MULTIPLE CONGENITAL ANOMALIES OF UNKNOWN ETIOLOGY : A RETROSPECTIVE STUDY & SYSTEMATIC REVIEW OF 94 CASES

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BY

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A Thesis/Practicum submitted to the Faculty of Graduate Studies of The University of Manitoba in partial fulfillment of the requirements of the degree of

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ABSTRACT

Approximately 2-3% of newborns will have an identifiable major congenital anomaly and 4-7 per thousand will have multiple congenital anomalies. Congenital anomalies are among the leading causes of infant mortality and contribute substantially to infant morbidity. Early and accurate diagnosis of a child with multiple congenital anomalies is important for patient management, providing useful genetic counselling regarding etiology and recurrence risk, prenatal diagnosis, screening and recommendation for evaluation of other family members. Unfortunately, providing a diagnosis for a child who presents with multiple congenital anomalies is a complex task and in many cases the etiology is unknown. The objectives of this study were: 1) to determine the value of a systematic review of patients with multiple congenital anomalies of unknown etiology, including addressing the success rate in making a diagnosis and to determine the factors that are associated with an increased chance of making a diagnosis and 2) to determine an appropriate recurrence risk estimate for infants with multiple congenital anomalies of unknown etiology.

At the time of this study over 35,000 patients had been referred to the Section of Genetics & Metabolism. Records were kept in the Section's database system including the reason for the referral. 2,681 cases underwent a chart review because of an indication of multiple congenital anomalies. Of those initial cases, 94 were included in the study for the following reasons: 75 were undiagnosed multiple congenital anomaly cases, 9 were

"new" diagnoses reported by members of the Section of Genetics & Metabolism and 10 were cases in which the diagnosis was made after one year's time from the initial contact.

All 75 cases of undiagnosed multiple congenital anomalies were re-evaluated by using LDDB, POSSUM and on-line databases such as OMIM and Medline. Of those 75 cases, 19 were given a new and/or confirmed syndrome diagnosis, 13 were given a new and/or confirmed association/sequence diagnosis and the remaining 43 cases remained unknown giving an overall success rate of 42.6%

Discriminant functional analysis was performed on demographic variables and on phenotypic traits to determine what factors potentially determine the likelihood of making a diagnosis. No demographic variables were found to have significant probability values. Three phenotypic traits were identified to have significant probability values. These traits were renal dysplasia/cystic kidneys, postaxial polydactyly and tracheal defects.

Recurrence risk estimates for infants with MCA of unknown etiology were performed. Two separate groups were analyzed, Group 1 – diagnosis made and Group 2 – no diagnosis made. In the cases in which a diagnosis was made, the estimated risk of recurrence was 14.8% and in the cases in which no diagnosis was made, the estimated risk of recurrence was 15.0%.

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LIST OF ABBREVIATIONS & ACRONYMS

A	Association & sequence diagnosis
ACC	Agenesis of the corpus callosum
AMA	Advanced maternal age
AS	Aqueductal stenosis
ASD	Atrial septal defect
BCD	Blepharo-cheilo-dontic syndrome
CA	Congenital anomaly
CFC	Cardio-facial-cutaneous syndrome
CHARGE	Coloboma, heart anomaly, choanal atresia, mental retardation, genital and ear anomalies
CLP	Cleft lip and palate
CNS	Central nervous system
CP	Cleft palate
CODAS	Cerebral, ocular, dental, auricular, skeletal anomalies syndrome
COFS	Cerebro-oculo-facial-skeletal syndrome
CS	Cockayne syndrome
DD	Developmental delay
DOB	Date of birth
DX	Diagnosis
EFE	Endocardial fibroelastosis
FAS	Fetal alcohol syndrome
FAV	Facio-auriculo-vertebral dysplasia
FHX	Family history
FISH	Fluorescence in situ hybridization
GAPO	Growth retardation, alopecia, pseudoanodontia and optic atrophy
GI	Gastrointestinal
IUGR	Intrauterine growth retardation
IWG	International Working Group
L	Left
LD	Late diagnosis
LDDB	London dysmorphology database
MART	Martsolf: skeletal dysplasia, polydactyly and Pierre Robin syndrome
MASA	Mental retardation, aphasia, shuffling gait and adducted thumbs
MAT	Maternal
MCA	Multiple congenital anomalies
MOTA	Manitoba oculotrichoanal syndrome
MR	Mental retardation
MURCS	Mullerian duct, renal agenesis and cervical thoracic somite dysplasia
N	New diagnosis

NER	Nucleotide-excision repair
NTD	Neural tube defect
OMIM	Online Mendelian Inheritance in Man
PAT	Paternal
PDA	Patent ductus ateriosus
POSSUM	Pictures of standard syndromes and undiagnosed malformation
R	Right
R-V FISTULA	Recto-vaginal fistula
S	Syndrome diagnosis
SAMS	Short stature, auditory canal atresia, mandibular hypoplasia and skeletal abnormalities syndrome
SCD	Spondylocostal dysostosis
SHH	Sonic hedgehog
SMA	Spinal muscular atrophy
TBS	Towns-Brocks syndrome
T-E FISTULA	Tracheo-esophageal fistula
TGV	Transposition of the great vessels
TOF	Teratology of fallot
T21	Trisomy 21
U	Unknown diagnosis
VATER	Vertebral anomalies, anal atresia, tracheo-esophageal fistula, radial ray and renal anomalies
VSD	Ventricular septal defect
YOB	Year of Birth

1. INTRODUCTION

1.1 MULTIPLE CONGENITAL ANOMALIES

Approximately 2-3% of newborns will have a recognizable major congenital anomaly and 4-7 per thousand children will be born with multiple anomalies. Major anomalies are defined as these of medical, surgical or cosmetic significance (Winter and Baraitser, 1984; Winter, Baraitser and Douglas, 1984; Patton, 1987; Evans, 1991). The incidence of major anomalies is even higher among spontaneous abortions and stillborn infants (Stevenson et al., 1993). In addition to these findings, 15% of newborns will have one or more minor anomalies (Marden et al., 1964). Minor anomalies are structural changes that are thought to pose no significant health or social consequences (Stevenson et al. 1993). Minor anomalies are of importance because, as the number of minor anomalies in a child increases, so does the risk for associated major malformations (Table 1). They can also provide critical clues that aid in the diagnosis of a specific syndrome.

TABLE 1 Concurrence of minor and major anomalies at birth in three series

# OF MINOR ANOMALIES	PERCENT WITH MAJOR ANOMALIES		
	Leppig et al. (1987)	Marden et al. (1964)	Meches (1983)
0	2.3	1.4	1.2
1	3.7	2.9	3.8
2	6.7	10.8	12.5
>3	19.6	90	26

Modified from Stevenson et al. (1993): Human Malformations and Related Anomalies

Congenital anomalies are among the leading causes of infant mortality and contribute

substantially to infant morbidity (Yoon et al., 1997). The overall frequency of birth defects has remained constant. However, the decline in infant mortality due to infections, poor prenatal or postnatal care, or nutritional factors has significantly heightened the importance of birth defects. Population-based studies have shown that birth defects and genetic diseases account for a high percentage (9-40%) of all pediatric hospitalizations (Scriver et al., 1973; Hall et al., 1978; Yoon et al., 1997). In addition to higher hospitalization rates, these children also tend to have longer hospital stays and higher readmission rates, and their hospitalizations are proportionally more costly then other types of pediatric hospitalizations (Cunniff et al., 1995).

Early and accurate diagnosis of a child with multiple congenital anomalies (MCA) is important for patient management, providing useful genetic counselling regarding etiology and recurrence risk, prenatal diagnosis, screening and recommendations for evaluation of other family members (Witt and Hall, 1985). Making a diagnosis in a child who presents with MCA can be a daunting task due to the complexity of these conditions with regard to understanding of the etiology and mechanism of action. Further, the large number of syndromes described in the literature makes the task that much more difficult. It has been estimated that a new syndrome is described at a rate of one or more a week (Toriello, 1988).

1.2 DYSMORPHOLOGY

Dysmorphology is the study of abnormal physical development by interpreting patterns of structural defects. The term "dysmorphic" is used to describe a body part that has not followed a normal pattern of growth or formation and it is often disproportionate when compared to normal development (Witt and Hall, 1985). A specific diagnosis is usually made on the overall pattern of anomalies. However, variations in the presentation

of an anomaly can arise from patient to patient and morphologic features can change over time, becoming more or less pronounced.

One of the most frequent tasks the dysmorphologist/clinical geneticist performs is to try and reach a diagnosis for a patient or family. In some cases, this can be done in one initial consultation with the patient. However, the majority of cases require a more extensive investigation. There are a number of steps that a dysmorphologist may take to try and reach a tentative diagnosis. Diliberti (1988) outlined the steps and procedures that a dysmorphologist typically takes. The first step usually involves a complete physical examination and detailed family and pre and postnatal history. If the diagnosis is not obvious, the next step is to review reference texts. With this, there are a number of approaches one can take. One strategy is to select a single physical feature and search reference texts for syndromes that contain that feature. Obviously this approach will yield a large number of possible diagnoses unless the physical feature is quite rare. From this, one can create a working list of candidate syndromes. Comparison of the patient's features with those of the candidate syndromes can shorten the list into a small number of potential diagnoses. The use of published reference material such as medical journals and photographs, and consultation with other dysmorphologists, in addition to performing a number of tests, e.g., radiographs, ultrasounds, chromosomal analysis and molecular tests, may also be necessary in order to reach or confirm a diagnosis (Winter and Baraitser, 1984).

Reference books such as Smith's textbook *Recognizable Patterns of Human Malformations* 5th edition (Jones, 1997) list only a small fraction of malformation syndromes. Computer technology has been able to offer some solutions for this problem. A number of computerized databases have been developed to allow the user to search a

large volume of syndromes by a variety of means.

1.3 MECHANISMS OF ABNORMAL MORPHOGENESIS

There are four categories that are often used to describe the major types of structural anomalies. These are malformation, deformation, disruption and dysplasia.

1.3.1 MALFORMATION

A malformation is defined as a " morphological defect which resulted from an intrinsically abnormal developmental process" (Thompson et al., 1991). These tend to be defects of organs, part of an organ or larger areas of the body (Witt and Hall, 1985). Malformations can be the result of chromosomal or monogenic defects, and can be grouped into three classes: incomplete morphogenesis, which occurs when there is developmental arrest (e.g. renal agenesis), redundant morphogenesis (e.g. polydactyly) and aberrant morphogenesis in which the malformation has no normal counterpart (e.g. paratesticular spleen) (Cohen, 1986).

1.3.2 DEFORMATION

A deformation is defined as an " abnormality in form or position of a body part caused by a non-disruptive mechanical force" (Thompson et al., 1991). These defects can be distinguished from malformations by the fact that they tend to be reversible and correctable and arise most often late in fetal development. Deformations may arise from malformational or functional causes (e.g. neurologic and muscle disturbances, connective tissue defects) and/or intrauterine constraint (Cohen, 1986). An important distinction must be made between malformations and deformations. Malformations arise in the

embryo during organogenesis and are primary errors in morphogenesis. Deformations tend to arise during the fetal stage of pregnancy and are changes in a shape of the previously normal structure. Perinatal mortality tends to be much higher in children with malformations as compared with those children with deformations. A final distinction that can be made between malformations and deformations is the potential for correction of the deformation defect either spontaneously or by intervention by posturing means. Malformations can not spontaneously revert back to the normal structure nor can they be corrected without major surgery or medical intervention (Cohen, 1986).

1.3.3 DISRUPTION

A disruption is defined as a " morphological defect resulting from breakdown of, or interference with, an originally normal developmental process" (Thompson et al., 1991). Disruptions are due to events that occur after embryogenesis; they tend to be sporadic events with a low recurrence risk. While disruptions are often environmental in nature, genetic factors may also be involved. For example, amniotic bands are strands of amniotic tissue that can adhere to the embryo or fetus causing constriction, amputation of limbs and digits as well as other defects such as facial clefts (Stevenson et al., 1993). Teratogens can also interfere with normal development of the fetus causing a wide range of anomalies. Fetal Alcohol Syndrome is an example of a common teratogenic syndrome.

1.3.4 DYSPLASIA

A dysplasia is defined as an " abnormal organization of cells into tissues and its morphological consequence" (Thompson et al., 1991). Dysplasias tend not to be restricted to specific sites or organs as the abnormality pertains to a specific tissue type.

Therefore anomalies tend to be tissue specific (e.g. Chondrodysplasia punctata) (Wynbrandt and Ludman, 1990).

1.4 PATTERNS OF ABNORMAL MORPHOGENESIS

Recognizing the specific patterns of birth defects can aid in the understanding of where and when in embryogenesis the defect(s) occurred. Understanding the type of pattern can influence how the family is counselled, and can play a role in patient management. Because it is important to understand and use the correct terminology when describing the patterns of abnormal development, the International Working Group (IWG) redefined and clarified the four terms used in dysmorphology: syndrome, sequence, association, and developmental field defects (Spranger et al., 1982).

1.4.1 SYNDROME

A syndrome is defined as a "pattern of multiple anomalies thought to be pathogenetically related and not known to represent a single sequence or a polytopic field defect" (Spranger et al., 1982). The use of the term "syndrome" indicates that a specific diagnosis has been made and that the natural history and recurrence risks are potentially known. That doesn't necessarily imply that the etiology is known or well understood. Syndromes tend not to be static entities as there is continuous expansion and revision of the phenotype through new case reports. Advances in both embryology and molecular genetics can also redefine the grouping of syndromes.

The term "syndrome" encompasses a diverse category of abnormal morphogenesis. To date, there are over two thousand syndromes described in the literature, of which the etiology can be chromosomal (10-15%), monogenic (6-8%), teratogenic (5-7%) or of

unknown etiology (50%) (Thompson et al., 1991; Stevenson et al., 1993).

1.4.2 SEQUENCE

A sequence is defined as a " pattern of multiple anomalies derived from a single known or presumed prior anomaly or mechanical factor" (Spranger et al., 1982), and that "a sequence is a pathogenic and not a causal concept" (Martinez-Frias et al., 1998). The secondary effects that result from the initial insult can be structural defects, functional defects or defects in form and growth. While the secondary effects are known to result from the primary defect, the etiology of the primary defect may not be understood.

1.4.3 ASSOCIATION

An association is a " non-random occurrence in two or more individuals of multiple anomalies not known to be polytopic field defects, sequence, or syndrome" (Spranger et al., 1982). An association is considered a statistical relationship, and not a pathogenetic or causal relationship. The concept of associations has been generally accepted; however, some authors have questioned whether or not associations are in fact developmental field defects (Opitz, 1994; Martinez-Frias, 1995). Associations are believed to not show altered sex ratio, tend to have low recurrence risks (usually thought to be sporadic in nature), are found in higher proportion in twins and tend to affect the midline (Opitz, 1993; Martinez-Frias and Frias, 1997).

1.4.4 DEVELOPMENTAL FIELD DEFECTS

The developmental field defect theory was first introduced by the IWG in 1982 (Spranger et al., 1982) and then clarified and amended at the International Congress of

Human Genetics in Berlin (Opitz et al., 1987). The developmental field defect concept is as follows: "a morphogenetic (or developmental) field is a region or part of the embryo which responds as a coordinated unit to embryonic induction and results in complex or multiple anatomic structures." Simply stated, a polytopic or developmental field defect is a pattern of anomalies that are caused by disruption of a single developmental field. Therefore, disruption in any field regardless of the size of the field, or stage of the development, whether due to teratogenic or mutation factors, will have morphological consequences (Martinez-Frias et al., 1998).

1.5 ETIOLOGY

Etiology simply means, "cause." The etiology of congenital anomalies can be the result of genetic factors, environmental factors, a combination of both genetic and environmental factors (here termed multifactorial inheritance), the twinning process or can be due to factors not yet known. Understanding the etiology may determine the manner in which the family is counselled and how patient management is conducted.

1.5.1 ENVIRONMENTAL

It is estimated that 5 to 7% of all congenital anomalies can be attributed to environmental teratogens, (Evans, 1991). A teratogen is any agent that can produce an anomaly or raise the population incidence of an anomaly. There are many known human teratogenic agents and they can be grouped into four main categories: infections, maternal disorders, drugs and ionizing radiation (Thompson et al., 1991).

There are a number of common characteristics that all teratogens share. Teratogens can only have their influence during fetal development, and only at the time of exposure.

They tend to be sporadic events with a low likelihood of recurrence unless exposure to the teratogen persists in subsequent pregnancies. They have a direct influence on development by interfering with cellular metabolism, disturbing regional vascular supply and killing cells (Stevenson et al., 1993). They are dose dependent such that the greater the length of time of exposure and the greater the amount of exposure during development, the greater the severity of the teratogenic effect to the fetus. Teratogens can also have an indirect influence by causing chromosomal aberrations or mutations (Thompson et al., 1991). Many well-recognized conditions are the result of teratogenic effects.

1.5.2 GENETIC

In all, 15-25% of cases of congenital anomalies can be attributed to genetic causes (Evans, 1991; Thompson et al., 1991; Stevenson et al., 1993). The genetic causes can be subdivided into two main categories, chromosomal or monogenic.

1.5.2.1 Chromosomal

Chromosomal aberrations are estimated to account for 10-15% of all cases of congenital anomalies (Stevenson et al., 1993). Chromosome based patterns of anomalies tend to share a number of common characteristics. Children with a chromosome abnormality tend to have growth retardation, both prenatally and postnatally, varying degrees of mental retardation, and tend to have multiple systems involved. There are two main types of chromosomal abnormalities: structural and numerical. These abnormalities can involve either the autosomes or sex chromosomes. They tend to be sporadic events, thus have a low risk of recurrence in future pregnancies. There are; however, cases of familial structural chromosome rearrangements. These rearrangements will have

different risks of recurrence depending on the type of rearrangement and the chromosomes involved (Gardner and Sutherland, 1996). There can be an increased incidence of recurrent spontaneous abortions in families with a chromosome abnormality.

1.5.2.2 Monogenic

It is estimated that 6-8% of all MCA can be attributed to the pleiotropic effects of single gene mutations (Evans, 1991; Stevenson et al., 1993). Disruptions in a gene's function tend to result in a distinct pattern of abnormalities that can be recognized and classified into a distinct syndrome. To date, there are well over two thousand non-chromosomal syndromes that have been described in the literature (Winter and Baraitser, 1987). Classification of these syndromes are based on their mode of inheritance: autosomal dominant, autosomal recessive or X-linked.

1.5.3 MULTIFACTORIAL

Multifactorial inheritance is based on the idea that both genetic and environmental factors work in an interrelated manner to influence phenotypic expression. This concept relies on the threshold theory, which is based on the concept that an individual is genetically predisposed, but that expression of the phenotype will only occur when environmental stress forces that predisposition beyond a certain point (i.e. the threshold) (Fraser, 1996). Multifactorial inheritance accounts for 25% of all birth defects and includes such anomalies as cleft lip/palate, spina bifida and congenital heart defects (Evans, 1991; Stevenson et al., 1993). While multifactorial inheritance accounts for a large number of isolated birth defects, it is not implicated in most cases of MCA (Witt and Hall, 1985).

1.5.4 UNKNOWN ETIOLOGY

Chromosomal, monogenic and multifactorial inheritance accounts for approximately 50% of anomalies in newborns. The remaining 50% of these cases are of unknown etiology. Being unable to determine the etiology impacts upon patient management, prognosis, and the way in which the individual/family is counselled with regard to risk of recurrence for future pregnancies, and risk to other family members. In those situations where a diagnosis is not made, parents are counselled with an estimated recurrence risk of 1 to 5%, and cautioned that the risk of recurrence maybe as high as 25% to 50% (to represent an unknown recessive or dominant disorder). While there have been many studies that have looked at empiric recurrence risks for single birth defects, there has been only one study to date that has looked at the recurrence risk following the birth of a child with MCA (Czeizel et al., 1988). This study found that sibs of the index patient born with MCA of unknown etiology had a 3.9% risk of having the same pattern of anomalies and that 3.5% of the sibs had at least one of the anomalies present in the index patient.

Hall et al. (1998) reported on a retrospective study of all cases of "unknown multiple congenital anomaly syndrome" seen at the University of Kentucky from 1981 to May 1998. They reviewed the number of follow-up visits each case had and the number of follow-ups (average of 2.3) required before a diagnosis was given, and broke those cases down into the type of condition (i.e. chromosome versus monogenic). They found that in, most cases, repeated follow-up was required to successfully diagnose an unknown MCA syndrome. They stated that this was due in part to: 1) phenotype change into a recognizable syndrome, 2) follow-up stimulated additional successful literature searches/matches, and 3) critical features/patterns initially missed became obvious. They suggested that periodic follow-up for cases of undiagnosed MCA syndromes should become a standard of practice.

To date, the Hall et al. (1998) review has been the only reported study in the literature to look at the value of a systematic re-evaluation of undiagnosed cases of MCA. One point that the report did not comment on was what impact did new advances in the field of human genetics, along with continuous reporting of "new" syndromes had on the success of reaching a diagnosis.

There have been a number of new advances made in diagnostic techniques and in recognition of multiple congenital syndromes. New syndromes are being continuously delineated and reported in journals, dysmorphology texts and other such references. Computerized database systems have been developed to aid in syndrome identification including online databases available through the World Wide Web on the Internet.

1.6 COMPUTERIZED DATABASES

The development of efficient computer databases opened the possibility of leaving the task of searching repetitively list of signs and syndromes in the hopes of finding the correct diagnosis to a computer. Research on computer-aided diagnosis started in the 1960s with Warner and his group and more specifically research in the field of computer-aided diagnosis for malformation syndromes began in the 1980s (Pelz et al., 1996). These computerized databases were designed to aid in the diagnosis of already well-known syndromes and to recognize rare or potentially new syndromes (Winter and Baraitser, 1987).

1.6.1 POSSUM

POSSUM stands for Pictures of Standard Syndromes and Undiagnosed Malformations. It is an Australian computer program developed in 1987 from the

Murdoch Institute for Research into Birth Defects, Melborn Australia (Stromme, 1991).

The current version, POSSUM 4, contains information on 2,120 syndromes with an atlas containing 1,331 traits. Each syndrome contains reference material that can direct the user to the original sources. In addition, the majority of the syndromes have illustrations of the clinical phenotype, examples of patients with the condition at different ages to demonstrate the variations of the condition, X-rays or radiographic findings, and some are accompanied by video-clips. To perform a search with POSSUM, the clinical features of the patient must be entered into the database. The clinical features can include malformations, minor anomalies, and neurological, biochemical, mental, chromosomal or other such characteristics. Once these features are coded into the database, it can then produce a list of syndromes compatible with those features and will rank them in order from most compatible (highest number of features found in both the patient and syndrome) to the least compatible. Using different parameters can modify the search. For example, one can modify the search by marking a particular feature as a major finding such that the list of candidate syndromes must contain that feature. One can perform a broad based search (use many features in the search all with equal "weight") or a narrow based search (by using only major features of the patient). Once the list of candidate syndromes has been generated, the clinical characteristics of each syndrome can then be studied and compared with the patient's findings.

1.6.2 LDDB

The London Dysmorphology Database (LDDB) was developed by Winter, Baraitser and Douglas in 1984. The 1995 version contains information on over 2,500 non-chromosomal syndromes with reference to the literature for each syndrome. Like POSSUM, most of the syndromes are illustrated with photographs. Information in the

LDDB database was obtained from a review of all genetic and pediatric journals from 1969 onwards. Included were all reported cases of patients with non-chromosomal MCA, including single case reports (Patton, 1987).

The fundamental principles of the LDDB system are the same as that of the POSSUM system. In order to search the LDDB database, identifying characteristics of the patient must be entered into the system. The LDDB database contains a master list of over 1,200 features that are arranged into three levels. The first level corresponds to the general clinical region (e.g. eyes), the second level refers to a subdivision of that region (e.g. iris) and the third level refers to a specific abnormality (e.g. coloboma). This allows the user to use broad or narrow search parameters (Evans, 1995). Once the clinical features have been entered into the system, a list of candidate syndromes can be produced. By a process of elimination, one may then arrive at a tentative diagnosis. The user can also modify their searches by using different key features, varying the number of features used as criteria and by changing the weight (i.e. importance) given to each clinical feature (Diliberti, 1988).

The role of both the LDDB and POSSUM is to function as a diagnostic tool for the user and to aid in syndrome identification. Both systems were designed with the intention of being used by specialists in the field of dysmorphology to aid in their decision making and not to make the diagnosis for the user. The authors of both LDDB and POSSUM systems have emphasized that a good approach to using these systems is to base a search around one key feature or anomaly together with general clinical features. The ability to search on general features is useful, as features tend to show considerable variability from patient to patient with the same syndrome.

Pelz et al. (1996) looked at the usefulness of both the LDDB and the POSSUM

systems. Two search strategies were used. A "novice's strategy" where all clinical finding were used in the search and an "expert's strategy" where only a select group of clinical features were used in the search. All cases used in the study already had a confirmed diagnosis. They found that, using the expert's strategy, the correct diagnosis was suggested by the LDDB in 68% of the cases and by POSSUM in 63% of the cases with the percentage being slightly lower for each when the novice strategy was used. This suggests that a "novice" use of both POSSUM and LDDB to aid in syndrome diagnosis is a valid approach.

