NUMERICAL CLASSIFICATION OF CHROMOSOMAL SYNDROMES DUE TO REARRANGEMENTS OF CHROMOSOME 3 IN HUMANS

By

ARMANSA GLODJO

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Department of Human Genetics
University of Manitoba
Winnipeg, Manitoba, Canada

THE UNIVERSITY OF MANITOBA

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DEDICATION

To my brother Arman

Thank you for your wisdom, love, and encouragement

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Firstly, I would like to gratefully acknowledge my parents, Ahmed and Finka Suzana, and brother Arman for their unlimited love, patience, and support. I also wish to thank my niece Talia for loving the pursuit of knowledge and loving me. To my friends, and Michael, your faith in me makes me strong. You are all the light in my life.

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ABSTRACT

This study of chromosomal syndromes was based on phenotypic data for two hundred and sixty-three individuals ascertained from case reports in the literature supplemented by unpublished reports. The individuals used in the study had at least one chromosomal duplication or deletion of a segment of chromosome 3, excluding a group of fifteen individuals with an unknown phenotypic etiology (Cornelia de Lange), which was used as a control group. Numerical taxonomy techniques were carried out on a data set based on one hundred and twelve structural phenotypic variables to generate and identify clusters containing individuals with like phenotypes. The results of the classification were then compared with the karyotypes of the individuals in each phenotypic group to identify a chromosomal basis for like phenotypes, as well as to identify components of a phenotype due to a recombinant chromosome 3 with a duplication of 3q and a deletion of 3p.

Four separate cluster analyses were carried out in this study. Cluster analysis of seven etiologic groups indicated a karyotypic basis for the classification of individuals within each cluster. Numerical taxonomy, or cluster analysis, was deemed a useful tool for the classification of chromosomal syndromes as well as the classification of the syndrome of unknown etiology.

Cluster analysis of dup(3q) and del(3p) individuals identified four separate clusters, with three potential subgroups for dup(3q) and two potential subgroups for del(3p). These karyotypic subgroups differed by the presence of an additional chromosomal aberration in one group while the majority of the other group had only the deletion of 3p or the duplication of 3q. Discriminant function analysis identified the top ten phenotypic variables that best define the differences between the four clusters.

Cluster analysis of dup(3q), del(3p) and rec(3) individuals showed a distribution of rec(3) cases in mainly two groups with no preferential clustering with either dup(3q) or del(3p). Simulated predicted re-classification of rec(3) individuals based on the top ten phenotypic variables from the previous analysis showed a marked preference for two clusters, where the rec(3) phenotype showed characteristics of both of its components, dup(3q) and del(3p). Phenotypic traits such as cardiovascular anomalies and thick eyebrows were attributed to genes in 3q, and traits such as ptosis and cervico-thoracic vertebral anomalies were attributed to genes in 3p.

Cluster analysis of rec(3) individuals showed a marked division into two phenotypic groups, with members of an inv(3) kindred showing representation in both clusters.

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1.0 INTRODUCTION

1.1 The concept of chromosomal syndromes

Conceptuses with chromosomal abnormalities have been estimated to account for between 8% (Alberman and Creasy 1977; Kajii et al. 1978) to 50% (Boué et al. 1975; Schesselman 1979) of all conceptuses. However the majority of these are spontaneously aborted in the first trimester of pregnancy, as few are compatible with life. Natural protective and selection factors such as fetal wastage, failure of germ cells to progress in meiotic cell division and maturation, and elimination of abnormal chromosomes in meiosis serve to reduce the number of chromosomally aberrant conceptuses (Chandley 1981). The majority of viable chromosomal aberrations result in progeny with multiple congenital abnormalities, with a spectrum of severity and survival rates. Such births can present a multitude of issues for families concerning the welfare and health of their children, as well as raise concerns about the families' reproductive futures if familial transmission of the chromosomal abnormality is a concern.

The study of syndromes resulting from chromosomal rearrangements is noteworthy in many respects. From the clinical aspect, it can serve to provide families with information about prognoses for future complications, as well as the severity of mental and physical handicap that will ultimately affect the child's quality of life. From the research perspective, syndrome classification and the study of dysmorphology helps to gain understanding of

human development and the regions of the genome that are expressed temporally and spatially in the growing fetus, as well as to provide some preliminary insight into the complex developmental pathways between a chromosomal aneuploidy and the resulting phenotype.

1.2 Syndromology

The study of syndromes has been a part of medicine for over 100 years. A syndrome can be defined as a pattern of multiple anomalies thought to be causally related (Spranger et al. 1982). As more information is gathered from new cases, syndrome delineation can be facilitated as well as impeded by the delienation of sub-groups within what was perceived to be one syndromic group, or by the possibility of identifying an additional distinct syndromic class. The classification and nomenclature of syndromes has historically depended on 1) the phenotypic spectrum of the syndrome, 2) the natural history, 3) the modes of inheritance and the risk of recurrence (Cohen 1976).

When the etiology of a syndrome is not as evident as in chromosomal aneuploidy syndromes, even the correct form of syndrome nomenclature has also been a focus of debate (Cohen 1976). Syndromes have been described in terms of four syndrome classes: the dysmetabolic syndrome, the dyshistogenetic syndrome, the malformation syndrome, and the deformation syndrome (Herrmann and Opitz 1974; Cohen 1982), where the deformation syndrome is at the top of a hierarchical inverted pyramid model. This

hierarchical view of syndromes spans the spectrum from the regional level to the molecular level and aids in classifying syndromes of various etiologies.

Chromosomal syndromes are in the class of malformation syndromes, where several organs or developmental fields have been affected and are primarily characterized by "embryonic pleiotropy in which the several malformation sequences are developmentally unrelated at the embryonic level" (Cohen 1982). Aside from trisomies 13, 18 or 21, few chromosomal syndromes are easily identifiable by visual inspection alone. Aside from one or two commonly occurring features, most phenotypic features associated with partial trisomy or monosomy appear to be non-specific and difficult to distinguish without the aid of karyotypic information.

1.2.1 Syndrome classification

The field of syndrome classification and dysmorphology has been a mixture of art and science as many features exhibited in various dysmorphic phenotypes overlap and may be ambiguous as to their origin. At a time when one or more newly recognized syndromes are being described per week (Cohen 1989a), attempts have been made to modulate and standardize syndrome delineation, while allowing the framework to remain flexible and open to change. For the purposes of delineation, syndromes are divided into syndromes of known and unknown etiology (Cohen 1977; Cohen 1982). Regarded as syndromes of known etiology, chromosomal syndromes are thought of as unique-pattern syndromes with clinical variability. The

occurrence of clinical variability as well as the aspect of non-specificity in malformation syndromes due to chromosomal aneuploidy emphasizes the need for detailed clinical information from new cases. Aside from traits such as mental retardation, most individuals with the same chromosomal abnormality do not exhibit exactly the same pattern of phenotypic features, with discordance being common even between siblings (Epstein 1986).

The effects of aneuploidy on the resulting phenotype can initially be attributed to gene dosage, that is an over-representation or under-representation of genetic material in the cell. It is presumed that under-expression of genetic material is more severe than over-expression. Such genetic instability can have effects on biochemical pathways and the ability of the cell to maintain cellular homeostasis. The loss of cellular homeostasis can ultimately lead to 1) an increase in variance of metric traits (e.g. skeletal maturation, height), 2) increased susceptibility for disturbance as compared to the same traits in the general population (e.g. palate length (Shapiro et al. 1967; Shapiro 1969)), 3) a decrease in physiological regulatory efficiency, and 4) an increase in morbidity (Shapiro 1983). Epstein (1986), however, argues that the mean, rather than the variance, is increased with aneuploidy due to the loss of cellular homeostatic buffering.

The non-specificity of chromosomal syndrome phenotypes can be attributed in part to the phenotypic 'noise' due to the large amount of trait variance occurring at the same time. This leads to a masking effect of the actual patterns of anomalies characteristic of a particular syndrome (Epstein

1986). Finding the 'signal' among the phenotypic 'noise' can allow for more careful assessment of phenotypic groups and sub-groups within a given syndrome due to aneuploidy. This is especially useful in the cases of double aneuploidy due to 1) a translocation involving two non-homologous chromosomes, resulting in trisomy of one chromosomal segment and monosomy of another chromosomal segment, 2) an uneven crossing over between two homologous chromosomes, resulting in an interstitial duplication and/or deletion of a chromosomal segment, and 3) an uneven number of crossover events in pericentric inversion loop in meiosis I, resulting in a duplication-deficient chromosome.

Moreover, the length of the chromosomal segment duplicated or deleted may be a significant factor in phenotypic attributes. For example, Montero and colleagues (1988) proposed that in cases of dup(3q), cardiac malformations are present in cases where the duplicated segment is proximal to 3q25. Searching for major phenotypic discriminators with tools designed to take an objective approach to syndrome delineation can facilitate finding the specific phenotypic 'signals' as well as the critical chromosomal regions for the purpose of phenotypic mapping.

1.2.2 Syndrome classification methods

1.2.2.1 Informal method: Univariate analysis

While experience and intuition were initially the sole aids in syndrome delineation, computer databases such as the London Dysmorphology

Database (LDDB) (Winter and Baraitser 1997) and Pictures of Standard Syndromes and Undiagnosed Malformations (P.O.S.S.U.M.) (Bankier et al. 1998) now assist dysmorphologists and physicians to narrow the search for a diagnosis when assessing a case. While most syndromologists find these databases invaluable tools, there can be discrepancies between results due to the subjectivity of the qualitative language initially entered into the database for search purposes.

Even though many phenotypic features of chromosomal syndromes are non-specific, some features are thought of as being good discriminators for a given chromosomal syndrome, and can significantly decrease the number of possible 'hits' in a given database search. For example, in dup(3p21.31→pter), the discriminating feature is a hypoplastic penis (Yunis and Lewandowski 1983). These discriminators are often deduced by frequency counts of features occurring in a number of cases. The univariate approach based on frequency counts does not have the capability to assess positive and negative association between anomalies found in chromosomal syndromes versus chance occurrences of given traits. The disadvantage of this analysis is a lack of method for building pathogenesis models for various malformation syndromes, especially in the case of chromosomal syndromes.

1.2.2.2 Formal method: Multivariate analysis

An example of how the univariate and multivariate approaches differ can be illustrated in the following scenario involving 20 cases of syndrome 'X', with ascertainment of three major phenotypic traits A, B, and C.

A) **Univariate analysis**:

e.g. 20 cases, syndrome 'X', traits A,B,C

13/20 have trait A

15/20 have trait B

5/20 have trait C

B) **Multivariate analysis**:

e.g. 20 cases, syndrome 'X', traits A,B,C

13/20 have trait A

15/20 have trait B

5/20 have trait C

8/20 have traits A and B

5/20 have traits A and C

0/20 have traits B and C

The multivariate approach yields the same information as the univariate approach while also assessing the relationship between traits. For example, with multivariate analysis one can observe that trait C always appears with trait A, but never with trait B. This added dimension to the phenotypic information can serve to identify positive or negative relationships between traits, yielding information about phenotypic sub-

groups as well as potential insight into patterns of anomalies. A multivariate classification method can emphasize the phenotypic 'signals' while lowering the phenotypic 'noise', especially with the use of a statistical classification approach such as numerical taxonomy.

1.3 Numerical Taxonomy

The roots of taxonomy and systematics can be traced back to Aristotle and the rules of logic (Cain 1958). Despite the historic origins of taxonomy and its use by systematists such as Linnaeus (1707-1778), the last 100 years have represented the period of the most significant growth and implementation of taxonomy, especially with the advent of the first theories of numerical taxonomy used for bacteria (Sneath 1957a; Sneath 1957b), and bees (Michener and Sokal 1957; Sokal and Michener 1958).

Numerical taxonomy is a complex, iterative statistical method of classifying members by virtue of the similarities and/or differences of variables possessed by each member, determined by the calculation of the coefficients of relationship of each member within and between clusters (Sneath and Sokal 1973). Sokal and Sneath (Sokal and Sneath 1963; Sneath and Sokal 1973) provided a formal method of classification that has been applied in bacterial taxonomy, ecology, psychiatry, DNA and evolutionary biology studies, and other fields. As technology has progressed, the use of statistical taxonomy computer software has significantly augmented the

scope of analysis, allowing a large number of variables to be compared simultaneously.

The basis of classification is that it functions both as the end and the means to the analysis, that is, by the act of classification, the end result is a classification (Sneath and Sokal 1973). In the context of phenotype delineation, classification is a method and a result of ordering individuals by virtue of their phenotypic features and relationships. The advantage of such classification is the development of a tool to apply to a set of unknown cases or individuals, and classify them by virtue of previously established classification parameters or discriminators (Sneath and Sokal 1973).

Based on ideas of Michael Adamson (1727-1806), seven fundamental principles of numerical taxonomy, or cluster analysis were established by Sneath (1958), namely:

1. The more information and characteristics or variables available to form the basis of classification, the better the resulting classification.
2. Initially, every variable or character is given equal weighting in the classification.
3. The total similarity between two individuals or cases is based on their similarities in each of the variables or characteristics that are being used for comparison.
4. Distinct clusters can be identified by virtue of the varying correlations of variables or characteristics within each cluster.

5. Inferences about phylogeny can be made by study of the cluster structure and can form the basis for the correlations between variables or characteristics that may yield insight into an evolutionary pathway or mechanism.
6. Taxonomy is deemed and carried out as an empirical science.
7. The classification is based on the similarity of phenotypic variables or characteristics.

The classification process generally involves four general steps: 1) selection of the variables or traits to be used for classification, 2) the calculation of relationship coefficients, 3) the creation of clusters, and 4), the general description of the aspects of each cluster (Sneath and Sokal 1973). While a monothetic classification method treats a specific set of variables as being necessary and sufficient to warrant classification of an individual into a particular cluster, a polythetic method attempts to maximize on the number of common variables in order to group individuals into a cluster. The latter method is flexible in terms of the dynamic state of features and characteristics that can classify an individual in a particular group, thereby avoiding any variable being necessary and sufficient to make a classification. For further information regarding the principles of numerical taxonomy, refer to Sneath and Sokal (1973).

1.3.1 Selection of characteristics

"If we are to compare 'apples and oranges,' we must compare them over a set of characteristics applicable to both of them (Sneath and Sokal 1973)." A unit character used for classification purposes can be defined as a characteristic possessing two or more states, that cannot be subdivided logically, except by coding of the character states (Sneath and Sokal 1973). The phenotypic features chosen should adhere to this definition, as well as have a large enough frequency to be deemed useful for the purposes of classification—that is, to avoid being present all or none of the time, while fitting into some frequency interval, for example between 5% to 95%. The variables chosen can be structural, morphological, functional, or behavioural in nature. Furthermore, the variables chosen ideally should include those with some kind of discriminating power, that is, variables that may assist in distinguishing one phenotypic group from another. Such guidelines for selection of variables or characteristics ultimately facilitate the classification process. For further information regarding the selection of variables, see Sneath and Sokal (1973).

1.3.2 Clustering methods

There are a number of different clustering methods available for the purposes of analysis, and they are characterized by the following eight different criteria (Sneath and Sokal 1973):

1. Agglomerative or divisive
2. Hierarchic or non-hierarchic
3. Overlapping or non-overlapping
4. Sequential or simultaneous
5. Local or global criteria
6. Direct or iterative
7. Weighted or unweighted
8. Adaptive or non-adaptive

Agglomerative methods work to sort data into fewer groups than present initially, whereas divisive methods begin with one group and work to subdivide the data. Generally, most analyses are carried out using agglomerative methods. Hierarchic methods imply that a member of a lower subgroup also belongs to the greater group, whereas members of the non-hierarchical method do not belong to such greater groups. Overlapping methods imply that membership to one subgroup is not mutually exclusive of the same member belonging to another group, whereas non-overlapping methods maintain group membership in one cluster mutually exclusive from another cluster. Sequential clustering implies a number of steps in the clustering analysis as opposed to a simultaneous treatment of the data. Local criteria measure the distances between minor clusters or variables close together, whereas global criteria attempt to achieve this task by measuring the distance between major clusters. Direct clustering methods attempt to cluster in a direct manner to achieve the best results, whereas sequential

methods search for optimization at each level of the cluster while not affecting other clustering levels. Weighting methods give different weights to variables at different levels of classification depending on the impact or classification value of a particular variable or the size of membership in a particular cluster, while unweighted clustering treats each variable in the same manner throughout the classification. Adaptive clustering methods are those that interact with the cluster structure in order to better estimate distances between clusters or members within clusters, while non-adaptive methods do not change the classification algorithm based on structure. For further information regarding classification methods, see Sneath and Sokal (1973).

Most classification methods used in biological studies employ an agglomerative, sequential, hierarchic, and non-overlapping approach to clustering. The basic units of classification are OTUs, or operational taxonomic units. In the agglomerative, hierarchical clustering techniques, two OTUs are combined into a new OTU and are then re-computed. The new OTUs are combined, re-computed, and are reused at the next hierarchical level. Eventually, all of the OTUs are merged into one at the lowest hierarchical level. The cluster diagram is converted into a classification by selecting a distinct level for each taxonomic rank. This allows for the identification of clusters that are distinct at the specified level as the taxa belonging to that particular rank. The selection of a classification method for analysis depends largely on the type of classification parameters that will

yield the optimal classification structure for interpretation. The main difference between the clustering techniques is the method by which the new similarity measures are sequentially calculated. The four most widely used clustering methods are 1) single linkage/nearest neighbor, 2) complete linkage/farthest neighbor, 3) group average, and 4) Ward's method.

1.3.2.1 Single linkage / Nearest neighbor method

The single linkage method identifies the nearest neighbors, that is, a single link is required between two cases in order for them to cluster together (McQuitty 1957; Sneath 1957). As each additional case is joined, one by one, to the existing cluster, it is related by its closest similarity to a member of the cluster. The advantage of single linkage is that the result will be the same even if the data are reordered in the analysis. The disadvantage of this method is that it is not a very useful method, as it generates a chaining effect due to the single linkage between a case and a cluster. The end result is a dendrogram with two clusters, a large cluster and a cluster containing one case (Aldenderfer and Blashfield 1984).

1.3.2.2 Complete linkage / Farthest neighbor method

The complete linkage method is the opposite of single linkage. Clusters are established by the similarity between a prospective case and all of the members of the cluster (Sokal and Michener 1958). This means that the prospective case must have similarity to the farthest neighbor, or the most dissimilar case in the cluster. This generates tight clusters with a high

degree of similarity within the clusters. However, cases of common diagnostic groupings are represented in different clusters. Thus, this method tends to exhibit membership overlap between the clusters (Aldenderfer and Blashfield 1984).

1.3.2.3 Average linkage / Group average method

This method uses the nearest neighbor principle in that a prospective case is joined to its nearest neighbor. However, once a cluster is formed, the similarity distances are re-calculated as a similarity average (Sokal and Michener 1958). The next prospective case is then assessed with the average similarity calculated. The advantage of this method is that this method incorporates aspects of both single linkage and complete linkage methods. The main disadvantage is that this method can generate reversal, that is, the joining of clusters may take place at a distance level less than that characterizing an earlier joining step (McKevley 1982). This can result in a confusing dendrogram organization.

1.3.2.4 Ward's method

This method designed by Ward (1963) optimizes the minimum variance between groups. The process used to generate similarity values is the within-groups sum of squares, or error sum of squares (ESS). Cases are joined if they result in the minimum increase in ESS. The clusters generated are hyperspherical and are roughly of equal size. Similar to complete linkage, this method can have membership overlap. Also, clusters can be ordered by

their overall elevation on the dendrogram, thereby generating solutions that are influenced by profile elevation, that is, the clustering level in the hierarchical classification (Aldenderfer and Blashfield 1984).

1.3.2.5 Comparison of clustering methods

Selecting a clustering method is based on knowing the inherent advantages and disadvantages of each method. Such knowledge is helpful when interpreting data, as each cluster method will generate different results. Studies known as the Monte Carlo studies have been carried out to compare cluster analysis methods and have been reviewed as a whole by Milligan (1981). In order to evaluate the various methods, a random number generator was employed as a source of data for examining the operating characteristics of the cluster techniques. Unfortunately, the results of the studies have contradictory results (Milligan 1981). The following four factors seem to influence the clustering methods: 1) the elements of cluster structure (shape, size, number of cases per cluster and the size differences between clusters), 2) the presence of outlier cases and the degree of coverage required, 3) the degree of cluster overlap, and 4) the choice of similarity measure (Aldenderfer and Blashfield 1984). While all of the cluster techniques have strengths and weaknesses, it is difficult to evaluate the cluster methods. Every scenario for evaluation changes the experiment, and thus, changes the results of the cluster method performance. Thus, the solution for the best cluster method is still unclear, and the user must still judge the cluster

methods by virtue of experience and personal preference for viewing the data generated by cluster analysis. For further reading on specific clustering methods, see Sneath and Sokal (1973).

1.3.3 Measuring techniques

1.3.3.1 Coefficient of similarity

A coefficient of similarity reflects the ratio of the number of variables that are shared by two members versus the total number of variables used in the analysis, notated by S, where S can have a value of zero (no similarity) to 1 (complete similarity). Conversely, 1-S signifies the dissimilarity coefficient.

1.3.3.2 Coefficient of association

A coefficient of association reflects the manner in which two members are related, notated by a, where a, can have a value of +1 (positive association) to -1 (negative association). Conversely, $(1-a)/2$ signifies the disassociation coefficient.

1.3.3.3 Euclidean distance

The distance between two characteristics can be described by a right angle triangle, where the sides at 90° to one another are one taxonomic unit apart, and the hypotenuse linking the two characteristics is $\sqrt{2}$ taxonomic units long. An added variable implies another dimension to create another right angle triangle with a hypotenuse of $\sqrt{3}$ taxonomic units. Additional variables or characteristics between two members implies additional

dimensions to the right angle triangle. Euclidean distance between two members is attained by use of Pythagorean theorem to calculate the square root of the sum of the squared differences in each dimension, where the values can range from zero (complete similarity) to very large values that depend on the number of variables and the amount of distance between them. For further information about measurement techniques, see Sokal and Sneath (1963).

1.3.4 Dendrograms

The visual representation of cluster analysis is a dendrogram, a tree diagram where the roots may be on the top or bottom, depending on the intent of the classification to be aggregative or divisive. The lowest levels of classification represent the highest similarity coefficients, while the nodes of the tree represent the division or aggregation of clusters determined by a measure that has divided the clusters. This measure can be due to a number of factors such as an increase of information within the subdivided cluster or an increase of the sum of squares within a cluster or between clusters.

1.3.5 Discriminant function analysis

While the dendrograms generated by the cluster analysis yield information regarding whether there are differences among cases in the analysis based on the phenotypic variables entered, a further step must be taken to yield information about how the clusters differ from one another. This question can be investigated with the identification of the top variables

that have the best discriminating power between the clusters. To identify the principal variables that differentiate the clusters, discriminant function analysis is used to add information about what separates the clusters. With respect to chromosomal syndromes, the top discriminating variables may be related to karyotypes found in a given cluster, and may indicate regions for potential developmental genes. For further reading about discriminant function analysis, see Sneath and Sokal (1973).

