Copy number variation-based gene set analysis reveals cytokine signaling pathways associated with psychiatric comorbidity in patients with inflammatory bowel disease

Svetlana Frenkel[1], Charles N Bernstein[2], Michael Sargent[2], Wenxin Jiang[1,3], Qin Kuang[1], Wei Xu[3], Pingzhao Hu[1,3,4,*]

[1]Department of Biochemistry and Medical Genetics and The George and Fay Yee Centre for Healthcare Innovation, University of Manitoba, Winnipeg, MB, Canada

[2]Department of Internal Medicine and the University of Manitoba IBD Clinical and Research Centre, University of Manitoba, Winnipeg, MB, Canada

[3]Division of Biostatistics, Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada

[4]Department of Electrical and Computer Engineering, University of Manitoba, Winnipeg, MB, Canada

*Correspondence:

Dr. Pingzhao Hu, Department of Biochemistry and Medical Genetics, Room 308 - Basic Medical Sciences Building, 745 Bannatyne Avenue, University of Manitoba, Winnipeg, Manitoba, R3E 0J9, Canada. Tel: 1-204-789-3229. Email: pingzhao.hu@umanitoba.ca.

Keywords: Inflammatory Bowel Disease, psychiatric comorbidity, cytokines, copy number variation, pathway enrichment

Running Title: Psychiatric comorbidity in inflammatory bowel disease

Abstract

Background: Recent studies discovered many genetic variants associated with both psychiatric and inflammatory disorders, but the role of genetic factors in the development of psychiatric comorbidity (PC) in inflammatory bowel disease (IBD) is underexplored. Particularly, it has been shown that some of the genetic variants have been linked to the concentrations of circulating cytokines and symptoms of the inflammatory cytokine-associated depression. We analysed genomic features of individuals with IBD by comparing IBD patients with PC with those who have IBD but without PC. We hypothesized that cytokine related signaling pathways may be significantly associated with the psychiatric comorbidity in patients with IBD.

Methods: Individuals enrolled in the Manitoba IBD Cohort Study were separated to two groups accordingly to the presence of PC. A sample set comprising 97 IBD individuals with PC (IBD+PC) and 146 IBD individuals without PC (IBD) was first used to identify copy number variations (CNVs) from genome-wide genetic data using three different detection algorithms. IBD+PC and IBD groups were compared by the number of CNVs overlapping each gene; deletions and duplications were analysed separately. Gene set overrepresentation analysis was then conducted using CNV-overlapped genes and the candidate gene sets of neurological and immunological relevance.

Results: Medium-sized CNV (size between 100 and 500 kilobase pairs)-burden is significantly higher in IBD+PC than IBD groups. Gene-based CNV association analysis did not show significant differences between the two IBD groups. Gene set overrepresentation analysis

demonstrated the significant enrichment of gene sets related to cytokine signalling pathways by the genes overlapped by deletions in the IBD individuals with PC.

Conclusion: Our results confirm the role of cytokine signalling pathways in the development of PC in IBD. Additionally, our results warrant further study with a larger sample size focusing on cytokine SNPs to further understand the relationship between inflammatory and psychiatric disorders.

1. Background

Inflammatory bowel disease (IBD) is one of the immune-mediated diseases characterised by chronic intestinal inflammation. The prevalence of IBD in Europe and North America exceeds 0.3%, and there is a rising incidence in newly industrialised countries (Ng et al., 2017). In turn, numerous studies reported a high frequency of psychiatric disorders, especially mood disorders in persons with IBD. It has been suggested that IBD activity is the critical factor of decreased subjective well-being and concomitant mood disorders, and not the disease itself (Lix et al., 2008). However, many IBD patients demonstrate symptoms of depression and anxiety in periods of remission (Cawthorpe, 2015; Keeton et al., 2015; Vidal et al., 2008; Walker et al., 2008). Other