There are some inherent problems associated with the use of computerized databases in syndrome identification. With both the LDDB and the POSSUM systems, there are concerns with regard to the inflexibility of the features represented in the master lists/atlas of traits. Concerns arise over the terminology and interpretation of how the features may be used or described (Diliberti, 1988; Evans, 1995; Harned et al., 1996; Pelz et al., 1996). The user is confined to using those traits listed in the master list.

Another problem is the lack of certainty with respect to individual features of a syndrome. What certainty does the user have in knowing whether or not an abnormality exists for those syndromes? For example, if the abnormality is only found in a small percentage of the cases for a particular syndrome, it may not be listed in the database as part of that syndrome. This may lead to some doubt as to the validity of the diagnosis in the patient who presents with the feature in question (Evans, 1995; Pelz et al., 1996).

Overall, computerized databases like POSSUM and LDDB, in addition to on-line databases such as OMIM (Online Mendelian Inheritance in Man), are valuable diagnostic tools. When these systems are used correctly, they are an effective step towards establishing a diagnosis in a patient with MCA of unknown etiology.

1.7 DUTY TO RECONTACT

The term "duty to recontact" refers to the possible ethical and /or legal obligations of genetic service providers to recontact former patients about advances in research that might be relevant to them (Fitzpatrick et al., 1999). Advances in medical genetics are occurring at an exponential rate. This is the result in part to the progress in the Human Genome Project and elucidation of the genetic bases of cancer and other genetic conditions. As a result of this growth, a concern has been raised that there is an ethical and potentially legal obligation of those in this field to recontact former patients when new advances occur.

Theoretically, recontacting patients when new information becomes available is an honorable goal to strive for. However, there are a number of problems associated with this concept. Likely the most substantial problem is the large task of recontacting patients. In order to recontact all patients who would potentially benefit from the new information, one would have to first identify these individuals. This may mean case/chart reviews, which would require a large effort in both time and funds. Most facilities would lack the resources to fulfill this task. Once those individuals were identified, one must than make contact with them. The concept of recontacting patients has raised some concerns. Does the benefit of recontacting patients out-weigh the possible burdens associated with recontacting patients, especially if a long period of time has elapsed since the last contact? The benefits of recontacting patients include improved patient care, reduced uncertainty in recurrence risk and renewed hope for the future. Possible negative outcomes would be patient anxiety and stress, intrusion of privacy and concerns about health/life insurance (Fitzpatrick et al., 1999). Some authors have advocated that it is the patient's responsibility to take a more active role in their medical care. This would mean patients would have more responsibility for keeping informed about research advances

(Fitzpatrick et al., 1999; Sharpe, 1999). This may not be a practical approach either, especially if the patient has limited understanding about his/her condition or if the patient does not have access to the information.

Regardless of which approach is taken, neither is optimal. Most centres do not have formal guidelines with respect to their duty to recontact patients. The concept of an ethical/legal duty to recontact may not even be a manageable or obtainable goal. However, as this study has demonstrated, there is a benefit in having some sort of systematic re-evaluation of patients. While it is not feasible to start re-evaluating all patients for every new advancement or breakthrough that occurs in the field of human genetics, it may be worth while for each centre to examine their demographics and determine what, if any, systematic re-evaluation of specific cases (i.e. unknown MCA) would be cost-effective and beneficial.

1.8 OBJECTIVES AND HYPOTHESES OF THE STUDY

The objectives of the study were as follows:

1. To determine the value of a systematic review of patients with MCA of unknown etiology. This included addressing the success rate in making a diagnosis and determining what factors were associated with an increased chance of making a diagnosis.
2. To determine an appropriate recurrence risk estimate for infants with MCA of unknown etiology.

There were two hypotheses tested in this study:

1. Advances in syndrome diagnosis will allow a significant number of new diagnoses to be made following a systematic review of previously undiagnosed multiple malformation cases.

2. Different patterns of abnormal morphogenesis are associated with different recurrence risks.

2. METHODS

2.1 CASE ASCERTAINMENT

When this study was initiated in 1997, over 35,000 patients had been seen in the Section of Genetics and Metabolism. Records of all of these patients were available in the Section's computerized database. Patient demographics, reason for referral, the geneticist who saw them and their diagnosis were recorded. Of these 35,000 patients seen, 2,681 cases underwent a chart review. These cases were ascertained through the Section of Genetics and Metabolism's database system using the following search criteria:

1. Referral for assessment of a patient affected with MCA without a specific diagnosis.
2. Referral for counselling because of a family history of MCA.
3. Referral to the Section of Genetics and Metabolism other than the General Genetics Clinic for assessment of or counselling for family history of MCA.
4. Referral to the cytogenetics laboratory for karyotype analysis because of MCA of unknown etiology.
5. Referral because the patient was affected with or had a family history of "congenital anomalies".
6. Referral for assessment because of a single congenital anomaly.

Of the initial 2, 681 cases, 94 were included in the study under one of three inclusion criteria:

1. The affected individual had at least two major malformations and did not have a known diagnosis and/or more than one potential diagnosis in the differential.
2. The affected individual had MCA, but a diagnosis had not been made within one year's time from the initial genetic assessment.
3. The affected individual had a provisionally "new" MCA syndrome that had been delineated and reported by a member of the Section of Genetics and Metabolism.

Of the 94 cases, 75 cases fell within the first criterion, 10 cases fell within the second criterion and 9 cases fell within the third criterion.

Figure one is a schematic summarization of the case ascertainment.

2.2 CASE EXCLUSION

Of the initial 2, 681 cases that underwent a chart review, 2,587 cases were excluded from the study based on the following reasons:

1. There was only one major anomaly in the index patient.
2. There was insufficient information available on the affected individual.
3. The case (affected individual) was previously ascertained into the study through previous search criteria (e.g. a relative of an affected individual was seen for counselling because of the family history of MCA). Lack of adequate information on the affected individual. The majority of the cases for this study were ascertained under the second referral method - referral to Genetics for a family history of MCA. There tended to be little information or documentation on the affected individual.
4. The referred individual was not seen or counselled by a member of the Section of Genetics and Metabolism (i.e. sample sent in to the cytogenetics laboratory for chromosome analysis without referral to Genetics).
5. The affected individual was thought to have a specific but tentative diagnosis due to atypical clinical features or unconfirmed diagnostic results.
6. Any case of MCA in which a chromosome abnormality had been demonstrated by chromosomal analysis.

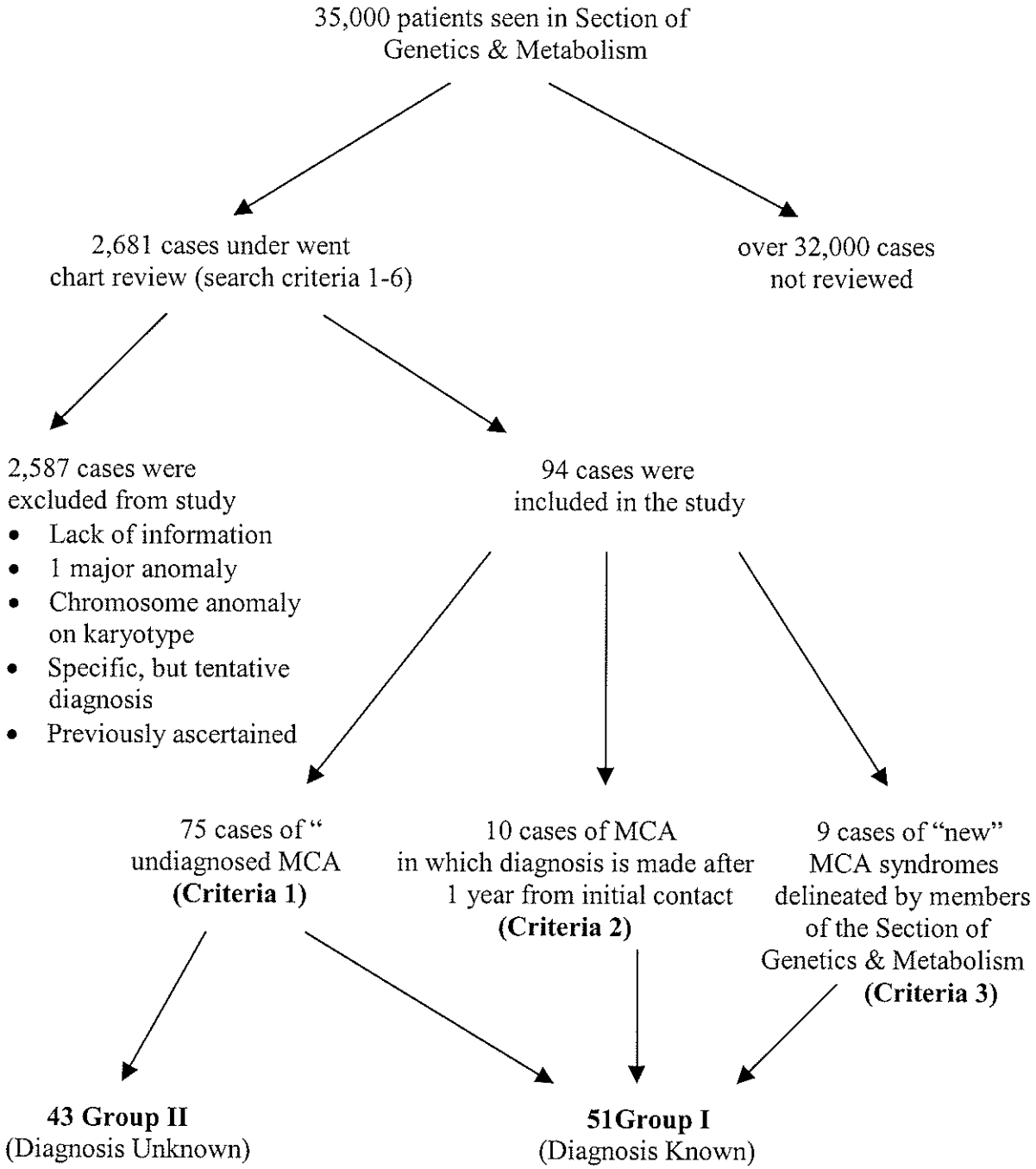

Figure 1. Schematic for case ascertainment and breakdown of cases into inclusion criteria

2.3 SYSTEMATIC RE-EVALUATION OF UNDIAGNOSED MCA: criteria 1

2.3.1 Retrospective Diagnosis

All 75 cases of undiagnosed MCA were re-evaluated using both the LDDB and POSSUM databases, on-line databases including OMIM, Medline and its subbranch PubMed, and reference material such as Smith's *Recognizable Patterns of Human Malformations* 5th Ed. (Jones, 1997). For each case, all clinical findings, including both major and minor anomalies, were entered into both the LDDB and POSSUM programs for analysis. All syndromes with a known chromosomal defect were excluded from the search. This was done as it was assumed that all cases in the study had a normal karyotype. However, 14 cases had not had a chromosomal analysis preformed. This was due to two main reasons: 1) failure of cell culture growth, or 2) chromosome analysis was not requested. A successful search required that there was a minimal match of two anomalies between the cases and the candidate syndromes. A number of searches were performed for each patient using various combinations of anomalies and weight (importance) given to each anomaly. Once a working list of candidate syndromes was identified, reference material, including original case reports if available, was used to reach a tentative diagnosis. If no diagnosis could be made, the case remained as an "unknown". All new diagnoses had to be agreed upon by two members of the Section of Genetics and Metabolism. A third member of the Section of Genetics and Metabolism was consulted if there was disagreement over a diagnosis. If possible, all diagnoses made in this study were confirmed by re-evaluating the patient in the Genetic Clinic and/or by cytogenetic, molecular or biochemical testing. Once a diagnosis was confirmed the new risk of recurrence was assessed and compared with the initial recurrence risk given to the family/patient. For these cases in which a diagnosis was made, two subdivisions were created to separate the cases based on the pattern of abnormal morphogenesis: 1)

syndromes and, 2) associations and sequences.

After re-evaluation of all 75 cases, the cases were grouped into two categories: Group one included all cases in which a diagnosis had been made and Group two included all cases that remained unknown. Included into Group one were all cases ascertained into study criteria two and three.

2.4 PREVIOUS MCA SYNDROME & ASSOCIATION DIAGNOSIS: criteria 2

Any MCA case with a definitive diagnosis, in which the length of time it took to make that diagnosis exceeded one year's time from the initial genetic assessment, was included into the study. All cases (10 cases in total) were evaluated to determine 1) the length of time it took from the initial assessment until a diagnosis was made and 2) why the diagnosis was delayed. These cases were also included in Group one for discriminant function analysis and recurrence risk estimations.

2.5 PROVISIONALLY NEW MCA SYNDROMES & ASSOCIATIONS: criteria 3

Any MCA case that was initially seen and reported as new MCA syndromes and/or associations by members of the Section of Genetics & Metabolism were included into this study. A total of 9 cases of "new" MCA syndromes and/or associations were delineated and reported by members of the Section of Genetics and Metabolism. These cases were also included in Group one for discriminant function analysis and recurrence risk estimations.

2.6 COMPUTERIZED DATABASE EVALUATION

For each case in which a diagnosis was made, the usefulness of computerized databases in helping to successfully make a diagnosis was evaluated. For each case that a diagnosis was made, each "search" was reviewed to determine what database(s) if any suggested the final diagnosis. The databases that were evaluated included POSSUM, LDDB, OMIM and PubMed. The success rate in percentage for each of the databases was calculated by taking the number of cases where the database was successful over the total number of cases in which a diagnosis was made (32 in total). This calculation was done for the above 4 databases. The total success rate was also calculated.

2.7 PHENOTYPIC & DEMOGRAPHICS ANALYSIS

2.71 Formation of the Phenotype & Demographic Sheet

A list of anomalies (traits) was obtained by review of the cases included in the study (95 cases in total as one "case" represented two affected individuals). Each trait was grouped into 10 main categories. These categories fell under two main groupings, systems or anatomical region: respiratory, cardiovascular, central nervous system (CNS), gastrointestinal, genitourinary, endocrine, musculoskeletal, craniofacial, skin and other. Most traits were retained for analysis with the exception of those traits that occurred fewer than four times. Additionally, for each case, demographic variables were included. The demographic variables used in this study were sex, year of birth, ethnicity, positive family history of similar anomalies, positive family history of other anomalies and symmetry of anomalies (i.e. anomalies occurring unilateral or bilateral).

This list of traits was used to create the phenotype sheet by categorizing each trait into appropriate system/region and by presentation of that trait. Each trait was coded as binary (present or absent) or multistate variable if applicable, e.g.:

Renal agenesis: No Left Sided Right Sided Bilateral

A listing of each trait classified by system/region and presentation can be found in Appendix 1.

2.7.2 Formation of the Coding Sheet

In order to accommodate the numerical parameters, each trait was correlated (coded) with a numerical value. Each multistate variable was coded such that the numerical value reflected the severity of the presentation with 0 equaling no involvement, e.g.:

Renal agenesis: No = 0 Left = 1 Right = 2 Bilateral = 3

A list of each trait with its associated numerical value (code) can be found in Appendix 2.

2.7.3 Discriminant Function Analysis

All numerical data from the coding sheet was entered into a Microsoft Access spreadsheet by case number. There were 71 variables per case. The presence or absence of each variable and the presentation of that variable if appropriate was indicated on the database. The 95 cases were divided into two groups as mentioned previously. Group one included all cases in which a diagnosis had been made and Group two included all cases in which no diagnosis was made. Discriminant function analysis was preformed to determine which variables might differentiate the two groups. Two separate analyses

were preformed. The first analysis evaluated the demographic variables and the second analysis evaluated the remaining 64 traits (anomalies). Probability values were derived for each trait/variable for both analyses.

2.8 RECURRENCE RISK ESTIMATION ANALYSIS

To determine an appropriate recurrence risk estimate for infants with MCA, each case (94) was reviewed and all indicated subsequent pregnancies were recorded (unless stated otherwise, all pregnancies in which the birth outcome was not known, were treated as "normal" outcomes). In 11 cases there was no information on subsequent pregnancies because: 1) the family/patient had been lost to follow up and thus subsequent pregnancy history was not available, or 2) the proband was seen once in the newborn period and the family was not brought back for follow- up counselling.

Each case was evaluated to determine if there had been a recurrence of a similarly affected sib(s) (affected same) or a recurrence of an affected sib(s) with malformations not similar to or associated with the proband's findings (affected other). The "affected other" category included both minor and major anomalies as well as multiple anomalies. This information was grouped into the two previously mentioned categories, diagnosis made (Group one) and diagnosis unknown (Group two). For Group one and Group two, the total number of "affected same" was compared to the total number of subsequent pregnancies to determine the percent of sibs with a recurrence. The same was done for the "affected other" category.

3. RESULTS

3.1 CASE ASCERTAINMENT: Breakdown per Referral Method

1) Of the 135 cases initially ascertained under category (1): referral made to the Section of Genetics and Metabolism because of MCA, 31 met the inclusion criteria for the following reasons: 23 cases had at least two major anomalies, 1 case was diagnosed after one year's time from their initial contact with genetics, 7 cases were new syndromes described by a member of the Section of Genetics and Metabolism.

2) Of the 149 cases initially ascertained under category (2): family history of MCA, 24 cases met the inclusion criteria for the following reasons: 23 cases had at least two major anomalies, and 1 case was diagnosed after one year's time from their initial contact with genetics.

3) Of the 121 cases initially ascertained under category (3): patient seen by a member of the Section of Genetics and Metabolism for MCA, outside of the regular general genetics clinic, 12 met the study's inclusion criteria for the following reasons: 10 cases had at least two major anomalies, and 2 cases were diagnosed after one year's time from their initial contact with the Section of Genetics and Metabolism.

4) Of the 52 cases initially ascertained under category (4): referral to the Section's cytogenetics laboratory for chromosomal analysis of a patient with MCA, none met the study's inclusion criteria.

5) Of the 13 cases initially ascertained under category (5): referral for "congenital

anomalies" none met the inclusion criteria.

6) Of the 2,211 cases initially ascertained under category (6): referral made for a single congenital anomaly (i.e. cleft lip/palate, limb anomaly, coloboma), 27 cases met the inclusion criteria for the following reasons: 19 cases had at least 2 major anomalies, 6 cases were diagnosed after one year's time from their initial contact with genetics, and 2 cases were new syndromes described by a member of the Section of Genetics and Metabolism.

In total, 75 cases were included in the study because of undiagnosed MCA. 10 cases were included in the study because a diagnosis was made after one year's time from the initial contact. Additional 9 cases were included in the study because a "new diagnosis" was made by the Section of Genetics and Metabolism (Table 2).

TABLE 2 The number of cases ascertained by each referral method per inclusion criterion

REFERRAL METHOD	# CASES ASCERTAINED	# CASES MET CRITERIA	2 OR MORE MCA	DIAGNOSED AFTER 1 YEAR	NEW SYNDROME
MCA affected	135	31	23	1	7
MCA family history	149	24	23	1	0
MCA other clinics	121	12	10	2	0
MCA cytogenetics lab	52	0	0	0	0
Congenital Anomalies	13	0	0	0	0
Single Anomalies	2211	27	19	6	2
TOTAL	**2681**	**94**	**75**	**10**	**9**

3.2 CASE EXCLUSION

Of the total number of cases that were excluded from the study, 983 cases were removed as the affected individual only had one major anomaly, 137 cases were removed due to insufficient information available on the affected individual, 1,364 cases already had a tentative or confirmed diagnosis, and 103 cases had been previously ascertained by one of the other search criteria. Table 3 summarizes the breakdown of these cases per referral method.

TABLE 3 Number of cases excluded from the study per exclusion criterion for each referral method

REFERRAL METHOD	1 CA	LACK OF INFO	DIAGNOSED	PREV. ASCERTAINED
MCA affected	34	13	57	0
MCA family history	19	17	64	25
MCA other clinics	20	19	68	2
MCA cytogenetics lab	13	10	26	3
Congenital Anomalies	1	2	7	3
Single Anomaly	896	76	1142	70
TOTAL	**983**	**137**	**1364**	**103**

3.3 SYSTEMATIC RE-EVALUATION OF UNDIAGNOSED MCA

The 75 cases included in the study under the first inclusion criteria (two or more major anomalies) were re-evaluated. Of the 75 cases, 19 were given a syndrome diagnosis, 13 associations or sequences were identified and the remaining 43 cases

remained unknown (Table 4).

TABLE 4 Summary of the 75 cases of MCA of unknown etiology after re-evaluation using POSSUM, LDDB, OMIM, Medline/PubMed and other references

STATUS	# OF CASES
Syndrome	19
Association or Sequence	13
Unknown	43

3.3.1 RETROSPECTIVE DIAGNOSIS: Syndromes

19 syndrome diagnoses were made (Table 5). In most cases, the original case report was obtained to help verify that the correct diagnosis had been reached. For each case a minimum of two major malformations had to correspond between the index patient and the clinical finding previously reported for the diagnosis in question. Once the diagnosis was confirmed, it was determined whether or not the mode of inheritance changed the risk of recurrence that the patient/family had been previously given (Table 6).

TABLE 5 List of syndromes diagnosed through re-evaluation including the number of major malformations present per case

CASE	# MCA	ANOMALIES	DIAGNOSIS
1-S	3	CNS/Brain Cleft palate Cardiac	COFS
2-S	3	Hydrocephalus Cardiac Tracheal stenosis	VACTERL-Hydrocephalus
3-S	3	Hirschsprung disease Microcephaly Hypospadias	Goldberg-Shprintzen
4-S	3+	Microcephaly Cleft lip/ palate Vertebral Renal	Diabetic Embryopathy
5-S	3	Coloboma Cleft palate VSD	Adducted Thumb syndrome
6-S	2	Renal agenesis Sacral defect	Diabetic Embryopathy
7-S	2	Cleft lip/palate Imperforate anus	Blepharo-Cheilo-Dontic
8-S	3	Club foot Brain Pulmonary stenosis	Cardio-Facio-Cutaneous
9-S	3+	Imperforate anus Polydactyly Renal Cardiac	Disorganization syndrome
10-S	3	Encephalocele Gastroschisis Radial hypoplasia	Disorganization syndrome
11-S	3	Agenesis of the corpus callosum NTD Cardiac	Lambotte syndrome
12-S	2	VSD Cleft palate	22q Deletion syndrome
13-S	3	ASD Syndactyly Cranium abnormality	Smith-Magenis syndrome
14-S	3+	Cleft lip/palate Renal agenesis Absent ribs Dandy -Walker malformation	Holzgreve-Thomas syndrome
15-S	a) 2 b) 2	Renal dysplasia Cleft lip/palate Horseshoe kidney Interrupted aortic arch	Holzgreve-Thomas syndrome
16-S	3	Iris coloboma Limb anomaly ASD	Ritscher-Schinzel
17-S	3	Congenital heart defect-VSD, ASD,PDA Hydrocephalus Cryptorchidism & Hypospadias	Alagille syndrome
18-S	3	Congenital heart defect Cleft lip/palate Coloboma	MOTA syndrome
19-S	3+	Microcephaly & Hydranencephaly Micrognathia Absent ribs	Seckel Syndrome

+ : number of major anomalies more than 3.

TABLE 6 Post-search mode of inheritance and associated risk of recurrence per newly diagnosed syndrome compared to pre-search risk estimates

CASE	PRE-SEARCH RISK ESTIMATE	POST-SEARCH MODE OF INHERITANCE	POST-SEARCH RISK OF RECURRENCE
1-S	25%	Autosomal Recessive	25%
2-S	0-25%	? Autosomal Recessive or X-linked	25%
3-S	0-25%	Autosomal Dominant *de novo*	2-5%
4-S	N/A*	Sporadic	2-5%
5-S	5-25%	Autosomal Recessive	25%
6-S	3%	Sporadic	2-5%
7-S	1-4% & 1-2%	Autosomal Dominant	Up to 50%[@]
8-S	5-25%	Autosomal Dominant *de novo*	2-5%
9-S	"extremely low"	Autosomal Dominant *de novo*	1-2%
10-S	1-2%	Autosomal Dominant *de novo*	1-2%
11-S	1-2%	? chromosomal	Up to 50%[#]
12-S	5%	Autosomal Dominant *de novo*	2-5%
13-S	N/A*	Autosomal Dominant *de novo*	2-5%
14-S	5%	Autosomal Recessive	25%
15-S	a) 0-25% b) 2-5%	Autosomal Recessive	25%
16-S	25%	Autosomal Recessive	25%
17-S	N/A	Autosomal Dominant *de novo*	2-5%
18-S	3-5%	Autosomal Recessive	25%
19-S	25-50%	Autosomal Recessive	25%

* Family lost to follow up and thus not counselled on risk of recurrence/family was not planning any future pregnancies
N/A Information was not available and/or recurrence risk was not given to family: reason unknown.
[@] Quoted "up to 50%" risk for recurrence as the condition has been shown to have reduced penetrance, hence a non penetrant carrier parent could not be ruled out.
can not rule out a subtelomeric translocation in the parents so recurrence may be as high as 50%

3.3.2 RETROSPECTIVE DIAGNOSIS: Associations & Sequences

13 new association or sequence diagnoses were made in this study (Table 7). As above, for each diagnosis to be made, there had to be a minimum of two major malformations found in both our patient and the corresponding "association or sequence". Literature searches were performed for each, and recurrence risks were re-evaluated (Table 8).