1.3.6 Numerical taxonomy and chromosomal syndromes

Despite the vast applicability of numerical taxonomy in biology, there has been little implementation of cluster analysis for the purpose of delineating human syndromes objectively. Preus employed numerical taxonomy for the identification and diagnosis of Cornelia de Lange syndrome (Preus and Rex 1983), Williams syndrome (Preus 1984), and chromosomal syndromes involving trisomies and monosomies of 4p and 9p (Preus and Ayme 1983). Subsequent applications of numerical taxonomy have included its use as a tool to further classify the del(4p) phenotype (Preus et al. 1985), and a guide to karyotypic interpretation of dup(9p) phenotypes (Preus et al. 1984). Numerical classification, when applied and interpreted with known principles of aneuploidy phenotypes, has been shown to be useful for the identification of phenotypic discriminators for the purpose of phenotype classification and delineation.

As a general guide to chromosomal syndromes, Epstein (1986) outlined 7 general principles of aneuploid phenotypes:

1. Although aneuploid phenotypes have many overlapping non-specific features, the phenotypes can be distinguished from one another.
2. Although any given aneuploidy syndrome may possess a great deal of variability in its phenotype, its overall pattern of defects is still specific.
3. Individual phenotypic features can often be mapped to specific chromosomal regions.
4. The features of segmental aneuploidies can sometimes be added together to generate the phenotypes of combined aneuploidies.
5. Chromosomal syndromes and anti-syndromes do not exist when homologous trisomies and monosomies are compared. A limited number of phenotypic features, however, may represent real counter-characters.
6. The less severe a trisomic phenotype, the more severe the corresponding tetrasomic phenotype is likely to be.
7. Lethality caused by an aneuploid state is a function of the amount of the active genome that is unbalanced. Certain chromosomal regions, which are probably few in number, may play a disproportionately large role.

For chromosomal syndromes, such general principles can be applied and tested with an objective approach to syndrome classification. The purpose of the analysis by Preus and Ayme (1983) was to ascertain the validity of the phenotypic discriminators chosen to distinguish between the four phenotypic groups, as well as test and confirm the non-validity of the

'anti-syndrome' hypothesis first proposed by Lejeune (1964). Epstein's principle number 5 (Epstein 1986) was tested and confirmed by Preus and Ayme as the difference between the trisomic and monosomic state was no larger than the difference between them and non-related pairs of chromosomal syndromes (Preus and Ayme 1983). However, certain phenotypic features have been regarded as having countertypes in the monosomic or trisomic state such as forehead shape in the case of 4p, or chin shape in 18q (Grouchy and Turleau 1977).

1.3.7 Limitations of phenotypic classification in cluster analysis

While phenotypic classifications carried out with cluster analysis have benefits over an informal approach, four problems have been noted as being associated with such analysis (Sneath and Sokal 1973), namely:

1. Discrepancy between clustering that is based on variables from different regions of the body, or comparing individuals at different stages of life. This is especially important in facial dysmorphologic classification as certain features change through the course of post-natal development and maturation, and can affect results.
2. Discrepancy in relationship estimation based on different values for the coefficients of similarity.
3. Discrepancy in interpretation of clusters generated by different clustering methods.

4. The impact of parallelism and convergence in terms of classification based on estimates of phenotypic or phenetic relationships.

While point 4 may initially seem irrelevant to the study of chromosomal syndromes in humans, it should be noted that it can be interpreted as an underlying basis for classification of certain individuals on the basis of their patristic similarity, that is, the similarity due to common ancestry (Cain and Harrison 1960). This is an important aspect to note in terms of any potential familial clustering, especially in the cases of consanguinity, or individuals coming from a large kindred such as a large inv(3) kindred from Newfoundland (Allderdice et al. 1975).

Other limitations may lie in the inability to perform analysis on specific traits due to the unknown genetic basis for many malformations such as cleft palate (Sneath and Sokal 1973). As a result, the concept of a 'pattern of anomalies' as opposed to specific anomalies has served as the basis for most informal syndrome delineation (Cohen 1989b). This general concept is especially important when assessing cases of double aneuploidy resulting in "composite phenotypes" (Epstein 1986). However, the knowledge of the specific etiology of a trait is not a prerequisite for its use in cluster analysis. Instead, the final classification can lead to models that may help in explaining the etiology of some traits.

Lastly, any objective analysis begins with some degree of subjectivity, mainly with the amount of detailed phenotypic information available for selection and the approach used to describe a clinical phenotype. Since verbal

data must be converted to numerical values for the purposes of analysis, value judgments can and do occur, and one must use caution when describing, interpreting, and generalizing the information in the clusters or groups generated by numerical classification.

1.4 Chromosome 3

Averaging 6.68% of the total human genome physical length (Morton 1991), the 214 Megabases of DNA comprising chromosome 3 make it a likely target for structural aberrations. It has been noted that regions of chromosome 3 play an important role in early embryonic development in humans (Jay et al. 1997), thus structural aberrations present a significant impediment in early developmental processes. The group A chromosomes appear to have less occurrences of hyper and hypohaploidy than statistically expected (Guttenbach et al. 1997). However, these chromosomes may present a likely target for structural rearrangements due to their length and hence the possibility for interruption of chiasma formation along the chromosome in meiosis I.

Chromosome 3, along with chromosome 7, appears to have an abundance in breakpoints that are involved in complex chromosomal arrangements, mainly in 're-entry', or chromosomal breaks that may serve to stabilize the genome after the initial chromosomal breaks (Lurie et al. 1994). This type of chromosomal behaviour in chromosome 3 involves breaks at 3pter, 3p25, 3p23, 3p11, 3q12, 3q23, 3q25, and 3q29, almost exclusively

consisting of Giemsa light bands. Despite the significant frequency of chromosome 3 involvement in these rearrangements, all of the breaks appear to occur in different locations (Lurie et al. 1994), thus not indicating any preferred sites of chromosomal breakage or specific 'hot-spots' (Gorski et al. 1988). However the possibility of 'hot-spots' or non-random chromosomal breaks on chromosome 3 has been suggested, namely clustering at 3p2 and 3q2 (Aula and von Koskull 1976), as well as an inducible fragile site on 3p14.2 (Wegner 1983).

In sperm, breaks involving chromosome 3 appear to be localized in G-light bands, but have no correlation to fragile sites in G-light bands, whereas in carriers of chromosomal aberrations, balanced and unbalanced gametes are produced at an equal frequency (Guttenbach et al. 1997). Also, an interchromosomal effect (where the abnormal chromosome causes further chromosomal instability within a cell) does not appear to be present at a higher rate in carriers of chromosomal aberrations than in males with a normal chromosomal complement (Guttenbach et al. 1997).

1.5 Genes on chromosome 3

It has been suggested that there is a negative correlation between the frequency of trisomy of an autosome and the gene content in that autosome (Kuhn et al. 1987). Chromosome 3, thus, is presumed to be a gene-rich chromosome, with a low frequency of trisomy when compared to chromosome 13 or 18. A study that isolated and mapped cDNAs expressed during early

human embryonic development indicated a high gene density in R-bands. More specific to chromosome 3, the regions of early embryonic gene expression appeared to be located at 3q14→p21, 3q24→p25, and 3p21.3, while the critical region for type II fibrillin maps to 3q24→p25 (Jay et al. 1997). This demonstrates an involvement of genes on various regions on chromosome 3 during early embryonic development in humans.

Some recently discovered genes on chromosome 3 play a role in development and can provide insight into patterns of malformation. cDNA homologues of the *Drosophila dishevelled* (*dsh*) polarity gene, DVL-1, and DVL-3. DVL-1 and DVL-3 appear to be expressed in fetal and adult heart, brain, skeletal muscle, kidney and lung tissue (Pizzuti et al. 1996). DVL-3 maps to 3q27 and is believed to function in neural and heart development. *WNT7A*, a gene involved in human limb development and cell transformation was mapped to 3p25 (Bui et al. 1997). Another gene in the *Wnt* family, *WNT5A*, was mapped to 3p14→p21.

3p25 is known to be an important region for disease, as the disease genes mapping to 3p25 include Marfan syndrome due to mutations in type II fibrillin (Collod et al. 1994), and dilated cardiomyopathy (Olson and Keating 1996). Another region of interest may be 3q22-q23, where blepharophimosis, ptosis, epicanthus inversus sequence has been mapped (Small et al. 1995). This is believed to be a contiguous gene syndrome encompassing genes involved in eyelid development.

The homologue to the *Drosophila* seven in absentia *Sina* gene, *SIAH2* is believed to play a role in vertebrate development and maps to 3q25 in humans (Hu et al. 1997). *SHOT*, a *SHOX*-related homeobox gene may play a role in limb, craniofacial, heart and brain development in humans and maps to 3q25-q26 (Blaschke et al. 1998). This gene, at present, is a candidate gene for Cornelia de Lange syndrome.

1.6 Parental origin of chromosomal rearrangements

Using chromosomal heteromorphisms, attempts have been made to determine the parental origin of various chromosomal abnormalities such as triploidy (Jacobs and Morton 1977), tetraploidy (Sheppard et al. 1982), structural abnormalities (Chamberlin and Magenis 1980), and autosomal trisomies (Mikkelsen et al. 1980; Hassold et al. 1984), with the majority focusing on cases of trisomy 21. A summary of new cases as well as cases in the literature showed a 13M:7P (13 maternal:7 paternal) ratio for Robertsonian translocations, a 5M:0P ratio for bisatellited 15s, and 4M:13P for other rearrangements (Chamberlin and Magenis 1980). While a relationship between parental age and chromosomal rearrangements was not apparent, there appeared to be a bias toward paternal origin of *de novo* chromosomal rearrangements. While it appears that trisomies and triploidies are primarily maternal in origin, most structural rearrangements seem to be paternal in nature (Chandley 1991). This is likely due to the inherent differences in the meiotic process in males and females, where, in males, the

increased amount of gamete production may lead to increased chromosomal breakage and thus increased frequency of chromosomal rearrangement (Chamberlin and Magenis 1980). It has also been suggested that the majority of partial trisomies may arise from incomplete disjunction of chromosomes during maternal meiosis I (Hassold et al. 1984).

1.7 Pericentric inversions in chromosome 3

Pericentric inversions have an frequency of 1 to 2% in liveborns (Kaiser 1984). This frequency in live births is attributed to the premise that pericentric inversions appear to result more often in fetal wastage than in live births with congenital malformations (Kaiser 1984; Francais 1986). Martin (1991) analyzed the sperm of a man heterozygous for an inv(3)(p25;q21). The length of the inversion exceeded 50% of the total chromosome length, thereby making it more likely to undergo unequal crossing over and hence lead to an increase of recombinant chromosomes when compared to chromosomes with an inversion segment measuring less than 30% of the total chromosome length (Guttenbach et al. 1997). Out of 144 sperm chromosome complements, 50 (37.6%) had normal a chromosome 3, 42 (31.6%) had a chromosome 3 with a balanced inversion, 18 (13.5%) had dup(3p)del(3q), and 23 (17.3%) had dup(3q)del(3p). Thirty-six of 144 (25.0%) complements had abnormalities unrelated to the inversion, with 3 (2.1%) being numerical and 33 (22.9%) being structural in nature (Martin 1991). It has also been suggested that there may be a preferential transmission of

abnormal chromosomes in fathers carrying a pericentric inversion (Boué and Gallano 1984).

1.8 Rec(3)

1.8.1 The rec(3) phenotype

Prior to more sophisticated chromosome identification and microscopy methods, the first cases of a recombinant chromosome 3 were mistakenly reported as translocations in the literature. The first such report was of an infant with multiple congenital abnormalities due to a t(2;3) translocation (Lee et al. 1964), with more individuals with the same chromosomal abnormality also being reported (Boon 1967). Hirschhorn and colleagues (1973) and Boué and colleagues (1974) reported a child with similar anomalies in a child with a (3;C) translocation, or a chromosome 3 with a pericentric inversion. With the advent of chromosome banding techniques, the chromosomal abnormality for these cases was determined to be del 3p25→pter, dup 3q21→qter, resulting from a pericentric inversion, inv(3)(p25q21). Allderdice and colleagues (1975) described the phenotypes of the individuals from the latter cases as well as those of 13 individuals from a large kindred from Newfoundland in which an inv(3)(p25q21) segregates. The primary phenotypic features of these individuals were generalized hirsutism, down-slanting oblique palpebral fissures, cleft lip and/or palate, micrognathia, omphalocele (umbilical hernia), spina bifida (sacral dimple), congenital heart defects, renal abnormalities, and club foot (Allderdice et al.

1975). Most individuals with this duplication-deficiency died early in life, most likely due to the combined effects of the duplication and the deletion in the chromosome.

Fineman and colleagues (1978), Sun and McAlpine (1994), and Siu and McAlpine (1997) have identified other cases of rec(3) belonging to this large kindred. While it has been stated that there is a very small chance of an identical duplication-deficiency syndrome occurring in more than one individual or kindred (Herrmann and Opitz 1974), other reports of duplication-deficient individuals due to inv(3)(p25q21) have been reported (Patil et al. 1978; Kawashima and Maruyama 1979; Migliori et al. 1983; Aughton 1997).

Other reports of recombinants resulting from inv(3) include del(3p25→pter) and dup(3q25→qter) (Fineman et al. 1978; Pope et al. 1979; Summitt 1966), del(3p25→pter) and dup(3q23→qter) (Mulcahy et al. 1979; Preus et al. 1986; Sutherland et al. 1981), and del(3p26→pter), dup(3q22→qter) (Lurie et al. 1974).

To date, the reciprocal recombinant with dup(3p25→pter) and del(3q21→qter) has never been detected in a liveborn presumably due to the overwhelming amount of genetic information that is deleted from the long arm of the chromosome, and phenotypic severity that would be likely to result (Allderdice et al. 1975).

1.8.2 Rec(3) chromosomal regions of interest

Since there is a duplication and deficiency present in the recombinant chromosome, there are two factors influencing the rec(3) phenotype: that of the deletion of p, and the duplication of q. Few studies have addressed the possibility that the duplication-deficient phenotype may be a composite phenotype of del(3p) and dup(3q) syndromes and mainly attribute the phenotypic features as those similar to dup(3q) individuals (Mulcahy et al. 1979). Kwasnicka (1997) compared the phenotype of rec(3) with that of del(p) and dup(q) cases, and attributed particular traits to either the duplication of q or deletion of p by virtue of the traits' frequency in each group. Whereas low-set ears, growth retardation, oblique palpebral fissures, and microcephaly were attributed to del(3p), traits such as cryptorchidism, a broad face with mid-facial hypoplasia, micrognathia, cleft palate/bifid uvula, club foot and renal anomalies were attributed to dup(3q). Traits such as congenital heart defects and sacral dimple were not informative as to the chromosomal segment to which traits could be attributed (Kwasnicka 1997).

1.9 Trisomy 3

1.9.1 Trisomy 3 phenotype

Full trisomy 3 is reported in about 1% of all karyotyped abortuses (Creasy et al. 1976). Most fetuses with a trisomy 3 chromosome complement are spontaneously aborted in the first trimester of gestation (Boué et al. 1976). As a result, there have been very few cases of liveborn trisomy 3

reported. All cases have been mosaic in nature, with frequencies of trisomic cells varying between 5% (Kuhn et al. 1987; De Keyser et al. 1988) and 86% (Smith et al. 1988) of the total cell population analyzed. The cases had multiple malformations, and mortality within the first two years of life was associated with the majority of cells in the karyotype having the additional chromosome 3. The phenotypes varied between individuals, thus trisomy 3 has not been delineated as a recognizable syndrome.

1.10 De Lange syndrome

1.10.1 De Lange phenotype

First described in two patients by Cornelia de Lange (1933), de Lange syndrome has been widely described in many comprehensive studies such as Berg and colleagues (1970), Hawley and colleagues (1985), Opitz (1985), and Jackson and colleagues (1993). The main phenotypic features of this syndrome are pre- and post-natal growth retardation; mental retardation; a characteristic facies including a low hairline, confluent eyebrows, upturned nostrils, prognathia, a long philtrum, and a down turned mouth; general hirsutism; and abnormalities of the upper limbs. Ireland and colleagues (1993) noted that that main phenotypic descriptors for de Lange syndrome are arched eyebrows with synophrys, thin down-turned lips, and a long philtrum. Post-puberty, this combination of features was seen in females but not in males.

De Lange syndrome has a variable phenotypic expression that appears to manifest over time. Jackson and colleagues (1993) noted a high proportion of de Lange patients as being mildly affected, with only 27% of cases having upper limb abnormalities. It has also been suggested that limb deficiencies in de Lange syndrome are present in only a minority of cases (Opitz 1993). Some 30 phenotypic discriminators have been proposed to differentiate between the various phenotypes in the de Lange spectrum (Preus and Rex 1983). A classification system for de Lange syndrome has been established to better distinguish from the classical and milder phenotypes (Van Allen et al. 1993). Type I de Lange phenotype includes limb abnormalities, growth retardation, and major abnormalities, and may be less compatible with survival. Type II phenotype is the milder form of de Lange syndrome, where the growth and mental retardation is less severe, and there are fewer major abnormalities or malformations. Type III phenotype is a de Lange phenocopy associated with exposure to teratogens, or due to chromosome abnormalities (Van Allen et al. 1993).

1.10.2 De Lange and chromosomal regions of interest

Despite the large number of clinical reports on the de Lange phenotype, the etiology of this syndrome still remains elusive. A chromosomal study of 45 de Lange patients revealed no structural chromosomal aberrations (Beck and Mikkelsen 1981). Despite the evidence of various chromosomal abnormalities associated with the de Lange phenotype

(Craig and Luzzatti 1965; Falek et al. 1966; Broholm 1968), ring chromosome 3 (Lakshminarayana and Nallasivam 1990), and more specifically with trisomy of 3q21→qter (Allderdice et al. 1975; Francke, 1978; Breslau 1981; Steinbach, 1981; Wilson, 1985), there still appears to be no conclusive cause and effect. Although the phenotypes of dup(3q) and de Lange individuals share many similarities, it has been established that they are separate syndromes. Characteristics such as IUGR, oligodactyly/phocomelia, and syndactyly of toes 2 and 3 appear to be more frequently seen in the de Lange syndrome, whereas cleft palate, craniosynostosis and genitourinary anomalies are more often associated with dup(3q). It is generally thought that the mutation responsible for de Lange phenotype is on 3q, as a patient with a severe de Lange phenotype was found to have a translocation at 3q26.3 and 17q23.1 (Ireland et al. 1991). Since 3q25.1→q26.1 was excluded from the de Lange region (Lopez-Rangel et al. 1993), it has been thought that the chromosomal region of interest for de Lange syndrome may be 3q26.3. It has been suggested that with the use of *in situ* hybridization and DNA molecular studies, the critical region for the Cornelia de Lange phenotype may be due to uniparental disomy, a microdeletion or microduplication of 3q, or imprinting (Kousseff et al. 1994).

1.11 Trisomy 3q

1.11.1 Dup(3q) phenotype

This syndrome was originally reported by Falek and colleagues, as a case of de Lange syndrome with a chromosomal abnormality (Falek et al. 1966). This phenotype associated with the dup(3q21→qter) syndrome is characterized by hirsutism; craniofacial dysmorphology such as microcephaly, tendency to synophrys, upward slant of palpebral fissures, small nose with anteverted nostrils, hypertelorism, micrognathia; glaucoma; short neck with redundant skin; severe cardiac, intestinal, and urogenital malformations, and skeletal abnormalities. Despite the similarity to the de Lange phenotype in facial dysmorphology, de Lange individuals have a much higher frequency of intrauterine growth retardation. There is a high rate of mortality within the first 12 months of life (Stengel-Rutkowski et al. 1979). As a large majority of dup(3q) cases are familial in nature, it has been suggested that relatives should be studied as well (Wilson et al. 1985). A case of leprechaunism with dup(3q) has also been reported (Iwasaki et al. 1978).

1.11.2 Dup(3q) and chromosomal regions of interest

Van Essen and colleagues (1991) suggested that the 3q22→q24 segment may be gene-poor, as the effects of the trisomic state of this region appears to be relatively mild to not apparent.

In recent years, studies have focused on molecular delineation of the critical chromosomal region for the required expression of the dup(3q)

phenotype. While 3q25→q26.2 appears to be excluded from the critical region for the dup(3q) phenotype (Rizzu et al. 1997), the distal 3q26 to proximal 3q27 region have been suggested as being critical to the dup(3q) syndrome phenotype (van Essen et al. 1991; Rizzu and Baldini 1994; Aqua et al. 1995). Montero and colleagues (1988) proposed that dup(3q21→qter) cases had cardiac malformations, while those cases with the trisomic segment at 3q25 or distal to 3q25 did not.

Fineman and colleagues (1978) first questioned whether the duplication-deficient chromosome 3 phenotype is due to the duplication of 3q, the deletion of 3p, or influence of both. In a review of dup(3q) cases by Steinbach and colleagues (1981), it was suggested that there is no significant difference in the phenotype of individuals with dup(3q) and individuals with dup(3q)del(3p).

1.12 Monosomy 3p

1.12.1 Del(3p) phenotype

The main features of the del(3p) phenotype are growth and mental retardation, generally decreased muscle tone, microcephaly, flat occiput, a triangular face shape, ptosis and epicanthal folds, thickened eyebrows with tendency to synophrys, long philtrum, downturned mouth with a thin upper lip, a broad, prominent nose, micrognathia, low-set, malformed ears, and postaxial polydactyly. Characteristics less frequently associated with the del(3p) phenotype are renal anomalies, rocker-bottom feet, cryptorchidism,

cardiovascular anomalies, and umbilical hernia. Three cases of deafness have been reported in conjunction with the del(3p) phenotype (Verjaal and De Nef 1978; Higginbottom et al. 1982; Narahara et al. 1990).

Although the del(3p) phenotype is often compared to that found in cases of ring(3), the variable phenotype associated with ring(3) does not appear to be similar in nature to del(3p) syndrome.

1.12.2 Del(3p) and chromosomal regions of interest

It appears that deletion of the 3p25.3 cytogenetic band plays an important role in the del(3p) phenotype (Narahara et al. 1990). While notable genes such as VHL (Von Hippel-Lindau syndrome) are known to be located in this region, the phenotypes associated with del(3p) do not appear to show any association with syndromes due to genes on 3p.

1.13 Ring 3

1.13.1 Ring 3 phenotype

Côté and colleagues (1981) coined the term "ring syndrome" in order to attempt to classify the phenotype commonly found in individuals with an autosomal ring chromosome, where the phenotype is independent of the autosome involved. The general features associated with the ring phenotype consist primarily of severe growth failure, and mild to moderate mental retardation (Kosztolanyi 1987).

It has been suggested that the ring syndrome phenotype can be the result of three aspects or events; the first being a result of the telomeric deletions that occur during ring formation. Secondly, the risk of aneuploidy due to chromosomal pairing and sister chromatid exchange with the ring chromosome, and thirdly, an incidence of cell death due to the aneuploidies being more incompatible with cell life by causing metabolic wastage (Côté et al. 1981). The larger the chromosome involved in the ring formation, the more severe growth retardation seems to be (Kosztolanyi 1987), as it appears the larger chromosomes have more opportunity for sister chromatid exchange, resulting in the aneuploidy and cell death (Côté et al. 1981). Moreover, the larger chromosomes (chromosomes 1 to 12) appear to be more "labile" than "stabile", thus suggesting a relationship between ring stability and growth failure (Kosztolanyi 1987).