TABLE 7 List of associations/sequences diagnosed through re-evaluation including the number of major malformations present per case

CASE	# MCA	ANOMALIES	DIAGNOSIS
1-A	3	Coloboma-Iris Encephalocele Cleft Palate	Holoprosencephaly sequence
2-A	3	ASD Ambiguous Genitalia Rib Anomalies	MURCS
3-A	3	Omphalocele Diaphragm Hernia PDA	Schisis
4-A	2	Duodenal Atresia Dextropositional Heart	Duodenal & Cardiac
5-A	3	Ectrodactyly Horseshoe Kidney Absent Thumb	Limb & Renal
6-A	2	Omphalocele ASD/Pulmonary Stenosis	Omphalocele & Cardiac
7-A	2	Omphalocele Transposition of Great Vessels	Omphalocele & Cardiac
8-A	3	Cleft Palate Omphalocele Cystic Hygroma	Schisis
9-A	2	Hydrocephalus Diaphragmatic Hernia	Schisis
10-A	3	Choanal Atresia Ectrodactyly Interrupted Aortic Arch	CHARGE
11-A	3	Horseshoe kidney Polysplenia Esophageal Cyst	VATER
12-A	3	Vertebral & Rib Anomaly Club Foot	FAV
13-A	3	Polysplenia Situs Inversus Cardiac Defect	Laterality sequence

TABLE 8 Post-search mode of inheritance and associated risk of recurrence per newly diagnosed associations & sequences compared to pre-search risk estimates

CASE	PRE-STUDY RISK ESTIMATE	POST-STUDY RISK OF RECURRENCE	DIAGNOSIS
1-A	5%	6%	Holoprosencephaly
2-A	N/A	4%	MURCS
3-A	N/A	4%	Schisis
4-A	"low"	2-5%	Duodenal & Cardiac
5-A	N/A	Low	Limb & Renal
6-A	1 – 2%	1-2%	Omphalocele & Cardiac
7-A	1 – 2%	1-2%	Omphalocele & Cardiac
8-A	5%	4%	Schisis
9-A	4% NTD 1-2% diaphragm	4%	Schisis
10-A	2%	1%	CHARGE
11-A	"low"	1%	VATER
12-A	N/A*	2-5%	FAV
13-A	5%	2-5%	Laterality sequence

N/A: the information regarding the risk of recurrence was not available in the chart when reviewed.
* Family lost to follow up and thus not counselled on risk of recurrence/family was not planning any future pregnancies.

3.3.3 UNDIAGNOSED CASES

Re-evaluation of the remaining 43 cases, which fell under inclusion criteria 1 was not successful in obtaining a diagnosis. These cases remained as a "MCA syndrome of unknown etiology". Table 9 summarizes these cases and includes any significant prenatal and family history along with each patient's clinical findings.

TABLE 9 Summary of Cases that remain unknown: medical/family history & major anomalies

CASE #	SEX	CONSANGUINITY	ETHNICITY	MATERNAL DISEASE	TERATOGEN EXPOSURE	FAMILY HISTORY	MAJOR ANOMALIES & CHROMOSOME ANALYSIS
1-U	F	? incest	Philippine	-	-	-	Imperforate anus recto-vaginal fistula microcephaly microphthalmia complex congenital heart disease (VSD ASD PDA TGV) 46,XX
2-U	F	-	Metis	-	-	-	Dysmorphic cerebral atrophy ASD VSD hypotonia DD 46,XX FISH for Smith-Magenis normal
3-U	M	-	N/A	-	-	Maternal uncle ? heart defect	Complex congenital heart disease (VSD PDA TGV hypoplastic R ventricle) duodenal atresia jejunum dysplasia 46,XY
4-U	F	-	Mennonite	Hypertension	-	Paternal uncle bowel malrot.	T-E fistula Complex congenital heart disease (VSD pulmonary stenosis anomalous L carotid) lobe lobation anomaly-extra 46,XX
5-U	F	-	European	N/A	N/A	-	Microcephaly micrognathia VSD dysmorphic 46,XX
6-U	M	-	Aboriginal	-	Alcohol-regular	Sib - VSD	Cleft lip/palate VSD hydrocephalus penile agenesis imperforate anus bar/hemivertebra dysmorphic 46,XY
7-U	M	-	N/A	-	-	Sib – similar anomalies	Polycystic kidneys VSD dysplastic incisor macrocephaly dysmorphic Sib- polycystic kidneys pulmonary stenosis dysmorphic macrocephaly 46,XY
8-U	F	2nd cousins	Irish/ Fr. Canadian	-	-	Sib – rhizomelic limbs	Gastroschisis imperforate anus recto-vaginal fistula ear pit No chromosome studies
9-U	M	2nd cousins	N/A	Gestational diabetes	N/A	1st cousin-T21	Potter sequence penile agenesis imperforated anus dysmorphic No chromosome studies
10-U	F	-	Mennonite /Scottish/ Japanese	-	-	Mat cousin-CP Pat cousin-hydrocephalus	Diaphragm hernia pulmonary hypoplasia duplicated uterus and vagina hypoplastic L lung complex congenital heart disease 46,XX
11-U	F	-	N/A	-	-	1st cousin Menke disease	Holoprosencephaly T-E fistula Macrocephaly No chromosome studies
12-U	M	-	Polish	-	-	Pat aunt T21	Syringomyelocele absent rib cryptorchidism hypospadias inguinal hernia 46,XY

13-U	M	N/A	N/A	-	N/A	Mat 1st cousin MCA	Microcephaly dysmorphic facies micrognathia MR hypospadias 46,XY
14-U	M	-	Dutch/ Romanian	-	-	Fhx of "webbed toes"	Renal dysplasia/cystic preaxial polydactyly of the foot 46,XY
15-U	M	-	German/ Irish/ Welsh	-	-	-	Absent R hand polymicrogyria AS hydrocephalus rib anomalies cryptorchidism hypoplastic R arm **No chromosome studies**
16-U	M	-	Welsh/ English/ Scottish	-	-	2nd cousin anencephaly	Hydrocephalus syndactyly of fingers bilateral amputation of mid feet **No chromosome studies**
17-U	M	N/A	Native	-	-	Sib atresia ear canal	Myelomeningocele bilateral renal agenesis absent ribs absent bladder agenesis lower lumbar/sacral hypoplastic limbs imperforate anus shawl scrotum 46,XY
18-U	M	-	French Canadian	-	-	-	R Radial aplasia absent R thumb IUGR syndactyly toes 46,XY
19-U	M	-	N/A	N/A	N/A	Sib polydactyly of all limbs	Postaxial polydactyly of R hand and both feet R ventricular hypertrophy pulmonary stenosis **No chromosome studies**
20-U	F	-	English/ Scottish	-	-	Mat grandfather cleft palate	VSD ear anomaly coarse facies postaxial polydactyly hands and feet microcephaly small stature 46,XX
21-U	M	-	English/ Dutch	-	-	-	Hypospadias ASD VSD ear tag 46,XY
22-U	M	-	Polish/ Native	-	-	Pat 2nd cousin CLP	Agenesis corpus callosum microcephaly micrognathia bilateral hypoplasia radia/thumbs dysmorphic facies MR 46,XY
23-U	M	-	Native	-	Alcohol until 4 mo.	-	Macrocephaly arachnodactyly hypoplastic scrotum cleft palate dysmorphic facies no speech 46,XY*
24-U	F	-	N/A	-	Alcohol until 2 mo.	Father with craniosynostosis	Microphthalmia postaxial polydactyly foot retrognathia macrocephaly dysmorphic facies 46,XX
25-U	F	-	German	-	-	-	VSD dysplastic kidneys duodenal atresia hearing loss annular pancreas **No chromosome studies**

26-U	M	-	German/ French	-	-	-	Duodenal atresia macrocephaly VSD extra ribs MR 46,XY
27-U	M	-	Native	-	Alcohol heavy	½ sib MCA dx unknown	AS hydrocephalus agenesis corpus callosum micrognathia glossoptosis microphthalmia IUGR **No chromosome studies**
28-U	M	-	Ukrainian	-	-	-	Polydactyly preaxial hand triphalangeal thumb hypospadias **No chromosome studies**
29-U	M	-	Irish/ Scottish	-	-	-	IUGR VSD polysplenia 46,XY
30-U	F	-	Caucasian	-	-	Sib pyloric stenosis/ DD	Short stature MR shorten upper limbs umbilical hernia FTT midface hypoplasia teeth anomalies 46,XX
31-U	M	-	Native	-	-	-	Joint laxity duodenal/jejunal atresia club feet microcephaly 46,XY
32-U	F	-	West Indian	-	Alcohol	-	Cataracts extra nipple double collecting system 46,XX
33-U	F	N/A	N/A	N/A	N/A	-	Hypoplastic L heart ASD VSD pulmonary hypoplasia renal hypoplasia dysmorphic facies diaphragm hernia encephalopathy 46,XX
34-U	F	-	Mennonite	-	-	-	Absent ribs vertebra anomalies duodenal atresia hypoplastic L heart IUGR dysmorphic facies 46,XX
35-U	M	-	French/ Scottish	-	-	Sib absent legs & arms	Radioulnar synostosis dysmorphic facies bilateral clinodactyly fingers and toes MR hearing loss 46,XY FISH William normal
36-U	F	-	N/A	Mother: karyotype 47,XXX	-	Father - Rieger syndrome	Dextrocardia asplenia Rieger anomaly dysmorphic facies ASD tracheal stenosis short sternum 46,XX
37-U	M	-	Native	-	-	-	Bilateral short femurs dysmorphic hydrocephalus cystic hygroma bilateral cystic kidneys 46,XY
38-U	F	N/A	N/A	N/A	N/A	Mother – uterine didelphis	MR VSD micrognathia high arched palate seizures double outlet R ventricle **No chromosome studies**
39-U	F	-	N/A	-	-	-	Bilateral syndactyly – toes & fingers omphalocele unilateral renal agenesis diaphragm agenesis rocker bottom feet dysmorphic amniotic band on 1 finger L atrophic testis malrotated intestines 46,XX

40-U	M	3rd cousins	Native	-	-	Mother & 2 nephews CLP	Macrocephaly micropenis & cryptorchidism micrognathia & glossoptosis camptodactyly metatarus adductus 46,XY
41-U	M	-	Scottish/ Irish	-	-	-	Postaxial polydactyly – hand TOF metatarsus varus dysmorphic DD 46,XY
42-U	M	-	Mennonite	-	-	Sib with CLP	Cleft lip & palate hypertelorism agenesis of corpus callosum Dandy Walker variant low-set ears arthrogryposis 46,XY
43-U	F	-	Ukrainian/ Swedish	-	-	-	ASD L hypoplastic thumb & 5th finger malformation L esotropia R syndactyly L ear microtia 46,XX

N/A: unable to obtain information.

- : absence of

* At the time of the study the chromosome analysis showed a normal male karyotype, however, the patient was re-investigated and extended chromosome analysis demonstrated a deletion on chromosome 9.

3.4 PREVIOUS MCA SYNDROME & ASSOCIATION DIAGNOSES

A total of 10 cases were ascertained by inclusion criterion (2): any MCA case in which the diagnosis of a syndrome/association was made more than 1 year after the initial assessment with the Section of Genetics and Metabolism. Table 10 summaries those cases and the length of time until a diagnosis was made.

TABLE 10 Summary of cases ascertained by criteria 2: MCA cases – diagnosis made after 1 year's time from initial contact

CASE	ANOMALIES	DIAGNOSIS	TIME PERIOD	REASON WHY DIAGNOSIS DELAYED
1-LD	VSD DD IUGR ACC dysmorphic	FAS	2.7 yr.	Atypical features
2-LD	Hypospadias hypertelorism short stature macrostomia spina bifida MR	Opitz G syndrome	5.1 yr.	Atypical features
3-LD	Arachnodactyly scoliosis bilateral dislocated radia	Beals syndrome	14.2 yr.	Initially thought Marfan syndrome
4-LD	Imperforate anus hypospadias shawl scrotum epicanthal folds	VATER	1.8 yr.	Atypical features
5-LD	Hypertelorism hearing loss DD dislocated hips joint hyperlaxity	Rieger syndrome	10.2 yr.	Previously unreported
6-LD	Macrocephaly hypertelorism DD scoliosis	Sotos syndrome	8.0 yr.	Initially thought to be SMA
7-LD	Short stature cryptorchidism club feet scoliosis short neck	Klippel-Feil syndrome	4.5 yr.	Initially thought neuromuscular
8-LD	VSD pulmonary stenosis hypertelorism hypospadias	Opitz syndrome	1.3 yr.	Initially thought chromosome etiology
9-LD	Short stature inguinal hernia dysmorphic	Aarskog syndrome	2.9 yr.	Initially thought features due to FAS
10-LD	Dysmorphic malformed ears DD hypotonia	22q Deletion	13.6 yr.	22q initially not well delineated

3.5 PROVISIONALLY NEW SYNDROMES & ASSOCIATIONS

A total of 9 cases was ascertained by inclusion criterion (3): provisionally "new" MCA syndromes/associations that were delineated and reported by members of the Section of Genetics and Metabolism. Table 11 summarizes the cases.

TABLE 11 Summary of the "new" syndromes/associations delineated by Members of the Section of Genetics & Metabolism

CASE	ANOMALIES	CONDITION	MODE OF INHERITANCE
1-N	Cleft palate micrognathia dysmorphic polydactyly vertebral anomalies	MART syndrome	Unknown
2-N	Vertebra anomalies DD rhizomelic shorting cataract teeth anomalies dysmorphic	CODAS	? Autosomal recessive
3-N	Bilateral tibial agenesis adactyly polydactyly PDA didelphus	Tibial agenesis – polydactyly	Unknown *? Autosomal recessive*
4-N	Cryptorchidism polydactyly radial & tibial agenesis imperforate anus	Tibial agenesis – polydactyly	Unknown *? Autosomal recessive*
5-N	Oligodactyly hypoplastic forearms hydrops absent ulna bilateral ear anomaly	Ulnar agenesis & EFE	Autosomal recessive
6-N	Short stature atretic ear canal micrognathia short humeri hypoplastic genitalia	SAMS	Autosomal dominant or autosomal recessive
7-N	ACC dysmorphic MR coarctation of aorta epibulbar dermoid	Dysgenesis of the Corpus Callosum	Autosomal dominant
8-N	Lissencephaly club feet microphthalmia cataract rib & vertebral anomalies	Walker – Warburg	Autosomal recessive
9-N	NTD penis agenesis hydrocephalus vertebral anomalies	Penile agenesis	Unknown

Case 1: Martsolf et al. (1977)
Case 2: Shebib et al. (1991)
Case 3 & 4: Evans and Greenberg (2002)
Case 5: Marles and Chudley (1990)
Case 6: Lemire et al. (1998)
Case 7: Evans and Chudley (1998)
Case 8: Evans et al. (1980)
Case 9: Evans et al. (1999)

3.6 COMPUTERIZED DATABASE EVALUATION

Table 12 illustrates each case that was successfully diagnosed indicating whether or not the computerized databases used in this study were effective in obtaining the diagnosis. As demonstrated computerized databases were instrumental in 26/32 of the cases. Table 12 also gives a breakdown of which database(s) was successful per case.

TABLE 12 Summary of all 32 diagnosed cases and the databases most useful for diagnostic purposes

CASE	DIAGNOSIS	DATABASE SUCCESS (Y/N)	DATABASE DESCRIPTION
1-S	COFS	N	-
2-S	VACTERL – Hydrocephaly	Y	POSSUM LDDB OMIM
3-S	Goldberg – Shprintzen	Y	OMIM
4-S	Diabetic Embryopathy	Y	POSSUM LDDB
5-S	Adducted thumb syndrome	Y	POSSUM LDDB OMIM
6-S	Diabetic Embryopathy	Y	POSSUM LDDB
7-S	Blepharo-Cheilo-Dontic	Y	PUBMED OMIM
8-S	Cardio-facio-cutaneous	Y	POSSUM LDDB OMIM
9-S	Disorganization syndrome	Y	POSSUM
10-S	Disorganization syndrome	Y	POSSUM
11-S	Lambotte syndrome	Y	PUBMED
12-S	22q Deletion syndrome	Y	POSSUM LDDB OMIM
13-S	Smith-Magenis syndrome	Y	PUBMED
14-S	Holzgreve-Thomas syndrome	Y	PUBMED
15-S	Holzgreve-Thomas syndrome	N	-
16-S	Ritscher-Schinzel	Y	POSSUM LDDB
17-S	Alagille syndrome	Y	PUBMED
18-S	MOTA syndrome	Y	OMIM
19-S	Seckel syndrome	N	-
1-A	Holoprosencephaly sequence	Y	POSSUM LDDB
2-A	MURCS	N	-
3-A	Schisis	N	-
4-A	Duodenal & Cardiac	Y	PUBMED
5-A	Limb & Renal	Y	PUBMED
6-A	Omphalocele & Cardiac	Y	PUBMED
7-A	Omphalocele & Cardiac	Y	PUBMED
8-A	Schisis	N	-
9-A	Schisis	Y	POSSUM LDDB
10-A	CHARGE	Y	POSSUM
11-A	VATER	Y	PUBMED
12-A	FAV	Y	POSSUM LDDB OMIM
13-A	Laterality Sequence	Y	POSSUM LDDB OMIM

- Indicates that no database was successful in suggesting a diagnosis

Table 13 gives the comparison in percentage of the success rate for each computerized database and the overall success rate of using computerized databases for this study.

TABLE 13 Success rate of computerized databases with comparison in percentage for POSSUM, LDDB, OMIM & PubMed

	DIAGNOSED CASES (32)	
Database Name	**N**	**%**
POSSUM	14	43.7
LDDB	11	34.3
OMIM	9	28.1
PubMed	10	31.2
None	6	18.7
Total success rate	**26**	**81.3**

N = number of cases

3.7 PHENOTYPIC & DEMOGRAPHIC ANALYSIS

Two separate analyses were preformed using discriminant function analysis to determine which, if any, variables could be used to differentiate Group one – diagnosis made, from Group two – diagnosis not made. The first analysis looked at the demographic variables. No variable was found to significantly differentiate the groups (Table 14). The second analysis compared all anomalies in both groups. Three anomalies were identified as being significantly less common in Group one (Table 15). Of note, only 80 of the original 95 cases were used in the discriminant function analysis as 15 cases had at least one missing discriminating variable in one of the 71 fields.

TABLE 14 The occurrence of demographic variables in Group 1 & Group 2: Comparison of probabilities

	Group 1	*Group 2*	*Probability*
Demographic Variables			
Number of Cases	43	37	
Sex (% M)	25 (58.1%)	19 (51.3%)	0.549
YOB: average time (years) from DOB to start of study (1997)	12	11	0.487
Ethnicity %			0.538
Caucasian	20 (46.5%)	21(56.7%)	
Aboriginal	10 (23.2%)	4 (10.8%)	
Other	16 (37.2%)	12 (32.4%)	
Family history same	2 (4.6%)	6 (16.2%)	0.166
Family history other	12 (27.9%)	18 (48.6%)	0.057
Symmetry			0.568
Partial asymmetry	9 (20.9%)	2 (5.4%)	
Full asymmetry	8 (18.6 %)	7 (18.9%)	
Symmetry	13 (30.2%)	11 (29.7%)	

TABLE 15 Renal dysplasia/cystic, Postaxial polydactyly and Tracheal defects: Comparison of frequency in Group 1 & Group 2

	Group 1	*Group 2*	*Probability*
Number of Cases	43	37	
Anomalies			
Renal dysplasia/cystic	0	5 (13.5%)	0.018
Postaxial polydactyly	0	4 (10.8%)	0.029
Tracheal defects	0	3 (8.1%)	0.069

3.8 RECURRENCE RISK ESTIMATION ANALYSIS

Recurrence risk estimates were derived by looking at all subsequent pregnancies per case (94) and totaling the number of similarity affected sibs. The number of sibs "affected other" (e.g. single birth defect(s) thought not to be associated with the proband's findings) was also included. Each case is identified as either diagnosis known (Group one) or as diagnosis unknown (Group two). Table 16 and Table 17 summarizes these findings.

TABLE 16 Recurrence of malformation(s) in sibling(s) of the proband: Comparison of Group 1 & Group 2

Database # & Case #	# Subsequent Pregnancies	Affected Same	Affected Other	Diagnosis
1 / 1-S	0	0	0	COFS
2 / 2-S	0	0	0	VACTERL-hydrocephalus
3 / 3-S	1	0	0	Goldberg-Shprintzen
4 / 4-S	N/A	-	-	Diabetic Embryopathy
5 / 5-S	1*	0	0	Adducted thumbs
6 / 39-U	0	0	0	Undiagnosed
7 / 12-A	1	0	0	FAV
8 / 6-S	1	0	0	Diabetic Embryopathy
9 / 7-S	0	0	0	BCD
10 / 8-S	*	-	-	CFC
11 / 13-A	0	0	0	Laterality sequence
12 / 9-S	0	0	0	Disorganization
13 / 10-S	3	0	0	Disorganization
14 / 40-U	*	-	-	Undiagnosed
15 / 11-S	2*	0	1	Lambotte
16 / 1-U	0	0	0	Undiagnosed
17 / 12-S	*	-	-	22q Deletion
18 / 13-S	0	0	0	Smith-Magenis
19 / 14-S	0	0	0	Holzgreve-Thomas
20 / 15-S	1	1	0	Holzgreve-Thomas
21 / 16-S	2	1	0	Ritscher-Schinzel
22 / 17-S	0	0	0	Alagille
23 / 18-S	1	0	0	MOTA

24 / 19-S	*	1	0	Seckel
25 / 1-A	0	0	0	Holoprosencephaly
26 / 2-A	N/A	-	-	MURCS
27 / 41-U	0	0	0	Undiagnosed
28 / 4-A	N/A	-	-	Duodenal & Cardiac
29 / 6-A	0	0	0	Omphalocele & Cardiac
30 / 3-A	*	-	-	Schisis
31 / 9-N	0	0	0	New Diagnosis
32 / 10-A	0	0	0	CHARGE
33 / 1-LD	N/A	-	-	FAS
34 / 2-LD	0	0	0	Opitz
35 / 3-LD	1	0	0	Beals
36 / 4-LD	N/A	-	-	VATER
37 / 5-LD	0	0	0	Rieger
38 / 6-LD	N/A	-	-	Sotos
39 / 7-LD	1	0	1	Klippel-Feil
40 / 8-LD	0	0	0	Opitz
41 / 9-LD	N/A	-	-	Aarskog
42 /10-LD	3	0	0	22q Deletion
43 / 1-N	N/A	-	-	New Diagnosis
44 / 2-N	0	0	0	New Diagnosis
45 / 3-N	N/A	-	-	New Diagnosis
46 / 4-N	0	0	0	New Diagnosis
47 / 5-N	0	0	0	New Diagnosis
48 / 6-N	0	0	0	New Diagnosis
49 / 7-N	0	0	0	New Diagnosis
50 / 2-U	N/A	-	-	Undiagnosed
51 / 3-U	*	-	-	Undiagnosed
52 / 4-U	0	0	0	Undiagnosed
53 / 5-U	0	0	0	Undiagnosed
54 / 6-U	3	0	1	Undiagnosed
55 / 7-U	1	1	0	Undiagnosed
56 / 8-U	1	0	1	Undiagnosed
57 / 9-U	*	-	-	Undiagnosed
58 / 8-N	1	1	0	New Diagnosis
59 / 10-U	*	-	-	Undiagnosed
60 / 11-U	*	-	-	Undiagnosed
61 / 12-U	N/A	-	-	Undiagnosed
62 / 13-U	0	0	0	Undiagnosed
63 / 14-U	0	0	0	Undiagnosed
64 / 15-U	0	0	0	Undiagnosed
65 / 16-U	0	0	0	Undiagnosed
66 / 17-U	1	0	1	Undiagnosed
67 / 18-U	0	0	0	Undiagnosed

68 / 19-U	1	1	0	Undiagnosed
69 / 20-U	0	0	0	Undiagnosed
70 / 21-U	0	0	0	Undiagnosed
71 / 22-U	0	0	0	Undiagnosed
72 / 23-U	0	0	0	Undiagnosed
73 / 24-U	0	0	0	Undiagnosed
74 / 25-U	0	0	0	Undiagnosed
75 / 26-U	0	0	0	Undiagnosed
76 / 27-U	2	1	0	Undiagnosed
77 / 28-U	0	0	0	Undiagnosed
78 / 29-U	0	0	0	Undiagnosed
79 / 30-U	1	0	1	Undiagnosed
80 / 31-U	0	0	0	Undiagnosed
81 / 32-U	1	0	0	Undiagnosed
82 / 33-U	0	0	0	Undiagnosed
83 / 34-U	0	0	0	Undiagnosed
84 / 35-U	2	0	0	Undiagnosed
85 / 36-U	0	0	0	Undiagnosed
86 / 37-U	2	0	0	Undiagnosed
87 / 38-U	0	0	0	Undiagnosed
88 / 39-U	*	-	-	Undiagnosed
89 / 11-A	1	0	1	VATER
90 / 43-U	0	0	0	Undiagnosed
91 / 7-A	1	0	0	Omphalocele & Cardiac
92 / 5-A	0	0	0	Limb & Renal
93 / 8-A	0	0	0	Schisis
94 / 9-A	1	0	0	Schisis
Total	**47**	**7**	**7**	-

N/A: Information on subsequent pregnancies unknown and/or unavailable
* Pregnancy – sex unknown

TABLE 17 Percentage of the occurrence of malformation(s) in the subsequent sibling of all 94 cases reviewed in the study: Comparison of Group 1 & Group 2

	Group 1	*Group 2*	*Total*
Number of Cases	27	20	47
Affected Same	4^{+} (14.8%)	3* (15.0%)	7(14.9%)
Affected Other	3^{++} (11.1%)	4** (20.0%)	7(14.9%)

ADDENDUM:

\+ Holzgreve-Thomas syndrome (case 15-S), Ritscher-Schinzel syndrome (case 16-S) Seckel syndrome (case 19-S) and Walker-Warburg (case 8-N) were the case that had a recurrence.

++ Lambotte syndrome (case 11-S): sib with multicystic dysplasic kidneys.

Klippel-Feil syndrome (case 7-LD): sib with a "major malformation" type/cause unknown.

VATER association (case 11-A): sib with unilateral diaphragmatic hernia.

* Case 7-U: sib with polycystic kidneys, pulmonary stenosis, macrocephaly, and micrognathia.

Case 19-U: sib with bilateral postaxial polydactyly of hands and feet.

Case 27-U: sib with microcephaly, IUGR, hypertelorism, DD, and clinodactyly.

** Case 6-U: sib with VSD.

Case 8-U: sib with rhizomelic shorting of all limbs.

Case 17-U: sib with atresia of the ear canal.

Case 30-U: sib with pyloric stenosis and DD.

1. CASE COMMENTARY: clinical description and review of cases

4.1 SYNDROMES

CASE 1-S

Patient 1 was born to a nonconsanguineous couple of Aboriginal background. She was seen by Genetics in consultation shortly after birth for MCA. Mother was G5P5. The pregnancy history was negative for any teratogen exposure and delivery was uneventful. The infant died shortly after delivery. The clinical finding included the following major and minor anomalies:

- CNS anomaly (neuroaxonal disease)
- Micrognathia
- Cloudy corneas
- Cleft palate
- Limb positional defects – club feet
- Short webbed neck with low set ears
- Cardiac defect (coarctation of the aorta & polypoid thickening of the valvula foraminus

The differential diagnoses included COFS syndrome (cerebro-oculo-facial-skeletal syndrome) and leukodystrophy. The family was counselled that this combination of features was most likely due to an autosomal recessive condition and they were given a 25% risk of recurrence. Chromosome analysis was normal, 46, XX and metabolic investigations were normal.

The diagnosis of COFS was considered based on the experience of the members of the Section of Genetics and Metabolism with this rare condition. COFS syndrome is a rare autosomal recessive condition associated with microcephaly, severe psychomotor retardation and death in early childhood. Other clinical findings include ocular

anomalies, dysmorphic facies, micrognathia, flexion contractors of the limbs and CNS anomalies (Del Bigio et al., 1997). COFS syndrome was originally described in Manitoba by Pena and Shokeir (1974) in 3 Aboriginal kindreds. Homozygous mutations in the ERCC6 gene are responsible for the COFS phenotype (Meira et al., 2000).

When the patient was initially seen by Genetics in 1984 the differential diagnosis included COFS and leukodystrophy. "Leukodystrophy" encompasses a group of white matter diseases that are characterized by progressive cerebral deterioration of the myelin of the central and peripheral nervous system. Leukodystrophy may or may not have other associated anomalies. Leukodystrophies are comprised of over 40 unique disorders, many of which are autosomal recessive in inheritance (OMIM). Hence the term "leukodystrophy" is more of a classification of disorders rather than an actual diagnosis.

Cockayne syndrome (CS), which falls under the grouping of leukodystrophy, shows similarities to COFS syndrome. Both are associated with neurodegeneration and cataracts. Initially COFS and CS were considered distinct entities as COFS syndrome eye defects were more severe than those found in CS patients and because cutaneous photosensitivity was not noted in the patients originally diagnosed with COFS syndrome. Recently, it has been demonstrated that COFS syndrome cases have mutations in the ERCC6 gene and Cockayne syndrome type B patients also have mutations in the ERCC6 gene (Meira et al., 2000). Graham (2001) demonstrated a mutation in the XPD gene, which is associated with the CS phenotype, in a patient clinically diagnosed with COFS. While they stated that COFS syndrome should remain a unique entity, it should be included in the spectrum of NER (nucleotide-excision repair) disorders along with Cockayne syndrome, xeroderma pigmentosum and trichothiodystrophy.

The diagnosis of COFS syndrome was suggested in this patient based on the

experience of members of the Section of Genetics & Metabolism with this rare disorder. Surprisingly, this diagnosis was not suggested by POSSUM, LDDB or OMIM searches. This may be due in part to the "handles" or clinical features used in the initial searches. We made the diagnosis of COFS syndrome in this patient based on the CNS findings, the ocular anomaly, flexion contractures, dysmorphic facies and the webbed neck. Cleft palate is not a common anomaly associated with COFS syndrome; however, it has been reported once before in another patient with COFS syndrome (Hamel et al., 1996). In addition to the clinical findings, the family was of North American Aboriginal background, which has a higher incident of COFS syndrome than the general population. A sample of DNA from this patient was obtained from tissue blocks and mutation analysis for the common COFS mutation found in this population was performed. A gene mutation was identified in the patient's sample. While only one mutation was identified this does not change the diagnosis of COFS syndrome for this patient, as only screening for the ethnic specific mutation was done and this patient may have a second unknown mutation. Mutation analysis is currently underway at an independent lab to try and identify the second mutation. The recurrence risk for this family remains the same with a 25% risk of recurrence. The diagnosis of COFS syndrome in this patient does not change the initial recurrence risk given to the family. We have, however, by confirming the diagnosis offered the possibility of prenatal diagnosis to the family and potentially carrier testing for other family members. One limitation is that, currently, the second mutation has not yet been identified in this patient.

CASE 2-S

Patient 2 was a stillborn born to a nonconsanguineous couple. The mother was of French / Ukrainian background and the father was of Ukrainian descent. The family was seen by genetics in consultation shortly after birth because of MCA. Review of the pregnancy and birth history was unremarkable. There was a positive family history of a

cousin who had Down syndrome and a more distantly related cousin, related through marriage only, who was though to have the VATER association. Routine chromosome analysis demonstrated a normal 46,XY karyotype. The clinical findings included the following:

- Hydrocephalus with aqueductal stenosis
- Hypoplastic left heart
- Trachea stenosis
- Transposition of the great vessels & single atrial ventricular valve
- Bronchopulmonary dysplasia
- Bilateral unilobular lungs

The differential diagnoses include VACTERL - hydrocephalus and Hydrolethalus syndrome. The family was counselled that this could be either an autosomal recessive condition or an X-linked condition with a 25% recurrence risk or that this was a sporadic event with a recurrence risk of 5%.

The diagnosis of VACTERL association with hydrocephalus was suggested by the OMIM database based on two clinical findings, aqueductal stenosis and cardiac defects. The only other diagnosis suggested by OMIM based on those two clinical findings was neurofibromatosis type 1, which the patient clearly did not have (lacked any other clinical features of NF1). VACTERL-hydrocephalus was also suggested by POSSUM and LDBB searches.

VACTERL – type anomalies associated with hydrocephalus was first delineated by Briard et al. (1984). They reported 16 patients who had this combination of findings. VACTERL association is an acronym for vertebral anomalies, anal atresia, cardiac defects, tracheosophageal fistula, renal anomalies and limb defects. VACTERL-hydrocephalus appears to be a separate entity associated with, in addition to the anomalies

seen in the VACTERL association, hydrocephaly, microphthalmia, micrognathia, branchial arch anomalies, lung lobation defects and spleen anomalies (Evans et al., 1989). VACTERL-hydrocephalus is frequently a lethal association as most children died in the newborn period or are stillborn.

The diagnosis of VACTERL-hydrocephalus was made in this patient based on the hydrocephalus, trachea stenosis, cardiac anomalies and lung lobe anomalies. VACTERL-hydrocephalus has been documented to have autosomal recessive and X-linked inheritance depending on the family (Evans et al., 1989; Sommer et al., 1989; Corsello and Giuffre, 1994). It is unclear whether or not this patient had the autosomal recessive or the X-linked form of VACTERL hydrocephalus. The parents were nonconsanguineous and this was their first pregnancy. Given that the couple was nonconsanguineous and that the affected was male, this could suggest either the X-linked or autosomal recessive form. In either situation, the couple would have a 25% risk of recurrence. It would be important to determine which mode of inheritance the patient had to better counsel other family members regarding their risk. Clearly, if this were the X-linked form then there would be a risk of carrier females on the maternal side having similarly affected children. The autosomal recessive form would have a much lower risk for other family members unless there was consanguinity. Some cases of VACTERL-hydrocephalus have been shown to have Fanconi anemia (Porteous et al., 1992; Wang et al., 1993; Rossbach et al., 1996). Fanconi anemia is associated with increased chromosome breakage and mutations in the Fanconi anemia complementation group C gene (Cox et al., 1997). Chromosome breakage and/or molecular analysis might be a consideration to help support the diagnosis of VACTERL-hydrocephalus in this patient.

The initial differential diagnosis included Hydrolethalus syndrome, although the patient was thought not to be typical for this condition. Hydrolethalus syndrome is a

lethal condition characterized by polydactyly and CNS malformations, stenosis of the airway and lung abnormalities (OMIM #236680). Our patient had a number of the features in common with this disorder including hydrocephalus, trachea stenosis and lung lobe abnormalities. Hydrolethalus syndrome was ruled out as a potential diagnosis based on the lack of any dysmorphic facial features in our patient. Hydrolethalus syndrome is associated with a typical facies including micrognathia, cleft palate/lip and broad nasal root. In addition, key characteristics of this condition, specifically polydactyly and the "key hole-shaped" opening at the base of the skull were not present in our patient (Jones, 1997).

CASE 3-S

Patient 3 was born to a nonconsanguineous couple of Polish and English background. A referral was made to genetics because of MCA. Pregnancy and birth history were reviewed and were unremarkable. Mother was G3P3. Routine chromosome analysis on the patient was normal, 46, XY. Upon examination the following anomalies were found:

- Hirschsprung disease
- Hypertelorism
- Ear anomaly
- Hypospadias
- Microcephaly
- Constitutional growth delay
- Cranial asymmetry
- Camptodactyly
- Developmental delay

The initial differential diagnosis included hypertelorism-hypospadias syndrome and VACTERL association. The family was counselled that this combination of anomalies might be a sporadic event or might represent an unknown autosomal recessive condition. They were given a 0-25% risk of recurrence. Unfortunately the patient died at age 2 year, six months due to complications of the Hirschsprung disease.

As previously documented, VACTERL association is characterized by vertebral anomalies, anal atresia, T-E fistula, renal anomalies and limb defects. Review of the patient's clinical findings did not support this diagnosis. The constellation of features are not typical for VACTERL association.

Hypertelorism-hypospadias syndrome (Opitz syndrome) is a condition associated with mild to moderate mental retardation, ocular hypertelorism, hypospadias and other anomalies (Jones, 1997). It can be an X-linked condition where carrier females can have hypertelorism or an autosomal recessive condition. While this patient did have the hallmark findings of Opitz syndrome - hypertelorism and hypospadias - there has not been a reported case of Opitz syndrome associated with Hirschsprung disease. In addition, microcephaly and camptodactyly are not characteristic findings in this condition.

The diagnosis of Goldberg-Shprintzen syndrome (Hirschsprung disease – Mental Retardation syndrome) was suggested by OMIM based on microcephaly, hypospadias and Hirschsprung disease. Goldberg-Shprintzen syndrome was first reported by Goldberg and Shprintzen (1981) who described a pair of sibs who had Hirschsprung disease, submucous cleft palate, microcephaly, short stature, hypertelorism, synophrys, prominent nose, thick eyelashes and fine sparse hair. They also had learning delay. Since that initial report, other cases of Goldberg-Shprintzen syndrome have been reported in the literature. Initial cases reports supported an autosomal recessive mode of inheritance (Hurst et al., 1988; Halal and Morel, 1990). However, Mowart et al. (1998) published 4 cases of Goldberg-Shprintzen syndrome that suggested an autosomal dominant mode of inheritance. Wakamatsu et al. (2001) later confirmed this by demonstrating that 3 out of 4 patients diagnosed with Goldberg-Shprintzen syndrome had heterozygous deletions in the SMAD1P1 gene, all of which occurred *de novo*.

The diagnosis of Goldberg-Shprintzen syndrome was made in this case based on the Hirschsprung disease, characteristic facies, microcephaly and short stature. Our patient also had other findings in common with the patient reported by Halal and Morel (1990). Their patient also had ear and genital anomalies. All cases of Goldberg-Shprintzen syndrome reported to date, including this patient, have had developmental delay. Given that there was no positive family history of any findings suggestive of Goldberg-Shprintzen syndrome in the parents or the siblings, this condition most likely occurred *de novo* in the affected. Barring gonadal mosaicism, the risk of recurrence for the family would be very low. Unfortunately, because the patient had died, molecular testing for the SMAD1P1 gene could not be offered to confirm the diagnosis.

The patient was initially seen by Genetics in 1976. At that time, only the X-linked form of Opitz syndrome was known and the Goldberg-Shprintzen syndrome had not yet been described in the literature. The family was lost to follow up until 1989 when the mother was seen for AMA counselling with a new partner. When reviewed by Genetics again, the differential diagnosis included Opitz syndrome (X-linked form only), an unknown MCA syndrome, Goldberg-Shprintzen syndrome and Jeshina-Koeda syndrome. A review of the literature could not identify any syndrome under that last name.

In 1989, the Goldberg-Shprintzen syndrome was considered to be an autosomal recessive condition. The family was counselled that the patient's phenotype was not characteristic of those reported at that time and that Goldberg-Shprintzen syndrome most likely did not explain his findings. In 1989 only 5 cases had been reported (Goldberg and Shprintzen, 1981; Hurst et al., 1988; Winter et al., 1984). This might be in part, why the diagnosis was not made at that time.

CASE 4-S

Patient 4 was delivered by cesarean section because of decreased fetal movement, to a nonconsanguineous couple. The mother was of East Indian descent and the father was of Ukrainian descent. The female infant was seen by genetics shortly after birth because of the presence of MCA. Mother did not have any prenatal care until 32 weeks gestation, at which time it was noted that the pregnancy was complicated by gestational diabetes with no blood sugar control. The rest of the pregnancy history was unremarkable. Mother had had a previous relationship that had resulted in one spontaneous abortion and one healthy child. In this current relationship, she and her partner, in addition to this child, had had another healthy child and three spontaneous abortions. Routine chromosome analysis on the patient revealed a normal karyotype: 46, XX. Parental karyotypes were not done. On examination and subsequent investigations, the following anomalies were noted:

- Cleft lip and palate
- Vertebral and rib anomalies (13 pairs of ribs)
- Microcephaly
- Unilateral renal agenesis

The differential diagnosis included an autosomal recessive condition with facial clefting, microcephaly and MR or an unknown MCA syndrome. Unfortunately the family was lost to follow up and they were never counselled regarding recurrence risks.

Due to the pregnancy history of gestational diabetes, diabetic embryopathy was suspected as the cause of the clinical finding in the affected. The results of the search supported the clinical suspicion of diabetic embryopathy. Diabetic embryopathy encompasses a large number and range of anomalies. Most common findings include CNS anomalies such as anencephaly, microcephaly, and hydrocephaly, cardiovascular defects, renal, rib and vertebral anomalies, and cleft lip/palate (Buyse, 1990). The

diagnosis of diabetic embryopathy was made based on the pattern of anomalies found in our patient and the fact that the mother had untreated gestational diabetes. One limitation of this diagnosis is that it is unknown how long the pregnancy was complicated by gestational diabetes. Why the diagnosis of diabetic embryopathy was not considered when the family was initially seen is not clear. Children of diabetic/gestational diabetic mothers have a 10 times higher frequency of congenital anomalies and the mothers have a 5 times higher frequency of spontaneous abortions (Nazer and Ramirez, 2000). The family was seen in 1992, at which time the effects of maternal gestational diabetes were well documented (Ramos-Arroyo et al., 1992; Hod et al., 1991; Kitzmiller et al., 1991). Diabetic embryopathy has a teratogenic effect and as such is a sporadic event. The risk of recurrence for this family would depend on how well the diabetes was controlled during subsequent pregnancies. A study by Steel et al. (1990) demonstrated that improved control in early pregnancy does lower the incidence of MCA in newborns of diabetic mothers.

CASE 5-S

Patient 5 was born to a nonconsanguineous couple, both of whom were of Cree background. The patient was seen in Genetics shortly after birth because of MCA. Review of the pregnancy and birth history was unremarkable. There was no exposure to any teratogens during the pregnancy. Family history was reviewed and showed that a sibling of the affected child had a cleft palate that was felt to be non-syndromic. There was also a first cousin who had been diagnosed with Rett syndrome. Routine chromosome analysis on this patient was normal with a 46,XY karyotype. On examination the following clinical findings were noted:

- Craniosynostosis - sagittal
- Iris coloboma
- Submucous cleft palate
- Ventricular septal defect

- Pyloric stenosis
- Adducted thumbs - bilateral
- Torticollis
- MR/autistic features
- Dysmorphic facies
- Neurosensory hearing loss

The differential diagnosis included CHARGE association, Adducted Thumb syndrome, Ritscher-Schinzel syndrome and an autosomal recessive MR/MCA condition reported by Pfeiffer (1987). The family was counselled that this most likely was an autosomal recessive condition with a 5 to 25% risk of recurrence.

CHARGE association is an acronym for coloboma of the eye, heart anomaly, choanal atresia, mental retardation, genital and ear anomalies. Facial clefting and dysmorphic facies are also common characteristics of CHARGE association (OMIM # 214800; Pagon et al., 1981). The patient had many of the criteria necessary to fulfill this diagnosis including iris coloboma, cardiac anomaly (VSD), ear anomaly (low-set ears) and MR. In addition, torticollis and neurosensory deafness have also been reported in a patient believed to have CHARGE association (North et al., 1995; Van Meter and Weaver, 1996). CHARGE association has a low risk of recurrence.

The diagnosis of CHARGE association was considered unlikely in this patient, as the overall clinical phenotype did not seem to be best explained by the CHARGE association. Specifically, the features that were not characteristic of CHARGE association were craniosynostosis and bilateral adducted thumbs. A review of the literature did not produce any reported cases of CHARGE with either of these two findings, although limb anomalies have been reported in patients with CHARGE association (Prasad et al., 1997).

Ritscher-Schinzel syndrome is an autosomal recessive disorder characterized by craniofacial, cerebral and cardiac defects. Cleft palate and ocular colobomas are also

common findings in this syndrome (Leonardi et al., 2001). This patient had a number of findings consistent with this syndrome, namely ocular coloboma, cleft palate, cardiac defects and MR. However, again our patient's overall gestalt did not seem to fit with this syndrome. The patient lacked any cerebral or structural CNS findings and craniosynostosis, adducted thumbs and hearing loss have not been reported in Ritscher-Schinzel syndrome. Therefore, it seems unlikely that this patient had this condition.

The third cardiocranial syndrome that was on the differential list was a case report by Pfeiffer et al. (1987) where he described two sibs with sagittal craniosynostosis, cardiac defects, micrognathia with mandibular ankylosis, genital defects, growth retardation and MR. Since that initial report, there have been a small number of other case reports similar to the Pfeiffer et al. report (Stratton and Parsons, 1989; Williamson-Kruse and Biesecker, 1995; Digilio et al., 1997). Review of the literature did not support this diagnosis in this patient. Hearing loss with ear anomalies, ocular coloboma and oral clefts have not been reported in this autosomal recessive condition.

MASA, a condition described by Bianchine and Lewis (1974) is an X-linked disorder associated with MR, aphasia, shuffling gait and adducted thumbs. Mutations in the LICAM gene are responsible for the clinical phenotype. MASA encompasses a number of previously described MCA conditions (OMIM #303350). Although one of the key features of this condition is "adducted thumbs", the overall clinical findings of our patient do not seem to fit into this spectrum.

Adducted Thumb syndrome was suggested by both the POSSUM and LDDB databases. It was also suggested by OMIM when "adducted thumb" was used as the search parameter. It was first described by Christian et al. (1971). They reported on 3 sibships in an Amish kindred with cleft palate, arthrogryposis, craniosynostosis and

microcephaly. Since that initial report additional cases have been reported (Fitch and Levy, 1975; Anderson and Breed, 1981; Kunze et al., 1983). The major diagnostic features for this condition are craniosynostosis, microcephaly, cleft palate and adducted thumbs (Buyse, 1990). Other findings, such as VSD defects, low-set ears, torticollis and MR have also been reported in this condition (Fitch and Levy, 1975). It is thought to be an autosomal recessive condition with a recurrence risk of 25%.

This patient has many of the clinical features of Adducted Thumb syndrome in addition to other findings not previously described in this syndrome (neurosensory hearing loss, pyloric stenosis and ocular coloboma). While there seems to be an overlap between the patient's clinical findings and both Adducted Thumb syndrome and CHARGE association, after review of the literature, this patient's overall clinical phenotype is more suggestive of the diagnosis of Adducted thumb syndrome. The patient's unique constellation of findings might be why the diagnosis was not made initially. His features certainly overlap with a number of syndromes. The recurrence risk for this family has been changed from a range of 5 to 25% to 25%. Unless there is consanguinity, the risk for other family members is low. Unfortunately, there is no molecular testing available for this condition as yet, so confirmational molecular diagnosis, carrier testing, or prenatal diagnosis is not an option for this family.

CASE 6-S

Patient 6 was born to a nonconsanguineous couple. The father was of Caucasian descent and the mother was of Aboriginal descent. The patient was seen shortly after birth by Genetics because of MCA. Review of the pregnancy and birth history was remarkable in that mother had had untreated gestational diabetes until the 4th month of her pregnancy. The family history was unremarkable. On examination the following clinical findings were noted:

- Unilateral renal agenesis
- Sacral dimple with associated hairy patch
- Bitemporal depression
- Limb length discrepancy

The differential diagnosis included caudal regression versus an early first trimester insult due to gestational diabetes. The family was counselled that this consolation of features most likely represented a sporadic event and they were given a 3% risk of recurrence.

As with patient 4-S, diabetic embryopathy was suspected as the mother had uncontrolled gestational diabetes throughout the pregnancy. A search using POSSUM and LDDB supported the clinical suspicion of diabetic embryopathy. As mentioned in case 4-S, diabetic embryopathy is associated with a large number and range of anomalies and certainly, renal agenesis and sacral defects are seen in this spectrum.

The diagnosis of diabetic embryopathy was considered in the initial differential diagnosis and it is unclear as to why this diagnosis was not given to the child. Caudal regression syndrome is a heterogeneous group. Its pattern of malformations includes incomplete development of the sacrum and lumber vertebrae, disruption of the distal spinal cord leading to secondary neurologic impairment and associated lower limb defects. Renal agenesis, anal anomalies, cleft lip/palate, and microcephaly are associated with this condition (Jones, 1997). These cases are usually sporadic, although it has been shown that a number (16%) occurred in infants of diabetic mothers (Rusnak and Driscoll, 1965; Passarge and Lenz, 1966; Stewart and Stoll, 1979; Goto and Goldman, 1994). Smith's *Recognizable Patterns of Human Malformation* 5th edition (Jones, 1997) considers this a caudal dysplasia sequence stating that the "caudal regression" most likely

is a secondary sequence of events with one of the known primary etiologies being maternal diabetes. Based on this statement, caudal regression in some cases is a clinical finding within the spectrum of diabetic embryopathy. As previously stated, it is important to clarify the primary cause of a birth defect(s) as it may have many etiologies and knowing which is specific to the case in question is necessary to provide accurate counselling to the family. With proper prenatal management of the mother's gestational diabetes, there would be a low risk of recurrence for this couple. One limitation in this case is that chromosome analysis was not done on this child, therefore a chromosome etiology can not be ruled out.

CASE 7-S

Patient 7 was seen by Genetics as a young child because of MCA. She was born to a nonconsanguineous couple of Caucasian background. Review of the pregnancy and birth history was unremarkable. There was a family history of cystic fibrosis on the maternal side. Routine chromosome analysis in the patient was normal: 46, XX. The following clinical features were noted on examination:

- Cleft lip and palate – bilateral
- Imperforate anus
- Bilateral lower lid ectropion
- Double row of eye lashes
- Short stature (5^{th} % for growth)
- Cone-shaped teeth with oligodontia

The family was originally counseled that this constellation of defects (cleft lip/palate and imperforate anus), represented two independent anomalies, both of which were multifactorial in inheritance. Two separate recurrence risk figures were given. A 4% risk of recurrence for cleft lip and palate and a 1-2% risk of recurrence for imperforate anus. Focal dermal hypoplasia (Goltz syndrome) was also mentioned in the differential diagnosis, although it was considered unlikely.

Goltz syndrome (focal dermal hypoplasia) is an X-linked dominant condition with in utero lethality in males. It is characterized by atrophy and linear pigmentation of the skin, herniation of fat through dermal defects, and multiple papillomas of the mucous membranes or skin. In addition, there is syndactyly, polydactyly, hypoplastic teeth, colobomas with microphthalmia and MR (OMIM #305600). This condition was first reported by Goltz et al. (1962). Review of the literature did not support the diagnosis in this patient as she lacked any of the skin findings, is developmentally normal and has other findings not consistent with this disorder (e.g. oral cleft and eye abnormalities).