Thus, ring chromosome 3 appears to be classified as a more labile chromosome that is prone to further instability and cell death resulting in more severe growth retardation. In the cases used in this report, the ring chromosomes are present in mosaic form representing 45% (Mukerjee and Burdette 1966), 75% (Picciano et al. 1972), 100% (Witkowski et al. 1978), 92% (Wilson et al. 1982), 77% (Kitatani et al. 1984), 87% (Narahara et al. 1990), and 84% of total lymphocytes studied (McKinley et al. 1991). One case of ring chromosome was also associated with a Cornelia de Lange phenotype (Lakshminarayana and Nallasivam 1990).

1.14 Monosomy 3q

1.14.1 Del(3q) phenotype

Only 7 cases of terminal del(3q) are known to have been reported in the literature (Alvarez Arratia et al. 1984; Sargent et al. 1985; Brueton et al. 1989; Jokiaho et al. 1989; Chitayat et al. 1996; Karimi-Nejad et al. 1996; Chandler et al. 1997). Most affected individuals died early in life. Aside from a few similarities, it is not possible to glean a discernible phenotype for this chromosomal abnormality. A few cases of interstitial deletions have been reported (Williamson et al. 1981; Franceschini et al. 1983; Martsolf and Ray 1983; Jenkins et al. 1985; Al-Awadi et al. 1986; McMorrow et al. 1986; Alvarado et al. 1987; Okada et al. 1987; Jewett et al. 1993; Genuardi et al. 1994; Chandler et al. 1997; Slavotinek et al. 1997), but have not been classified into a syndrome due to lack of phenotypic uniformity. Although the most common phenotypic features appear to be blepharophimosis, ptosis, epicanthus inversus syndrome (BPES), other phenotypic features found in cases of terminal 3q deletions include hypotonia, microdolichocephaly, protruding occiput, scant hair, eyebrows and eyelashes, telecanthus, bilateral micropthalmia, high nasal bridge, bilateral cleft lip and palate, retromicrognathia, low-set malformed ears, short neck, cardiomegaly, clenched hands and feet, hypoplastic nails, vertebral and rib abnormalities, short stature, developmental delay, hypotonia, angiomata, strabismus, broad nose, long smooth philtrum, high arched palate, and kyphosis.

1.14.2 Del(3q) and chromosomal regions of interest

Fujita and colleagues (1992) described a boy with blepharophimosis, ptosis, epicanthus inversus syndrome with a 3q12→q23 deletion. BPES has also been noted in 4 other cases where 3q23 appears to be deleted (Williamson et al. 1981; Martsolf and Ray 1983; Al-Awadi et al. 1986; Alvarado et al. 1987; Okada et al. 1987). Thus, 3q23 appears to be a critical region for BPES, and BPES is thought to be a contiguous gene syndrome (Fujita et al. 1992).

1.15 Trisomy 3p

1.15.1 Dup(3p) phenotype

First described by Yunis (1978), trisomy 3p is a well-characterized syndrome with characteristic facies often characterized by microcephaly, frontal bossing, hypertelorism, square-shaped face, prominent cheeks, and bilateral temporal indentation. Reiss and colleagues (1986) summarized the major and minor phenotypic features from the literature on dup(3p). The major clinical features of dup(3p) syndrome were psychomotor retardation, brachycephaly, frontal bossing, temporal indentation, square facies, hypertelorism, and micro/retrognathia, cardiac defects, and genitourinary abnormalities in males such as hypospadias, cryptorchidism, and micropenis. Minor findings were intrauterine and post-natal growth retardation, and cleft lip/palate. Unique cases have been described with micropthalmia, postaxial hexadactyly, and sex reversal.

There are also cases of holoprosencephaly associated with duplication of 3p (Martin and Steinberg 1983; Van Regemorter et al.1983; Gimelli et al. 1985; Gillerot et al. 1987; Kurtzman et al. 1987; Bürrig et al. 1989; Dallapiccola and Ferranti 1990; Chen et al. 1996b). Gillerot and colleagues (1987) reported a few dup(3p) cases; one case with holoprosencephaly, another case with arrhinencephaly, and a case with a normal face and skull, with all three cases from same family.

Although 42% of the cases reviewed by Reiss and colleagues (1986) did not survive beyond two years of age, the facial features of dup(3p) in survivors appear to be less pronounced as patients get older. The survival appears to depend mainly on the severity of brain and organ malformations. 3p trisomies appear to be predominantly maternally derived.

1.15.2 Dup(3p) and chromosomal regions of interest

Reiss and colleagues (1986) noted cleft lip +/- palate was found mainly in cases with dup(3p21→3pter) and dup(3p23→3pter), holoprosencephaly/cyclopia in cases with dup(3p21→3pter) and dup(3p25→3pter), and early death in cases with dup(3p21→3pter). Cleft lip and palate have been observed in dup(3p21→pter) and dup(3p23→pter) but not in dup(3p25→pter). Thus, the critical region for cleft lip and palate may be between 3p23 and 3p25 (Scarbrough et al. 1987). Also, there may be genes influencing forebrain and mid-face development on terminal regions of 3p.

The major phenotypic features in the syndromes mentioned are summarized in Table 1.

Table 1 An overview of the major phenotypic features noted in the eight etiologic groups in the study

Etiologic group	Phenotypic features
dup(3q)	hirsutism, cleft palate, microcephaly, glaucoma, upturned nose, congenital heart and intestinal malformations, bushy eyebrows, synophrys, high neonatal mortality
del(3p)	microcephaly, cleft lip, ptosis, short palpebral fissures, long philtrum, low-set, malformed ears, postaxial polydactyly, cryptorchidism
ring(3)	intrauterine and postnatal growth retardation, mental retardation
trisomy 3	multiple non-specific anomalies
del(3q)	BPES, microdolichocephaly, diffuse hair, high nasal bridge
rec(3)	cataracts, glaucoma, broad depressed nasal bridge, micrognathia, club foot, heart malformations, sacral dimple
de Lange	hirsutism, synophrys, upturned nose, downturned thin lips, limb deficiencies, microcephaly
dup(3p)	square head, temporal indentations, protruding forehead, large mouth

1.16 Objectives

The objectives of this project have been to implement numerical taxonomy as a formal, objective method of syndrome classification to:

1) **Classify the phenotypes due to various duplications and deletions of the long and short arms of chromosome 3.** Testing the validity of the phenotypic discriminators ascertained by the cluster analysis for their separating power of eight different etiologic groups.

2) **Using the phenotypic discriminators defined by the analysis, classify a duplication-deficient phenotype with respect to the dup(3q) and del(3p) phenotypes.** The classification of the dup(3q)del(3p) phenotype with respect to dup(3q) and with del(3p) can indicate whether the recombinant phenotype is experiencing an additive effect from the trisomy of 3q as well as monosomy of 3p.
3) **Classify a syndrome of unknown etiology.** Testing the phenotypic discriminators and their ability to classify De Lange syndrome with respect to dup(3q) syndrome.
4) **Identify regions of chromosome 3 that may contain genes involved in human fetal development and affect the loss of cellular control due to aneuploidy.** Phenotypic discriminators that are determined to be the 'signals' in each phenotype may indicate underlying patterns of malformation and their relationship with a specific monosomic or trisomic segment.

2.0 METHODS

2.1 Data selection

The data set consisted of 263 cases. Cases were collected from case reports in the literature, as well as 6 unpublished case reports (Sun and McAlpine 1994; Allderdice 1997; Aughton 1997; Barr Jr. 1997; Howard 1997; Siu and McAlpine 1997; Wulfsberg and McAlpine 1997). The goal was to gather as many cases as possible for the analysis, with the main inclusion criteria being the karyotype (including breakpoints whenever possible), the sex of the individual, and some specific phenotypic information. Therefore, case reports referring to craniofacial anomalies as 'unusual facies' were excluded whenever possible. Some karyotypic groups such as ring(3) and trisomy 3 had few reported cases in the literature, therefore all of the cases found were included in the study. Rather than choosing cases of Cornelia de Lange syndrome from different case reports, one report was chosen (Filippi 1989). The 15 cases reported in the study were ascertained by different examiners, and the phenotypic information was presented in detailed tables. The quantity of information was large and detailed enough to warrant inclusion of these 15 cases as a control group. For a complete listing of karyotypes and citations, see Appendix 1.

The 263 cases were each given a number and were classified into eight etiologic groups as shown in Table 2.

Table 2 Distribution of cases by etiologic group

Etiologic Group	Number of Cases
dup(3q)	49
del(3p)	57
ring(3)	8
trisomy 3	6
del(3q)	18
dup(3q)del(3p)	43
de Lange	15
dup(3p)	67
Total	263

After data had been submitted for cluster analysis, it was discovered that 5 cases had erroneously been duplicated in the database, thus reducing the actual number of cases to 258 (see Appendix 1). All of the cases were retained for cluster analysis.

2.2 Selection of phenotypic traits

A list of phenotypic variables was gathered from review of the case reports. The variables were classified in groups such as systems or physical regions—craniofacies, central nervous system (CNS), cardiovascular, respiratory, gastrointestinal, genitourinary, musculo-skeletal including hands and feet, dermatological, and behaviour/growth. In an effort to retain as many traits as possible, only uniquely occurring traits were not included in the list of variables.

2.3 Creation of phenotype sheet

The list of phenotypic variables formed a basis for a phenotype sheet, listing variables by category, and if possible, by spectrum e.g.:

'Eyebrows': Thin Normal Thick

The phenotypic traits for each case were transferred onto the phenotype sheets by circling the appropriate variables, and any additional information was written in the margins of the sheets. A phenotypic coding sheet is presented in the Appendix 2.

2.4 Creation of coding sheet

In order to accommodate the numerical parameters of cluster analysis, phenotypic traits were coded numerically, e.g.:

'Eyebrows': Thin = 0 Normal = 1 Thick = 2

A listing of definitions used for the field names and numerical coding is listed in Appendix 3.

2.5 Creation of numerical database

The numerical data were entered into a Microsoft Excel spreadsheet by case number. The spreadsheet consists of 184 variables per case, including a comment field for any additional information.

2.6 Descriptive statistics

Preliminary descriptive statistics were carried out with SPSS statistical software (SPSS Inc. 1997) to determine which phenotypic variables

would be used as discriminators in cluster analysis. Two criteria were used to select variables: a frequency of 5% to 95%, and statistically significant variability for a variable between etiologic groups, where $p < 0.001$ was deemed significant. The frequency of a given discriminator was important as a variable occurring in very few or a large number of cases would not be informative with respect to discriminating one phenotypic group from another. Statistically significant variability between etiologic groups for a given variable was deemed important to ensure that the chosen variables would have discriminating power in the cluster analysis. Descriptive statistics for phenotypic variables were calculated and karyotypic information collected for the entire data set of 258 cases.

2.7 Cluster analysis

2.7.1 List of analyses performed

Four separate cluster analyses were performed. Information regarding the etiologic groups and the number of cases included in each study are listed in Table 3.

Table 3 Description of the four cluster analyses in the study with respect to the etiologic groups and the number of cases in each cluster analysis

Cluster analysis number	Groups in analysis	Number of cases in analysis
1	dup(3q), del(3p), ring(3), trisomy 3, del(3q), de Lange, dup(3p)	220
2	dup(3q), del(3p)	106
3	dup(3q), del(3p), rec(3)	149
4	rec(3)	43

2.7.1.1 Cluster analysis 1

The first analysis was carried out to test the capability of numerical taxonomy to organize individuals based on phenotype, with no karyotypic data included in the analysis. Also, this initial analysis would indicate if the phenotypic variables chosen would be adequate discriminators for the classification analysis. The de Lange cases were used as an internal control to test the validity of the initial cluster analysis, as the cases belong to a well-described syndrome. The rec(3) cases were omitted from the first analysis and were retained as test cases for comparison with del(3p) and dup(3q) cases. The database was then modified accordingly for submission for cluster analysis.

2.7.1.2 Cluster analysis 2

The second cluster analysis included cases from dup(3q) and del(3p) etiologic groups. This cluster analysis was carried out for the purpose of grouping phenotypes that may be composites of the rec(3) phenotype. Also, discriminant function analysis was carried out on this group to determine the top phenotypic variables that separated the clusters.

2.7.1.3 Cluster analysis 3

The third cluster analysis included cases from dup(3q), del(3p), and rec(3) etiologic groups. The clustering information in this analysis would yield information about where the recombinant cases are clustering with respect to individuals who partially share the karyotype, with either dup(3q) or del(3p).

Also, rec(3) individuals in this analysis would be re-classified according to the top discriminant features identified in analysis 2 as described above.

2.7.1.4 Cluster analysis 4

This cluster analysis consisted of rec(3) cases only. This analysis was carried out to determine how individuals sharing very similar karyotypes would cluster, especially those individuals belonging to the large inv(3) kindred from Newfoundland.

2.7.2 Execution of cluster analysis

The cluster analyses were carried out using SYNTAX 5 taxonomy software on a Pentium 100 computer processor using set parameters as per instructions in the software literature (Podani 1993). For settings used in the cluster analysis, refer to the SYNTAX 5 operations manual.

2.7.3 Selection of clustering method

Six different clustering methods were initially used for 220 cases in analysis 1: Ward's method, complete link, average link, single link, minimum between/within, and simple average. The six dendrograms generated were analyzed by visual inspection to determine which clustering method yielded the best dendrogram for determining clusters. Ward's method was selected as the optimum method for determining clusters due to the tight clustering of data on the dendrogram, and was subsequently employed for cluster analyses 2, 3 and 4. For illustration of the dendrograms, see figures 1, 2, 3, and 4.

2.7.4 Selection of optimal clusters

Analysis to determine the level of the dendrogram tree would yield the optimal number of clusters was determined by inspection of values yielded for separating power per variable. The greatest number of positive values for separating power, and the greatest value for total separating power would determine the optimal hierarchical level of clustering. For analysis 1, the optimal level of clusters was calculated by computer according to the cluster level with the greatest number of variables showing positive values, as well as the greatest cumulative separating power for all variables. Optimal cluster levels for the subsequent analyses were determined by visual inspection.

2.7.5 Discriminant function analysis

For the purposes of identifying whether the rec(3) phenotype is a composite phenotype of the discrete dup(3q) and del(3p) phenotypes, discriminant function analysis was carried out on the dup(3q) and del(3p) cluster analysis to identify the top phenotypic discriminators for the four clusters identified in this analysis. As per protocol, the number of discriminators is limited to approximately 10% of the number of cases being classified, thus the number of top discriminators would be limited to 10 in this analysis. With the identification of the top discriminating variables in this analysis, an algorithm could potentially be created by which the rec(3)

cases could then be assessed by the process of a simulated re-classification based on the key variables identified.

3.0 RESULTS

3.1 Descriptive statistics

The final group of variables chosen for cluster analysis consisted of 112 variables restricted to structural abnormalities, as data for variables such as 'impaired hearing' and behavioral traits were deemed inconclusive or were inconsistently reported.

3.1.1 Karyotypes

3.1.1.1 The frequency of two affected chromosomes in the karyotype

Descriptive statistics indicated that the frequency of positive results in the field for 'other chromosome' differed significantly between etiologic groups. It was thought that noting which etiologic groups had a high frequency of another abnormal chromosome in the karyotype might clarify if this factor was influencing the clustering of certain groups. Cases where the information was not known were not counted in the total. The total frequency of additional chromosomal imbalances are listed in Table 4.

Table 4 The frequency of an additional chromosomal imbalance in the eight etiologic groups

Etiologic Group	Yes	No	Unknown	Total (%)
dup(3q)	39	10	0	39/49 (79.6)
del(3p)	16	36	5	16/52 (31.0)
ring(3)	1	7	0	1/8 (12.5)
trisomy 3	0	6	0	0/6 (0)
del(3q)	3	15	0	3/18 (16.7)
rec(3)	0	43	0	0/43 (0)
de Lange	0	15	0	0/15 (0)
dup(3p)	61	5	1	61/66 (94.0)
TOTAL	120	73	6	120/258 (46.5)

Dup(3q) and dup(3p) cases were most likely to have other chromosomal aberrations involved. In such cases, the double aberrations were usually due to a translocation or a complex rearrangement.

3.1.1.2 The preferential sites of breakage in chromosomal rearrangements

Since most of the inv(3) cases had a recombinant chromosome due to an inversion of 3p25→3q21, the sites evaluated for the frequency of chromosome breakage and rearrangement were 3q21 and 3p25. The etiologic groups counted were dup(3q), del(3q), dup(3p), del(3p), and rec(3), where the duplications and deletions represent individual portions of the recombinant chromosomes generated by an inversion. When counting non-redundant chromosomal breaks in each etiologic group, individuals belonging to one family were counted once, as the chromosomal rearrangement itself occurred once in the gametes of the original carrier, and was then passed on to carrier

progeny as well as affected individuals. The frequency of non-redundant chromosome breaks at these sites are listed in Table 5.

Table 5 The frequency of non-redundant chromosome breaks at 3q21 and 3p25 in cases of dup(3q), del(3q), dup(3p), del(3p), and rec(3)

Etiologic Group (N)	Number of breaks at 3q21 (% of total)	Number of breaks at 3p25 (% of total)
dup(3q) (44)	16 (36.4)	0
del(3q) (17)	6 (35.2)	0
dup(3p) (51)	0	10 (19.6)
del(3p) (45)	0	30 (66.7)
rec(3) 3p25 (13)	0	5 (38.5)
rec(3) 3p25 and 3q21 (13)	7 (53.4)	7 (53.4)
TOTAL (183)	29/74 (39.2)	52/109 (47.7)

The results shown in the table indicate that 3q21, and especially 3p25 are common sites of chromosome breakage in chromosomal rearrangements such as translocations, direct duplications, direct deletions, and inversions. 3q25 was also frequent in the dup(3q) population used in the study (16 of 44 or 36.4%), however the majority of cases showed preferential breakage sites at 3p25 and 3q21.

3.1.2 Karyotype and mortality

3.1.2.1 Dup(3q)

Four of fourteen cases having a duplication of 3q21→qter (29%) were alive at the time of report, with most of the deaths having occurred in the neonatal period. When the duplication was distal to 3q21, the rate of survival increased. For example, where the duplication spanned 3q25→qter, 6 out of 8 (75%) cases were alive at the time of report, while 4 out of 7 (57%) dup(3q)

(q26→qter) cases and all cases of dup(3q)(q27→qter) were alive at the time of report. This indicates that duplication of 3q21 may increase the risk of a more severe phenotype and a higher mortality rate.

3.1.2.2 Del(3p)

Cases of del(3p) appear to have a higher survival rate than those of dup(3q), with 28 out of 32 (87.5%) alive in cases of del(3p)(p25→pter), and 8 out of 9 (88.9%) alive in cases of del(3p)(p26→pter). Cases with deletions proximal to 3p25 were low in number, but had slightly higher mortality. For example, in cases with del(3p)(p13→p21), 2 out of 4 (50%) were alive at the time of report.

3.1.2.3 Rec(3)

The duplication-deficient phenotype has a very high mortality rate in comparison to cases of dup(3q) or del(3p). This may be due to the effect of two chromosomal segments contributing to the karyotypic imbalance. The survival rate for cases involving dup(3q)(q21→qter) and del(3p)(p25→pter) was 7 out of 34 (21%) cases. Most of the deaths occurred in the neonatal period or the first year of life. Out of the 5 cases involving dup(3q)(q25→qter) and del(3p)(p25→pter), 2 (40%) were alive at the time of report, with the deaths occurring in childhood and adulthood.

3.1.2.4 Del(3q)

Fifteen out of 18 (83.3%) of del(3q) cases were alive at the time of report. The three deaths occurred in the first 2 ½ years of life and were limited to cases with distal deletions involving 3q27→qter and 3q28 (Alvarez Arratia et al. 1984; Sargent et al. 1985; Chitayat et al. 1996).

3.1.2.5 Dup(3p)

Mortality was very high for cases where the duplication included 3p21→pter, 3p22→pter, or 3p23→pter, with survival rates of 10 out of 21 (47.6%), 2 out of 3 (66.6%), and 8 out of 17 (47.1%), respectively. Where the duplication included 3p24→pter or 3p25→pter, the survival rates were 5 out of 5 (100%) and 8 out of 10 (80%) at the time of report, respectively. This indicates that duplication of bands proximal to 3p24 may have a more severe effect on the phenotype and survival.

3.2 Cluster Analysis 1—7 groups excluding rec(3)

The result of the cluster analysis revealed that the Ward's clustering method was the best method for viewing the cluster data. The optimal separating level would have a positive separating value for each variable, with a maximum cumulative separating power. The separating power was calculated as being greatest at 4 clusters, with all of the variables having a positive separating power, and a cumulative separating power of 12.93617. The results of the separation are listed in Table 6.

Table 6 The cumulative separating power at a cluster hierarchy of 2, 3, 4, and 5 clusters in the dendrogram of cluster analysis 1

Number of clusters	Cumulative separating power
2	8.62827
3	1.74961
4	12.93617
5	8.01871

The 10 highly ranked variables with respect to separating power in this analysis were: 'other genitourinary abnormalities', 'rocker-bottom feet', 'cervico-thoracic abnormalities', 'posteriorly-rotated ears', 'clinodactyly', 'small feet', 'delayed bone maturation', other musculo-skeletal abnormalities', 'full cheeks', and 'jaw characteristics', with separating power of .289, .271, .260, .243, .232, .232, .224, .223, .204, and .202 respectively. The dendrogram for cluster analysis 1 is shown in Figure 1.