As suggested by OMIM and a Medline search using "distichiasis and ectropion" as search parameters, the diagnosis of Blepharo-Cheilo-Dontic (BCD) syndrome was made. Allanson and McGillirray (1985) reported a family with 4 generations of individuals with cleft lip and palate, ectropion of lower eyelids and conical teeth. This large kindred demonstrated an autosomal dominant inheritance with marked clinical expression. Falace and Hall (1988) reported on a 5-generation family that had a combination of oral clefting with eye and teeth anomalies supporting the suggestion that this was a distinct autosomal dominant syndrome. Gorlin et al. (1996) in his 8 patient case report termed this condition the "Blepharo-Cheilo-Dontic (BCD) syndrome." In addition to the oral clefting, eyelid and teeth findings, sparse scalp hair, minor digit anomalies, poor growth with short stature, ear anomalies and imperforate anus have all been reported (Allanson and McGillivray, 1985; Martinez et al., 1987; Falace and Hall, 1988; Korula et al., 1995; Gorlin et al., 1996; Guion-Almeida et al., 1998; Valdez-de la Torre et al., 1999). The case reported by Falace and Hall (1988) demonstrated a pedigree where a father had 4 affected children and his mother was affected. However, he himself had no clinical findings of BCD syndrome, suggesting that this condition also shows incomplete penetrance.

The diagnosis of BCD syndrome was made in this patient based on her eye findings, specifically the bilateral lower lid ectropion with double row of eye lashes, as well as the cone-shaped teeth and cleft lip and palate. As mentioned above, short stature and imperforate anus have also been described in this syndrome. Unfortunately, the exact genetic defect of this condition has not been identified. The risk to this family, as this patient appears to be a sporadic case, is most likely low. However, as demonstrated by Falace and Hall (1988) one of the parents may be a non-penetrant carrier, so there may be a higher risk (50%) of having other affected children. This patient has up to a 50% risk of recurrence for each of her future pregnancies (noting that there is decreased penetrance).

In the initial assessment, BCD syndrome was considered (at that time the syndrome was report in OMIM as a MCA with clefting, eyelid ectropion and conical teeth). However, the diagnosis was thought to be unlikely. This was because the patient also presented with imperforate anus and at the time of the initial assessment, the association of imperforate anus with BCD syndrome was not known.

CASE 8-S

Patient 8 was delivered by cesarean section to a nonconsanguineous couple of Norwegian and French Canadian background respectively. He was seen by Genetics shortly after birth because of MCA. Mother was G2P2. An ultrasound examination done during the pregnancy revealed a cystic hygroma and polyhydramnios. Amniocentesis was carried out to rule out a chromosome abnormality and demonstrated a normal 46,XY karyotype. A second ultrasound in pregnancy revealed bilateral pleural effusions and ascites, and confirmed the polyhydramnios. There was no history of teratogen exposure during the pregnancy. On examination and subsequent investigations, the following clinical features were revealed:

- Cryptorchidism
- Talipes equinovarus
- Polymicrogyria
- Palmoplantar hyperkeratosis
- Short stature and rhizomelic shorting
- Polysplenia
- Encephalopathy
- Large fontanelle
- Short up-turned nose
- Hypertelorism and small ears
- Gut malrotation
- Hydrops
- Dysmorphic facies
- Short webbed neck
- Pulmonary stenosis, ASD & cardiomegaly

The initial differential diagnoses included GAPO syndrome and Noonan syndrome. The family was counselled that this might be a sporadic event with a recurrence risk of 5% or that this might an autosomal recessive condition with a recurrence risk of 25%.

GAPO syndrome was initially suggested in the original differential diagnosis. GAPO is an acronym for growth retardation, alopecia, pseudoanodontia and optic atrophy (OMIM #230740). It is an autosomal recessive condition with bone age retardation (Tipton and Gorlin, 1984). Review of this patient's clinical findings did not seem to suggest this diagnosis. One limitation of our re-evaluation is that this patient died at age 2 months so it is not know whether or not he would have developed alopecia, delayed teeth eruption and/or optic atrophy. However, the extent of the clinical findings in this patient did not suggest the diagnosis of GAPO syndrome.

As suggested by POSSUM, LDDB and OMIM, the diagnosis of Cardio-facial-cutaneous (CFC) syndrome was made in this patient. Cardio-facial-cutaneous syndrome (CFC) was first described by Reynolds et al. (1986) in 8 patients, all of who were from different families. These 8 individuals all had heart defects (pulmonary stenosis and ASD), characteristic facies, ectodermal abnormalities, and growth failure. Since that

initial report, the phenotype has expanded to include other findings such as hyperkeratosis to severe generalized ichthyosis-like skin findings, dysmorphic facies with high large forehead and bitemporal narrowing, depressed nasal bridge with ear abnormalities, sparse fine hair and a variety of neurological findings (OMIM #115150).

A condition that overlaps phenotypically with CFC syndrome is Noonan syndrome. There have been debates in the literature as to whether or not CFC syndrome and Noonan syndrome represent the same entity (Fryer et al., 1991; Ward et al., 1994; Leichtman, 1996). Noonan syndrome is characterized by hypertelorism, down slanting palpebral fissures with low-set ears, short stature, short and/or webbed neck, cardiac anomalies, deafness and motor delay (OMIM #163950). Rauen et al. (2000) reported a patient with CFC syndrome who had an interstitial deletion at 12q21.2-q22, which is proximal to the critical region for Noonan syndrome. This suggests that CFC syndrome is a distinct entity from Noonan syndrome. CFC syndrome and Noonan syndrome are still recognized as separate entities in the literature.

This patient did have features that overlap with Noonan syndrome. Those features include short stature, hypertelorism, web neck, cardiac anomalies and cryptorchidism. However, our patient's overall phenotype seems much more severe than that of a typical Noonan syndrome patient. For example, neurologic defects are not typical in Noonan syndrome (Jones, 1997). A search of the literature did not produce any reports of polymicrogyria (or other gyral defects) associated with Noonan syndrome. Our patient also had skin findings typical of those seen in CFC patients, but not in Noonan syndrome. The overall gestalt of the patient did not suggest the diagnosis of Noonan syndrome.

Grebe and Clericuzio (2000) proposed a set of criteria to aid in making the diagnosis of CFC syndrome. The criteria included macrocephaly, characteristic facies, growth

retardation, cardiac defects, sparse curly hair, neurologic impairment/developmental delay, ocular abnormalities, a history of polyhydramnios in pregnancy and hyperkeratosis. Using these criteria, this patient certainly fits into this spectrum. The diagnosis was made based on the following criteria:

Growth – short stature

Head & neck – prominent large forehead with hypertelorism and short upturned nose with depressed nasal bridge

Genital – cryptorchidism

Cardiovascular – ASD, pulmonary stenosis and cardiomegaly

Abdomen – spleen abnormalities

Ectodermal – hyperkeratosis

Neurologic – polymicrogyria

Pregnancy history – polyhydramnious

All cases of CFC syndrome reported to date have been sporadic. Therefore, CFC syndrome is thought to be an autosomal dominant condition with all cases occurring *de novo*. Given that gonadal mosaicism can occur, the recurrence risk for this condition is 5%.

CFC syndrome may not have been suggested when the patient was originally seen by Genetics for the following reasons. First, the patient is a severe case of CFC syndrome with specific neurologic abnormalities not previously reported for this condition. Second, the patient died at 2 months of age and may not have "grown" into the full phenotype of CFC syndrome (e.g. lack of hair findings).

CASE 9-S

Patient 9 was stillborn to a nonconsanguineous couple of unknown ethnic background. Genetics saw the infant because of MCA. The pregnancy and birth history were reviewed and were unremarkable. The family history was significant for two other members of the

family on the maternal side that had pregnancies that ended in stillbirths. The mother was also found to have a Meckel diverticulum. Chromosome analysis on the patient was not done. The following anomalies were noted on examination:

- Imperforate anus
- L postaxial polydactyly and R adactyly – hands
- Sacral and coccygeal agenesis
- Popliteal fossa at the end of the left leg
- Absent L foot
- Ectopic kidney – bilateral
- Cardiac anomaly – pulmonary vein defect
- Incomplete development of vocal cords
- Genital malformation – scrotum & penis

The family was counselled that this was most likely an unknown MCA syndrome and that it was a sporadic event. They were given an "extremely low" risk of recurrence.

Disorganization syndrome was suggested by POSSUM. Review of the literature supported this diagnosis in this patient. Donnai and Winter (1989) described 6 patients with MCA that they suggested might have resulted from a mutated gene that is the homolog of the mouse mutant disorganization (DS) gene first described by Hummel (1985, 1986). Mutations in this gene in mice have been shown to cause a wide range of abnormalities from facial clefting, limb abnormalities (duplication, reduction and polydactyly), urogenital abnormalities, gastroschisis and hamartomas (Winter and Donnai, 1989). The patient Winter and Donnai (1989) reported had polydactyly of the right foot, a "digit" arising out of the right side of the abdominal wall, which contained bone and muscle and had a nail, and unilateral renal agenesis. The right leg also had shorting of the upper and lower segments with flexion of the knee and popliteal webbing. They suggested that the diagnosis of "disorganization" should be made when limb and

digit anomalies (i.e. extra limbs, appendages or hamartomatous structures) occur in association with polydactyly or duplication/reduction of limbs with urogenital, body wall and craniofacial abnormalities (i.e. clefting).

Since that initial report by Donnai and Winter (1989), there has been a number of cases reported in the literature (Lowry and Yong, 1991; Hennekam, 1992; Kabra et al., 1994; Sabry et al., 1995). The anomalies seen in these cases can not be explained by amniotic disruption sequence, though some of the findings (i.e. clefting and digit/limb amputations) are reminiscent of findings in that disorder. The diagnosis of Disorganization syndrome was made in this patient based on the imperforate anus, polydactyly, renal abnormalities, adactyly, absent foot, popliteal fossa on the left leg and genital abnormalities, all of which have been described in this condition. Vertebral anomalies have also been reported (Donnai and Winter, 1989).

Disorganization syndrome is thought to be an autosomal dominant condition with decreased penetrance. The parents of the patient had a normal physical exam. Therefore, this condition most likely occurred *de novo* in this patient. However, one must be cautious when giving the family a low (1-2%) risk of recurrence, as one of the parents might be a nonpenetrant carrier. To date, the human disorganization gene has not been identified, thus molecular testing is not available. One limitation in this case is that chromosome analysis was not done. Although it seems unlikely that a chromosome defect could account for the range and severity of the defects found in the patient, it can not be ruled out.

CASE 10-S

A young nonconsanguineous couple of Mennonite background was seen by Genetics following a termination at 20 weeks for MCA found on ultrasound. Until the

identification of the anomalies on ultrasound, the pregnancy was unremarkable. There was a male first cousin with MR on the mother's side and the mother's mother had had a number of first trimester pregnancy losses. The fetus was examined at the time of delivery and the following anomalies were noted (also documented on autopsy):

- Encephalocele - occipital
- Gastroschisis
- Contratures of shoulders, elbows and wrists
- Micrognathia & microglossia
- Cleft palate (midline)
- Abnormal liver
- Scoliosis
- Malrotated kidneys
- Partial amputation of the left second & third digits of the hand
- Absent right radius & right first radial ray

The differential diagnoses included amniotic band disruption and VATER association. The family was counselled that this was a sporadic event and given a 1-2% risk of recurrence. The fetus had normal chromosomes, 46, XX.

As with the previous case, Disorganization syndrome came up in the POSSUM search and review of the literature again seem to support this diagnosis in this patient. The diagnosis was made in this patient based on the abnormal wall defect, the adactyly, cleft palate and radial agenesis. Amniotic band disruption was suggested as a potential diagnosis for this case as "apparent bands" (quoted in the autopsy report) were found on the left second to fifth digits and in the mouth. The diagnosis of amniotic band disruption was rejected, as this would not explain some of the other findings in our patient. Specifically, the anomalies that could not be explained by amniotic bands were the hypoplastic liver, malrotated kidney, absent right radius and first radial ray. Donnia and Winter (1989) have argued that some cases of amniotic band disruption sequence might

represent cases of Disorganization syndrome as some of the clinical findings can not be explained by amniotic bands (e.g. unilateral renal agenesis).

VATER association was also suggested as a potential diagnosis. Again the spectrum of anomalies seen in this patient does not suggest the diagnosis of VATER association. The radial ray defect fits into this spectrum. However, the remaining findings are not typical.

The couple went on to have a second normal pregnancy. As with the previous case, a nonpenetrant carrier parent can not be ruled out. The recurrence risk for this couple would be low (1-2%).

CASE 11-S

Patient 11 was born to a nonconsanguineous couple. The mother was of English/Scottish/ Aboriginal background and the father was of German descent. Genetics was asked to see the child because of MCA. The mother was a 28 year old G7P2 SA1 TA4. Pregnancy history was positive for alcohol exposure once at 16 weeks (amount unknown). At the time when the patient was seen, there were no other remarkable findings in the family or pregnancy history. Routine chromosome analysis revealed a normal karyotype of 46, XY. The following clinical findings were found on examination and subsequent investigations:

- IUGR
- Microcephaly
- Agenesis of the corpus callosum
- NTD- myelomeningocele
- Transposition of the great vessels
- Hydrocephalus with an Arnold-Chiari malformation
- Unusual facies with broad tipped nose

The diagnosis given at that time was a "cardiac and neural tube defect association." The family was counselled that this was a multifactorial defect and they were given a recurrence risk of 1-2%. The mother went on to have another pregnancy that resulted in a son with multicystic dysplasic kidneys. This was considered to be unrelated to her previous child's findings.

A PubMed search suggested the Lambotte syndrome and review of the literature supported this diagnosis for this patient. Lambotte syndrome was first described by Verloes et al. (1990) in an Arabic sibship from Morocco in which four children presented with IUGR, microcephaly, large ears, telecanthus and/or hypertelorism, hooked nose, narrow mouth with retrognathia, semilobar holoprosencephaly and severe neurologic problems. One of the sibs was stillborn and the other 3 died within the first 2 years of life. Given that the affected cases were from one sibship in which the parents shared the same family name and came from the same village, autosomal recessive inheritance was suggested.

Thakker and Donnai (1991) reported on another sibship that appeared to have Lambotte syndrome. Two sibs born to first cousin parents seemed to support Verloes' initial suggestion that the Lambotte syndrome was an autosomal recessive condition. The findings in their patient included normal karyotypes, IUGR, hypertelorism, large long ears, TGV, ACC, vertebral anomalies (Klippel-Feil), GI anomalies (R-V fistula), renal malformations (bilateral hydronephrosis), unusual nose with bulbous tip, small mouth, dilatation of the ventricular system without an Arnold-Chiari malformation and occult spina bifida. The authors commented on the striking similarities of their patients' facies with at of Verloes' patients.

Herens et al. (1997) reported on the same sibship of that in Verloes' 1990 paper after an unaffected sister to the affected sibs had a child born with the same findings. They showed, with in situ hybridization analysis and chromosome painting techniques, a subtle t (2;4) (q37.1;p12.2) translocation in the mother of the affected child. They proposed that all affected children had a combination of 2q/4p trisomy/monosomy that was undetectable by conventional banding techniques. The mother went on to have a second pregnancy and on amniocentesis they demonstrated an abnormal karyotype of 46, XX, -4 + der (4), t (2;4) (q37.1;p16.2), confirming their previous statement. Therefore, the Lambotte syndrome appears to be the result of a cryptic subtelomeric rearrangement and not an autosomal recessive condition as previously suggested.

The mother of this patient was seen again in another pregnancy. She was informed that her son most likely had Lambotte syndrome and based on the information at that time, was given a low risk of recurrence. She was counselled that Lambotte syndrome was an autosomal recessive condition (she was not longer with her previous partner). In light of the new information, this patient may have had a cryptic rearrangement not previously detected by chromosome analysis. The parents should have chromosome painting to determine whether either of them are carriers for a subtle subtelomeric translocation. The mother did go on to have a normal pregnancy, although the child had not been seen by genetics. Given the risk of an unknown chromosome rearrangement, the risk of recurrence is unclear, but may be higher than previously counselled.

CASE 12-S

Patient 12 was born to a nonconsanguineous couple of Cree background. The patient was seen in Genetics at the age of 8 months because of MCA. The pregnancy and birth histories were reviewed and were unremarkable. The mother was a 28 year old, G6P5 SA1. Family history was significant in that a first cousin on the maternal side had MR of

unknown etiology. On examination/investigation the following anomalies were noted:

- Ventricular septal defect
- Mild dysmorphic facies with hypertelorism and short palpebral fissures, unusual nose with overhanging columella & midline distal nasal groove
- Posteriorly rotated ears with overfolded upper helices
- Hypotonia
- Short neck with low posterior hairline
- Cleft palate

The differential diagnosis included "a prenatal insult" or Toriello-Carey Syndrome. The family was counselled that this was most likely a sporadic event and given a 5% risk of recurrence.

22q Deletion Syndrome (Velo-Cardio-Facial Syndrome) was suggested by POSSUM, LDDB and OMIM and this concurred with our clinical suspicion upon review of the case. The diagnosis of 22q Deletion syndrome was suspected based on the patient's heart anomaly and cleft palate. Blood was obtained from the patient and sent for FISH analysis of the 22q region. FISH analysis confirmed that the patient had a deletion in the 22q11.2 region, confirming the diagnosis of 22q Deletion Syndrome. Parental bloods were not obtained. 22q Deletion syndrome is inherited in an autosomal dominant fashion. However, most cases are sporadic events and the family was counselled with a low risk of recurrence for future pregnancies. The family was counselled that their daughter had a 50% risk of transmitting the deletion in future pregnancies.

The diagnosis of 22q Deletion syndrome was originally not considered. This is most likely due to the fact that the patient was initially assessed in 1991 at which time 22q Deletion syndrome, also know as Velo-cardio-facial syndrome or Shprintzen syndrome

was not yet well defined in the literature. The patient was seen before FISH analysis was available to confirm the diagnosis.

The differential diagnosis included Toriello-Carey syndrome, which is a MCA syndrome described by Toriello and Carey (1988). The features include ACC, telecanthus, short palpebral fissures, small nose with anteverted nares, Pierre Robin sequence, cardiac defects and hypotonia. It is believed to be an autosomal recessive condition. This diagnosis was originally considered because of the similarity of the patient's features with that of this syndrome.

CASE 13-S

Patient 13 was born to a nonconsanguineous couple of unknown ethnic background. The patient was seen in Genetics at the age of 21 because of MCA and behavior problems. The pregnancy and birth histories were reviewed and were unremarkable. Family history was significant for two relatives with MR of unknown etiology and a history of neonatal deaths. No further information was available. Routine chromosome analysis revealed a normal karyotype of 46, XX. On examination/investigation the following anomalies were found:

- Ventricular septal defect
- Syndactyly and clinodactyly
- Microcephaly with prognathism
- Prominent low-set ears
- Blepharophimosis
- Mental retardation and self mutilating behaviour

The differential diagnoses included a chromosome abnormality (ruled out by a normal chromosome constitution on G-banding), FAS and Fragile X syndrome. FAS syndrome is unlikely as there was no evidence of alcohol use during pregnancy and Fragile X

syndrome was rule out by a DNA analysis (normal number of FMR CGG repeats). The patient was lost to follow up and therefore not given any counselling regarding risk of recurrence and/or potential diagnosis.

A review of the literature with PubMed using the behavioral phenotype of the patient suggested the diagnosis of Smith-Magenis syndrome. Smith et al. (1986) first described Smith-Magenis syndrome. They showed an interstitial deletion of 17p in 9 unrelated patients. Juyal et al. (1995) used FISH analysis to demonstrate a deletion in 17p11.2 that was not detected by conventional cytogenetic techniques in a Smith-Magenis patient. The main clinical findings in Smith-Magenis syndrome are brachycephaly, broad nasal bridge with midface hypoplasia, congenital heart defects, brachydactyly and neurologic findings. Most patients have behavioural problems including self-destructive behaviour (e.g. head banging and wrist biting), onychotillomonia (pulling out nails), polyembolokoilamonia (insertion of foreign bodies into body orifices), sleep disturbances and decreased pain sensitivity.

The diagnosis of Smith-Magenis syndrome was made in our patient based on the self-mutilating behavior, MR and autistic like behaviors, speech delay, prognathia and dysmorphic facies. As this is a microdeletion syndrome, FISH analysis could confirm the diagnosis. However, repeated attempts to re-contact the patient failed and no sample was obtained, thus the diagnosis was not confirmed cytogenetically. Chromosome analysis was done previously; however, it was done with G-banding and an interstitial deletion could have been missed. Recurrence risk is low, as most cases of Smith-Magenis syndrome occur *de novo*.

CASE 14-S

Patient 14 was seen by Genetics for counselling following a termination of a pregnancy. Review of the family history was unremarkable and there was no consanguinity. Both parents were of Aboriginal heritage. Mother was G6P6. The pregnancy had been unremarkable until an ultrasound at 20 weeks gestation detected MCA. On autopsy, the following anomalies were found:

- Dandy-Walker malformation
- Cervical hemivertebrae with absent rib
- Scoliosis
- IUGR
- Short fingers
- Cleft lip and palate
- Bilateral renal agenesis

Chromosome analysis done on cardiac blood showed a normal 46,XY karyotype. The couple was counselled that the constellation of anomalies was most likely due to a primary abnormality of the embryonic midline resulting from a single insult to the fetus early on in the pregnancy. The couple were counselled that this was a sporadic event and given a 5% empirical risk of recurrence.

After careful review of the literature (using PubMed) the diagnosis of Holzgreve-Thomas syndrome was made in our patient. Holzgreve et al. (1984) first described this condition in a fetus with Potter sequence, heart defect, cleft palate, polydactyly and skeletal defects including vertebral abnormalities and extra/missing ribs. Since that initial report, there have been other case reports in the literature (Bonnet et al., 1987; Legius et al., 1988; Thomas et al., 1993; Zlotogora et al., 1996). The cardiac defects range from VSD to more complex defects such as Tetralogy of Fallot. Almost all cases reported have renal anomalies that range from bilateral renal agenesis to small sized kidneys. Thomas et al. (1993) reported on a family who had 2 affected children, one with hypoplastic left

heart syndrome and small kidneys and the other child with bilateral cleft lip and palate, complex heart defect and bilateral renal agenesis. This case report emphasizes the variation in expression of this condition from a relatively mild form to a much more severe lethal form. Zlotogora et al. (1996) suggested that their patient along with the sibs reported by Thomas et al. (1993) represented a distinct syndrome and were not the same condition first presented by Holzgreve. This was based on the lack of polydactyly in the affected patients.

These cases however, probably represent the same syndrome with variable expression. Thus, for this report, no distinction is made between the patients reported in these cases. The diagnosis of Holzgreve-Thomas syndrome was made in our patient based on the bilateral renal agenesis, cleft lip and palate and the vertebral and rib anomalies. Holzgreve-Thomas syndrome is thought to be an autosomal recessive condition due to the familial recurrence of this condition in two phenotypically normal parents. Therefore our family would have a 25% risk of recurrence. As this family was lost to follow up, it is unknown if they had any further pregnancies.

CASE 15-S

The mother of patient 15 was seen by Genetics because of a history of MCA in a previous pregnancy. Her third pregnancy had ended in the birth of a fetus with MCA. The history of this pregnancy was reviewed and there was the occasional use of alcohol throughout the pregnancy. There were no other teratogenic exposures. The couple was unsure as to whether or not they might be related. Both parents were of Aboriginal heritage. Autopsy had revealed the following anomalies:

- Bilateral cystic renal dysplasia
- Cleft lip and palate
- Bilateral clinodactyly

Chromosome analysis done on fetal blood showed a normal 46,XX karyotype. The differential diagnoses included a "possible unknown autosomal recessive condition given the possibility that there was consanguinity". They were counselled that the risk of recurrence might be as high as 25%.

The parents were seen in Genetics for a second time after the birth of another affected child. This birth resulted in a live full term female who was noted to have the following anomalies at birth:

- Interrupted aortic arch
- Horseshoe kidney
- Depressed nasal bridge with anteverted nares
- Short neck with low posteriorly rotated ears
- Short stature

Chromosome studies and FISH for 22q were done to rule out 22q Deletion Syndrome based on the cardiac finding; both were normal. The differential diagnoses included DiGeorge syndrome (22q Deletion syndrome), Turner Syndrome and Fetal Alcohol Effects. The DiGeorge and Turner syndrome were ruled out by a normal chromosome and FISH results. The couple was counselled that this most likely was a sporadic event related to the use of alcohol in pregnancy.

Given the previous case and the similarity between the affected individuals, the diagnosis of Holzgreve-Thomas syndrome was made in this family. The first affected fetus had bilateral cystic kidneys and cleft lip and palate, which was consistent with the other case reports of Holzgreve-Thomas syndrome. The second affected child also had renal and cardiac findings. While this patient's particular renal anomaly have not been

previously reported, aortic arch anomalies are the main cardiac finding in patients with Holzgreve-Thomas syndrome. Given the more classical Holzgreve-Thomas syndrome in the first sib, we believe the second sib also had this condition. This case lends additional support to an autosomal recessive mode of inheritance, giving this family a 25% risk of recurrence. One factor that should be considered was that there was occasional use of alcohol during both pregnancies. The effects of the alcohol, while unclear, may have had some impact on the development of the fetus in addition to the underlying genetic disorder. It can be quite difficult to tease out teratogenic effects from that of genetic effects.