Figure 1 **Dendrogram showing the 4 clusters generated by Ward's cluster analysis of seven etiologic groups: dup(3q), del(3p), del(3q), dup(3p), ring (3), trisomy 3, and de Lange cases. The clusters are numbered 1 to 4 from left to right.**

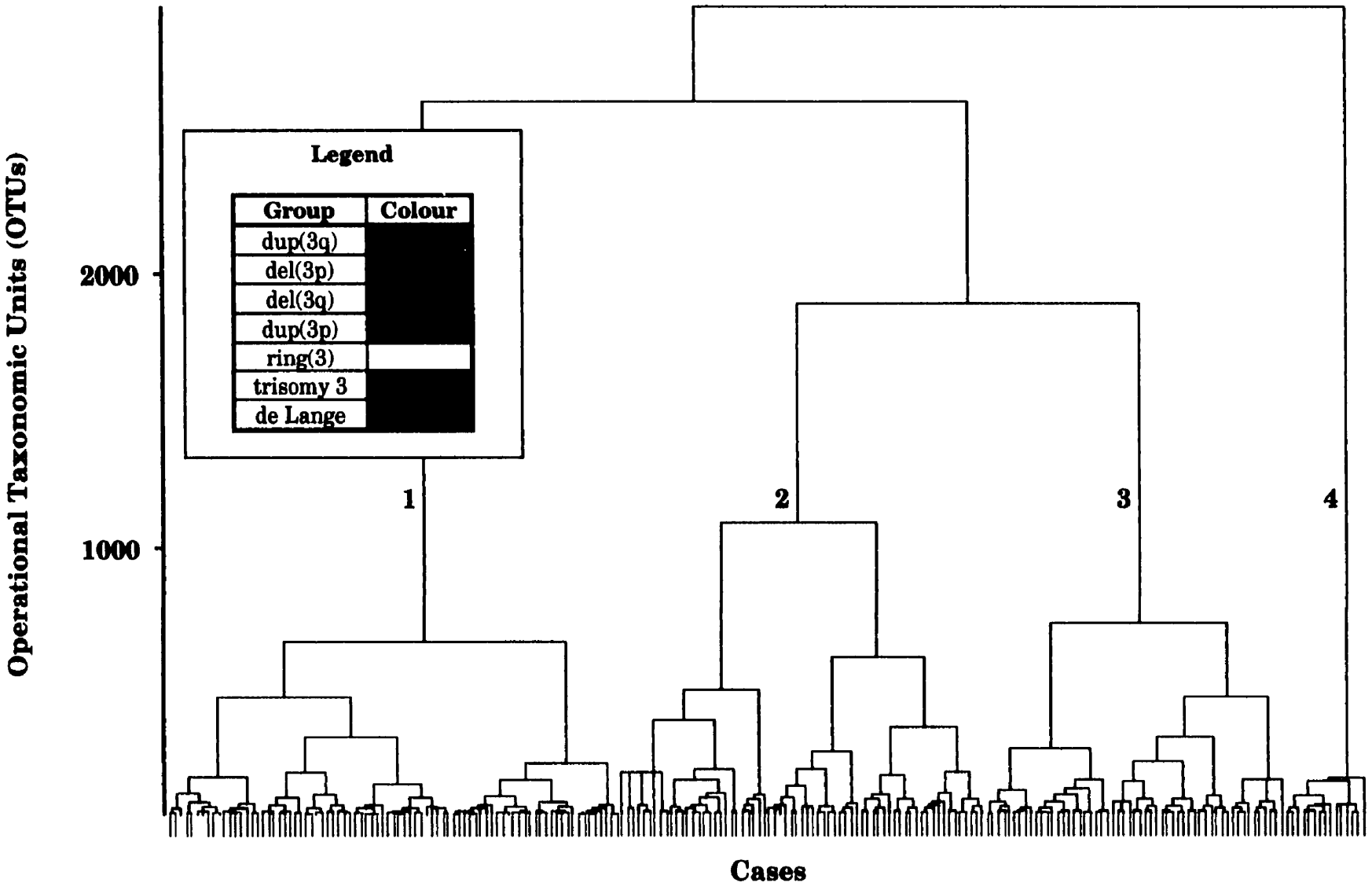

Table 7 List of clusters and case numbers for cluster analysis 1

CLUSTER 1	CLUSTER 2	CLUSTER 3	CLUSTER 4
1	2	37	156
118	5	38	157
96	30	108	158
64	27	186	159
238	36	171	160
100	121	192	161
101	102	195	162
107	69	194	163
71	122	193	164
113	6	94	165
60	10	199	166
181	95	201	167
182	52	234	168
230	84	191	169
104	239	232	170
240	93	204	
241	109	217	
11	57	231	
33	87	222	
119	110	223	
31	90	212	
32	91	213	
214	4	228	
22	14	117	
24	9	175	
34	13	226	
35	7	221	
97	3	197	
211	26	235	
86	243	200	
116	55	202	
124	46	227	
245	79	188	
248	89	189	
47	16	190	
120	115	209	
66	8	210	
67	247	215	
68	20	233	
219	21	58	
61	39	174	
65	40	187	
80	82	105	
237	76	216	
205	12	218	
62	56	15	
63	17	28	
99	85	29	
196	23	103	
112	18	172	
176	49	178	
207	81	229	
25	59	184	
242	92	224	
106	74	198	
180	48		
203	50		
111	249		
183	73		
114	70		
51	53		
244	206		
98	54		
88	83		
177	123		
208	126		
236	125		
72			
185			
220			
19			
173			
225			
179			
246			
41			
75			
77			
78			

The case numbers are listed in descending order as read from left to right on the dendrogram.

3.2.1 Description of clusters—Analysis 1

Table 8 illustrates the distribution of seven etiologic groups in the four clusters in the dendrogram created by Ward's cluster analysis:

Table 8 Distribution of etiologic groups in 4 clusters generated by Ward's cluster analysis 1

Etiologic Group	Cluster Number (% total)			
	1	2	3	4
dup(3q)	17 (34.7)	26 (53.1)	6 (12.2)	0
del(3p)	24 (42.1)	31 (54.4)	2 (3.5)	0
ring(3)	7 (87.5)	1 (12.5)	0	0
trisomy 3	2 (33.3)	2 (33.3)	2 (33.3)	0
del(3q)	11 (61.1)	6 (33.3)	1 (5.6)	0
de Lange	0	0	0	15 (100)
dup(3p)	22 (32.8)	1 (1.5)	44 (65.7)	0

3.2.2 Cluster 1

Cluster 1 is a very heterogeneous group consisting of members from all of the etiologic groups except those cases belonging to the de Lange group. The majority of del(3q) cases (61.1%) are in this cluster, and a large portion of dup(3q) and del(3p) cases (34.7% and 42.1% respectively). Seven out of 8 ring (3) cases are located in cluster 1, as well as one-third of all trisomy 3 cases (2 cases in each of clusters 1, 2, and 3).

3.2.2.1 Cluster 1: dup(3q) karyotypes

With the exception of three cases (Fryns et al. 1978; Oorthuys et al. 1981; Williamson et al. 1981), all of the dup(3q) cases in cluster 1 had trisomy of 3q25 or bands distal to 3q25.

3.2.2.2 Cluster 1: del(3p) karyotypes

With the exception of two cases with interstitial deletions on 3p (Kogame and Kudo 1979; Short et al. 1986), all of the del(3p) cases in cluster 1 had a deletion of 3p23→pter or 3p25→pter.

3.2.2.3 Cluster 1: del(3q) karyotypes

In cluster 1, four cases of del(3q) with deletion distal to 3q23 were present, along with four cases with 3q23 deleted, as well as three cases where the deletion was proximal to 3q23.

3.2.2.4 Cluster 1: dup(3p) karyotypes

Approximately one-third of all dup(3p) cases are located in cluster 1, with 9 out of 10 cases with holoprosencephaly or cyclopia being in this cluster. These cases include trisomy of 3p21→pter, 3p22.1→pter, and 3p23→pter. Aside from four cases where the extent of the 3p duplication was not known, all of the dup(3p) cases in this cluster have trisomy of 3p23, and represent a larger duplication than the majority of dup(3p) cases located in clusters 2 and 3.

3.2.3 Cluster 2

Cluster 2 is also a heterogeneous cluster, with a marked absence of dup(3p) cases in this group except for the case reported by Orye and Laureys (1984). There is a large population of dup(3q) and del(3p) cases in this cluster, comprising 53.1% and 54.4% of the total etiologic group, respectively.

3.2.3.1 Cluster 2: dup(3q) karyotypes

Apart from one case (Fryns et al. 1978), all of the dup(3q21→qter) cases are located in cluster 2. A large number of dup(3q) cases involving 3q25 or 3q26 are located in cluster 2, indicating the possibility that there may be a distinct phenotypic subset of these cases, which differs from the group of cases in cluster 1.

3.2.3.2 Cluster 2: del(3p) karyotypes

There is a very large number of del(3p) cases with monosomy of 3p25→pter or 3p25.3 in cluster 2, indicating that there may be a distinct phenotypic subset of del(3p) cases that include the deletion of 3p25, apart from del(3p) cases in cluster 1. The majority of interstitial 3p deletions and proximal deletions (proximal to 3p25) also cluster in this group.

3.2.3.3 Cluster 2: del(3q) karyotypes

Aside from one case where the deletion spanned 3q27→qter (Chitayat et al. 1996), five out of six del(3q) cases in cluster 2 included the deletion of 3q23.

3.2.3.4 Cluster 2: dup(3p) karyotypes

One case of dup(3p) is located in cluster 2 and involves a duplication of 3p21→p22 (Orye and Laureys 1984). This case is unique in the dup(3p) group in the sense that the duplication does not include bands that are duplicated

in all other proximal duplications (3p14) or more distal deletions (3p23). This may explain why this particular case is classified by itself in cluster 2.

3.2.4 Cluster 3

Aside from a large dup(3p) population (65.7% of all dup(3p) cases), cluster 3 is relatively underrepresented by the other etiologic groups, with only 12.2% of dup(3q) cases and 3.5% of del(3p) cases being present in this cluster.

3.2.4.1 Cluster 3: dup(3q) karyotypes

Only six cases of dup(3q) are located in cluster 3. The karyotypes found in this cluster include trisomy of 3q26.2→qter, 3q25→qter, 3q21→q26, and 3q21→qter.

3.2.4.2 Cluster 3: del(3p) karyotypes

Only two cases of del(3p) are located in cluster 3, both being proximal interstitial deletions of 3p11→p14.1 (Crispino et al. 1995), and 3p12→p14.2 (Neri et al. 1984). This may indicate that certain proximal 3p deletions exhibit a clinical phenotype distinct from that due to deletions of 3p25.

3.2.4.3 Cluster 3: del(3q) karyotypes

One case of del(3q) is located in cluster 3, with a deletion of 3q28 (Alvarez Arratia et al. 1984).

3.2.4.4 Cluster 3: dup(3p) karyotypes

Cluster 3, containing approximately two-thirds of all dup(3p) cases, has widely varying dup(3p) karyotypes, including duplication of 3p21, 3p22, 3p23, 3p24, 3p25, with most duplications spanning to 3pter.

3.2.5 Cluster 4

Cluster 4 is exclusively comprised of the 15 cases of de Lange syndrome. This may be because the de Lange cases were described in a similar manner, or that the phenotype of the individuals is a distinct entity from the six other etiologic groups used in this analysis.

3.2.6 The clustering of siblings/relatives

The following table (Table 9) indicates the frequency of groups of siblings/relatives in each etiologic group and the frequency of familial clustering in cluster 1.

Table 9 The number of related groups and the frequency of similar clustering of related groups in cluster analysis 1

Etiologic Group	Number of related groups	Number of related groups similarly clustered (%)
dup(3q)	5	5 (100)
del(3p)	3	1 (33.3)
del(3q)	0	0
dup(3p)	10	9 (90)

With the exception of four groups of related dup(3p) individuals, all of the related cases were clustered side by side in the same cluster. This may indicate either familial similarity in the phenotype, or a bias in the ascertainment of phenotypic information for the related individuals.

3.3 Cluster Analysis 2—dup(3q), del(3p)

3.3.1 Description of clusters—Analysis 2

The following table (Table 10) illustrates the distribution of dup(3q) and del(3p) cases in four clusters in the dendrogram created by Ward's cluster analysis:

Table 10 Distribution of dup(3q) and del(3p) cases in 4 clusters generated by Ward's cluster method

Etiologic Group	Cluster Number (% total)			
	1	2	3	4
dup(3q)	29 (59.2)	0	6 (12.2)	14 (28.6)
del(3p)	9 (15.8)	18 (31.6)	2 (3.5)	28 (49.1)

Figure 2 **Dendrogram showing the 4 clusters generated by Ward's cluster analysis of dup(3q) and del(3p) cases. The clusters are numbered 1 to 4 from left to right.**

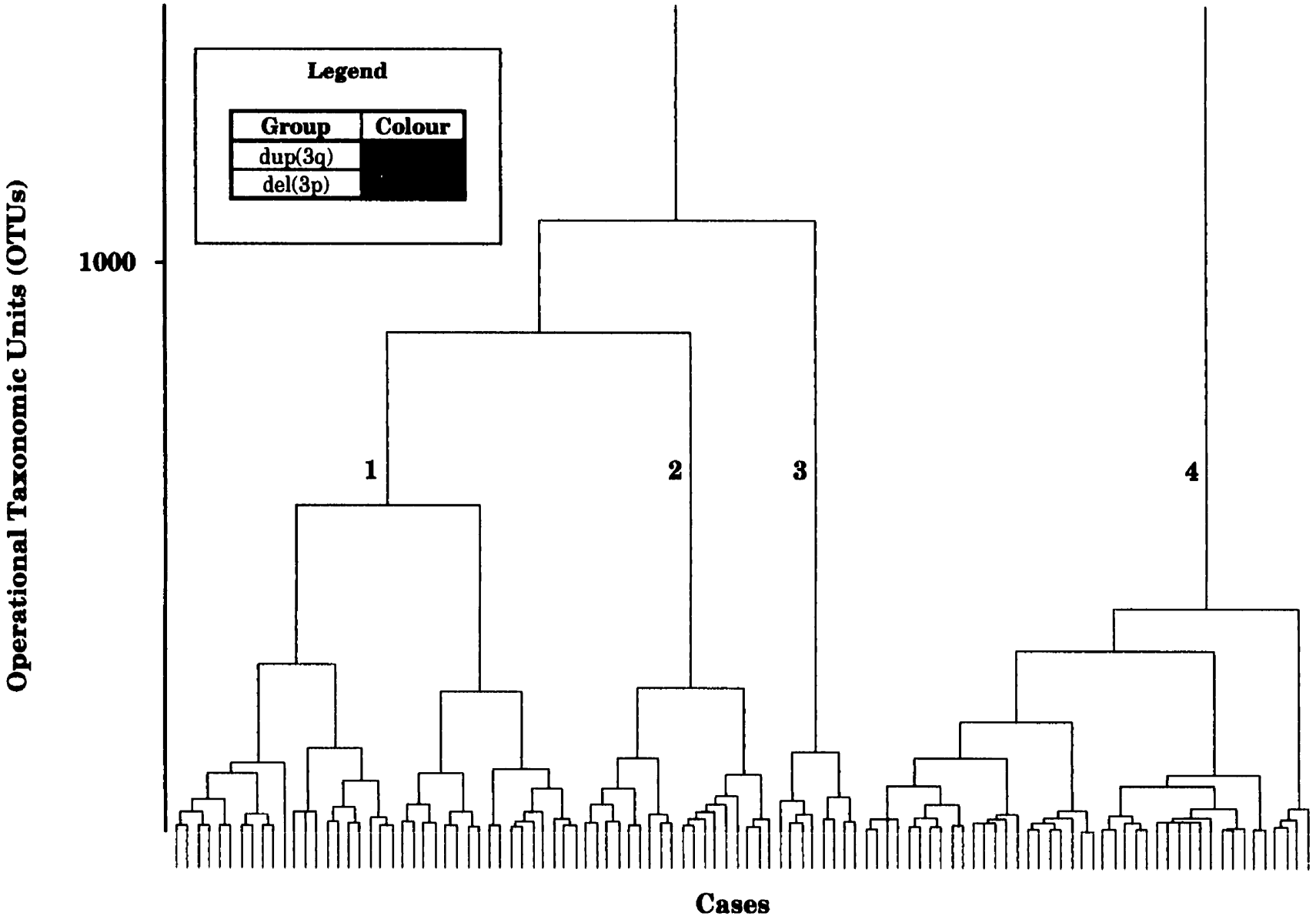

Table 11 List of clusters and case numbers for cluster analysis 2

CLUSTER 1	CLUSTER 2	CLUSTER 3	CLUSTER 4
1	46	7	25
86	79	4	242
17	49	14	241
23	81	9	240
22	54	13	52
104	83	102	64
3	69	90	60
26	58	91	71
11	89		84
24	48		239
18	50		31
5	85		32
27	249		63
36	73		33
6	70		94
30	59		41
53	92		44
55	74		42
15			43
28			75
29			77
2			78
16			34
12			35
56			47
8			51
247			244
20			45
21			62
10			61
95			65
19			80
88			236
246			66
103			67
57			68
87			37
93			38
			39
			40
			82
			76

The case numbers are listed in descending order as read from left to right on the dendrogram.

3.3.2 Cluster 1

Cluster 1 was comprised mostly of dup(3q) cases (29 of 38 or 76.3%), and the majority of all dup(3q) cases (29 of 49 or 59.2%), clustered here.

3.3.2.1 Cluster 1 karyotypes

For the dup(3q) cases in this cluster, 26 of 29 (89.7%) had another chromosome affected other than chromosome 3, thus indicating that the phenotype in this cluster may well be affected by a chromosome other than chromosome 3. With respect to del(3p) cases, 8 of 9 (88.9%) did not have

another chromosome affected, and 5 of 9 (55.6%) had proximal deletions not distal to 3p21 (Sichong et al. 1981; Mitter et al. 1984; Short et al. 1986; Hertz et al. 1988; Karimi-Nejad et al. 1990).

3.3.3 Cluster 2

Cluster 2 was a very homogeneous cluster, comprising solely of del(3p) cases.

3.3.3.1 Cluster 2 karyotypes

Of the 18 cases belonging to cluster 2, only 2 of 18 (11.1%) had a deletion proximal to 3p25 (Wyandt et al. 1980; Neri et al. 1984). Likewise, only 2 of 18 (11.1%) of cases in this cluster had a chromosomal segment affected other than the deletion of chromosome 3p (Schroer and Phelan 1988; Chen et al. 1996c).

3.3.4 Cluster 3

Cluster 3 contained the least cases (8 in total), with 6 of 8 (75%) being dup(3q) cases.

3.3.4.1 Cluster 3 karyotypes

Of the 6 dup(3q) cases, 4 (66.7%) had another chromosome affected, and 5 of 6 (83.3%) had a duplication spanning 3q21→qter or 3q27/29. The two del(3p) cases had proximal deletions of 3p12→3p21.2 (Wieczorek et al. 1997) and 3p12→3p14.2 (Naritomi et al. 1988).

3.3.5 Cluster 4

The largest cluster in the analysis, cluster 4 contains 42 cases, 28 of 42 (66.7%) being del(3p) cases.

3.3.5.1 Cluster 4 karyotypes

Of the 14 dup(3q) cases in this cluster, all (100%) have duplications distal to 3q21, with 13 of 14 (92.9%) having duplications from 3q25 or more distal. 8 of 14 (57.1%) of dup(3q) cases have another chromosome affected. Comprising two-thirds of the cluster, 10 of 28 (35.7%) del(3p) cases have another chromosome affected. 27 (96.4%) del(3p) cases in this cluster also have a deletion from 3p25 or more distal.

3.4 Cluster Analysis 3—dup(3q), del(3p), rec(3)

3.4.1 Description of clusters—Analysis 3

The following table (Table 12) illustrates the distribution of dup(3q), del(3p), and rec(3) cases in five clusters in the dendrogram created by Ward's cluster analysis.

Table 12 Distribution of dup(3q), del(3p), and rec(3) cases in 5 clusters generated by Ward's cluster method

Etiologic Group	Cluster Number (% total)				
	1	2	3	4	5
dup(3q)	13 (26.5)	3 (6.1)	16 (32.7)	12 (24.5)	5 (10.2)
del(3p)	14 (24.6)	28 (49.1)	8 (14.0)	2 (3.5)	5 (8.8)
Nfld.	13 (48.1)	1 (3.7)	1 (3.7)	2 (7.4)	10 (37.0)
rec(3),inv(3) (p25q21)	2 (28.6)	1 (14.3)	1 (14.3)	1 (14.3)	2 (28.6)
other rec(3)	3 (33.3)	2 (22.2)	2 (22.2)	2 (22.2)	0

Figure 3 **Dendrogram showing the 5 clusters generated by Ward's cluster analysis of dup(3q), del(3p), and rec(3) cases. The clusters are numbered 1 to 5 from left to right.**

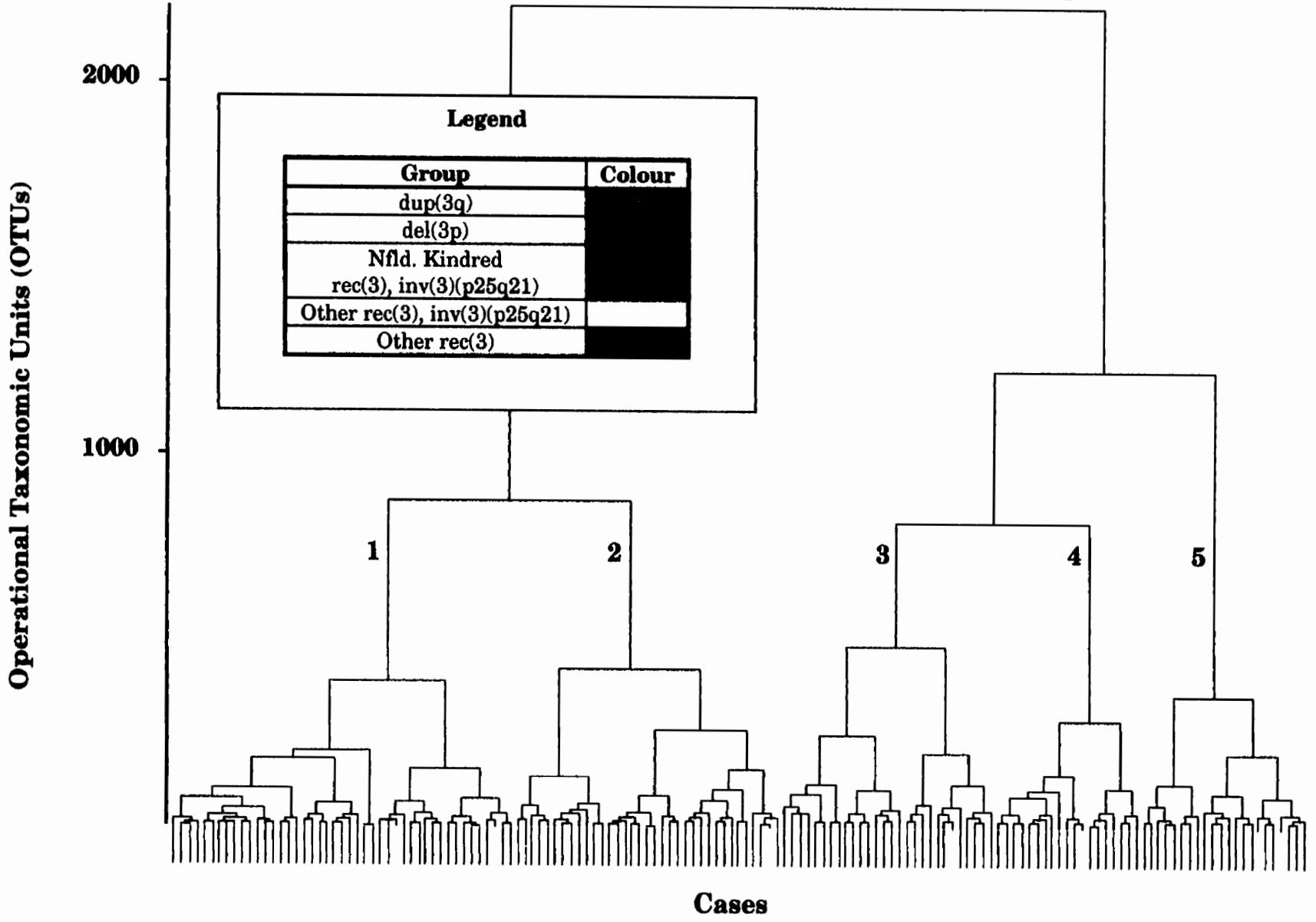

Table 13 List of clusters and case numbers for cluster analysis 3

CLUSTER 1	CLUSTER 2	CLUSTER 3	CLUSTER 4	CLUSTER 5
1	12	2	3	5
66	56	69	26	27
67	81	16	17	57
68	84	89	23	87
25	239	58	22	93
242	52	142	24	90
62	60	10	104	91
61	71	95	148	102
65	255	8	18	36
80	79	247	30	130
252	240	20	246	261
236	241	21	251	259
51	41	46	39	133
244	44	53	40	134
34	45	55	82	155
35	42	70	76	150
144	43	4	129	6
11	77	14	131	257
47	78	13	147	154
31	73	7		253
32	86	9		260
33	143	146		256
63	48	151		
64	50	127		
94	85	15		
37	249	28		
38	59	29		
88	92	103		
128	74			
152	54			
263	83			
19	49			
137	75			
138	145			
254	149			
258				
132				
135				
136				
139				
140				
141				
153				
250				
262				

The case numbers are listed in descending order as read from left to right on the dendrogram.