CASE 16-S

Patient 16 was born to a consanguineous couple (first cousins) of Aboriginal ethnic background. The patient was seen by Genetics because of MCA. Pregnancy and birth history were not available. There was a positive family history of stillbirths and spontaneous abortions. The couple's first pregnancy resulted in a stillbirth. Their second born child was diagnosed with Herpes encephalitis and their fourth pregnancy was lost at 8 weeks gestation. On examination/investigation, the following anomalies were noted in this patient:

- Mental retardation
- Hypotonia
- Iris coloboma
- Cryptorchidism
- Low-set ears with hypertelorism and down-slanting palpebral fissures
- Seizure
- Small stature with failure to thrive
- Macrocephaly
- Syndactyly and camptodactyly with adducted thumbs
- ASD

Chromosome analysis revealed a normal male karyotype: 46,XY. The diagnosis given

to the family was "an unknown autosomal recessive condition unique to this family" based on the consanguinity. The couple was counselled with a 25% risk of recurrence.

Ritscher-Schinzel syndrome (also called craniocerebello cardiac syndrome) was suggested by POSSUM and LDDB database searches. Review of the literature supported this diagnosis in the patient. In addition, this family was from a geographic region where this condition is found in high prevalence.

Ritscher et al. (1987) reported on two sisters with similar craniofacial anomalies, brain malformations and congenital heart defects. The craniofacial anomalies included macrocephaly with prominent forehead and occiput, hypertelorism with down-slanting palpebral fissures, depressed nasal bridge and low-set ears. Both sibs had mild MR. In this report, they suggested that this was an autosomal recessive condition.

Marles et al. (1995) reported on eight native children with craniofacial anomalies, congenital heart defects and CNS findings consistent with those found in Ritscher-Schinzel syndrome. These children had a variety of ocular colobomas, hand anomalies (adducted thumbs), macrocephaly and cardiac anomalies. These patients were from a specific isolated geographic region. All of the parents were clinically normal, lending support to the autosomal recessive mode of inheritance.

Leonardi et al. (2001) reviewed all reported cases of Ritscher-Schinzel syndrome and reported on four patients who they considered had this condition. They concluded that cleft palate and ocular anomalies were the most readily ascertained findings. They proposed that all cases must have a normal chromosome analysis and the following traits to confirm the diagnosis: cardiac malformation, cerebellar malformation, cleft palate or ocular coloboma, or four of the seven following traits: prominent forehead, prominent

occiput, hypertelorism, down-slanting palpebral fissures, low-set ears, depressed nasal bridge and micrognathia.

Based on the above criteria, the diagnosis of Ritscher-Schinzel can be made in this patient. The features include bilateral iris colobomas, ASD, hypertelorism, low-set ears, down-slanting palpebral fissures and a normal chromosome karyotype. One limitation is that the patient did not have any investigations to determine whether there was any brain malformations as are found in the majority of patients with Ritscher-Schinzel syndrome. This is an autosomal recessive condition with a 25% risk of recurrence. This diagnosis has not changed the initial recurrence risk that the family was given when they were seen by Genetics. Making a diagnosis does however, allows for better medical management of this child (e.g. cranial imaging). Making a diagnosis also allows for more accurate counselling for other family members.

CASE 17-S

Patient 17 was seen by Genetics as a consult because of dysmorphic facies, IUGR and ambiguous genitalia. He was born at 34 weeks to a G1P 16-year-old Aboriginal woman. Pregnancy history was remarkable in that there was no prenatal care until 23 weeks' gestation, use of marijuana, hash and LSD (one exposure in the first two trimesters) and alcohol use on 3 to 4 occasions. The mother was also exposed to varicella virus during the third trimester. The parents were second cousins once removed. The family history was unremarkable. On examination/investigation, the following clinical features were noted:

- Congenital heart defect – VSD, ASD
- IUGR
- Hydrocephalus
- Cholestatic liver disease with secondary rickets
- History of hyperbilirubinemia

- Hypospadias
- Macrocephaly with large fontanelle
- Mental retardation
- Dysmorphic facies with hypertelorism and micrognathia

The differential diagnosis included Hypertelorism-Hypospadias syndrome, Alagille syndrome and DiGeorge syndrome. Recurrence risks for this family was not commented on. Routine chromosomal analysis revealed a normal male karyotype of 46,XY. He also had a normal ophthalmologic examination.

A search using PubMed suggested Alagille syndrome and review of the literature supported this diagnosis in the patient. Alagille syndrome is characterized by retinal pigmentary changes, pulmonary stenosis/arterial stenosis, vertebral anomalies (butterfly vertebrae), absent deep tendon reflexes, learning delays, characteristic facies with broad forehead, pointed mandible and bulbous tip of the nose and digit abnormalities (primarily shorting). In addition, many Alagille patients have cholestatic liver disease (Watson and Miller, 1973; Alagille et al., 1975; Rosenfield et al., 1980; Berman et al., 1981). Oda et al. (1997) and Li et al. (1997) demonstrated that Alagille syndrome is caused by heterozygous mutations in the JAG 1 gene, which encodes a ligand for NOTCH 1. Deletions in the region of the JAG 1 gene have also been found in some Alagille patients (Krantz et al., 1997). These results confirmed the autosomal dominant inheritance of Alagille syndrome.

Our patient had had an extensive work up regarding his cholestatic liver disease and no cause could be determined. He had a liver biopsy that was non-informative. Renal ultrasound and eye exams were normal. The patient did not have any skeletal X-rays. Despite the lack of other investigations, the diagnosis of Alagille syndrome was made in this patient based on the cholestatic liver disease, cardiac abnormalities, failure to thrive

and characteristic facies with broad forehead and hypertelorism, and mild MR. Our patient also had hypospadias, which, based on review of the literature, has not been previously reported in Alagille syndrome patients.

The initial differential diagnosis included hypertelorism-hypospadias syndrome and DiGeorge syndrome (22q deletion). Based on a review of the literature, hypertelorism-hypospadias and DiGeorge syndrome seemed unlikely. Neither condition was suggested in any of the database searches and our patient's overall clinical picture does not fit with either of these conditions, which were discussed in previous cases. This case is complicated by the exposure of alcohol (although limited), marijuana/hash and LSD during pregnancy. While there is no debate over the teratogenic effects of alcohol, the exposure was small with three to four exposures throughout out the pregnancy. Marijuana, hash and LSD have not been shown to have teratogenic effects on the developing fetus (Friedman and Polifka, 1994). Thus, it seems unlikely that these factors would have contributed to this patient's clinical findings.

Alagille syndrome is an autosomal dominant condition with a recurrence risk of 50%. Most likely, this condition occurred *de novo* in this patient as neither parent had any clinical findings of Alagille syndrome. Therefore, the risk for this family of having a recurrence is low. The risk to the patient of having an affected child is 50%. The diagnosis of Alagille could be confirmed by DNA analysis; however, molecular testing has not yet been pursued. Although the risk to the family for having another affected child is low, prenatal diagnosis with DNA analysis would be a possibility if a mutation were identified in this patient.

CASE 18-S

Patient 18 was seen in the newborn period by Genetics because of a cleft lip and palate and minor anomalies. He was born to a nonconsanguineous couple (although from the same small community) of Aboriginal heritage. Review of the family history revealed that there was a first cousin who was developmentally delayed with minor dysmorphic facies. This was thought to be due to the maternal drug abuse during pregnancy. This patient's birth and pregnancy history were unremarkable. The patient had a normal karyotype: 46, XY. On examination/investigation the following clinical features were found:

- Eyelid coloboma both upper & lower lids of right eye
- Bilateral cleft lip & palate
- Hypertelorism
- Hypoplastic toe nail
- Anterior lying hairline on right side
- Pulmonary stenosis

The differential diagnosis included Fraser syndrome, Marles (MOTA) syndrome, median cleft facies and amnion disruption sequence. The family was counselled with a 3-5% recurrence risk for any future pregnancies.

MOTA syndrome (also known as Marles syndrome) was suggested by OMIM when the clinical finding "aberrant hair line" was used as a search parameter. Review of the literature on this condition supported this diagnosis in this patient. During this study, the patient was re-evaluated and the family was counselled regarding this new diagnosis and given a 25% recurrence risk.

MOTA syndrome is an autosomal recessive condition, which has been described in 6 Manitoba Indian children by Marles et al. (1992). This syndrome is comprised of

hypertelorism, unilateral eye malformations (colobomas), aberrant anterolateral scalp hairline, nasal and anal anomalies (MOTA stands for Manitoba oculotrichoanal syndrome). All affected were from related families. The most interesting anomaly was the anomalous wedge of scalp hair, which extended from the frontotemporal region to the eyebrow/eye region. One of the patients described had an upper eyelid coloboma with a wedge of scalp hair extending down to her eyebrow. Review of the clinical findings and clinical photographs strongly supported the diagnosis of MOTA syndrome in our patient. The diagnosis was made on the unique abnormal scalp hairline and the coloboma of the upper and lower eyelid. This patient also had a bilateral cleft lip and palate, which has not been previously described in this syndrome. Growth and development was normal in this patient as has been documented in other cases of MOTA syndrome.

The initial differential diagnoses included Fraser syndrome. This is an autosomal recessive condition first described by Fraser (1962). It is a MCA condition characterized by cryptophthalmos, absent/malformed lacrimal ducts, ear malformations, hypertelorism, laryngeal stenosis, kidney and genital malformations. It has also been called the cryptophthalmos-syndactyly syndrome (Lurie and Cherstroy, 1984). This patient's spectrum of clinical findings does not fit into this pattern of defects. This patient lacks any of the main features of this condition, specifically ear malformations, cryptophthalmos, laryngeal stenosis/atresia, genital and renal anomalies and syndactyly. Interestingly, this condition is also associated with lateral scalp hair growth extending to the lateral eyebrow (Jones, 1997).

Amnion band sequence is a sporadic event that occurs when small strands of amnion encircle or adhere to developing structures of the fetus. This can cause a range of defects from clefting to limb amputation. The features of amnion band sequence should all be "surface" defects; thus there should not be internal malformations. Evidence of the

amniotic bands is also usually present. Given the clinical picture of this patient, amnion band sequence does not seem to fit. There was no history of oligohydramnious from amnion leakage (sometimes seen), no evidence of amniotic bands and there were other malformations, which would no be explained by amniotic bands (i.e. aberrant hairline, pulmonary stenosis and hypertelorism).

Median cleft facies is generally a sporadic event with a wide spectrum of clinical findings. Affected persons can have mild ocular hypertelorism with a broad nasal tip to a completely divided nostril with a median cleft lip (Jones, 1997). The inheritance of this condition is uncertain. Again, a literature review of this condition did not support this diagnosis for this patient. This diagnosis was most likely originally suggested, as there is a slight resemblance between our patient's facial features (hypertelorism and board nasal root) with that of Median cleft facies.

MOTA was initially suggested in the differential diagnosis. However, because of atypical features, MOTA syndrome was thought unlikely.

CASE 19-S

Patient 19 was born to a 21-year-old G2P1 nonconsanguineous couple, both of whom were of Caucasian background. They had had one previously healthy child. On ultrasound examination at 16 weeks, IUGR and an unusual head shape were noted. The child was stillborn at 39 weeks with weight, length and head circumference below the 3rd percentile. The family history was unremarkable. The couple went on to have another pregnancy that was terminated at 21 weeks when severe IUGR and microcephaly were detected on ultrasound. The clinical findings noted on this patient were:

- Sloping forehead
- Protuberant nose & low-set ears

- Cloudy corneas
- Marked micrognathia & high arched palate
- 5th finger clinodactyly with single crease
- Hydranencephaly with cerebral & cerebellar hypoplasia
- Non-fixation of the ascending colon
- Hypoplastic lungs
- Dysplastic cartilaginous foci both kidneys
- Sacral dimple
- Absent ribs (11 pairs)
- Hypoplastic/non-ossified bones on radiography
- Scoliosis

The differential diagnosis included cerebro-costo-mandibular syndrome and Seckel syndrome. The family was given a 25 to 50% risk of recurrence. The family was lost to follow up after this initial consultation and the outcome of the second pregnancy was not reviewed with the family. The patient had a normal karyotype 46,XX and the parental karyotypes were also normal.

Based on clinical suspicion, the diagnosis of Seckel syndrome was suggested and review of the literature supported this diagnosis. Seckel first described "Seckel syndrome" in 1960 as a severe short stature MCA condition. The clinical findings of this condition are prenatal onset of growth retardation and postnatal growth delay, microcephaly with receding forehead, prominent nose, micrognathia, low-set malformed ears, large eyes with down slanting palpebral fissures, clindodactyly of the 5th finger with simian crease and absent ribs (only 11). It may also be associated with cleft palate and mental retardation. Sugio et al. (1993) reported on 2 Japanese cases of Seckel syndrome with severe brain dysplasia. Shanske et al. (1997) reported on 2 siblings with Seckel syndrome who also had neurological findings including dysgenetic cerebral cortex with pachygyria, agenesis of the corpus callosum and hypoplasia of the cerebellar. Seckel

syndrome is an autosomal recessive condition with many examples of recurrences in families.

The diagnosis of Seckel syndrome was made in this patient based on the craniofacial findings (microcephaly with sloping forehead, protuberant nose, large low-set ears and micrognathia), the neurological findings (cerebellar and cerebral anomalies) and severe IUGR. Our patient also had other findings that have been described in this condition (11 pairs of ribs and 5^{th} finger clinodactyly). The recurrence of a similarly affected sibling with severe IUGR and microcephaly supports the autosomal recessive nature of Seckel syndrome. This patient seems to fit into the severe end of the Seckel syndrome spectrum.

The differential diagnosis included cerebro-costo-mandibular syndrome (also called rib-gap syndrome). This condition was initially described by Smith et al. (1966). It is defined by postnatal growth deficiency, MR and speech problems, severe micrognathia with glossoptosis, palate defects, bell-shaped small thorax with gaps between posterior ossified ribs and rudimentary ribs with other rib anomalies, microcephaly and other anomalies (e.g. cardiac defects) are found occasionally. Half died with in the first year of life due to the severity of the thoracic defects. The main findings of this condition tend to be the thorax-rib and micrognathia anomalies (Silverman et al., 1980; Plotz et al., 1996; Kirk et al., 1999).

This patient did have micrognathia, IUGR, hydranencephaly, microcephaly and a high arched palate, all of which have been described in cerbro-costo-mandibular syndrome (Jones, 1997). However, this patient's rib anomalies (absent ribs) are not the rib anomalies commonly associated with this condition. The rib anomalies found in cerebro-costo-mandibular syndrome tend to be lack of ossification and short ribs with "gaps". Plotz et al. (1996) reviewed the literature and showed that respiratory distress, gaps of

posterior ribs and micrognathia were almost always present. Heart and kidney defects were uncommon. While the clinical findings in this patient overlap those found in cerbro-costo-mandibular syndrome, after review of the literature, it seems unlikely that our patient and her sibling fit into this syndrome. In addition to lacking the typical rib findings, our patient had renal and ocular anomalies, dysmorphic facies, severe micrognathia and GI findings not usually associated with this condition.

The clinical similarity between Seckel syndrome and cerebro-costo-mandibular syndrome along with the fact that the family was lost to follow up, is most likely why the diagnosis was not made initially. Seckel syndrome is an autosomal recessive condition and as such has a 25% recurrence risk. Cerebo-costo-mandibular syndrome has been shown to be both autosomal recessive and autosomal dominant in different families. The family was initially counselled with a potential recurrence risk of 25%. Making a diagnosis of Seckel syndrome has supported the 1 in 4 recurrence risk. Currently there is no molecular testing available for this condition, thus DNA based prenatal counselling and testing is not an option at this time. There is a low risk for extended family members unless they were consanguineous.

4.2 ASSOCIATIONS & SEQUENCES

CASE 1-A

Patient one was born to a nonconsanguineous Caucasian couple. The patient was seen by Genetics because of the presence of an encephalocele at birth. The pregnancy and birth history were reviewed and revealed that the mother was on Nadolol for hypertension but that it was discontinued once she was aware she was pregnant. Nadolol was not believed to be a teratogen. The family history was reviewed and was unremarkable. The patient had two older healthy brothers. On examination/investigation, the following anomalies were identified:

- R coloboma – iris and retinal
- Cleft palate
- Mental retardation
- Midface hypoplasia
- Short stature
- Encephalocele
- Absent crista galli
- Single incisor
- Cerebral atrophy

The differential diagnosis included holoprosencephaly sequence and CHARGE association. The family was counselled and given a 5% risk of recurrence.

Holoprosencephaly sequence was suggested by both the POSSUM and LDDB searches. Review of the literature supported this diagnosis in the patient. The patient presented with a single incisor, coloboma and cleft palate. This combination of findings has been previously reported and has been suggested to be manifestations of the holoprosencephaly sequence (Liberfarb et al., 1987). Nanni et al. (2001) performed molecular studies in 13 patients with single incisor without holoprosencephaly and

demonstrated mutations in the SHH gene (Sonic Hedgehog gene), which had previously been demonstrated to be associated with holoprosencephaly (OMIM # 600725), suggesting that these patients fit into the holoprosencephaly spectrum. Other features of this condition include short stature and mild craniofacial defects (e.g. retrognathia). The combination of occipital encephalcele and holoprosencephaly has been reported in the literature (Hutchison et al., 1979; Saatci et a., 1998; Elgin et al., 2001).

The differential diagnoses included CHARGE association. The findings of this patient were reviewed and compared to those features found in CHARGE association and it seems unlikely that he fits into this spectrum. This patient does not have any heart, genital or ear anomalies. Nor does he have choanal atresia. Recurrence risk for holoprosencephaly sequence is estimated to be about 6%.

CASE 2-A

Patient 2 was seen in the Genetics Clinic at the age of 6 years because of MCA. She was born to parents of unknown ethnic background and unknown consanguinity. Birth history and prenatal history were unremarkable. Family history was unknown. On examination/investigation, the following anomalies were noted:

- Ambiguous genitalia (enlarged clitoris, fused labia minora & one urogenital sinus opening)
- Left-sided ribs fused & hypoplastic right rib
- ASD
- Hydronephrosis and malrotated kidneys with bifid renal pelvis
- Short phalanges with short flat nails & tapered digits
- Epicanthal folds

Chromosome analysis showed a normal female karyotype 46,XX. The initial

differential diagnosis included adrenogenital syndrome (congenital adrenal hyperplasia) and gonadal dysgenesis due to adrenal insufficiency, which were subsequently ruled out by endocrine studies. The recurrence risk quoted to the family at that time was unknown.

Review of the patient's findings with members of the Section of Genetics identified a potential diagnosis known as the MURCS association. Review of the literature on this condition supported this diagnosis in our patient. The MURCS association consists of mullerian duct and renal agenesis and cervicothoracic somite dysplasia (OMIM# 223340). It was first reported by Duncan et al. (1979) who documented a nonrandom occurrence of these malformations in 30 patients, 28 from previously reported cases and 2 of their own cases. The common findings in this association include small stature, cervicothoracic vertebral defects (including Klippel-Feil malformation), hypoplastic/absent vagina, uterus and/or ambiguous genitalia, ectopic and/or renal agenesis, rib anomalies, upper limb defects, GI, cardiac and craniofacial anomalies (Greene et al., 1986; Braun-Quentin et al., 1996; Jones, 1997; Geipel et al., 2001). The diagnosis of MURCS association was made in this patient based on the absent vagina and ambiguous genitalia, rib anomalies and renal findings.

The initial differential diagnosis included adrenogenital syndrome (congenital adrenal hyperplasia) and adrenal insufficiency, which were ruled out by normal endocrine investigations. Neither diagnosis would account for the patient's other findings (i.e. rib and digit anomalies).

Our patient was initially seen by Genetics in 1977, before the MURCS association was delineated by Duncan et al., in 1979. After initial consultation with Genetics, she was lost to follow up. The MURCS association is sporadic in most cases, however there have been reports of familial cases. The recurrence risk for this family is approximately 4%

(Jones, 1997).

CASE 3-A

Patient 3 was born to a couple of Scottish/English ethnic background. The patient was seen in the Genetics clinic for evaluation because of possible Marfan syndrome. Review of the prenatal and birth history showed that the mother had had one abnormal glucose tolerance test late in pregnancy. This was not thought to be a significant finding and the mother was not treated. The rest of the prenatal and birth history was unremarkable. The family history was reviewed. The father had macular degeneration. There were two first cousins on the maternal side with clubfeet. The patient had a sibling who had had multiple pregnancy losses. On examination/investigation, the following features were noted:

- R sided diaphragmatic hernia with agenesis of the anterior medial diaphragm
- Developmental delay
- Omphalocele
- PDA
- Contractures of the lower limbs
- Abnormal lobation of the liver
- IUGR
- Dysmorphic facies with ptosis and malar hypoplasia

A differential diagnosis was not mentioned on review of the chart nor was the risk of recurrence noted. Chromosome analysis showed a normal male karyotype: 46,XY. Parental chromosomes were also normal.

The patient's phenotype was reviewed with members of the Section of Genetics and Schisis association was suggested. Review of the literature supported this diagnosis in this patient. In 1981, Czeizel reported and reviewed the nonrandom occurrence of birth

defects known as the Schisis association. These defects are NTD (anencephaly, encephalocele and spina bifida), oral clefts (cleft lip and palate), omphalocele and diaphragmatic hernias. In this paper, Czeizel suggested that the diagnosis of Schisis association could be made when 2 or more of the above anomalies are found in absence of other major congenital anomalies. His analysis suggested a recurrence risk of 4%.

A second epidemiology paper was presented by Martinez-Frias et al. (1997) and using Czeizel's methods, they re-evaluated the Schisis association using the Spanish Collaborative Study of Congenital Malformations. They also demonstrated the nonrandom association of Schisis defects. They argued that schisis-like defects represent a primary developmental field defect. This then lead to the argument by some authors that some or all associations are also primary field defects (Martinez-Frias, 1997).

The diagnosis of Schisis association was made in this patient based on the diaphragmatic defects and the omphalocele in the absence of any other major malformations. The recurrence risk for this family is 4%.

CASE 4-A

Patient 4 was born to parents of unknown ethnic background and unknown consanguinity. She was seen at birth because of duodenal atresia. Pregnancy history and birth history were unremarkable except that she was born prematurely at 34 weeks. The family history was not remarked upon. The following features were noted on examination:

- Duodenal atresia
- Dextropositional heart
- Ectopic anus

The constellation of defects was thought to be due to an early embryonic insult of unknown etiology. The family was counselled that there was a "low" risk of recurrence for future pregnancies. No chromosomal studies were carried out this patient. However, her findings were not thought to be due to Down syndrome as she lacked any of the typical facial features of
Down syndrome.

Hancock and Wiseman (1989) discussed the association between duodenal anomalies and cardiac anomalies. They looked at 34 patients with duodenal atresia and 8 out of those 34 patients had associated cardiac anomalies. They suggested the occurrence of duodenal atresia and cardiac anomalies were a real "association". Duodenal atresia is associated with other anomalies in 50 – 70% of the cases. Duodenal atresia is associated with gastrointestinal anomalies (e.g. imperforate or ectopic anus) in about 26% of the patients. An additional 20% have congenital heart defects (Romero et al., 1988). After review of the literature on this association, it was decided that this patient's clinical findings fit into this category. This association has a recurrence risk of 2-5%.

CASE 5-A

Patient 5 was born to a consanguineous couple (second cousins) of Cree background. The pregnancy history was reviewed and was unremarkable. Family history was also unremarkable. On examination the following features were noted:

- Bilateral split hand anomalies with absent thumb & absent metacarpals
- L radial agenesis
- Developmental delay
- Elbow contracture – bilateral
- Horseshoe kidney

The differential diagnosis included an "unknown autosomal recessive skeletal disorder" and Fanconi anemia. The latter was ruled out by a normal chromosome breakage analysis. The recurrence risk was not commented on in the chart.

PubMed identified a paper by Leiter and Lipson (1975) and a more recent paper by Evans et al. (1994) that described the association between limb deficiency defects and renal anomalies. The literature was reviewed and the limb-renal association diagnosis was made in this patient.

Dicker and Opitz (1969) first noted the association between limb and renal anomalies. They described three unrelated males with a range of limb and renal anomalies. Since that original report other authors have reported on this "association" (Leiter and Lipson, 1975; Siegler et al., 1980; Evans et al., 1994). An article by Leiter and Lipson (1975) reported a child with ectrodactyly (lobster claw syndrome) and genitourinary anomalies. They pointed out in their paper that there is a well known embryological association between renal and limb-bud development. However, given this embryonic association, this combination of defects is not overly reported on in the literature. As far as this writer is aware, this is the first report of the combination of ectrodactyly and horseshoe kidney. While it is not clear from the literature, it is likely, as in most associations, a low risk of recurrence.

CASE 6-A

Patient 6 was born to a nonconsanguineous couple of mixed European background. The mother was G2P2 with an unremarkable pregnancy history. Family history was unremarkable. The patient had a CT scan that showed lucency of the anterior thalamus, which was thought to be gliosis. He had a normal chromosome analysis: 46, XY. The following anomalies were noted:

- Omphalocele
- ASD with pulmonary stenosis
- Mild left hemiparesis
- Growth delay
- Microcephaly with developmental delay
- IUGR

The initial differential diagnosis included an unknown syndrome or an isolated omphalocele. The family was counselled with a recurrence risk of 1-2% for the recurrence of the omphalocele.

A search using PubMed suggested an omphalocele-cardiac association. A paper by Gilbert and Nicolaides (1988) reported on 30 cases of omphalocele with associated malformations. Fourteen had cardiac defects, all of which had normal chromosome studies. Eleven of these cases also had other malformations, but the types of anomalies were not documented. There have been other reports that have documented the association between omphalocele and cardiac defects, the most common of which are septal defects (ASD and VSD) and Tetralogy of Fallot. It is estimated that cardiac defects are found in 47% of cases of omphaloceles (Romero et al., 1988). These cases also tend to have IUGR (about 20%). The recurrence risk for this family would be 1-2%.

CASE 7-A

Patient 7 was born to a nonconsanguineous couple of German/English ethnic background. The patient was seen in the newborn period because of an omphalocele and congenital heart defect. Pregnancy and birth histories were reviewed and were unremarkable. There was a positive family history on the paternal side for congenital heart disease of unknown etiology in a first cousin. The patient was seen by Genetics and the following anomalies were noted:

- Transposition of great vessels with VSD/ASD, tricuspid stenosis, R hypoplastic ventricle
- Omphalocele
- Intestinal duplication with malrotation

The family was counselled that this most likely represented two sporadic anomalies and was non-syndromic. They were given a recurrence risk of 1-2% for complex congenital heart anomalies in future pregnancies. Chromosome analysis was normal: 46,XY. The patient died at 2 years of age.

As in the previous case the omphalocele-cardiac association was suggested for this patient. The recurrence risk for this family would be 1-2%.

CASE 8-A

The parents of patient 8 were seen after MCA were detected on an ultrasound done for dating. They were a nonconsanguineous couple. The mother was of Cree descent and the father was of German/Yugoslav background. Pregnancy history was reviewed and was unremarkable. There was a positive family history on the mother's side of a half cousin who had MCA. That individual was said to have facial paralysis with micrognathia and missing fingers and toes. This individual had not been assessed by Genetics. The parents were seen for counselling regarding recurrence risk in future pregnancies. The patient was not seen by Genetics. However, the autopsy was reviewed with the family. On review the following anomalies were noted:

- Cystic hygroma
- Midline cleft palate
- Omphalocele
- Scoliosis

The family was counselled that this constellation of anomalies might represent a chromosome defect or an unknown autosomal recessive syndrome. Chromosome analysis was not done on the patient. The family was given a 5% risk of recurrence.

This case was reviewed with the members of the Section of Genetics and the diagnosis of Schisis association was suggested. Review of the literature supported this diagnosis in this patient. As Schisis association was discussed previously, it will not be reviewed in detail here. The diagnosis was made based on the omphalocele and the midline cleft palate. One limitation in this case was that chromosome analysis was not done, thus one is unable to rule out a chromosomal etiology for this constellation of features. Cystic hygroma can be associated with chromosome syndromes (e.g. Turner syndrome). However, the overall gestalt of the patient's clinical features did not fit into any recognized chromosomal syndrome. The recurrence risk for Schisis association is 4%.

CASE 9-A

Patient 9 was born to a consanguineous couple (second cousins) of Aboriginal ethnic background. The pregnancy and birth history were reviewed and were unremarkable. There was a positive family history of early onset heart disease of unknown etiology on both sides of the family. The patient died at 2 years of age due to complications of her congenital anomalies. The patient was not seen by Genetics, but the parents were seen for counselling regarding recurrence in future pregnancies. The child did have a chromosome analysis and had a normal female karyotype of 46, XX. No autopsy was preformed. Review of the patient's hospital chart revealed the following anomalies:

- Hydrocephalus
- Spina bifida
- Diaphragmatic hernia

The family was counselled that this combination of anomalies most likely represented two sporadic anomalies. The family was counselled with a recurrence risk of 4% for neural tube defect and a recurrence risk of 1-2% for diaphragmatic hernia.

Schisis association was suggested in both the POSSUM and LDDB database queries for this patient. Schisis association was reviewed and the diagnosis of Schisis was made in this patient based on the spina bifida and diaphragmatic hernia. The recurrence risk for this family is 4%.

CASE 10-A

Patient 10 was born to a nonconsanguineous couple of Scottish/French Canadian background. The mother smoked one half pack of cigarettes per day throughout the pregnancy. The birth history and family history were unremarkable. Chromosome analysis was normal: 46,XY. The infant died at 2 weeks of age. The infant was seen by Genetics shortly after birth and the following anomalies were noted then or found on subsequent investigations:

- Choanal atresia
- Complex congenital heart with interrupted aortic arch
- Ectrodactyly – R hand
- Low set simple ears
- Absent median ray – R hand

The initial differential diagnosis included CHARGE association and DiGeorge syndrome. The family was counselled with a low risk of recurrence (2%).

CHARGE association was suggested by the POSSUM database search. Review of the clinical findings and the literature supported this diagnosis in this patient. CHARGE association has been reviewed in a previous case so it will not be discussed in detail here.

The diagnosis was made for this patient based on the following features: choanal atresia, cardiac anomaly, and the ear anomaly. This patient also had ectrodactyly with absent median ray. Limb defects in combination with CHARGE association has been described in the literature (Meinecke et al., 1989; Williams and Rooney, 1996; Prasad et al., 1997). Williams and Rooney (1996) reported on two patients who had atypical split hand/split foot deformities as part of the CHARGE phenotype. The recurrence risk for this family would be low (1%). However, familial cases of CHARGE association have been reported (Mitchell et al., 1985).

In the initial differential diagnoses, DiGeorge sequence was suggested. After review of the literature, it seems unlikely that this patient fit into this spectrum. DiGeorge sequence patients typically have hypoplasia/aplasia of the thymus and parathyroids in association with conotruncal defects. If it is associated with a deletion of 22q.11 (known as 22q Deletion syndrome), there is usually a dysmorphic facies as well (Jones, 1997). FISH for 22q might have helped to rule out this condition.

CASE 11-A

Patient 11 was born to a nonconsanguineous couple of German/English/Irish heritage. Pregnancy history showed borderline gestational diabetes with one abnormal glucose tolerance test; this was treated effectively with diet. Labour was induced at 38 weeks. The patient suffered a cardiac arrest at 31 hours of age and resuscitation attempts failed. Family history was reviewed and showed that the couple had had a previous child with unilateral diaphragmatic hernia and an intrauterine death at 16 weeks. The paternal grandfather had syndactyly of one hand. Chromosome analysis was done on the parents and was normal for both. Chromosome analysis on the patient was normal 46,XX. The following anomalies were noted on exam and autopsy:

- Large infant
- Hypopharyngeal/ esophageal cyst
- Horseshoe kidney
- Accessory spleen

The family was counselled that the esophageal cyst was a sporadic developmental error and that the other anomalies were nonsyndromic (i.e. the kidney and spleen findings were incidental findings). The couple was given a low risk of recurrence.

Because esophageal cyst is an uncommon finding, a search using that specific anomaly with PudMed was performed. A paper by Goktay et al. (1999) reported on a case of esophageal cyst, Bochdalek hernia and polysplenia in a 4 month – old girl. Because esophageal cyst is an unusual finding, the association of this finding with accessory spleen and renal anomaly, such as those found in this patient, suggested the diagnosis of VATER association. VATER association consists of vertebral anomalies, anal atresia, tracheo-esophageal fistula or esophageal atresia, radial ray and renal anomalies. Other anomalies can be found in the VATER association including spleen anomalies (Botto et al., 1997). Horseshoe kidney has also been reported in the VATER association (Unuvar et al., 1998). This patient has an atypical presentation of VATER association with a rarer esophageal anomaly (not a T-E fistula or esophageal atresia), a renal defect and associated spleen anomaly. VATER association has a 1% risk of recurrence.

CASE 12-A

Patient 12 was born to a nonconsanguineous couple. The mother was of English/Scottish heritage and the father was of Mennonite background. The patient was seen by Genetics in the newborn period because of MCA. Review of the pregnancy and birth history was essentially unremarkable. Family history revealed that a sibling of the patient had pectus excavatum and that several children on the father's side of the family had "turned-in feet". Routine chromosome analysis demonstrated a 46, XX, 13 S++

karyotype and this finding was thought to be a normal variant. During examination and subsequent investigation the following clinical findings were noted:

- Vertebral anomalies with tethered cord and fused ribs
- Asymmetric facies
- Plagiocephaly with torticollis
- Talipes equinovarus and pes cavus
- Motor and developmental delay

The initial differential diagnosis included VACTERL association and spondylocostal dystostosis. The family was counselled that the patient's clinical findings most likely were the result of a sporadic event. The family was not planning on having any more children so they were not counselled about recurrence risks.

Spondylocostal dysostosis (SCD) is associated with vertebral and rib malformations. It is thought by some authors to be a subtype of the Jarcho-Levin syndrome, which is represented by variations in the severity of expression (OMIM #277300). It is a lethal short trunk dwarfism associated with rib (fused) anomalies, dysmorphic facies and genital – urinary anomalies (Jones, 1997). It is thought to be an autosomal recessive condition.

Review of this patient's clinical findings, while consistent with the vertebral and rib anomalies seen in SCD, did not seem to suggest the diagnosis of SCD. Other clinical findings, (e.g. asymmetric crying facies) suggests that our patient falls under the Facio-auriculo-vertebral (FAV) dysplasia (also known as Goldenhar and Hemifacial-microsomia dysplasia). Searches were performed using both the POSSUM and LDDB databases and both analyses supported the clinical suspicion of FAV. The features of this condition include asymmetric facies (hemifacial microsomia with or without microsomia and micrognathia), ear anomalies consisting of ear pits or ear tags and microtia and

vertebral anomalies. Other associated findings such as developmental delay, rib anomalies, and positional limb defects have also been reported (Avon and Shively, 1988; Rodriguez et al., 1993). Rodriguez et al. (1993) reported a patient with FAV dysplasia who had rib and vertebral anomalies similar to those found in SCD syndrome. They pointed out that these malformations are associated with both FAV dysplasia and SCD syndrome and made for a diagnostic problem. SCD syndrome is considered to be an autosomal recessive condition (25% risk of recurrence) whereas FAV dysplasia is heterogeneous with most cases occurring sporadically. Therefore the estimated recurrence risk for this family would be 2-5%.

The diagnosis of VACTERL association was not considered for this patient, as the only finding consistent with VACTERL association was the vertebral anomalies. Renal ultrasound ruled out any renal abnormalities. Duncan and Shapiro (1993) pointed out the association between the phenotype of hemifacial microsomia (FAV dysplasia) and VATER association. They suggest that a subgroup of FAV patients may represent a hemifacial-VATER phenotype. They did not suggest whether or not this is a distinct entity or whether these patients fit under the VATER association phenotype with associated hemifacial findings.

Townes-Brock syndrome (TBS) consists of auricular anomalies, features of FAV dysplasia, (e.g. ear tags), radial – ray defects with anal and renal anomalies (Jones, 1997). It is an autosomal dominant condition with marked variability of expression. It has long been noted that there is clinical overlap between TBS and the FAV spectrum (Gabrielli et al., 1993; Johnson et al., 1996) and the VATER association (OMIM #164210). In a retrospective study, Keegan et al. (2001) demonstrated mutations in the SALL 1 gene (which is associated with TBS) in a subgroup of patients who had been clinically diagnosed with FAV dysplasia. They noted, however, that these patients had additional

findings commonly seen in Townes-Brock syndrome. Our patient does not have any of the typical TBS features (e.g. ear anomalies, anal anomalies or digit defects). It seems unlikely our patient fits into this spectrum of defects. Mutation analysis of the SALL 1 in this patient might not be beneficial (i.e. negative results would not necessary rule out TBS).

Although there is some debate in the literature over the grouping of these clinical features (VATER verses SCD verses TBS verses FAV) at this time, the patient's findings are most representative of the FAV spectrum. Therefore, the recurrence risk for this family is likely low (2-5%).

CASE 13-A

Patient 13 was stillborn to a nonconsanguineous couple of Mennonite background. The couple was seen by Genetics shortly after the birth of this child who had MCA. The pregnancy and birth histories were unremarkable. The family history was positive in that a paternal great aunt had died of a congenital heart defect. Routine chromosome analysis on the patient revealed a normal male karyotype, 46,XY. The following clinical features were noted on examination and autopsy:

- Hypoplastic L heart, patent ductus arteriosus and dextrocardia
- Polysplenia
- Situs inversus and bowel-malrotation
- Bilateral liver
- Lung lobation anomaly: bilobed R lung and a trilobed L lung

The differential diagnoses included an unknown autosomal recessive condition with a recurrence risk of 25%; Kartagener syndrome, which is also thought to be an autosomal recessive condition with a recurrence risk of 25%, or a multifactorial condition with a 2%

risk of recurrence. The family was counselled with a 5% risk of recurrence for future pregnancies.

Laterality sequence was suggested by POSSUM, LDDB and OMIM databases. It was first described by Mathias et al. (1987) in a group of patients who had complex cardiac defects, situs inversus and asplenia/polysplenia. In that initial description, X-linked inheritance was suggested. Since then autosomal recessive and autosomal dominant modes of inheritance have also been documented (Nikkawa et al., 1983; Mikkila et al., 1994; Casey et al., 1996). There is some debate in the literature as to whether or not the different modes of inheritance should remain as distinct entities or one entity acknowledging it to be heterogeneous in nature. OMIM recognizes each as a separate condition. Asplenia with cardio-vascular anomalies, also known as Ivemark or polysplenia syndrome, is characterized by asplenia/polysplenia, complex cardiovascular abnormalities and GI and lung lobe abnormalities. It is inherited in an autosomal recessive fashion (OMIM # 208530). The laterality X-linked form is characterized by complex cardiac malformations, situs inversus and asplenia/polysplenia (OMIM # 306955).

This patient's findings certainly cluster into the "laterality" spectrum with complex cardiac malformations, polysplenia, situs inversus, liver and lung lobe anomalies. The difficulty lies in counselling the family accurately in term of risk of recurrence. The family history is essentially unremarkable with the exception of the paternal great aunt who had a congenital heart defect, although there was little information on the type of defect that she had. The parents were not known to be consanguineous, although they were from the same ethnic background and the same community. Their risk may be low (less then 1% for a new dominant mutation in the child) to 25% due to autosomal recessive or X-linked inheritance. The overall risk of recurrence for this family is most

likely between 2-5%.

Kartagener syndrome was suggested in the initial differential diagnosis at the initial assessment. It is an autosomal recessive condition characterized by bronchiectasis, situs inversus, asplenia, characteristic facies, dextrocardia and infertility (OMIM #244400). It is also characterized by defects in the cilia (Afzelius, 1980; Jonason et al., 1982). It is unlikely that this patient had Kartagener syndrome given the constellation of the findings including the complete cardiac anomalies, which are not usually found in this condition. However, without EM studies to look for abnormalities of the cilia, this condition can not be completely ruled out.

5. DISCUSSION

5.1 CASE ASCERTAINMENT

As noted in the Methods section, potentially all cases of MCA were reviewed. Ideally, all cases seen in the Section of Genetics and Metabolism are entered and coded into the Section's database by "reason for referral" (e.g. case would be coded as "MCA affected") along with other demographics. A search through the Section's database using the 6 search criteria noted in the Methods section, should have potentially identified all cases of MCA be it "affected," "family history of" or "other". However, during the study, two MCA cases were found that had not been ascertained into the study because they were incorrectly coded into the database. Presumably, other cases were missed for the same reason, although this would likely involve a small number of cases. Overall, there should be a good representation of all MCA cases that have been seen and evaluated by members of the Section of Genetics and Metabolism in this study.

5.2 SYSTEMATIC RE-EVALUATION OF UNDIAGNOSED MCA

As outlined in the Methods section, all 75 cases of undiagnosed MCA cases were re-evaluated using the previously described methods (computerized databases, reference material etc.). After re-evaluation, a total of 32 syndrome, association and sequence diagnoses were made. The diagnoses were broken down into 2 main categories: 1) syndrome diagnoses, and 2) association/sequence diagnoses. For each category, the

recurrence risks were re-evaluated to determine if the diagnosis changed the previously given recurrence risk. In the first category (syndrome diagnosis), 19 syndrome diagnoses were made. Of the 19 diagnoses, 7 cases had autosomal recessive inheritance. Of these 7 cases, making the diagnosis altered the original recurrence risk estimates in 5 of the cases. In these 5 cases the families had been previously counselled with: 1) an estimated risk of 2-5% (one was quoted as 3-5%), 2) a range of risk from 0 to 25%, and 3) a range of risk from 25 to 50%. The remaining two cases (case 1-S and 16-S) had been previously counselled with a 25% recurrence risk based on the belief that the patient represented an unknown autosomal recessive MCA condition.

In total, 8 cases had autosomal dominant inheritance with 7 of the cases occurring *de novo*. In those 7 cases, the previous recurrence risks estimations were: 1) generally low ("low" to 5%) in 4 cases, 2) a 0-25% recurrence risk was given in case 3-S, and 3) in cases 13-S and 17-S initial risk estimates were unknown. For the 7 cases that occurred *de novo*, the new recurrence risk estimates (1-2% and 2-5%) did not significantly alter the initial recurrence risk estimates. Of the one autosomal dominant condition (7-S) that is known to have decreased penetrance (thus the potential for a nonpenetrant carrier parent) the recurrence risks would remain 1-2% while recognizing that it may be higher due to the uncertainly of the nonpenetrant parent (hence up to 50%).

The remaining 4 cases were: 1) sporadic with a recurrence risk of 2-5% (cases 4-S and 6-S), 2) mode of inheritance heterogeneous with a recurrence risk of 2-5% (case 2-S), and 3) query chromosome etiology with a risk of recurrence estimate as high as 50% based on a potential for a carrier parent (case 11-S). The previous recurrence risks were not

significantly altered by the diagnoses in cases 2-S and 6-S (initial recurrence risk estimations were 0-25% and 3% respectively). In case 4-S the initial risk estimate was unknown and in case 11-S the new recurrence risk estimate (which may be as high as 50%) is higher than the initial 1-2% risk given.

In summary, out of the 19 syndrome diagnoses, 6 cases (31.5%) had the previous estimated recurrence risks significantly altered. These cases were Seckel syndrome, MOTA syndrome, Holzgreve-Thomas syndrome (both cases), Lambotte syndrome, and the BCD syndrome cases.

In the second category (association/sequence diagnoses), 13 diagnoses were given. Of those 13 cases, 2 were sequences and the remaining 11 were associations. When previous recurrence risk estimates were compared, no significant differences were noted. As association and sequences etiologies are usually unknown and most cases occur sporadically, recurrence risks are based on estimated risks and are usually low. For example, the VATER association has a 1% recurrence risk and the holoprosencephaly sequence has a 6% recurrence risks. As the patients that fell into this category were previously given low recurrence risk, making a diagnosis did not impact on the recurrence risks for these families.

Besides altering the recurrence risks, making a diagnosis does impact the family and /or patient in other ways.

1) It clarifies the recurrence risks for the immediate family members and the patient, and also clarifies any risk to extended family members. For example, if the

diagnosis given shows autosomal recessive inheritance, then the risks to extended family members is low unless there is consanguinity.

2) Once a diagnosis is made, molecular and/or cytogenetic testing may be available to confirm the diagnosis and may allow prenatal diagnosis in subsequent pregnancies (by molecular, cytogenetic or ultrasound means).
3) Confirming or making a diagnosis impacts on family planning. For example, in the MOTA syndrome case, the parents had previously been counselled that there was a 3-5% risk of recurrence. When the family was re-counselled with the 25% risk of recurrence, the parents decided not to have any more children. Making a diagnosis can have psychosocial issues that should be considered.
4) Confirming or making a diagnosis impacts on patient management. For many conditions the natural history of the condition as well as other risks associated with that condition, are well documented. Knowing this information can influence patient management and can aid in proper work-up by indicating what investigations are necessary. For example all patients with Ritscher-Schinzel syndrome should have cranial imaging and all patients with VATER association should have abdominal ultrasounds.

There are a number of limitations that are inherent in a retrospective study such as this one. There are 3 main limitations in this study in regards to making retrospective diagnoses.

1) All information obtained in this study was gathered from patient charts/records. This type of data gathering has drawbacks. Family and medical history records can be incomplete. There tends to be little information on subsequent pregnancies

and outcomes. In addition, when one is seeing a patient because of MCA, reporting of all findings, both major and minor malformations are key factors in making a diagnosis. One problem with retrospectively assessing a patient is if a particular feature is not commented on, does that imply that it was normal? This is particularly important when it is a key feature in the diagnosis in question. As stated in the Methods, there were a number of MCA cases that had to be excluded from the study because of lack of adequate information.

2) Many of the cases were seen only for one or two follow-ups. As some syndrome's phenotype changes over time with age or as some features become evident (e.g. hair abnormalities in CFC syndrome), without continuous follow-up, phenotypic changes would not be noted.
3) Due to the extended period of time from which the patient was initially seen by Genetics to the start of the study for a number of cases, recontacting the families/patients to offer follow-up counselling and testing was limited to a few cases (4 in total). Many families/patients are lost to follow-up.
4) As noted previously, 14 of the 75 cases did not have chromosomal analysis for various reasons. Therefore a chromosome etiology can not be completely ruled out for these cases. To correct for this, these 14 MCA cases could be removed from the study.

Ideally, in a retrospective study, one would want to reassess all patients/families to: 1) update pedigree and medical history, 2) re-counsel families/patients regarding recurrence risk and mode of inheritance, and 3) offer molecular or cytogenetic testing to confirm the diagnosis and to offer extended family member testing/counselling.

The first objective of the study was to determine the value of a systematic review of patients who present with MCA of unknown etiology. Of the 75 cases that underwent a systematic review and re-evaluation, 32 were given a specific diagnosis, and 43 cases could not be given a diagnosis after re-evaluation. Of the 32 diagnoses made, 10 had been previously suggested in the initial differential diagnosis. Thus, out of the 32 cases, 22 were a true "new" diagnosis and 10 diagnoses were confirmation of a diagnosis that had been initially suggested in the differential diagnosis. Of the 32 cases, 19 were syndrome diagnosis and 13 were association/sequence diagnosis (Table 18). This study demonstrated that a systematic review of infants with MCA of unknown etiology could yield a relatively good success rate, supporting the idea of periodic re-review of these cases.

TABLE 18 Success rate of a systematic review & re-evaluation of 75 cases:

MCA of unknown etiology

	Percentage of Cases (75)
Diagnosis	
Syndrome	19 (25.3%)
Association/sequence	13 (17.3%)
Total	**32 (42.6%)**

5.3 PREVIOUS MCA SYNDROME DIAGNOSES

Included in the study were all cases of MCA of unknown etiology in which the length of time from initial contact with the Section of Genetics and Metabolism to diagnosis exceeded one year's time. As stated in the Introduction, ideally when a child presents with MCA, one would want to make a diagnosis during that initial session or shortly afterwards. In many cases a diagnosis is not made during that time period. Determining what factors influence the eventuality of making a diagnosis and also determining how long or the number of follow-up sessions required before a diagnosis is made was briefly looked at in this study. Follow-ups usually occurred once a year, thus the length of time chosen in the study is approximately equivalent to the number of follow-ups.

Ten cases fell into this inclusion criteria and had an average length of time from initial contact to diagnosis of 6.4 years with a range of 1.3 years to 14.2 years. Three of these cases were initially not given a diagnosis because the patient's overall pattern of malformations although was suggestive of a specific diagnosis, were considered atypical features not known to be associated with that diagnosis. It was not until repeated follow-up and subsequent reporting in the literature of those features in association with the condition, that the diagnosis was given to the patient/family (FAS, Opitz G syndrome and VATER association). In 2 cases, the patients were given a diagnosis only after clinical reports appeared in the literature recognizing the pattern of malformations as a distinguishable "new" MCA condition with a known etiology allowing for confirmation by molecular and/or cytogenetic analysis (Rieger syndrome and 22q Deletion syndrome). The remaining 5 cases were undiagnosed initially as the patient was thought to have a

different although tentative diagnosis. It was not until continuous reinvestigation that the "correct" diagnosis was given (Aarskog syndrome, Beals syndrome, Sotos syndrome, Opitz syndrome and Klippel-Fiel syndrome). In 2 of these 5 cases, the diagnosis was not obvious until the patient had "grown" into the phenotype

As Hall et al. (1998) demonstrated in their retrospective study of undiagnosed MCA, periodic follow-up of cases of undiagnosed MCA syndromes does allow for a number of successful diagnoses. Success is due in part to: 1) the advent of new technology and the ability to confirm the diagnosis with molecular or cytogenetic methods, 2) reporting of new or previously described conditions with expansion of the phenotype, and 3) phenotypic changes over time into recognizable syndromes. As illustrated here, it may require a significant length of time and continuous follow-up before a diagnosis is made. Hall et al. (1998) found that among the 50 cases that were diagnosed, 36% had chromosomal anomalies or microdeletions, including 22q Deletion syndrome and Smith-Magenis syndrome. Their findings are similar to that of this study. Two cases of 22q Deletion syndrome and one case of Smith-Magenis syndrome were retrospectively diagnosed. As stated by Hall et al. (1998) and supported by this study, periodic follow-up should become a standard of practice at least for this group of patients.

5.4 PROVISIONALLY NEW MCA SYNDROMES & ASSOCIATIONS

A total of 9 new syndromes and associations were reported and delineated by members of the Section of Genetics and Metabolism. Toriello (1988) had estimated that a new syndrome is described in the literature at a rate of one or more a week. This illustrates the

above mentioned point that reporting of "new" previously undescribed conditions allows for the diagnosis in other patients with the same/similar findings. It is only through continuous follow-up of these "unknown" patients that subsequent literature searches would identify these newly delineated conditions. Certainly, additional case reports have been described in the literature since the initial reporting of some of these "new" MCA conditions diagnosed by the Section, further illustrating the above mentioned point (Harbord, Baraitser and Wilson, 1989; Baltaci et al., 1999). Continuous investigation could also lead to the identification of the etiology and/or mode of inheritance.