3.4.2 Cluster 1

Cluster 1 contained a large representation of dup(3q) cases as well as del(3p) cases. Cluster 1 also contained 18 of 43 (41.9%) rec(3) cases, in particular, 13 of 27 (48.1%) cases belonging to the Newfoundland kindred.

3.4.2.1 Cluster 1 karyotypes

Of the dup(3q) cases in this cluster, 11 of 13 cases (84.6%) had duplications of 3q25→3qter, or bands more distal. Also, 11 of 13 cases (84.6%) had a chromosomal imbalance in another chromosome. Of the del(3p) cases in

this cluster, with the exception of 3 cases, the deletion spanned 3p23→pter or 3p25→pter. 8 of 14 (57.1%) del(3p) cases also had another chromosome affected. Almost half (48.1%) of the rec(3) cases belonging to the inv(3) Newfoundland kindred were in cluster 1, thus the majority of rec(3) cases in this cluster had a deletion of 3p25→pter and a duplication of 3q21→qter. Three cases had a rec(3) karyotype with break points different than those of the Newfoundland kindred (Lurie et al. 1974; Fineman et al. 1978; Pope et al. 1979).

3.4.3 Cluster 2

Almost half (49.1%) of all del(3p) cases clustered in cluster 2, thereby forming the majority of cases in this cluster. There was representation of dup(3q) cases as well as rec(3) cases in this cluster as well.

3.4.3.1 Cluster 2 karyotypes

The chromosomal region deleted in the del(3p) cases was almost uniform for all of the cases in cluster 2, ranging from 3p25→3pter or 3p26→3pter. 4 of the 28 del(3p) cases (14.3%) had another chromosome affected. The 3 dup(3q) cases in this cluster involved a duplication of 3q25→3q26 (Rizzu et al. 1997), and 3q26→3qter (Steinbach et al. 1981), of which only the latter involved another affected chromosome. Of the rec(3) cases in this cluster, one belonged to the Newfoundland kindred, one case shared the same breakpoints, and two cases had different karyotypes.

3.4.4 Cluster 3

This cluster predominantly contains dup(3q) and del(3p) cases, with almost two-thirds of all dup(3q) cases located in cluster 3.

3.4.4.1 Cluster 3 karyotypes

10 of 16 (62.5%) dup(3q) cases in this cluster involve a duplication of 3q21→3qter, and 11 of 16 (68.8%) have duplications ranging from bands more proximal than 3q25. Only 2 dup(3q) cases did not have another chromosome affected (Stengel-Rutkowski et al. 1979; Gustashaw et al. 1985). Of the del(3p) cases, 3 were cases involving an interstitial deletion while the others were deletion of 3p25→3pter, with one case having another chromosome affected (Yunis et al. 1977). Of the rec(3) cases, all had deletions of 3p25→pter, while the duplications included 3q21→3qter, 3q23→3qter and 3q24→3qter.

3.4.5 Cluster 4

Similarly to cluster 3, this cluster contains mainly dup(3q) cases, but with representation from all of the etiologic groups.

3.4.5.1 Cluster 4 karyotypes

The karyotypes of dup(3q) cases in this cluster do not show any similarity, as there is a variation in the size of the duplicated 3q segment, although one-third of the dup(3q) cases do not have another chromosome

affected. The two del(3p) cases have a deletion of 3p25→3pter. The breakpoints for the rec(3) cases are 3p25, and 3q25 or 3q21.

3.4.6 Cluster 5

This cluster contains 10 of 27 (37.0%) of rec(3) cases belonging to the Newfoundland kindred, as well as representation from other etiologic groups.

3.4.6.1 Cluster 5 karyotypes

Apart from one case, all of the dup(3q) cases had duplications from 3q21 or more proximal, and all of the cases had another chromosome affected. All of the del(3p) cases in this cluster were cases with an interstitial deletion ranging from 3p11, 3p12 or 3p13→3p14.2, 3p21 or 3p21.2, with no other chromosome affected. In addition, all but one of the rec(3) cases in this cluster belonged to the Newfoundland kindred.

3.5 Cluster Analysis 4—Rec(3)

3.5.1 Description of clusters—Analysis 4

The following table (Table 14) illustrates the distribution of rec(3) cases in two clusters in the dendrogram created by Ward's cluster analysis.

Table 14 Distribution of rec(3) cases in 2 clusters generated by Ward's cluster analysis

Etiologic Group	Cluster Number (% total)	
	1	2
Nfld.	15 (55.6)	12 (44.4)
rec(3),inv(3) (p25q21)	3 (42.9)	4 (57.1)
other rec(3)	8 (88.9)	1 (11.1)

Figure 4 **Dendrogram showing the 2 clusters generated by Ward's cluster analysis of rec(3) cases. The clusters are numbered 1 and 2 from left to right.**

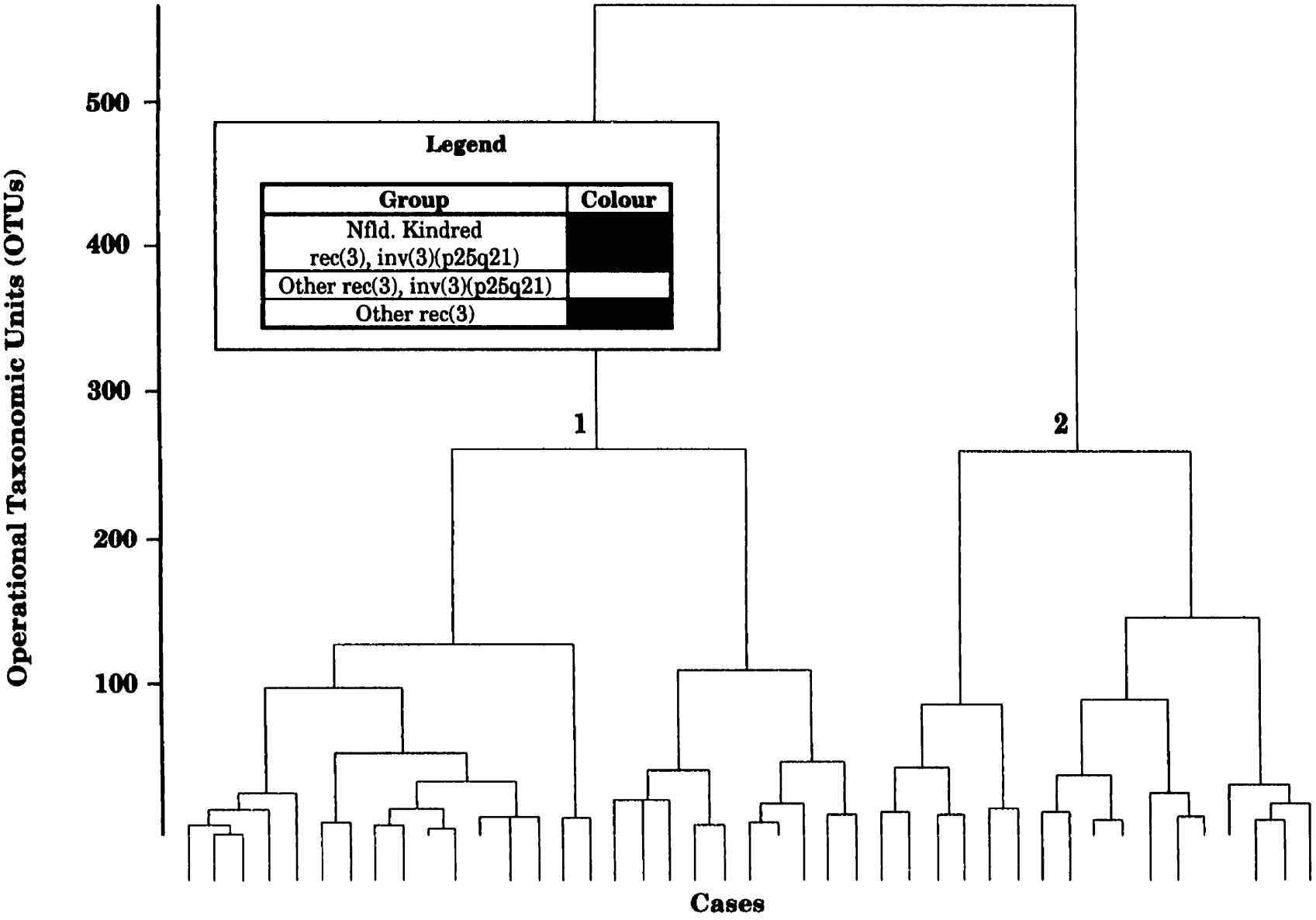

Table 15 List of clusters and case numbers for cluster analysis 4

CLUSTER 1	CLUSTER 2
127	133
130	146
131	259
136	261
148	138
128	140
129	139
143	141
147	153
151	251
252	142
254	137
258	154
135	145
263	253
132	260
144	256
134	
250	
262	
149	
150	
155	
255	
257	

The case numbers are listed in descending order as read from left to right on the dendrogram.

The dendrogram generated by the cluster analysis indicates a true split between the rec(3) cases, where the cases belonging to the Newfoundland kindred are split almost evenly across the two clusters. For the cases where the chromosomal rearrangement breakpoints differ from these of the Newfoundland kindred, all but one case (Mulcahy et al. 1979) are clustered in cluster 1.

3.6 Discriminant function analysis—Cluster analysis 2

3.6.1 Identification of top discriminating variables

The top 10 phenotypic variables identified by discriminant function analysis of the dup(3q) and del(3p) cluster analysis data set are listed in Table 16.

Table 16 The top 10 discriminating phenotypic variables identified from the dup(3q) and del(3p) cluster analysis

Rank	Variable name
1	hypoplastic nails
2	eyebrows
3	ptosis
4	other cardiovascular anomalies ♣
5	other foot anomalies ♦
6	camptodactyly—hands
7	short palpebral fissures
8	neck characteristics
9	micrognathia
10	cervico-thoracic vertebral anomalies

♣ includes anomalies not individually listed in coding sheet (see appendix 2)
♦ includes anomalies not individually listed in coding sheet (see appendix 2)

3.6.2 Identifying differences between clusters

Using the 10 variables identified by the discriminant function analysis, the clusters were identified qualitatively according to the variables. The following table (Table 17) illustrates the differences between the clusters based on the phenotypic variables.

Table 17 Qualitative descriptions of the four clusters based on the top 10 discriminating variables identified in the dup(3q) and del(3p) cluster analysis

Variables	1	2	3	4
Hypoplastic nails	No	No	Bilateral	No
Eyebrows	Thick	Normal	Normal	Normal
Ptosis	No	Yes	No	1/3 Yes
Other cardiovascular anomalies	1/3 Yes	No	All	No
Other foot anomalies	No	No	Yes	No
Camptodactyly hands	No	No	Yes	None
Short palpebral fissures	No	1/4 Yes	No	None
Neck characteristics	Short	Short	Short and webbed	Short
Jaw characteristics	1/3 Micrognathia	Normal	All normal	Micrognathia
Cervico-thoracic vertebral anomalies	No	No	None	No

3.6.3 Cluster 1—Qualitative description

According to the information generated by the qualitative description of the clusters, it seems apparent that cases in cluster 1 are defined by thick eyebrows, some cardiovascular anomalies, a short neck, and, in some cases, with micrognathia. Features absent in the group are hypoplastic nails, ptosis, foot anomalies, camptodactyly of hands, short palpebral fissures, and cervico-thoracic vertebral anomalies. As mentioned previously, cluster 1 contains mainly dup(3q) cases. It is known that thick, bushy eyebrows are associated with the dup(3q) phenotype, thus it is not surprising to see this variable as an important discriminating feature for most of the dup(3q) cases. It is also known that cardiovascular anomalies are sometimes associated with dup(3q), thus there is some incidence of cardiovascular anomalies in cluster 1.

3.6.4 Cluster 2—Qualitative description

While thick bushy eyebrows are absent in cases in cluster 2, ptosis is present in all of the cases in this cluster. Also, one-fourth of the cases in this cluster have short palpebral fissures. The other phenotypic variables are absent in this group. This cluster was identified as consisting exclusively of del(3p) cases, therefore it is expected to identify ptosis and short palpebral fissures associated with this group. Also, this group was identified as cases who did not have any other chromosomes affected, thus the phenotype is not being affected by the duplication of another chromosomal segment.

3.6.5 Cluster 3—Qualitative description

This cluster is primarily identified by all of the cases having bilateral hypoplastic nails, all having cardiovascular anomalies, and none having micrognathia. This cluster contains mainly dup(3q) cases with duplication of 3q21 or bands more proximal, and almost all of them have an additional chromosomal imbalance. Some of the anomalies listed under the 'other cardiovascular anomalies' variables in these cases were: a closed ductus Botalli, valvular and infundibular stenosis, a 'riding' aorta with supravalvular dilatation (Stengel-Rutkowski et al. 1979), a single right ventricle and atrio-ventricular valve, a small pulmonary artery (Gustashaw et al. 1985), coarctation of the aorta (Sod et al. 1978), a bicuspid pulmonary valve (Steinbach et al. 1981), double renal arteries, pulmonary artery hypertension (Wilson et al. 1985), right axis deviation, enlargement of right atrium (Naritomi et al. 1988), stenosis and sclerosis of the intrapulmonary pulmonary arteries (Wieczorek et al. 1997). The anomalies listed under the 'other foot anomalies' variable were: long toes, bilateral aplasia of all middle phalanges (Stengel-Rutkowski et al. 1979), bilateral terminal prominence of distal phalanges II to IV, bilateral distal phalanx of toes II to IV (Steinbach et al. 1981), overlapping of 3rd and 4th toes (Sod et al. 1978), accessory flexion creases in antecubital fossae, distal femoral epiphyses (Steinbach et al. 1981), and a 'sandal' gap between the 1st and 2nd toes (Naritomi et al. 1988; Wieczorek et al. 1997).

3.6.6 Cluster 4—Qualitative description

Cluster 4 differs from cluster 2 by cases not having any short palpebral fissures, and most cases having micrognathia. Cluster 4 is the cluster containing most of the other del(3p) cases, therefore similarities would be expected. However, there are differences in phenotype as well as karyotype. Most of the del(3p) cases having another chromosomal imbalance are in cluster 4, and of the dup(3q) cases, most of the cases not having another chromosome affected are also in this cluster and represent distal 3q duplications.

3.7 Predicted clustering of rec(3) cases in cluster analysis 2

Based solely on the top 10 discriminating phenotypic variables, the rec(3) cases were classified using the discriminant function algorithms derived from cluster analysis 2, the cluster analysis containing only dup(3q) and del(3p) cases. The classification was simulated to determine in what clusters the rec(3) cases would be classified according to the top 10 phenotypic variables in relation to dup(3q) and del(3p) cases. The following table (Table 18) illustrates the result of the simulated re-classification of rec(3) cases.

Table 18 Predicted clustering for rec(3) cases in cluster analysis 2

Rec(3) Cases	1	2	3	4	Total
ALL	18	0	2	23	43
Nfld. kindred	12	0	0	15	27
Other p25q21	2	0	0	5	7
Other rec(3)	4	0	2	3	9

Based on the simulated re-classification, the rec(3) cases clustered almost exclusively to cluster 1 and 4. Cluster 1 is predominantly represented by dup(3q) cases. Conversely, cluster 4 is predominantly represented by del(3p) cases. Also, the majority of dup(3q) and del(3p) cases in clusters 1 and 4 respectively have another chromosome affected. Thus it appears that the rec(3) phenotype shares components of both dup(3q) and del(3p) phenotypes when the phenotypes are affected by another chromosomal aberration.

3.8 Identifying differences between clusters for the simulated re-classification of rec(3) cases

The qualitative descriptors identifying the differences between the clusters where rec(3) cases clustered are shown in Table 19.

Table 19 Qualitative descriptions of groups where rec(3) cases were predicted to cluster in cluster analysis 2.

Variables	Group 1	Group 3	Group 4
Hypoplastic nails	None	All bilateral	No
Eyebrows	Normal	Normal	Normal
Ptosis	None	1/2 No, 1/2 Yes	No
Other cardiovascular anomalies	Yes	None	No
Other foot anomalies.	2/3 bilateral	All bilateral	None
Camptodactyly	No	None	None
Short palpebral fissures	None	None	None
Neck characteristics	1/2 short, 1/2 short and webbed	1/2 normal, 1/2 short	normal
Micrognathia	1/2 Yes, 1/2 No	1/2 Yes, 1/2 No	1/2 Yes, 1/2 No
Cervico-thoracic vertebral anomalies	No	None	No

Rec(3) cases appeared to cluster to cluster 1, 3 and 4, where cluster 2, the homogeneous del(3p) cluster, was completely absent of rec(3) representation. In comparison to the previous qualitative description of

dup(3q) and del(3p) cases, differences as well as similarities between those cases and rec(3) cases are noted.

3.8.1 Cluster 1—Qualitative description

The obvious differences between the rec(3) profile in cluster 1 and that of dup(3q) and del(3p) cases in the cluster is the absence of thick, bushy eyebrows, a majority of cases having other cardiovascular anomalies, two-thirds having other foot anomalies, and some cases having a short neck with redundant skin. The absence of bushy eyebrows indicates that this dup(3q)-associated phenotypic trait is not present in the majority of rec(3) cases. However, the presence of cardiovascular anomalies and redundant skin are dup(3q)-like traits.

3.8.2 Cluster 3—Qualitative description

The key differences between the cases in the original analysis and rec(3) cases is the presence of ptosis in half of the rec(3) cases in this cluster, combined with the absence of cardiovascular anomalies and camptodactyly of the hands. The similar variable is the presence of other foot anomalies. The presence of ptosis in the rec(3) cases appears to be a del(3p)-like phenotypic trait, as well as the absence of camptodactyly of the hands. The foot anomalies listed under 'other foot anomalies' were: small feet with a dorsiflexed 1st toe (Preus et al. 1986), and short feet (Fineman et al. 1978).

3.8.3 Cluster 4—Qualitative description

While cluster 4 originally included cases who did not have any of the top 10 phenotypic anomalies present except for most cases having a short neck and micrognathia, half of the rec(3) cases in the cluster have micrognathia and none of the other traits present. Cluster 4 appears to be a 'no' cluster with respect to the presence of many traits and thus most of the rec(3) cases with no sign of the top 10 phenotypic variables were clustered in cluster 4.

3.9 Comparative analysis of dup(3q), del(3p), and rec(3)

The following two tables (Table 20 and 21) illustrate the frequency of the top 10 phenotypic discriminators for cases of dup(3)(q21→qter), del(3)(p25→pter), and rec(3) respectively. The frequency of a given phenotypic trait for dup(3q) and del(3p) cases indicates whether 3q or 3p is the chromosomal segment that most influences a particular phenotype, and thus contains the gene or genes that potentially play a role in the phenotype observed.

Table 20 The frequency of the top 10 phenotypic discriminators in the dup(3)(q21→qter) and del(3)(p25→pter) cases and the chromosomal segment contributing to the phenotype

Variables	Dup(3q) N=16 (%)	Del(3p) N=37 (%)	Contributing chromosomal segment
Hypoplastic nails	6 (38.0)	0	3q
Eyebrows	4 (25.0) thick, 1 (6.3) thin	4 (10.8) thick	3q
Ptosis	0	23 (62.1)	3p
Other cardiovascular anomalies	7 (44)	7 (18.9)	3q
Other foot anomalies	5 (31.3)	4 (10.8)	3q
Camptodactyly of hands	5 (31.3)	1(2.7)	3q
Short palpebral fissures	1 (6.3)	5 (13.5)	3p
Neck characteristics	2 (12.5) short, 10 (63.0) short & webbed	5 (13.5) short, 1 (2.7) short & webbed	3q
Micrognathia	10 (63.0)	20 (54.1)	3p/3q
Cervico-thoracic vertebral anomalies	0	2 (5.4)	3p

Table 21 The frequency of the top 10 phenotypic discriminators in the rec(3) cases and the chromosomal segment most influential to the phenotype

Variables	Rec(3), inv(3)(p25q21) N=34 (%)	Rec(3), inv(3)(p25q23), (p25q25), & (p26q22) N=9, (%)	Contributing chromosomal segment	Rec(3) shares features with
Hypoplastic nails	1 (2.9)	2 (22.2)	3q	dup(3q)
Eyebrows	3 (8.8) thick, 1 (2.9) thin	2 (22.2)	3q	dup(3q)
Ptosis	0	2 (22.2)	3p	del(3p)
Other cardiovascular. anomalies	13 (38.2)	3 (33.3)	3q	dup(3q)
Other foot anomalies	5 (14.7)	4 (44.4)	3q	dup(3q)
Camptodactyly of hands	3 (8.8)	1 (11.1)	3q	dup(3q)
Short palpebral fissures	0	0	3p	dup(3q)
Neck characteristics	5 (14.7) short, 5 (14.7) short & webbed	2 (22.2) short, 1 (11.1) short & webbed	3q	dup(3q)
Micrognathia	16 (47.0)	4 (44.4)	3p/3q	del(3p)/dup(3q)
Cervico-thoracic vertebral anomalies	3 (8.8)	3 (33.3)	3p	del(3p)

It appears that rec(3) cases share phenotypic features of both dup(3q) as well as del(3p). Based on the assumption that 3q or 3p contributes to a given phenotype, rec(3) cases have both p-like and q-like phenotypic features, with those being derived from 3q comprising 7 to 8 of the 10 traits. The one trait that differs between individuals where the inversion spans 3p25→3q21 and those individuals where the inversions may span 3p25→q23, 3p25→3q25, and 3p26→3q22 is the higher frequency of ptosis in individuals with an inversion other than that of the Newfoundland kindred. Indeed, the two individuals (siblings) who have ptosis also have a recombinant chromosome 3 due to an inv(3)(p25q25) (Fineman et al. 1978). While this phenotypic trait is not found in other cases of rec(3), the trait itself is influenced by 3p and its presence in the rec(3) phenotype is a result of del(3p).

4.0 DISCUSSION

4.1 Case ascertainment

4.1.1 Validating the methodology

As mentioned as part of the limitations of numerical taxonomy analysis, the analysis requires as little incomplete and subjective data as possible to attain maximum objectivity. However, bias cannot be avoided as cases are derived from case reports that may or may not have been complete in their description of the patient. To avoid introducing bias from the beginning of the analysis, phenotypic information would have to be entered in a detailed sheet listing many phenotypic abnormalities by means of checking off relevant information from the first time the individuals were examined, including any changes in phenotype during growth, changes in medical conditions, and finally including information derived from autopsy. The cases used in the four analyses in this study were included based solely on the karyotype, and not the phenotypic information contained. Thus, the basis on which the cases were collected was as uniform as possible, and was not biased due to the amount of phenotypic information present in the report. The de Lange cases were collected from one research paper (Filippi 1989), but the cases themselves were derived from separate sources and were then tabulated according to the same phenotypic criteria, thereby reducing bias of ascertainment. Some of the cases thought to initially be 2;3 translocations

(Lee et al. 1964; Summitt 1966; Boon 1967) were indeed clarified as being cases of rec(3), inv(3)(p25q21) (Allderdice et al. 1975). The data set of 263 cases is a large set for cluster analysis, however, the number of phenotypic variables employed (112) enabled the taxonomy software to have a large matrix of information upon which to formulate the hierarchical tree.

4.2 Descriptive statistics

4.2.1 3q21 and 3p25 are preferential sites of breakage in chromosomal rearrangements involving chromosome 3

Comprising 39.2% and 47.7% of all 3q and 3p non-redundant chromosomal breaks respectively, 3q21 and 3p25 appear to be preferred sites of breakage during chromosomal rearrangements. When stained with Giemsa, 3q21 and 3p25 are both observed as G-light bands. It is known that G-light bands are usually preferred sites of breakage; however, the frequency of breakage at 3q21 and 3p25 in particular may indicate a biological preference for these two chromosomal regions for breakage during chromosomal rearrangements. These bands appear to be frequent sites of breakage and reunion in inversions and translocations involving chromosome 3.

4.3 Cluster Analysis

4.3.1 The effect of two chromosomal aberrations on phenotypes

Descriptive statistics indicated that there are trends associated with particular phenotypes with respect to the presence of another chromosomal imbalance due to a balanced translocation or a duplication-deficient chromosome due to an inversion. Such a 'double aberration' was known to potentially affect the phenotype of an individual. However, cluster analysis revealed that such cases can be and are clustered separately from those that have only one chromosomal aberration. The most striking example is in cluster analysis 2, where the majority of del(3p) with an additional chromosome imbalance were located in a cluster separate from cases where the deletion of 3p was the sole chromosomal imbalance. For example, two siblings with der(5)t(3;5)(q27;p15.1)pat, had trisomy of 3q27→qter, as well as monosomy of 5p15.1→pter. These two cases were diagnosed with Cri-du-chat syndrome, and exhibited a phenotype reflective of that diagnosis (Aqua et al. 1995). It appears that the deletion of the 5p segment had a greater effect on the phenotype than the duplication of 3q. Similarly, other cases with translocations resulting in imbalances in chromosomes other than chromosome 3 may be clustering separately from 'pure' deletions or duplications due to the effect of the other chromosome. By using cluster analysis to classify cases on the basis of phenotype alone, phenotypic 'signals'

may be identified and traced back to the chromosomal segment most influential in the expression of a phenotypic trait.

4.3.2 Siblings and relatives similarly cluster

The high frequency of siblings and relatives clustering together may be due to two influencing factors. Firstly, family members cluster together due to a shared phenotype caused by the same chromosomal abnormality as well as many shared genes. Secondly, familial clustering occurs due to bias in ascertainment, whereby siblings or relatives are ascertained along the same limited criteria and are compared mainly to one another and not other cases of the syndrome. While it is not surprising to locate relatives clustering in the same cluster, or side by side, it is important to note how the cases were ascertained and evaluated as well as to observe the phenotypic similarity in visual documentation.

4.3.3 Cluster Analysis 1

4.3.3.1 Validating the methodology

Based on the outcome of the first cluster analysis involving seven different etiologic groups, it appears that cluster analysis can identify differences between phenotypes due to different etiologies without any karyotypic data included in the analysis. When referring to the karyotypes of the individuals in each cluster, there is an underlying basis to the groupings that can be traced back to the karyotypes. This follows the reasoning that the

phenotypic or dysmorphologic information used in the cluster analysis has its roots in the karyotypic abnormalities of the data set. For example, distal 3q duplications were mostly grouped separately from the proximal 3q duplications; cases with cyclopia or holoprosencephaly were grouped together, apart from other dup(3p) cases. Also, many of the del(3p) cases were clustered separately from dup(3p) cases, indicating the possibility that secondary analysis such as discriminant function analysis may indicate a distinct differences between phenotypes with monosomy and trisomy of the same segment. De Lange cases, serving as internal controls, grouped separately in their own cluster. The results observed in cluster analysis 1 validated the use of cluster analysis to attempt to classify phenotypes due to chromosomal aberration, and therefore warranted further analysis.

4.3.3.2 The de Lange phenotype is different than the trisomy 3q phenotype

Cluster analysis 1 indicated that the 15 de Lange cases in the study clustered separately from the other six etiologic groups (Figure 1). While frequently compared to the dup(3q) phenotype, the de Lange phenotype appears to be a distinct and separate phenotype from that of dup(3q). The distinct and early separation of the de Lange cluster from the other three in cluster analysis 1 confirms that this syndrome is due to a very small region governing a very specific gene or genes. It is known that de Lange syndrome is caused by the duplication or deletion of a very small region in 3q26.3, and

the disturbance of a larger segment of 3q would yield a phenotype having attributes of de Lange syndrome, but with a different overall presentation.

4.3.4 Cluster Analysis 2

4.3.4.1 There are distinct phenotypic differences between the dup(3q) and del(3p) phenotypes

Discriminant function analysis identified the top 10 phenotypic traits that had the highest discriminating power for cluster analysis 2. These top 10 traits may not necessarily be the most frequent traits or the most evident traits in the syndromes. However, they best describe how the clusters themselves differ and provide some insight into the relationship between phenotype and karyotype in the clusters. Based on the findings of the discriminant function analysis, it is apparent that there are differences between the del(3p) and dup(3q) phenotypes. Dup(3q) cases have bushy eyebrows and more cardiovascular anomalies, whereas del(3p) cases have ptosis and short palpebral fissures. Some of the differences in the physical features of individuals with dup(3q) and del(3p) are apparent upon observation, however by using an objective approach such as numerical taxonomy, these differences can be delineated by a method free from preconceived biases.

4.3.4.2 *An indication of recognizable subgroups within the dup(3q) and del(3p) chromosomal syndromes*

In cluster analysis 2 (dup(3q) and del(3p) cases), discriminant function analysis indicates the possibility that cluster analysis may have identified clinical subgroups within what were previously thought to belong to one syndromic group. For del(3p) individuals, there appear to be two distinct subgroups. In cluster 2, del(3p) individuals have ptosis, short palpebral fissures, a short neck and no micrognathia. In cluster 4, some del(3p) individuals have ptosis, a short neck, and micrognathia. When examining the karyotypes of individuals in these clusters, there may be a possible 'true del(3p)' phenotype located in cluster 2. This cluster is a very homogeneous cluster where individuals located in this group have virtually no other chromosome affected in the karyotype. Cluster 4, however, appears to contain individuals with a del(3p) phenotype that is also being influenced by the effect of another chromosomal imbalance other than that of chromosome 3. While almost all of the del(3p) cases in cluster 4 do contain distal 3p deletions, many do have another chromosome affected and therefore are not 'pure' 3p deletions and are classified apart from the ones in cluster 2. The phenotypic 'signal' that would normally be expressed by the deletion of 3p may be somewhat masked or altered by another chromosomal imbalance.

For the dup(3q) cases, there appear to be three subgroups in the cluster analysis. Cluster 1 contains dup(3q) individuals who have thick, coarse eyebrows, a short neck, and micrognathia. Cluster 3 contains dup(3q)

individuals with bilateral hypoplastic nails, multiple cardiovascular anomalies, short necks with redundant skin, and no micrognathia. Cluster 4 contains dup(3q) individuals with a short neck, no 'other' cardiovascular anomalies, and micrognathia. For the dup(3q) cases, it appears that there may be a 'true dup(3q)' phenotype in cluster 4 where the duplicated region is at 3q25 or more distal, and half of the dup(3q) cases in cluster 4 do not have another chromosome affected. In cluster 1, however, the cases that may be more greatly affected by the presence of another chromosomal imbalance are located in this cluster. In cluster 3, dup(3q) cases with cardiac anomalies are clustered together, indicating that genes involved in heart development may be located in 3q21 or in a region more proximal to 3q21. Montero and colleagues (1988) indicated the possibility that cardiac genes are located in this region, as cases with duplications of 3q25 or more distal do not present with cardiac anomalies. Thus, it is possible that 3q21 is a location for genes involved in fetal heart development.

4.3.5 Cluster Analysis 3

4.3.5.1 The rec(3) phenotype may be a composite of the dup(3q) and del(3p) phenotypes

Based on the predicted classification of the rec(3) cases with only the top 10 discriminating phenotypic variables, it is apparent that the rec(3) cases share features of both the dup(3q) cases as well as the del(3p) cases. Using the weighted algorithm, rec(3) cases clustered almost exclusively to

cluster 1 and 4. Cluster 1 is predominantly represented by dup(3q) cases. Conversely, cluster 4 is predominantly represented by del(3p) cases. Most of the dup(3q) cases involve duplications of 3q21→3qter, and most of the del(3p) cases in cluster 4 involve deletions of 3p25→3pter. This corresponds to the regions affected in the majority of rec(3) cases. However, in both clusters 1 and 4, the majority of dup(3q) and del(3p) cases have another chromosome affected. Thus it appears that the rec(3) phenotype shares components of both dup(3q) and del(3p) phenotypes, whereas the dup(3q) or del(3p) cases have an additional chromosomal aberration.

When the frequency of each phenotypic variable is tabulated for cases of dup(3)(q21→qter), and del(3)(p25→pter), one can estimate which chromosomal segment influences the phenotype for a given trait. For example, while hypoplastic nails, thick, bushy eyebrows, 'other' cardiovascular anomalies, 'other' foot anomalies, camptodactyly of hands, and a short, webbed neck may be due to the duplication of genes in 3q21, short palpebral fissures and ptosis may be due to the deletion of genes in 3p25. Micrognathia was present in the majority in cases of dup(3q) and del(3p), therefore was not conclusive as to whether 3q or 3p was the major contributing chromosomal segment. Rec(3) cases showed 'q-like' features for all phenotypic variables except for ptosis. No cases with short palpebral fissures were found in the rec(3) group, indicating that rec(3) shares the phenotype with cases of dup(3q) for this trait.

4.3.5.2 *3q is more influential than 3p in the expression of the rec(3) phenotype*

With the tabulation of the frequency of the top 10 phenotypic features for rec(3) cases, it appears that many of the traits are influenced by 3q rather than 3p. This may be due to the difference in the sizes of the chromosomal segments duplicated and deleted in the rec(3) phenotype. For example, dup(3)(q21→qter) can be estimated to span more than one-third of the chromosome or approximately 71.3 Megabases of DNA, and thus may contain one-third of all genes in chromosome 3. 3p25→pter is a much smaller chromosomal region by comparison, and thus may be gene poor when compared to the larger 3q region. From a developmental perspective, duplication of genes in the 3q21→qter region would have a greater disruption of normal fetal development and thereby would yield a more severe phenotype with a greater chance of mortality within the first year of life. This is indeed true when examining the infant mortality rate of del(3p) and dup(3q) individuals. The mortality rate among dup(3q) individuals was much greater than those individuals with del(3p). Among dup(3p) cases themselves, the mortality rate increased as the size of the duplication increased. The more severe cardiovascular anomalies associated with dup(3q), along with ptosis in the del(3p) group, are some of the phenotypic 'signals' identified and associated with chromosomal regions with the use of cluster analysis.

4.3.6 Cluster Analysis 4

4.3.6.1 There may be two subgroups of the rec(3) phenotype

While the discriminant function analysis was not carried out on this data set, the information generated by cluster analysis 4 created a dendrogram with a distinct split of the rec(3) cases into two groups. This indicates that further analysis such as discriminant function analysis should be carried out to identify the major discriminating variables that differentiate the two groups. In addition, identification of the degree of relationship among the members of the inv(3) Newfoundland kindred would be helpful to interpret the division of cases by revealing the familial factors in the nature of clustering.

5.0 FUTURE WORK

5.1 Identification of genes in chromosomal regions of interest

With information such as specific phenotypic discriminators that appear to be influenced by a specific chromosomal region, future initiatives may identify genes that may play a role in development in these regions. For example, genes involved in cardiac function and development located on 3q21 should be evaluated by searching in databases for human expressed sequence tags (ESTs) that express in the heart.

5.2 Discriminant function analysis for rec(3) cluster analysis

The dendrogram of the rec(3) cluster analysis indicates a split of the cases into two distinct clusters. Secondary analysis identifying the top 10% of discriminating features should be carried out to identify the differences in the sub-groups in the rec(3) phenotype. Also, individuals belonging to the Newfoundland kindred should be identified according to how they are related to each other. Such identification could initiate studies into the relationship between familial phenotypes and how this affects cluster analysis.

5.3 Testing the 'anti-syndrome' hypothesis

While cluster analysis 1 did classify many etiologic groups separately from one another, secondary analyses such as 1) cluster analysis with dup(3q) and del(3q), and 2) cluster analysis with dup(3p) and del(3p) could be

carried out. Discriminant function analysis would reveal the top phenotypic discriminators for these groups, and might indicate a difference in a particular phenotypic trait due to the number of gene copies present in the karyotype. These differences might provide support for a syndrome/anti-syndrome phenotype spectrum for a given trait or traits previously not observed.

6.0 SUMMARY

1. Cluster analysis is a valid method of classifying individuals with dysmorphology due to chromosome imbalance, as it can classify individuals based on phenotype as well as classify the well-described de Lange phenotype as a separate and distinct syndromic group.
2. 3q21 and 3p25 are preferential sites of breakage in chromosomal rearrangements involving chromosome 3.
3. Two chromosomal aberrations can affect the phenotype such that it can potentially create a clinical group that differs from the 'pure' phenotype.
4. There are phenotypic differences between the dup(3q) and del(3p) phenotypes. Discriminant function analysis indicated that the duplication of 3q contributes to multiple cardiovascular anomalies, while the deletion of 3p contributes to ptosis.
5. There may be recognizable subgroups within the dup(3q) and del(3p) chromosomal syndromes. Discriminant function analysis indicated that dup(3q) with an additional chromosomal imbalance cluster separately from those where the duplication is the only imbalance in the karyotype.
6. The rec(3) phenotype may be a composite of the dup(3q) and del(3p) phenotypes. Rec(3) individuals have dup(3q)-like traits such as multiple cardiovascular anomalies and redundant skin, and del(3p)-like traits such as ptosis and cervico-thoracic vertebral anomalies.
7. There may be two subgroups of the rec(3) phenotype.

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Appendix 1 Cases and their karyotypes

Case #	Karyotype	Monosomic Segment	Trisomic Segment	Reference
1	46,XX,der(2)t(2;3)(q37;q21)	2q37→qter	3q21→qter	(Fryns et al. 1978)
2	46,XY,der(8)t(3;8)(q21;p23)	8p23→pter	3q21→qter	(Kondo et al. 1979)
3	46,XX,der(21)t(3;21)(q21;pter)mat	21pter	3q21→qter	(Yunis et al. 1979)
4	46,XY,inv ins(3)(q21q29q21)		3q21→q29	(Gustashaw et al. 1985)
5	46,XX,-18,+t(3;18)(q12;p11)	18p11→pter	3q12→qter	(Salazar et al. 1979)
6	46,XX,t(3;13)(q21;q34)mat	13q34→qter	3q21→qter	(Fear and Briggs 1979)
7	46,XX,dir dup(3q2100→q2700)		3q21→q27	(Stengel-Rutkowski et al. 1979)
8	46,XY,der(6)t(3;6)(q21;p25)pat	6p25→pter(?)	3q21→qter	(Ismail et al. 1991)
9	46,XY,der(22)t(3;22)(q21;p11)mat	22p11→pter	3q21→qter	(Sod et al. 1978)
10	46,XY,-14,+der(14)t(3;14)(q13;q32)	14q32→qter	3q13→qter	(Mulcahy et al. 1979)
11	46,XX,der(15)t(3;15)(q25;p13)mat	15p13→pter	3q25→qter	(Montero et al. 1988)
12	46,XY,der(15)t(3;15)(q26;p12)mat	15p12→pter	3q26→qter	(Steinbach et al. 1981)
13	46,XY,der(12)t(3;12)(q21;q24)mat	12q24→qter	3q21→qter	(Steinbach et al. 1981)
14	46,XX,der(5)t(3;5)(q21;p15)pat	5p15→pter	3q21→qter	(Steinbach et al. 1981)
15	46,XX,der(9)t(3;9)(q25;p24)mat	9p24→pter	3q25→qter	(Steinbach et al. 1981)
16	46,XY,der(2)t(2;3)(q37;q25)pat	2q37→qter	3q25→qter	(Steinbach et al. 1981)
17	46,XX,der(2)t(2;3)(q37;q25)	2q37→qter	3q25→qter	(Steinbach et al. 1981)
18	46,XX,inv dup(3)(pter→q28::q28→q25::q28→qter)		3q25→q28	(van Essen et al. 1991)
19	46,XY,-15,der(15)t(3;15)(q26;q26)mat	15q26→qter	3q26→qter	(Chrousos et al. 1988)
20	46,XY,-16,der(16)t(3;16)q25;p13)mat	16p13→pter	3q25→qter	(Annéren and Gustavson 1984)
21	46,XX,-16,der(16)t(3;16)q25;p13)mat	16p13→pter	3q25→qter	(Annéren and Gustavson 1984)
22	46,XX,der(9)t(3;9)(q26.1;p23)mat	9p23→pter	3q26.1→qter	(Tranebjaerg et al. 1987)
23	46,XX,der(2)t(2;3)(q37;q25)pat	2q37→qter	3q25→qter	(Centerwall et al. 1977)
24	46,XX,-15,der(15)t(3;15)(q26;p13)mat	15p13→pter	3q26→qter	(Elorza Arizmendi et al. 1989)
25	46,XY, dup(3)(q22.1→q24),dir ins(11;3)(q22;q22.1q24)mat		3q22.1→q24	(Williamson et al. 1981)
26	46,XX,dup(3)(pter→q27::23→27::27→qter)		3q23→q27	(Sciorra et al. 1979)
27	46,XX,-10,t(3;10)(q21;p15)pat	10p15→pter(?)	3q21→qter	(Blumberg et al. 1980)

Case #	Karyotype	Monosomic Segment	Trisomic Segment	Reference
28	46,XX,dup(3)(pter→q26::21→26::qter)	3q27→q29(?)	3q21→q26	(Rosenfeld et al. 1981)
29	46,XX,der(2)t(2;3)(p25;q21)mat	2p25→pter	3q21→qter	(Chiyo et al. 1976)
30	46,XX,dup(3q),t(3;14)(q21;q32)(inv 9)	14q32→qter	3q21→qter	(Ayral et al. 1984)
31	46,XX,der(5)t(3;5)(q27;p15.1)pat	5p15.1→pter	3q27→qter	(Aqua et al. 1995)
32	46,XY,der(5)t(3;5)(q27;p15,1)pat	5p15.1→pter	3q27→qter	(Aqua et al. 1995)
33	46,XY,der(5)t(3;5)(q27;p15.3)mat	5p15.3→pter	3q27→qter	(Aqua et al. 1995)
34	46,XY,der(2)dup q, t(2;3)(q37;q27)mat	2q37→qter	3q25→qter	(Fineman et al. 1978)
35	46,XX,der(2)dup q, t(2;3)(q37;q27)mat	2q37→qter	3q25→qter	(Fineman et al. 1978)
36	46,XX,der(21)t(3;21)(q26 or 27;q22)pat	21q22→qter	3q26→qter	(Iwasaki et al. 1978)
37	46,XX,der(18)t(3;18)(q26.2;p11.1)mat	18p11.1→pter	3q26.2→qter	(Rubin et al. 1994)
38	46,XX,der(18)t(3;18)(q26.2;p11.1)mat	18p11.1→pter	3q26.2→qter	(Rubin et al. 1994)
39	46,XY,inv dup(3q)(pter→q29::q29→q25::q29→qter)		3q25→q29	(Wilson et al. 1978)
40	46,XX,dir dup(3p)(pter→p27::q29→q25::p27→qter)		3q25→q29	(Wilson et al. 1978)
41	46,XX,del(3)(qter→3p25:)	3p25→pter(?)		(Phipps et al. 1994)
42	46,XX,del(3)(qter→3p25:)	3p25→pter(?)		(Phipps et al. 1994)♦
43	46,XX,del(3)(qter→3p25:)	3p25→pter(?)		(Phipps et al. 1994)♣
44	46,XX,del(3)(qter→3p25:)	3p25→pter(?)		(Phipps et al. 1994)♥
45	46,XX,del(3)(qter→3p25:)	3p25→pter(?)		(Phipps et al. 1994)♠
46	46,XX,del(3)(p25.3pter)	3p25.3→pter		(Narahara et al. 1990)
47	46,XX,del(3),t(3;18)(3qter→3p13::18q23→18qter;18pter→18q23::3p21→3pter)	3p13→p21		(Kogame and Kudo 1979)
48	46,XY,del(3)(p25pter)	3p25→pter(?)		(Mowrey et al. 1993)
49	46,XY,del(3)(p25pter)	3p25→pter		(Verjaal and De Nef 1978)
50	46,XX,del(3)(p25pter)	3p25→pter		(Schwyzer et al. 1987)
51	46,XX,del(3)(p25pter)	3p25→pter		(Tazelaar et al. 1991)
52	46,XY,del(3)(p25pter)	3p25→pter		(Tazelaar et al. 1991)
53	46,XX,der(3)t(1;3)(q32;p25)	3p25→pter	1q32→qter	(Yunis et al. 1977)
54	46,XX,del(3)(p25pter)	3p25→pter		(Zergollern and Hitrec 1983)
55	46,XX,del(3)(p25pter)	3p25→pter		(Witt et al. 1985)
56	46,XY,del(3)(p25pter)	3p25→pter		(Reifen et al. 1986)
57	46,XY,del(3)(pter→p14.2::p11→qter)	3p11→p14.2		(Hertz et al. 1988)

Case #	Karyotype	Monosomic Segment	Trisomic Segment	Reference
58	46,XY,del(3)(pter→p14.2::p12→qter)	3p12→p14.2		(Neri et al. 1984)
59	46,XY,-3,+der(3)t(2;3)(p25.3;p25)mat	3p25→pter	2p25.3→pter	(Chen et al. 1996c)
60	46,XY,der(3)t(3;20)(p25;13.1)	3p25→pter	20q13.1→qter	(Nielsen et al. 1986)
61	46,XX,der(3)t(3;20)(p25;13.1)pat	3p25→pter	20q13.1→qter	(Nielsen et al. 1986)
62	46,XX,der(3)t(3;20)(p25;13.1)pat	3p25→pter	20q13.1→qter	(Nielsen et al. 1986)
63	46,XY,der(3)t(3;20)(p25;13.1)pat	3p25→pter	20q13.1→qter	(Nielsen et al. 1986)
64	46,XY,der(3)t(3;20)(p25;13.1)mat	3p25→pter	20q13.1→qter	(Nielsen et al. 1986)
65	46,XX,der(3)t(3;20)(p25;13.1)mat	3p25→pter	20q13.1→qter	(Nielsen et al. 1986)
66	46,XX,der(3)t(1;3)(q25;p23)mat	3p23→pter	1q25→qter	(McCarthy et al. 1986)
67	46,XY,der(3)t(1;3)(q25;p23)mat	3p23→pter	1q25→qter	(McCarthy et al. 1986)
68	46,XX,der(3)t(1;3)(q25;p23)pat	3p23→pter	1q25→qter	(McCarthy et al. 1986)
69	46,XX,del(3)(p25pter)	3p25→pter		(Gonzales et al. 1980)
70	46,XX,del(3)(p25pter)	3p25→pter		(Ramer et al. 1989)
71	46,XY,del(3)(p25pter)	3p25→pter		(Ramer et al. 1989)
72	46,XX,der(4)t(3;4)(p22.1;q35)pat	4q35→qter	3p22.1→pter	(Dallapiccola and Ferranti 1990)
73	46,XY,del(3)(p25pter)	3p25→pter		(Meinecke 1990)
74	46,XY,del(3)(p25pter)	3p25→pter		(Nienhaus et al. 1992)
75	46,XY,del(3)(pter→p25:)	3p25→pter		(Smith and Sachdeva 1980)
76	46,XY,del(3)(p25.3pter)	3p25.3→pter		(Merrild et al. 1981)
77	46,XX,del(3)(p25pter)	3p25→pter		(Garcia Sagredo et al. 1981)
78	46,XX,del(3)(p25pter)	3p25→pter		(Garcia Sagredo et al. 1981)
79	46,XY,del(3)(3p25pter)	3p25→pter		(Tolmie et al. 1986)
80	46,XX,-3,+rec(3)(qter→q29::p25→p13::q11→p13::q11→qter)mat	3p25→pter		(Ward et al. 1982)
81	46,XY,del(3)(p25pter)	3p25→pter		(Beneck et al. 1984)
82	46,XY,der(3)rcp(1;3)(q32;p25)mat	3p25→pter	1q32→qter	(Schinzel 1981)
83	46,XY,del(3)(p25pter)	3p25→pter		(Higginbottom et al. 1982)
84	46,XY,del(3)(p25.3pter)	3p25.3→pter		(Asai et al. 1992)
85	46,XY,del(3)(p25pter)	3p25→pter		(Bueno et al. 1987)
86	46,XX,del(3)(p25→pter)	3p25→pter		(Fineman et al. 1978)