5.5 COMPUTERIZED DATABASES

As discussed in the Introduction, the utility of computerized databases for syndrome diagnoses has been debated in the literature. The usefulness of these tools was evaluated in this study. Of the 32 cases in which a diagnosis was made, 26 of the diagnosis were suggested by at least one of the 4 databases used in this study (POSSUM, LDDB, OMIM and PubMed). POSSUM ranked the highest with a 43.7% success rate with LDDB ranking second with a 34.3% success rate, PubMed had a 31.2% success rate and OMIM had a 28.1% success rate. The accumulative success rate was 81.3% when all databases were used. Overall, each program was fairly equivalent in regards to their success rate and usefulness. As shown in this study, the combination of at least two or more databases yields the best success rate and also allows for comparison of the list of candidate syndromes generated by each search, which can be helpful when trying to narrow down the list to one potential diagnosis.

These programs are meant to function as diagnostic tools/aids and are not meant to provide a diagnosis. Each program generates a list of candidate syndromes that must be reviewed at length in order to arrive at a potential diagnosis. As discussed in the Introduction, the "novice strategy" to use of these tools has been shown to be valid. Therefore, there should not have been any additional biases introduced into the study (i.e. reduced usefulness of the databases and thus reduced number of syndrome diagnosis) by the author using the "novice strategy" as compared to the "expert strategy."

The success rate demonstrated in this study is similar to that of the study carried out by Pelz et al. (1996). They looked at POSSUM and LDDB success rates and found 63% and 68% respectively. One major difference between their study and this one was that they re-evaluated cases in which a diagnosis was already known, to determine the program's success rate. This may account for the slightly lower values in this study as compared to their study.

5.6 PHENOTYPIC & DEMOGRAPHIC ANALYSIS

Two separate discriminant function analyses were preformed looking at: 1) demographic variables, and 2) phenotypic traits (anomalies). In the first analysis, no differences could be identified between Group 1 and Group 2. For both groups, most of the demographic variables had approximately equivalent values with nonsignificant probability values. When the percentage of males (and thus conversely females) were compared, 58.1% of the cases in Group 1 were males and 51.3% of the cases in Group 2 were males. The average time from date of birth to start of the study (thus looking at the

age of the individual) was also similar with an average age of 12 years for Group 1 and an average age of 11 years for Group 2. No ethnic variable could be demonstrated to be significant, nor could these two groups be differentiated in terms of "family history same" or in terms of symmetry of anomalies. The only demographic variable that was somewhat significant was "family history other" with a probability value of 0.057. Group 2 had almost double the frequency (48.2%) of occurrence of other anomalies then Group 1 (27.9%). This finding would suggest then that those families, in which siblings of the proband presented with malformation(s) different from those in the proband, decreased the likelihood of making a diagnosis. This may suggest that there are other genetic and/or environmental factors that are influencing the expression of certain malformation(s), thus complicating the situation. Over all, other than potentially family history of other anomalies, none of the demographic variables looked at in this study could be used to distinguish the two groups nor could they be used to determine what factor(s) influence the ability to make a diagnosis.

The phenotypic traits were compared between Group 1 and Group 2. Three anomalies were found to have significant probability values. These 3 anomalies were renal dysplasia/cystic, postaxial polydactyly and tracheal defects. In the 80 cases examined, these 3 anomalies were not found in any of the 43 cases in which a diagnosis had been made (Group 1) whereas renal dysplasia/cystic anomalies occurred in 13.5%, postaxial polydactyly in 10.8% and tracheal defects in 8.1% of the cases in which no diagnosis had been made (there were a total of 37 cases in Group 2).

Ideally, one would want discriminant function analysis to identify those anomalies that

would have differentiated Group 1 from Group 2 such that one could determine what factors influenced the ability to achieve a diagnosis rather than what factors are associated with failure to achieve a diagnosis. Three anomalies were identified, which suggested that, the occurrence of these anomalies in a child who presents with MCA is associated with a lower likelihood of making a diagnosis. This does not follow logical reasoning. However, when one looks at the anomalies identified by the discriminant function analysis there is some reasoning to support this finding. Few syndromes are associated with tracheal anomalies. A search using OMIM only identified 2 syndromes that are commonly associated with tracheal defects: Pfeiffer syndrome (OMIM #101600) and Hydrolethalus syndromes (OMIM #236680). Besides the VATER association, there are few other conditions that have tracheal defects as a common characteristic. This may be why tracheal defects were found in Group 2 only. Presumably, for the cases in Group 2, any of the known syndromes and associations with tracheal defects would have been ruled out. When the 3 undiagnosed cases with tracheal defects were re-reviewed none of them were typical for the VATER association (or the above two mentioned syndromes). All 3 cases had other malformations not typically associated with VATER (e.g. holoprosencephaly).

Renal dysplasia/cystic and postaxial polydactyly were found in Group 2 but not in Group 1. This may be due to the fact that both anomalies are associated with a large number of conditions. For example, an OMIM search was performed using renal dysplasia and renal cystic. Over two hundred different conditions were suggested, many of which were MCA syndromes. Similarly, one hundred entries were found in OMIM that had postaxial polydactyly as one of the features. This suggests that both of these

features are nonspecific common malformations (as opposed to tracheal defects). It may be that having either of these 2 anomalies in a patient, who presents with MCA, makes the task of achieving a diagnosis that much more complex.

A limitation of this discriminant function analysis was that, not all of the original 95 cases underwent analysis. In 15 of the cases, there was at least one missing discriminanting variable. These cases were removed from the analysis. When the original data was reviewed the following was noted: 1) one case from Group 1 had a tracheal defects and was removed from the analysis, 2) one case from Group 1 had a renal dysplasia/cystic anomaly and was removed from the analysis, and 3) one case from Group 1 had postaxial polydactyly and was removed from the analysis. Therefore, in actuality, each of these anomalies occurred in Group 1 with a frequency of 2.3%. While this is a relatively low value as compared to the frequencies of these anomalies in Group 2, the probability values might not be as significant as originally stated in table 15.

5.7 RECURRENCE RISK ESTIMATION ANALYSIS

The second objective in this study was to determine an appropriate recurrence risk estimate for infants with MCA of unknown etiology. To do this, all subsequent pregnancies in the 94 cases that were recorded in the patient charts were tabulated to determine an estimation of the recurrence risk for persons with MCA. In all, 47 subsequent pregnancies were reported. There were 7 cases of a recurrence in which the sibling had a similar pattern of malformations and 7 cases in which the sibling had a dissimilar malformation. This information was then broken down into the two groups,

diagnosis made (Group 1, which had 51 in total) and diagnosis unknown (Group 2, which had 43 in total). Group 1 had 27 subsequent pregnancies with 4 recurrences of similarly affected sibs (14.8%) and 3 occurrences of other malformations (11.1%). The 4 cases in which there was a recurrence included the Holzgreve-Thomas syndrome case, the Ritscher-Schinzel syndrome case, the Seckel syndrome case and the Walker-Warburg syndrome case. All 4 conditions are thought to be autosomal recessive inheritance and thus it is not surprising that there were recurrences in the family.

Surprisingly, Group 2 had 3 recurrences out of a total of 20 subsequent pregnancies (15.0%) of similarly affected siblings. This might be due to the fact that some of the families had a new private autosomal recessive MCA syndrome. Recurrence of an affected sib with normal parents is suggestive of an autosomal recessive condition. However, when these cases were re-reviewed, none of the families were consanguineous, which would have suggested a private autosomal recessive MCA condition. This group also had 4 occurrences of other malformations (20.0%).

These figures are much higher than Czeizel et al. (1988) study. They found a 3.9% risk of recurrence in the siblings of patients with MCA of unknown etiology. The discrepancy between Czeizel et al. (1988) study and the recurrence risk estimates in this study are most likely due to a number of reasons:

1) There was inadequate or lack of information on subsequent pregnancies for 11 of the cases, thus potentially under-estimating the true number of subsequent pregnancies.
2) Information on subsequent pregnancies was obtained by review of the patient chart.

Ideally, to obtain accurate information on all subsequent pregnancies, the families/patients need to be recontacted to up date the family and pregnancy histories and outcomes. In many of the cases, they were only seen once, thus any subsequent pregnancies would not have been known or recorded in the patient's chart.

3) Families were more likely to be seen in the Section of Genetics and Metabolism a second time if there was a recurrence of an affected sib. This could lead to an over estimate of recurrences of affected sibs. Normal pregnancies are less likely to come to the attention of the Section of Genetics and Metabolism.

It is likely that 47 subsequent pregnancies is an under estimation of the true number of pregnancies. This would account for the discrepancy between the recurrence risk estimation (15.0%) for patients with MCA of unknown etiology in our study and Czeizel et al. (1988) recurrence risk estimation of 3.9%.

There was a total of 7 (14.9%) recurrences of siblings who had other malformations (both minor and major malformations), 3 in Group 1 and 4 in Group 2. This figure should presumably reflect the population frequency of both minor and major malformations in newborns. The finding of 14.9% is fairly representative of the expected population frequencies. One limitation of this analysis was that minor and major malformations were not distinguished from each other, thus the 14.9% is the combined frequency. A second limitation is, as stated previously, 47 subsequent pregnancies is most likely not the true pregnancy number for this group and therefore, the 14.9% may be an under or over estimation.

6. FUTURE WORK

6.1 CLUSTER ANALYSIS

Given that all anomalies for each case have been recorded in a phenotype sheet and entered into a Microsoft Access spreadsheet, cluster analysis can now be performed to identify those groups that would fall into the same subgroups, and to identify those cases that were most similar. Discriminant function analysis could be used to determine which phenotypic traits (anomalies) could be used to distinguish between cases. This analysis may give further insight into the pattern of malformation in those cases in which the diagnosis remains unknown. Preliminary cluster analysis did demonstrate 4 main clustering of cases (appendix 3).

6.2 RECONTACTING FAMILIES

Ideally, the families and patients in this study should be recontacted so that family and medical history can be updated. Families and patients can be re-counselled in regards to the recurrence risk, and mode of inheritance so that one can identify those family members at risk and offer testing and/or subsequent investigations. Recontacting these families could also help validate the diagnosis given to the patient/family.

7. SUMMARY

1. A systematic re-evaluation of previously undiagnosed cases of MCA yielded a relatively high success rate (42.6 %) of syndrome/association/sequence diagnosis.
2. Computerized databases both online and software forms (POSSUM, LDDB, PubMed and OMIM) are valid and useful diagnostic tools in dysmorphology.
3. Continued follow-up of undiagnosed MCA cases, as well as detailed description and reporting of clinical features including minor dysmorphic features, contribute to the likelihood of identifying a syndrome/association diagnosis.
4. Reporting of "new" MCA syndromes contributes to the success of syndrome diagnosis in other patients who present with MCA of unknown etiology.
5. No demographic variables that were looked at in this study could be used to determine the likelihood of making a diagnosis. Renal dysplasia/cystic, postaxial polydactyly and tracheal defects were negatively associated with the likelihood of being able to make a diagnosis.
6. Recurrence risk estimations were found to be 14.8% for cases in which a diagnosis was known and 15.0% for cases in which no diagnosis was made.

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APPENDIX 1 Phenotype sheet of all traits grouped by system/region and by presentation.

SYSTEM / REGION **PRESENTATION**

Diagnosed: Y/N
Sex: M/F
Year of Birth:
Ethnicity: Caucasian Aboriginal Other
Family history similar: Y/N
Family history other: Y/N
Anomalies symmetrical: N/A Partial asymmetry Full asymmetry symmetrical

RESPIRATORY

Trachea:	Normal	Stenosis		TE fistula
Lung – lobed anomaly:	No	L	R	Bilateral
Other anomalies:	Y/N			

CARDIOVASCULAR

Patent ductus ateriosus:	Y/N			
Dextroposition heart:	Y/N			
Transposition of great vessels:	Y/N			
Ventricle hypoplasia:	No	L	R	Bilateral
Preductal coarctation:	Y/N			
Atrial septal defect:	Y/N			
Ventricular septal defect:	Y/N			
Other cardiac anomalies:	Y/N			
Other vessel anomalies:	Y/N			

CNS

Microcephaly:	Y/N		
Macrocephaly:	Y/N		
Corpus callosum:	Normal	Agenesis	Hypoplastic
Hydrocephalus:	No	Hydrocephalus	Aqueductal Stenosis
Neural tube defect:	Meningomyelocele		Encephalocele
	Tethered Cord		Spina Bifida
Other anomalies:	Y/N		

GASTROINTESTINAL

Intestinal tract:		Normal	Malrotated	Duplicated
Intestinal atresia:	No	Foregut	Midgut	Hindgut
Abdominal wall defect:		No	Omphalocele	Gastroschisis Other
Anus:			Normal	Ectopic Imperforate
Other anomalies:			Y/N	

GENITOURINARY

Scrotum:	N/A	Normal	Hypoplastic	Shawl
		AbN	Absent	
Penis:	N/A	Normal	Micro	Agenesis AbN
Cryptorchidism:	N/A	Y/N		
Hypospadias:	N/A	Y/N		
Renal:	Normal	Malrotated	Horseshoe	
Renal dysplasia:		No	L	R Bilateral
Renal agenesis:		No	L	R Bilateral
Other urinary tract anomalies:		Y/N		
Other GU anomalies:		Y/N		

ENDOCRINE

Spleen:	Normal	Absent	Polysplenia
Other anomalies:	Y/N		

MUSCULOSKELETAL

Vertebral:	Normal	Segmental defects	Absent	Extra
		Fistula	Not Specified	
Rib:	Normal	Absent	Extra	Malformed
		Not Specified		
Diaphragm:	Normal	Agenesis	Hypoplastic	Hernia
Limb positional defect:		Y/N		
Limb – short:		No	Upper	Lower Both
Limb contracture:		No	Upper	Lower Both
Radial – Ray defects:		No	L	R Bilateral
Scoliosis:		Y/N		
Joints:	Normal	Laxity	Hyperextensible	Dislocation
		Ankylosis	Synostosis	
Hernia:		No	Umbilical	Inguinal Both

Polydactyly – preaxial:	No	L	R	Bilateral	
Polydactyly – postaxial:	No	L	R	Bilateral	
Other limb deficiencies defects:	No	Transverse	Longitudinal	Central defect	Other
Other digit anomalies:	No	Syndactyly	Malformed	Absent	Adducted

CRANIOFACIES

Skull defect:		Y/N			
Head shape:	Normal	Brach	Trig	Turri	Dolich
Ears:		Normal	Abnormal		
Epicanthal folds:		Y/N			
Eye spacing:	Normal	Hypertelorism	Hypotelorism		
Micrognathia:		Y/N			
Coloboma:		No	Iris	Retina	Eyelid
Eye anomalies:	No	Rieger's anomaly	Cataracts	Other	
		Microphthalmia	Anophthalmia		
Oral anomalies:	No	Glossoptosis	Macrostomia		
Cleft lip:		No	L	R	Bilateral
Cleft palate:	Normal	High arched palate	Cleft		

SKIN

Ectodermal defects:	No	Teeth	Skin	Nail	Hair

OTHER

Hearing loss:	Y/N
Short stature:	Y/N
Failure to thrive:	Y/N
Other anomalies:	Y/N

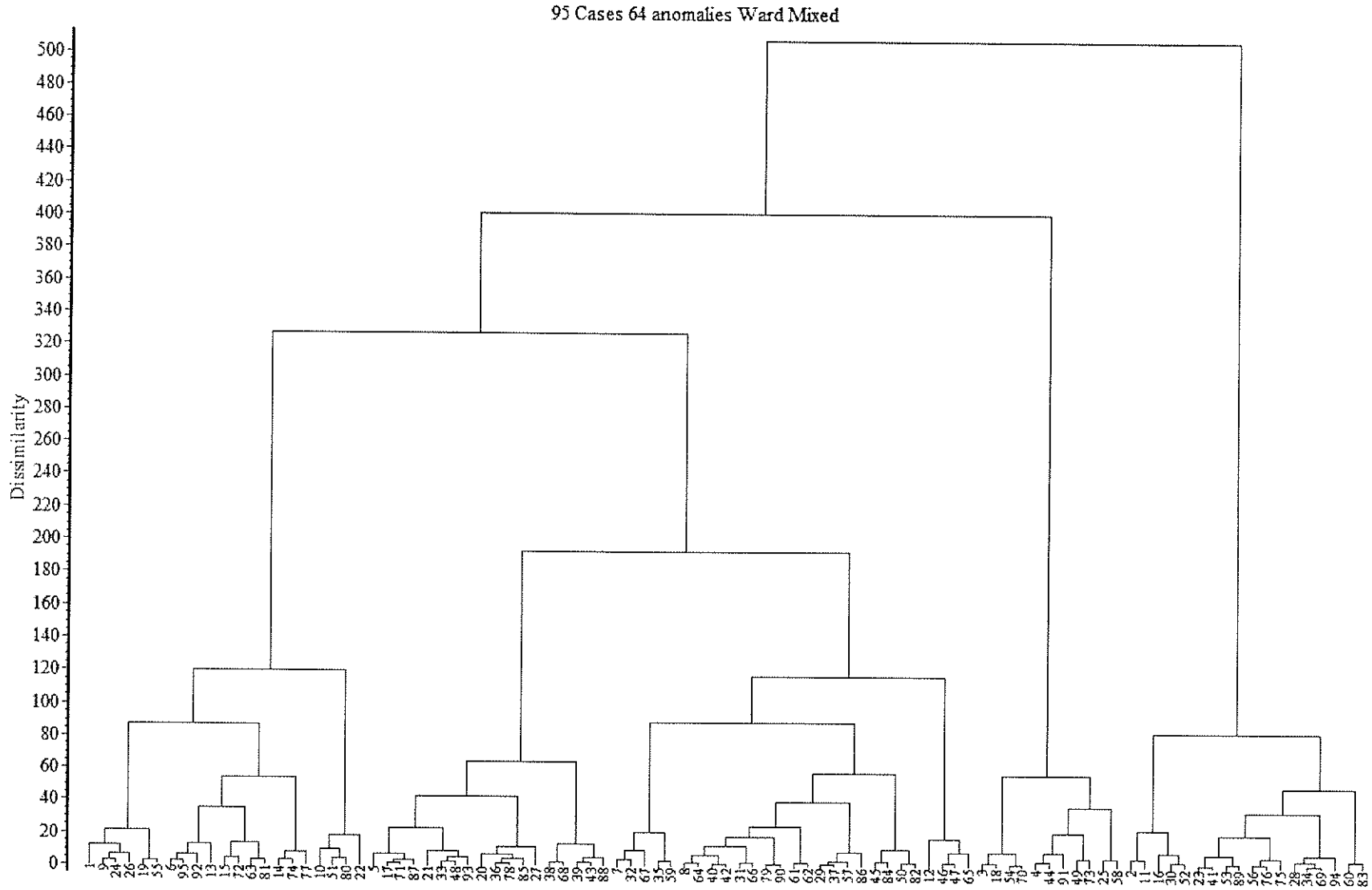
APPENDIX 2 CODING SHEET: Definitions, Field names and Codes per trait.

DEFINITION	FIELD NAME	CODE
Diagnosed	DX	Y=1 N=0
Sex	SEX	M=1 F=0
Year of Birth	YOB	Numerical
Ethnicity	ETHNC	Caucasian=0 Aboriginal=1 Other=2
Family history similar	FHXS	Y=1 N=0
Family history other	FHXO	Y=1 N=0
Anomalies symmetrical	SYMM	N/A=0 Partial asymmetry=1 Full asymmerty=2 symmetrical=3
1. Trachea	TRACH	Normal=0 Stenosis=1 TE fistula=2
2. Lung – lobed anomaly	LOBEL	No=0 Left=1 Right=2 Bilateral=3
3. RESP other anomalies	RESP	Y=1 N=0
4. Patent ductus ateriosus	PDA	Y=1 N=0
5. Dextroposition heart	DEXTRO	Y=1 N=0
6. Transposition of great vessels	TGV	Y=1 N=0
7. Ventricle hypoplasia	VENTS	No=0 Left=1 Right=2 Bilateral=3
8. Preductal coarctation	COARC	Y=1 N=0
9. Atrial septal defect	ASD	Y=1 N=0
10. Ventricular septal defect	VSD	Y=1 N=0
11. Other cardiac anomalies	CVS	Y=1 N=0
12. Other vessel anomalies	VESS	Y=1 N=0
13. Corpus callosum	CORPU	Normal=0 Hypoplastic=1 Agenesis=2
14. Hydrocephalus	HYDRO	No=0 Hydrocephalus=1 Aqueductal stenosis=2
15. Neural tube defect	NTD	No=0 Tethered Cord=1 Spina Bifida=2 Encephalocele=3 Meningomyelocele=4
16. CNS other anomalies	CNS	Y=1 N=0

17. Intestinal tract	INTEST	Normal=0 Malrotated=1 Duplicated=2
18. Intestinal atresia	ATRES	No=0 Foregut=1 Midgut=2 Hindgut=3
19. Abdominal wall defects	OMPHA	N=0 Omphalocele=1 Gastroschisis=2 Other=3
20. Anus	ANUS	Normal=0 Ectopic=1 Imperforate=2
21. GI other anomalies	GI	Y=1 N=0
22. Scrotum	SCROT	N/A=99 Normal=0 Hypoplastic=1 Shawl=2 AbN=3 Absent=4
23. Penis	PENIS	N/A=99 Normal=0 Micro=1 AbN=3 Agenesis=4
24. Cryptorchidism	CRYP	N/A=99 Y=1 N=0
25. Hypospadias	SPAD	N/A=99 Y=1 N=0
26. Renal	RENAL	Noraml=0 Malrotated=1 Horseshoe=2
27. Renal dysplasia/cystic	REND	No=0 Left=1 Right=2 Bilateral=3
28. Renal agenesis	AREN	No=0 Left=1 Right=2 Bilateral=3
29. Other urinary tract anomalies	TRACT	Y=1 N=0
30. GU other anomalies	GU	Y=1 N=0
31. Spleen	SPLEN	Normal=0 Polysplenia=1 Absent=2
32. ENDO other anomalies	ENDO	Y=1 N=0
33. Vertebral	VERTCT	Normal=0 Segmental defects=1 Extra=2 Absent=3 Fistula=4 Not specified=5
34. Rib	RIB	Normal=0 Malformed=1 Extra=2 Absent=3 Not specified=4
35. Diaphragm	DIAPH	Normal=0 Hypoplastic=1 Hernia=2 Agenesis=3
36. Limb positional defect	LIMB	Y=1 N=0
37. Limb – short	LIMBS	No=0 Upper=1 Lower=2 Both=3
38. Limb contractures	LIMBC	No=0 Upper=1 Lower=2 Both=3
39. Radial – Ray defects	RADIA	No=0 Left=1 Right=3 Bilateral=3
40. Scoliosis	SCOLI	Y=1 N=0
41. Joints	JOINT	Normal=0 Laxity=1 Hyperextensible=2 Dislocate=3 Ankylosis=4 Synostosis=5
42. Hernia	HERNIA	No=0 Umbilical=1 Inguinal=2 Both=3
43. Polydactyly – preaxial	POLPH	No=0 Left=1 Right=2 Bilateral=3
44. Polydactyly – postaxial	POLTH	No=0 Left=1 Right=2 Bilateral=3

45. Other limb deficiencies defects	DEFIC	No=0 Transverse=1 Longitudinal=2 Central=3 Other=4
46. Other digit anomalies	DIGIT	No=0 Adducted=1 Malformed=2 Syndactyly=3 Absent=4
47. Skull defects	CRANA	Y=1 N=0
48. Head shape	HEAD	Normal=0 Brach=1 Trig=2 Turri=3 Dolich=4
49. Microcephaly	MICRO	Y=1 N=0
50. Macrocephaly	MACRO	Y=1 N=0
51. Ears	EAR	Normal=0 Abnormal=1
52. Cleft lip	CL	No=0 Left=1 Right=2 Bilateral=3
53. Cleft palate	CP	Normal=0 High arched=1 Cleft=2
54. Epicanthal folds	EPICN	Y=1 N=0
55. Micrognathia	GNATH	Y=1 N=0
56. Oral anomalies	ORAL	No=0 Macrostomia=1 Glossoptosis=2
57. Eye spacing	ESPAC	Normal=0 Hypertelorism=1 Hypoterlorism=2
58. Coloboma	COLOB	No=0 Iris=1 Retina=2 Eyelid=3
59. Eye anomalies	EYE	Normal=0 Rieger's anomaly=1 Cataracts=2 Microphthalmia=3 Anophthalmia=4 Other=5
60. Ectodermal defects	ECTO	No=0 Teeth=1 Skin=2 Nail=3 Hair=4
61. Hearing loss	HEAR	Y=1 N=0
62. Short stature	SHORT	Y=1 N=0
63. Failure to thrive	FTT	Y=1 N=0
64. Other anomalies	OTHER	Y=1 N=0

Note: For each field, 99 or 999 = not applicable



APPENDIX 3 Dendrogram showing Ward's Mixed Cluster analysis of 95 Cases: Preliminary Results