Case #	Karyotype	Monosomic Segment	Trisomic Segment	Reference
87	46,XX,del(3)(p11p14.2)	3p11→p14.2		(Sichong et al. 1981)
88	46,XY,del(3)(p13.2p21)	3p13.2→p21		(Short et al. 1986)
89	46,XY,del(3p)(pter→p21.1::p13.5→qter), ins inv(3)(pter→p25.5::p13.5→p21.1::p25.5→p21.1::p13.5→qter)pat	3p13.5→p21.1		(Wyandt et al. 1980)
90	46,XY,-3,+del(3)(pter→p21.2::p12→qter)	3p12→p21.2		(Wieczorek et al. 1997)
91	46,XY,del(3)(p12p14.2)	3p12→p14.2		(Naritomi et al. 1988)
92	46,XX,-3,+der(3)t(X;3)(p11.3;p26)mat	3p26→pter	Xp11.3→pter	(Schroer and Phelan 1988)
93	46,XX,del(3)(pter→p21::p13→qter)	3p13→p21		(Mitter et al. 1984)
94	46,XY,t(3;20)(p14.2;p12.2),del(3)(p11p14.1)	3p11→p14.1		(Crispino et al. 1995)
95	46,XY,del(3)(p21.1;p13)	3p13→p21.1		(Karimi-Nejad et al. 1990)
96	46,XY,r(3)	ring(3), bands unknown		(Witkowski et al. 1978)
97	46,XY,r(3)(p26q29)	3p26→pter; 3q29→qter		(Wilson et al. 1982)
98	46,XY,r(3)	ring(3), bands unknown		(Picciano et al. 1972)
99	46,XX,r(3)(p26.2q29)	3p26.2→pter; 3q29→qter		(McKinley et al. 1991)
100	46,XX,r(3)(p26.1q29)	3p26.1→pter; 3q29→qter		(Narahara et al. 1990)
101	46,XX,-3,+r(3)(p26q29)	3p26→pter; 3q29→qter		(Kitatani et al. 1984)
102	46,XY,der(15)t(3;15)(q11;p11)mat	15p11→pter	3q11→qter	(Wilson et al. 1985)
103	46,XY,der(13)t(3;13)(q25;q32)pat	13q32→qter	3q25→qter	(Wilson et al. 1985)
104	47,XX,+der(14)(14pter→q12::3q27→qter)mat		3q27→qter, 14q12→qter	(Wilson et al. 1985)
105	46,XX/47,XY,+3		Trisomy 3	(Sarri et al. 1997)
106	46,XX/47,XX,+3		Trisomy 3	(De Keyser et al. 1988)
107	46,XX/47,XX,+3		Trisomy 3	(Smith et al. 1988)
108	46,XX/47,XX,+3		Trisomy 3	(Kuhn et al. 1987)
109	46,XX/47,XX,+3		Trisomy 3	(Metaxotou et al. 1981)

Case #	Karyotype	Monosomic Segment	Trisomic Segment	Reference
110	46,XY/47,XY,+3		Trisomy 3	(Sinha 1968)
111	46,XY,del(3)(pter→q12::q21→qter)	3q12→q21		(McMorrow et al. 1986)
112	46,XX,del(3)(pter→q12::q21→qter)	3q12→q21		(Okada et al. 1987)
113	46,XX,r(3),t(X;3)	ring(3), bands unknown		(Mukerjee and Burdette 1966)
114	46,XX,del(3)(pter→q23::q26→qter)	3q23→q26		(Franceschini et al. 1983)
115	46,XX,del(3)(q23q25)	3q23→q25		(Martsolf and Ray 1983)
116	46,XX,del(3)(pter→q11::q21→qter)	3q11→q21		(Jenkins et al. 1985)
117	46,XX,del(3)(q2800)	3q2800		(Alvarez Arratia et al. 1984)
118	46,XY,del(3)(pter→q27:)	3q27→qter		(Sargent et al. 1985)
119	46,XY,del(3)(pter→q27:)	3q27→q29		(Brueton et al. 1989)
120	46,XX,del(3)(pter→q27:)	3q27→qter		(Jokiaho et al. 1989)
121	46,XX,del(3)(pter→q27:)	3q27→qter		(Chitayat et al. 1996)
122	46,XY,del(3)(q13.12q21.3)	3q13.12→q21.3		(Genuardi et al. 1994)
123	46,X,t(Y;1;3)(Yqter→Yp11::1q21→1qter;1pter→1q21::3q25→3qter;3pter→3q23:)	3q23→q25		(Al-Awadi et al. 1986)
124	46,XY,del(3)(q21.3q23)	3q21.3→q23		(Jewett et al. 1993)
125	46,XX,del(3)(q23q25)	3q23→q25		(Alvarado et al. 1987)
126	46,XY,del(q22.1q24),dir ins(11;3)(q22;q22.1q24)pat	3q22.1→q24		(Williamson et al. 1981)
127	46,XY,rec(3)dup(3q)inv(3)(p25q23)mat	3p25→pter	3q23→qter	(Preus et al. 1986)
128	46,XY,rec(3)dup(3q)inv(3)(p25q25)mat	3p25→pter	3q25→qter	(Pope et al. 1979)
129	46,XY,rec(3)dup(3q)inv(3)(p25q21)mat	3p25→pter	3q21→qter	(Allderdice et al. 1975)
130	46,XY,rec(3)dup(3q)inv(3)(p25q21)pat	3p25→pter	3q21→qter	(Allderdice et al. 1975)
131	46,XX,rec(3)dup(3q)inv(3)(p25q21)mat	3p25→pter	3q21→qter	(Allderdice et al. 1975)
132	46,XY,rec(3)dup(3q)inv(3)(p25q21)mat	3p25→pter	3q21→qter	(Allderdice et al. 1975)
133	46,XY,rec(3)dup(3q)inv(3)(p25q21)mat	3p25→pter	3q21→qter	(Allderdice et al. 1975)
134	46,XY,rec(3)dup(3q)inv(3)(p25q21)pat	3p25→pter	3q21→qter	(Allderdice et al. 1975)
135	46,XX,rec(3)dup(3q)inv(3)(p25q21)mat	3p25→pter	3q21→qter	(Allderdice et al. 1975)
136	46,XY,rec(3)dup(3q)inv(3)(p25q21)mat	3p25→pter	3q21→qter	(Allderdice et al. 1975)

Case #	Karyotype	Monosomic Segment	Trisomic Segment	Reference
137	46,XY,rec(3)dup(3q)inv(3)(p25q21)mat	3p25→pter	3q21→qter	(Allderdice et al. 1975)
138	46,XX,rec(3)dup(3q)inv(3)(p25q21)mat	3p25→pter	3q21→qter	(Allderdice et al. 1975)
139	46,XY,rec(3)dup(3q)inv(3)(p25q21)pat	3p25→pter	3q21→qter	(Allderdice et al. 1975)
140	46,XY,rec(3)dup(3q)inv(3)(p25q21)pat	3p25→pter	3q21→qter	(Allderdice et al. 1975)
141	46,XX,rec(3)dup(3q)inv(3)(p25q21)pat	3p25→pter	3q21→qter	(Allderdice et al. 1975)
142	46,XY,rec(3)dup(3q)inv(3)(p25q21)mat	3p25→pter	3q21→qter	(Fineman et al. 1978)
143	46,XX,rec(3)dup(3q)inv(3)(p25q25)pat	3p25→pter	3q25→qter	(Fineman et al. 1978)
144	46,XY,rec(3)dup(3q)inv(3)(p25q25)mat	3p25→pter	3q25→qter	(Fineman et al. 1978)
145	46,XY,rec(3)dup(3q)inv(3)(p25q21)mat	3p25→pter	3q21→qter	(Patil et al. 1978)
146	46,XX,rec(3)dup(3q)inv(3)(p25;q23)mat	3p25→pter	3q24→qter	(Mulcahy et al. 1979)
147	46,XY,rec(3)dup(3q)inv(3)(p25q25)mat	3p25→pter	3q25→qter	(Summitt 1966)
148	46,XX,rec(3)dup(3q)inv(3)(p25q25)mat	3p25→pter	3q25→qter	(Summitt 1966)
149	46,XY,rec(3)dup(3q)inv(3)(p25q23)pat	3p25→pter	3q23→qter	(Sutherland et al. 1981)
150	46,XX,rec(3)dup(3q)inv(3)(p25q21)mat	3p25→pter	3q21→qter	(Kawashima and Maruyama 1979)
151	46,XX,rec(3)dup(3q)inv(3)(p25q21)pat	3p25→pter	3q21→qter	(Hirschhorn et al. 1973)
152	46,XX,rec(3)dup(3q)inv(3)(p25q21)pat	3p25→pter	3q21→qter	(Boué et al. 1974)
153	46,XX,rec(3)dup(3q)inv(3)(p25q21)mat	3p25→pter	3q21→qter	(Migliori et al. 1983)
154	46,XX,rec(3)dup(3q)inv(3)(p25q21)mat	3p25→pter	3q21→qter	(Aughton 1997)
155	46,XY,rec(3)dup(3q)inv(3)(p25q21)mat	3p25→pter	3q21→qter	(Lee et al. 1964)
156	46,XY	?	?	(Filippi 1989)◊
157	46,XY	?	?	(Filippi 1989)◊
158	46,XY	?	?	(Filippi 1989)◊
159	46,XY	?	?	(Filippi 1989)◊
160	46,XX	?	?	(Filippi 1989)◊
161	46,XX	?	?	(Filippi 1989)◊
162	46,XY	?	?	(Filippi 1989)◊
163	46,XX	?	?	(Filippi 1989)◊
164	46,XY	?	?	(Filippi 1989)◊
165	46,XY	?	?	(Filippi 1989)◊
166	46,XX	?	?	(Filippi 1989)◊
167	46,XX	?	?	(Filippi 1989)◊

Case #	Karyotype	Monosomic Segment	Trisomic Segment	Reference
168	46,XY	?	?	(Filippi 1989)◊
169	46,XX	?	?	(Filippi 1989)◊
170	46,XX	?	?	(Filippi 1989)◊
171	46,XY,-6,+der(6)t(3;6)(p23;q27)mat	6q27→qter	3p23→pter	(Gimelli et al. 1985)
172	46,XY,-6,+der(6)t(3;6)(p23;q27)mat	6q27→qter	3p23→pter	(Gimelli et al. 1985)
173	46,XX,-2,+der(2)t(2;3)(p25;p23)mat	2p25→pter	3p23→pter	(Gimelli et al. 1985)
174	46,XX,der(4)t(3;4)(p23;p16)mat	4p16→pter	3p23→pter	(Ballesta and Vehi 1974)
175	46,XY,der(22)t(3;22)(p21.2;q13.3)	22q13.3→5	3p21.2→p27	(Yunis 1978)
176	46,XX,der(12)dup 3p,t(3;12)mat	12q, bands unknown	3p, bands unknown	(Sachdeva et al. 1974)
177	46,XY,der(12)dup 3p,t(3;12)mat	12q, bands unknown	3p, bands unknown	(Sachdeva et al. 1974)
178	46,XY,der(22)t(3;22)(p2;q13)pat	22q13→qter	3p2→pter	(Surana et al. 1977)
179	46,XY,der(2)t(2;3)(q37;p21)pat	2q37→qter	3p21→pter	(Chen et al. 1996b)
180	46,XY,der(2)t(2;3)(q37;p21)pat	2q37→qter	3p21→pter	(Chen et al. 1996b)
181	46,XX,der(2)t(2;3)(q37;p21)pat	2q37→qter	3p21→pter	(Chen et al. 1996b)
182	46,XX,der(7)t(3;7)(p23;q36)	7q36→qter	3p23→pter	(Chen et al. 1996b)
183	46,der(X)t(X;3)(p22.2;p22)mat	Xp22.2→pter	3p22→pter	(Donnenfeld et al. 1990)
184	46,Y,der(X)t(X;3)(p22.3;p21)mat	Xp22.3→pter	3p21→pter	(de Almeida et al. 1989)
185	46,XY,-7,+der(7)t(3;7)(p23;q36)pat	7q36→qter	3p23→pter	(Bürrig et al. 1989)
186	46,XX,der(6)t(3;6)(p25;p25)pat	6p25→pter	3p25→pter	(Lurie et al. 1987)
187	46,XY,der(9)t(3;9)(p21.33;p22.1)mat	9p22.1→pter	3p21.33	(Fryns et al. 1986)
188	46,XY,der(1)t(1;3)(q43;p21)pat	1q43→qter	3p21→pter	(Reiss et al. 1986)
189	46,XX,der(1)t(1;3)(q43;p21)pat	1q43→qter	3p21→pter	(Reiss et al. 1986)
190	46,XY,der(1)t(1;3)(q43;p21)mat	1q43→qter	3p21→pter	(Reiss et al. 1986)
191	46,XX,-12,+der(12)rcp(3;12)(p25.1;p13.31)pat	12p13.31→pter	3p25.1→pter	(Rivas et al. 1985)
192	46,XX,der(5)rcp(3;5)(p23;p153)mat	5p153→pter	3p23→pter	(Schwanitz and Zerres 1984)
193	46,XX,der(5)rcp(3;5)(p23;p153)mat	5p153→pter	3p23→pter	(Schwanitz and Zerres 1984)
194	46,XX,der(5)rcp(3;5)(p23;p153)pat	5p153→pter	3p23→pter	(Schwanitz and Zerres 1984)

Case #	Karyotype	Monosomic Segment	Trisomic Segment	Reference
195	46,XY,der(5)rcp(3;5)(p23;p153)	5p153→pter	3p23→pter	(Schwanitz and Zerres 1984)
196	46,XX,der(10)t(3;10)(p21;p26)mat	10q26→qter	3p21→pter	(Van Regemorter et al. 1983)
197	46,XY,der(10)t(3;10)(p21;p26)mat	10q26→qter	3p21→pter	(Van Regemorter et al. 1983)
198	46,XX,der(11)t(3;11)(p21;q25)mat	11q25→qter	3p21→pter	(de Pina Neto and Ferrari 1980)
199	46,XY,dir dup(3)(p25→pter)		3p25→pter	(Kotzot et al. 1996)
200	46,XX,-6,+t(3;6)(6pter→6q27::3p21→3pter)mat	6q27→qter	3p21→pter	(Braga and Schmidt 1982)
201	46,XX,-9,+der(9)t(3;9)(p25;p23)mat	9p23→pter	3p25→pter	(McClure et al. 1996)
202	46,XX,-8,+der(8)t(3;8)(p21;p23)	8p23→pter	3p21→pter	(Scarbrough et al. 1987)
203	46,XX,-10,+der(10)t(3;10)(p21;q26)pat	10q26→qter	3p21→pter	(Gillerot et al. 1987)
204	46,XY,-4,+der(4)t(3;4)(p25;q35)mat	4q35→qter	3p25→pter	(Martin and Steinberg 1983)
205	46,XY,dup(3p)		3p, bands unknown	(Allen and Foster 1996)
206	ins(4;3)(4pter→4p15.3::3p22→3p21::4p15.2→4qter) or inv ins(4;3)(4pter→4p14.3::3p21→3p22::4p14.1→4qter)		3p21→p22	(Orye and Laureys 1984)
207	46,XY,dup(3p)		3p, bands unknown	(Suzuki et al. 1996)
208	46,XY,der(7)t(3;7)(p24.1;p22)	7p22→pter	3p24.1→pter	(Conte et al. 1995)
209	46,XX,der(15)t(3;15)(p23;p12)mat	15p12→pter	3p23→pter	(Say et al. 1976)
210	46,XY,der(15)t(3;15)(p23;p12)mat	15p12→pter	3p23→pter	(Say et al. 1976)
211	46,XX,der(7)t(3;7)(p243;p221)mat	7p22.1→pter	3p24.3→pter	(Baeteman et al. 1985)
212	46,XY,der(11)t(3;11;18)(p23;q25;q21.1)mat		3p23→pter	(Voss et al. 1984)
213	46,XX,der(11)t(3;11;18)(p23;q25;q21.1)mat		3p23→pter	(Voss et al. 1984)
214	46,XY,dir dup(3)(pter→p25::p25→p21.3::p25→qter)		3p21.3→p25	(Zhang and Wang 1984)
215	46,XY,der(12)t(3;12)(p21;p13)pat	12p13→pter	3p21→pter	(Cointin et al. 1985)
216	46,XY,dup(3p),inv ins(7;3)(q31;p21p26)mat		3p21→p26	(Rethoré et al. 1972)
217	46,XX,dup(3p),inv ins(7;3)(q31;p21p26)mat		3p21→p26	(Rethoré et al. 1972)
218	46,XY,dup(3p),inv ins(7;3)(q31;p21p26)mat		3p21→p26	(Rethoré et al. 1972)
219	46,XY,rec(3)(dup(p14.2p11.1),dir ins(3)(pter→p26.2::p14.2→p11.1::p26.2→qter)mat		3p11.1→p14.2	(Watson et al. 1990)
220	46,XX,der(7)t(3;7)(p21;q36)	7q36→qter	3p21→pter	(Kurtzman et al. 1987)

Case #	Karyotype	Monosomic Segment	Trisomic Segment	Reference
221	46,XY,der(4)t(3;4)(p23;q35)mat	4q35→qter	3p23→pter	(Schinzel et al. 1978)
222	46,XY,der(18)t(3;18)(p25;q23)mat	18q23→qter	3p25→pter	(Parloir et al. 1979)
223	46,XY,der(18)t(3;18)(p25;q23)mat	18q23→qter	3p25→pter	(Parloir et al. 1979)
224	46,XX,der(12)t(3;12)(?;p21)	12p, bands unknown	3p21→pter	(Charrow et al. 1981)
225	46,XX,der(X)t(X;3)(p22.3;p23)mat	Xp23→pter	3p22.3→pter	(Bettio et al. 1994)
226	46,XX,der(13)t(3;13)(p22;p12)pat	13p12→pter	3p22→pter	(Francke 1978)
227	46,XY,t(3;6)(p21;q11),11q+mat	11q23→qter	3p23→pter	(Neu et al. 1988)
228	47,XY,+der(15)t(3;15)(p25;q11)pat	15q11→qter	3p25→pter	(Hersh et al. 1980)
229	46,XY,der(18)t(3;18)(p21;11)mat	18p11→pter	3p21→pter	(Buchinger et al. 1981)
230	46,XX,der(18)t(3;18)(p21;11)pat	18p11→pter	3p21→pter	(Buchinger et al. 1981)
231	46,XX,-9,+der(9)t(3;9)(p24;p22)mat	9p22→pter	3p24→pter	(Game et al. 1990)
232	46,XY,dup(3p),ins(4;3)(p15;p14p22)mat		3p14→p22	(Kleczkowska et al. 1984)
233	46,XY,-18,der(18)t(3;18)(p24;q22)mat	18q22→qter	3p24→pter	(Tsukino et al. 1981)
234	46,XX,+3p,t(3;14)(3pter→3p24.1::14qter)pat		3p24.1→pter	(Frankova et al. 1991)
235	46,XX,der(11)t(3;11)(p21;q25)mat	11q25→qter	3p21→pter	(Suzumori et al. 1983)
236	46,XX,der(12)t(3;12)(q27;p13)mat	12p13→pter	3q27→qter	(Howard 1997)
237	46,XY,der(8)t(3;8)(p21;p23.2)	8p23.2→pter	3p21→pter	(Howard 1997)
238	46,XY,del(3)(q25q25)	3q25		(Slavotinek et al. 1997)
239	46,XY,-3,+der(3)t(3;6)(p26;p21)pat	3p26→pter	6p21→pter	(Pagano et al. 1980)
240	46,XY,dup(3)(3q25q26)mat		3q25→q26	(Rizzu et al. 1997)
241	46,XX,dup(3)(3q25q26)		3q25→q26	(Rizzu et al. 1997)
242	46,XX,dup(3)(q25.1q26.1)		3q25.1→q26.1	(Lopez-Rangel et al. 1993)
243	46,XY,r(3)	ring(3), bands unknown		(Lakshminarayana and Nallasivam 1990)
244	46,XX,inv(3)(pterp25)	3pter, region unknown		(Wulfsberg and McAlpine 1997)
245	46,XX,del(3)(q23q25)	3q23→q25		(Chandler et al. 1997)
246	46,X,der(X)t(X;3)(Xter→p21::3q12→3qter)	Xp21→qter	3q12→qter	(Oorthuys et al. 1981)
247	46,XX,der(11)t(3;11)(q21;q23)mat	11q23→qter	3q21→qter	(Chen et al. 1996a)

Case #	Karyotype	Monosomic Segment	Trisomic Segment	Reference
248	46,XX,t(X;3)(p22;q21)	3q21→qter, mosaic(?)		(Karimi-Nejad et al. 1996)
249	46,XY,del(3)(p26pter)	3p26→pter		(Lizcano-Gil and Figuera 1994)
250	46,XX,rec(3)dup(3q)inv(3)(p25q21)pat	3p25→pter	3q21→qter	(Allderdice et al. 1975)∞
251	46,XX,rec(3)dup(3q)inv(3)(p25q21)mat	3p25→pter	3q21→qter	(Boon 1967)
252	46,XX,rec(3)dup(3q)inv(3)(p26q22)mat	3p26→pter	3q22→qter	(Lurie et al. 1974)
253	46,XX,rec(3)dup(3q)inv(3)(p25q21)pat	3p25→pter	3q21→qter	(Allderdice 1997)
254	46,XX,rec(3)dup(3q)inv(3)(p25q21)mat	3p25→pter	3q21→qter	(Allderdice 1997)
255	46,XY,rec(3)dup(3q)inv(3)(p25q21)mat	3p25→pter	3q21→qter	(Allderdice 1997)
256	46,XX,rec(3)dup(3q)inv(3)(p25q21)mat	3p25→pter	3q21→qter	(Allderdice 1997)
257	46,XY,rec(3)dup(3q)inv(3)(p25q21)pat	3p25→pter	3q21→qter	(Allderdice 1997)
258	46,XX,rec(3)dup(3q)inv(3)(p25q21)mat	3p25→pter	3q21→qter	(Allderdice 1997)
259	46,XY,rec(3)dup(3q)inv(3)(p25q21)mat	3p25→pter	3q21→qter	(Allderdice 1997)
260	46,XX,rec(3)dup(3q)inv(3)(p25q21)pat	3p25→pter	3q21→qter	(Allderdice 1997)
261	46,XY,rec(3)dup(3q)inv(3)(p25q21)mat	3p25→pter	3q21→qter	(Allderdice 1997)
262	46,XY,rec(3)dup(3q)inv(3)(p25q21)pat	3p25→pter	3q21→qter	(Siu and McAlpine 1997)
263	46,XX,rec(3)dup(3q)inv(3)(p25q21)pat	3p25→pter	3q21→qter	(Sun and McAlpine 1994)

KEY TO APPENDIX 1:

◊ Cornelia de Lange cases
♦ same as case 79 (Tolmie et al. 1986)
♣ same as case 71 (Ramer et al. 1989)
♥ same as case 70 (Ramer et al. 1989)
♠ same as case 50 (Schwyzer et al. 1987)
∞ same as case 141 (Allderdice et al. 1975)

Appendix 2 Phenotype sheet for trisomy 3q, monosomy 3p, duplication 3q/deletion 3p, trisomy 3p, monosomy 3q, trisomy 3, ring 3, and de Lange syndrome

REFERENCE:

CASE #:

Father's age (yrs):	Mother's age (yrs):	Sex: M F N/A
SB NND ID Child Adult	Birth Order: G P SA TA SB NND	
Age of 1st examination:	Autopsy: Y/N	Photographs: Y/N
Birth weight(g):	Gestation(wk.):	Twin: No MZ DZ NK
Karyotype:	Origin: *De Novo* Maternal Paternal	
Affected sibs/relatives: Y/N	#:	

CRANIOFACIES

Cranial sutures:	Wide	Normal	Closed	
Head shape:	Normal	Brach	Trig	Turri Dolich
Microcephaly:	Y/N			
Face:	Normal	Square	Round	Triangular
Forehead:	High	Normal	Low	
	Wide	Normal	Narrow	
	Bossed	Normal	Flat	
	Sloped	Normal		
Coarse features:	Y/N			
Thick, coarse eyebrows:	Y/N			
Synophrys:	Y/N			
Long, coarse eyelashes:	Y/N			
Palpebral fissure:	Downslanting	Normal	Upslanting	Short
Epicanthal folds:	Y/N			
Hypertelorism:	Y/N			
Ptosis:	Y/N			
Ears:	Low-set	Normal	Posteriorly angulated	
Ear size:	Small	Normal	Large	
Preauricular dimple:	Y/N			
Dysplastic auricles:	Y/N			
Nasal root/bridge:	Broad/flat	Normal	Prominent	
Nose:	Small	Normal	Large	
	Short	Normal	Long	
Philtrum size:	Short	Normal	Long	
Anteverted nostrils:	Y/N			
Jaw characteristics:	Retrognathia	Normal	Prognathia	
Micrognathia:	Y/N			
Lips:	Thin	Normal	Thick	
Downturned lips:	Y/N			
High arched palate:	Y/N			
Cleft palate:	Y/N			
Prominent palate ridges:	Y/N			
Harelip:	Y/N			
Dental abnormalities:	Y/N/NA			
Neck characteristics:	Short	Normal	Short & webbed	
Other anomalies:	Y/N			

CNS

Hydrocephalus:	Y/N				
Congenital glaucoma:	Normal	Left		Right	Bilateral
Cataract:	Normal	Left		Right	Bilateral
Convergent strabismus	Y/N				
Nystagmus:	Y/N				
Impaired hearing:	Normal	Left		Right	Bilateral
Impaired vision:	Normal	Left		Right	Bilateral
Other anomalies:	Y/N				

CARDIOVASCULAR

Cardiomegaly:	Y/N				
Patent ductus arteriosus:	Y/N				
Patent foramen ovale:	Y/N				
Atrial septal defect:	Y/N				
Ventricular septal defect:	Y/N				
Ventricular hypertrophy:	Normal	L	R	Inter	Bilateral
Cardiac murmurs:	Y/N				
Other anomalies:	Y/N				

RESPIRATORY

Cyanosis:	Y/N
Bronchopneumonia:	Y/N
Apnea:	Y/N
Pulmonary stenosis:	Y/N
Other anomalies:	Y/N

GASTROINTESTINAL

Anal canal stenosis:	Y/N			
Anteriorly placed anus:	Y/N			
Anus:	Normal		Ectopic	Imperforate
Omphalocele:	Y/N			
Incomplete rotation of large gut:	Y/N			
Hepatomegaly:	Y/N			
Splenomegaly:	Y/N			
Other anomalies:	Y/N			

GENITOURINARY

Kidney hypoplasia:	No	L	R	Bilateral	
Kidney dysplasia:	No	L	R	Bilateral	
Renal cysts:	No	L	R	Bilateral	
Double ureter:	Y/N				
Hydroureter/hydronephrosis:	Y/N				
Cryptorchidism:	Y/N/NA				
Short penis:	Y/N/NA				
Absent testes:	No	L	R	Bilateral	N/A
Dysplastic testes:	Y/N/NA				
Double vagina:	Y/N/NA				
Duplication of cervix:	Y/N/NA				
Duplication of uterus:	Y/N/NA				
Hypoplastic ovaries:	Y/N/NA				
Germ cells absent:	Y/N				
Other anomalies:	Y/N				

HANDS/FEET

Polydactyly:	Hands	No	L	R	Bilateral
	Feet	No	L	R	Bilateral
Syndactyly:	Hands	No	L	R	Bilateral
	Feet	No	L	R	Bilateral
Camptodactyly:	Hands	No	L	R	Bilateral
	Feet	No	L	R	Bilateral
Clinodactyly:	Hands	No	L	R	Bilateral
Broad hands:		No	L	R	Bilateral
Broad feet:		No	L	R	Bilateral
Thumb abnormalities:		No	L	R	Bilateral
Hypoplastic nails:		No	L	R	Bilateral
Dislocation in fingers:		No	L	R	Bilateral
Abnormal palmar creases:		No	L	R	Bilateral
Club foot:		No	L	R	Bilateral
Varus position of feet:		No	L	R	Bilateral
Valgus position of feet:		No	L	R	Bilateral
Other hand anomalies:		No	L	R	Bilateral
Other foot anomalies:		No	L	R	Bilateral

MUSCULOSKELETAL

Vertebral/rib anomalies:	Y/N		
Congenital hip dysplasia:	Y/N		
Joint flexibility:	Inflexible	Normal	Overflexible
Short arms:	Y/N		
Short legs:	Y/N		
Muscle tone:	Decreased	Normal	Increased
Herniae/diastasis recti:	Y/N		
Other anomalies:	Y/N		

DERMATOLOGICAL

Nevi on skin:	Y/N			
Hirsutism:	No	Head	Trunk	Generalized
Persistent lanugo:	Y/N			
Dermatoglyphic anomalies:	Y/N			
Cutis marmorata:	Y/N			
Redundant skin:	Y/N			
Sacral dimple:	Y/N			
Wide spaced nipples:	Y/N			
Hypoplastic nipples:	No	L	R	Bilateral
Hemangioma:	Y/N			
Other anomalies:	Y/N			

BEHAVIOUR/GROWTH

Short stature:	Y/N/NA		
Failure to thrive:	Y/N/NA		
Abnormal cry or whimpering:	Y/N/NA		
Poor feeding/sucking:	Y/N/NA		
Mental retardation:	Y/N/NA		
Tone:	Hypotonic	Normal	Hypertonic
EEG abnormalities:	Y/N/NA		
Seizures:	Y/N/NA		

Appendix 3 Field names, definitions, and codes

Note: In each field, 98 or 998=not known, 99= not applicable

Case	Case number	**Numerical**
Group	Group number (phenotypic group)	**Numerical**
Citnum	Citation reference number for Endnote	**Numerical**
Refnum	Case reference number within article	**Numerical**
PID	Personal Identification number (Newfoundland kindred)	**Numerical**
Linknum	Link number (Newfoundland kindred)	**Numerical and Alphabetical code**
Karyo	Karyotyped	**Yes or No**
Matage	Maternal age	**Numerical (years)**
Patage	Paternal age	**Numerical (years)**
Sex	Sex of case	**Male=1 Female =2**
Vitstat	Vital status at time of report	**SA=1, SB=2, TA=3, NND=4, D6mo=5, Dinf=6, Dchild=7, Dadult=8, Alive=9**
Ageex	Age at examination in months	**Numerical (months)**
Bweight	Birth weight in grams	**Numerical (g)**
Blength	Birth length in centimeters	**Numerical (cm)**
OFC	Occipitofrontal circumference in centimeters	**Numerical (cm)**
Gestat	Time of gestation in weeks	**Numerical (weeks)**
IUGR	Intrauterine growth retardation	**Y=1 N=0**
Inherit	Parental inheritance of abnormality	***De Novo*=1 Maternal=2 Paternal=3**
Parorig	If *de novo*, parental origin	**Maternal=1, Paternal=2**
Gpinher	Grandparental inheritance of abnormality	**Maternal=1, Paternal=2**
Type	Type of abnormality (Translocation, ring, etc.)	**Translocation=1, Ring=2, Inversion=3, Isolated duplication=4 Isolated deletion=5, Trisomy=6, Complex Chromosomal Rearrangement=7**
Larm	Long arm of chromosome	**Deletion=0, Normal=1, Duplication=2**
Distbl	Distal band on long arm	**Numerical, Telomere(ter)=100**
Proxbl	Proximal band on long arm	**Numerical, Telomere(ter)=100**
Sharm	Short arm of chromosome	**Deletion=0, Normal=1, Duplication=2**
Distbs	Distal band on short arm	**Numerical, Telomere(ter)=100**
Proxbs	Proximal band on short arm	**Numerical, Telomere(ter)=100**
Otherch	Other chromosomes affected	**Y=1 N=0**

Affrel	Affected relatives			**Y=1**		**N=0**		
Cransut	Cranial sutures		**Closed=0**			**Normal=1**		**Wide=2**
Headshp	Head shape	**Normal=0**	**Brach=1**		**Trig=2**		**Turri=3**	**Dolich=4**
Mircocep	Microcephaly			**Y=1**		**N=0**		
Occiput	Occipital characteristics			**Flat=0**		**Normal=1**		**Prominent=2**
Anthairl	Low anterior hairline			**Y=1**		**N=0**		
Posthairl	Low posterior hairline			**Y=1**		**N=0**		
Face	Shape of face	**Normal=0**	**Square=1**		**Round=2**		**Triangular=3**	
Forhgt	Forehead height			**Low=0**		**Normal=1**		**High=2**
Forwdt	Forehead width		**Narrow=0**		**Normal=1**		**Wide=2**	
Forsurf	Forehead surface			**Flat=0**		**Normal=1**		**Bossed=2**
Forangle	Forehead angle			**Sloped=1**		**Normal=0**		
Tempind	Temporal indentations			**Y=1**		**N=0**		
Coarfeat	Coarse features			**Y=1**		**N=0**		
Eyebr	Eyebrow characteristics		**Thin=0**			**Normal=1**		**Thick=2**
Synoph	Synophrys			**Y=1**		**N=0**		
Eyelash	Long, coarse eyelashes			**Y=1**		**N=0**		
Eyes	Eye size			**Small=0**		**Normal=1**		**Large=2**
Palpfiss	Palpebral fissure slant	**Downslanting=0**		**Normal=1**		**Upslanting=2**		
Shpalp	Short palpebral fissures			**Y=1**		**N=0**		
Narpalp	Narrow palpebral fissures			**Y=1**		**N=0**		
Folds	Eye folds	**Epicanthic=0**		**Normal=1**		**Inverse epicanthic=2**		
Hypertel	Hypertelorism/telecanthus			**Y=1**		**N=0**		
Ptosis	Ptosis of eyes			**Y=1**		**N=0**		
Earsls	Low-set ears			**Y=1**		**N=0**		
Earspa	Posteriorly angulated ears			**Y=1**		**N=0**		
Earsize	Ear size		**Small=0**		**Normal=1**		**Large=2**	
Preauric	Preauricular dimple/sinus/tag	**Normal=0**	**Dimple=1**		**Sinus=2**		**Tag=3**	
Dyspaur	Dysplastic auricles			**Y=1**		**N=0**		
Narbht	Height of nasal root/bridge			**Broad/flat=0**		**Normal=1**		**Prominent=2**
Narblt	Length of nasal root/bridge			**Short=0**		**Normal=1**		**Long=2**
Nosesize	Nose size			**Small=0**		**Normal=1**		**Large=2**
Nosshp	Nose shape			**Upturned=1**		**Normal=0**		
Philsize	Philtrum size			**Short=0**		**Normal=1**	**Long=2**	
Philtext	Philtrum texture			**Flat=0**		**Normal=1**	**Prominent=2**	
Nostrils	Nostril slant			**Anteverted=0**		**Normal=1**	**Everted=2**	

Fullchk	Full cheeks			**Y=1**		**N=0**			
Mouth	Mouth size			**Small=0**		**Normal=1**		**Large=2**	
Maxilla	Maxilla size			**Small=0**		**Normal=1**		**Large=2**	
Upplip	Upper lip thickness			**Thin=0**		**Normal=1**		**Thick=2**	
Cleftlip	Cleft lip			**Y=1**		**N=0**			
Downmt	Downturned mouth			**Y=1**		**N=0**			
Palate	Palate characteristics	**Normal=0**	**High arched=1**		**Bifid uvula=2**		**Cleft=3**		
Prompr	Prominent palatal ridges			**Y=1**		**N=0**			
Lagtong	Large tongue			**Y=1**		**N=0**			
Dentabn	Dental abnormalities			**Y=1**		**N=0**			
Jawchar	Jaw characteristics		**Retrognathia=0**		**Normal=1**		**Prognathia=2**		
Microgn	Micrognathia			**Y=1**		**N=0**			
Neckch	Neck characteristics			**Normal=0**		**Short=1**		**Short & webbed=2**	
Cfoth	Other cranio-facial abnormalities			**Y=1**		**N=0**			
Hydrocep	Hydrocephalus			**Y=1**		**N=0**			
Midline	Midline characteristics	**Normal=0**	**Arrhinencephaly=1**		**Holoprosencephaly=2**			**Cyclopia=3**	
Glaucom	Glaucoma		**Normal=0**	**Left=1**		**Right=2**		**Bilateral=3**	
Catar	Cataracts		**Normal=0**	**Left=1**		**Right=2**		**Bilateral=3**	
Strabis	Strabismus		**Normal=0**	**Left=1**		**Right=2**		**Bilateral=3**	
Nystag	Nystagmus		**Normal=0**	**Left=1**		**Right=2**		**Bilateral=3**	
Imphr	Impaired hearing		**Normal=0**	**Left=1**		**Right=2**		**Bilateral=3**	
Impvis	Impaired vision		**Normal=0**	**Left=1**		**Right=2**		**Bilateral=3**	
CNSoth	Other CNS abnormalities			**Y=1**		**N=0**			
Cardiom	Cardiomegaly			**Y=1**		**N=0**			
Pda	Patent ductus arteriosus			**Y=1**		**N=0**			
Pfo	Patent foramen ovale			**Y=1**		**N=0**			
Asd	Atrial septal defect			**Y=1**		**N=0**			
Vsd	Ventricular septal defect			**Y=1**		**N=0**			
Venthyp	Ventricular hypertrophy	**Normal=0**	**Left=1**	**Right=2**		**Inter=3**		**Bilateral=4**	
Carmur	Cardiac murmurs			**Y=1**		**N=0**			
Pulsten	Pulmonary stenosis			**Y=1**		**N=0**			
Cvoth	Other cardiovascular abnormalities			**Y=1**		**N=0**			
Cyano	Cyanosis			**Y=1**		**N=0**			
Respinf	Respiratory infections			**Y=1**		**N=0**			
Apnea	Apnea			**Y=1**		**N=0**			
Roth	Other respiratory abnormalities			**Y=1**		**N=0**			

Ancsten	Anal canal stenosis		**Y=1**	**N=0**		
Antplan	Anteriorly placed anus		**Y=1**	**N=0**		
Anus	Anus characteristics		**Normal=0**	**Ectopic=1**	**Imperforate=2**	
Intmal	Intestinal/organ malrotation		**Y=1**	**N=0**		
Hepato	Hepatomegaly		**Y=1**	**N=0**		
Spleno	Splenomegaly		**Y=1**	**N=0**		
Gioth	Other gastrointestinal abnormalities		**Y=1**	**N=0**		
Kidapl	Kidney aplasia	**Normal=0**	**Left=1**	**Right=2**	**Bilateral=3**	
Kidhyp	Kidney hypoplasia	**Normal=0**	**Left=1**	**Right=2**	**Bilateral=3**	
Kiddys	Kidney dysplasia	**Normal=0**	**Left=1**	**Right=2**	**Bilateral=3**	
Rencyst	Renal cysts	**Normal=0**	**Left=1**	**Right=2**	**Bilateral=3**	
Doubur	Double ureter	**Normal=0**	**Left=1**	**Right=2**	**Bilateral=3**	
Hydroun	Hydroureter/hydronephrosis	**Normal=0**	**Left=1**	**Right=2**	**Bilateral=3**	
Crypto	Cryptorchidism	**Normal=0**	**Left=1**	**Right=2**	**Bilateral=3**	**N/A=99**
Penis	Penis characteristics	**Hypoplastic=0**	**Normal=1**	**Short=2**	**N/A=99**	
Hyposp	Hypospadias		**Y=1**	**N=0**	**N/A=99**	
Abstest	Absent testes	**Normal=0**	**Left=1**	**Right=2**	**Bilateral=3**	**N/A=99**
Doubva	Double vagina		**Y=1**	**N=0**	**N/A=99**	
Dupcer	Duplication of cervix		**Y=1**	**N=0**	**N/A=99**	
Dupute	Duplication of uterus		**Y=1**	**N=0**	**N/A=99**	
Hypoov	Hypoplastic ovaries		**Y=1**	**N=0**	**N/A=99**	
Guoth	Other genitourinary abnormalities		**Y=1**	**N=0**		
Polyha	Polydactyly of hands	**Normal=0**	**Left=1**	**Right=2**	**Bilateral=3**	
Polyft	Polydactyly of feet	**Normal=0**	**Left=1**	**Right=2**	**Bilateral=3**	
Brahan	Brachydactyly of hands	**Normal=0**	**Left=1**	**Right=2**	**Bilateral=3**	
Braft	Brachydactyly of feet	**Normal=0**	**Left=1**	**Right=2**	**Bilateral=3**	
Synha	Syndactyly of hands	**Normal=0**	**Left=1**	**Right=2**	**Bilateral=3**	
Synft	Syndactyly of feet	**Normal=0**	**Left=1**	**Right=2**	**Bilateral=3**	
Campha	Camptodactyly of hands	**Normal=0**	**Left=1**	**Right=2**	**Bilateral=3**	
Campft	Camptodactyly of feet	**Normal=0**	**Left=1**	**Right=2**	**Bilateral=3**	
Clinodac	Clinodactyly of hands	**Normal=0**	**Left=1**	**Right=2**	**Bilateral=3**	
Smhand	Small hands	**Normal=0**	**Left=1**	**Right=2**	**Bilateral=3**	
Smfeet	Small feet	**Normal=0**	**Left=1**	**Right=2**	**Bilateral=3**	
Brhand	Broad hands	**Normal=0**	**Left=1**	**Right=2**	**Bilateral=3**	
Brfeet	Broad feet	**Normal=0**	**Left=1**	**Right=2**	**Bilateral=3**	
Thumab	Thumb abnormalities	**Normal=0**	**Left=1**	**Right=2**	**Bilateral=3**	

Nailabn	Nail abnormalities	**Normal=0**	**Left=1**	**Right=2**	**Bilateral=3**
Abpacrs	Abnormal palmar creases	**Normal=0**	**Left=1**	**Right=2**	**Bilateral=3**
Clubft	Clubfeet	**Normal=0**	**Left=1**	**Right=2**	**Bilateral=3**
Robtft	Rocker bottom feet	**Normal=0**	**Left=1**	**Right=2**	**Bilateral=3**
Varus	Varus position of feet	**Normal=0**	**Left=1**	**Right=2**	**Bilateral=3**
Valgus	Valgus position of feet	**Normal=0**	**Left=1**	**Right=2**	**Bilateral=3**
Hoth	Other hand abnormalities	**Normal=0**	**Left=1**	**Right=2**	**Bilateral=3**
Foth	Other foot abnormalities	**Normal=0**	**Left=1**	**Right=2**	**Bilateral=3**
Derma	Dermatoglyphic abnormalities		**Y=1**	**N=0**	
CTVab	Cervico-thoracic vertebral abnormalities		**Y=1**	**N=0**	
Lsab	Lumbo-sacral vertebral abnormalities		**Y=1**	**N=0**	
Rib	Rib abnormalities		**Y=1**	**N=0**	
Hipdys	Hip dysplasia		**Y=1**	**N=0**	
Jflex	Joint flexibility	**Inflexible=0**		**Normal=1**	**Overflexible=2**
Jdisl	Joint dislocation		**Y=1**	**N=0**	
Bonmat	Bone maturation delay		**Y=1**	**N=0**	
Sharms	Short arms		**Y=1**	**N=0**	
Shleg	Short legs		**Y=1**	**N=0**	
Mustone	Muscle tone	**Decreased=0**	**Normal=1**		**Increased=2**
Herndr	Hernia/diastasis recti		**Y=1**	**N=0**	
Chest	Chest characteristics	**Narrow=0**	**Normal=1**	**Wide=2**	**Excavatum=3**
Ldefael	Limb deficiencies above elbow		**Y=1**	**N=0**	
Ldefbel	Limb deficiencies below elbow		**Y=1**	**N=0**	
Umbher	Umbilical hernia/omphalocele		**Y=1**	**N=0**	
Msoth	Other musculo-skeletal abnormalities		**Y=1**	**N=0**	
Edema	Edematous extremities/trunk/face		**Y=1**	**N=0**	
Nevi	Nevi on skin		**Y=1**	**N=0**	
Hirsut	Hirsutism	**No=0**	**Head=1**	**Trunk=2**	**Generalized=3**
Cutmar	Cutis marmorata		**Y=1**	**N=0**	
Redskin	Redundant skin		**Y=1**	**N=0**	
Sacdimp	Sacral dimple		**Y=1**	**N=0**	
Pilsin	Pilonidal sinus		**Y=1**	**N=0**	
Widspni	Widely spaced nipples		**Y=1**	**N=0**	
Hypnip	Hypoplastic nipples	**Normal=0**	**Left=1**	**Right=2**	**Bilateral=3**
Hemang	Hemangioma	**No=0**	**Head=1**	**Trunk=2**	**Generalized=3**
Doth	Other dermal abnormalities		**Y=1**	**N=0**	

Shstat	Short stature/growth retardation		**Y=1**	**N=0**	
Fathriv	Failure to thrive		**Y=1**	**N=0**	
Abcry	Abnormal cry		**Y=1**	**N=0**	
Pfeed	Poor feeding		**Y=1**	**N=0**	
Psmot	Psychomotor retardation		**Y=1**	**N=0**	
Mr	Mental retardation		**Y=1**	**N=0**	
Pspeech	Poor speech		**Y=1**	**N=0**	
Lresp	Lack of responsiveness		**Y=1**	**N=0**	
Tone	Body tone	**Hypotonic=0**		**Normal=1**	**Hypertonic=2**
EEG	EEG abnormalities		**Y=1**	**N=0**	
Seizure	Seizures		**Y=1**	**N=0**	
Comments	Special notes				