66 immune-mediated inflammatory disorders, such as rheumatoid arthritis, psoriasis, and
67 cardiovascular diseaseare were also associated with increased risk of psychiatric comorbidity
68 (Andreoulakis et al., 2012; Hare et al., 2014; Margaretten et al., 2011; Tyring et al., 2006). Recent
69 studies have reported elevated incidence rates of depression, anxiety disorder, bipolar disorder and
70 schizophrenia in patients with IBD specifically as well as in a cohort of persons with any of IBD,
71 multiple sclerosis and rheumatoid arthritis (Bernstein et al., 2018; Marrie et al., 2017). An
72 increased incidence of depression and anxiety has been reported in the years prior to diagnosis of
73 IBD suggesting that psychiatric comorbidity is not only a mental health response to a chronic
74 disease but it may be that psychiatric disease and IBD share inflammatory aetiologies (Marrie et
75 al., 2017; Walker et al., 2008). Depression and decreased well-being have also been associated
76 with higher relapse rates in IBD (Long et al., 2014; Persoons et al., 2005). The symptoms of
77 depression and anxiety and accompanying fatigue significantly deteriorate the patients' quality of
78 life and contribute to work impairment (Enns et al., 2018; Graff et al., 2011). Brain gut connections
79 are considered the underpinning of the association between IBD and psychiatric disorders. These
80 interactions include neural, immune and endocrine communication pathways with an impact on
81 the gut microbiome, all of which may direct intestinal inflammation (Abautret-Daly et al., 2017;
82 Bonaz and Bernstein, 2013). There are a number of possible environmental risk factors common
83 for both IBD and mood disorders, such as stress, sleep disturbances, vitamin D deficiency,
84 microbiome alterations and dietary changes (Ananthakrishnan, 2015; Anglin et al., 2013; Foster
85 et al., 2017; Franzen and Buysse, 2008; Westover and Marangell, 2002). Alterations in
86 concentrations of circulating pro-inflammatory cytokines in response to different environmental
87 triggers may be a unifying mechanism through which psychiatric disease and IBD are linked
88 (reviewed in Berk et al., 2013). Through the activation of the inflammatory pathways in the brain

parenchyma, cytokines can influence the monoamine, glutamate and neuropeptide systems (Felger and Lotrich, 2013; Lotrich, 2015). The activation of the immune system and increasing blood cytokine levels have been observed in numerous psychiatric disorders including depression and anxiety disorder, posttraumatic stress disorder, schizophrenia and autism (Berk et al., 2013; Filiano et al., 2015; Kim et al., 2016; Kronfol, 2000; Uçar et al., 2018). Inflammatory cytokines can cause the depressive-like symptoms induced by cytokine-based treatment for certain cancers and viral infections (Lotrich, 2009). Moreover, inflammatory cytokine-associated depression may be a specific major depression subtype warranting specific treatment (Lotrich, 2015).

Chronic inflammatory disorders such as IBD, as well as psychiatric disorders, are complex conditions with contributions by multiple genes with small effect sizes. Numerous genome-wide association studies (GWAS) have identified more than 200 IBD risk loci (de Lange et al., 2017; Liu et al., 2015). Some of the IBD-associated genes are involved in activation of T-, B-, and NK-cells, response to molecules of bacterial origin, JAK-STAT signalling pathway and other processes, which may be linked to the regulation of host response to intestinal microbes (Jostins et al., 2012; Kostic et al., 2014). In a previous study, we found few copy number variation (CNV) loci linked to susceptibility to IBD. These CNVs were involved in T-cell immune responses and cellular signal transduction pathways in IBD pathogenesis. Similarly to the inflammatory diseases, depression and anxiety disorders have been linked to multiple risk SNP and CNV alleles; some of these alleles were associated with multiple mood, neurodevelopmental and neurodegenerative disorders (Gratten et al., 2014; Green et al., 2016; Guyatt et al., 2018; Hyde et al., 2016; Marshall et al., 2017; O'Dushlaine et al., 2014; Perlis et al., 2012; Pinto et al., 2010; Wray et al., 2018). In addition, several SNPs have been linked to the concentrations of circulating cytokines and symptoms of the inflammatory cytokine-associated depression. The genes mapped to these

112 variants are related to the immune signalling molecules, neurotransmitters, neuropeptides and
113 growth factors (Ahola-Olli et al., 2017; Felger and Lotrich, 2013).

114 The role of genetic factors in the development of psychiatric comorbidity in IBD is significantly
115 underexplored. We reasoned that IBD patients with psychiatric comorbidity (IBD+PC) might
116 represent a genetically different group than those with IBD who never had PC (IBD). Given that
117 inflammatory cytokines have been shown strong associations with IBD and depression-related
118 disorders as discussed above, we hypothesized that cytokine related signaling pathways may be
119 significantly associated with the psychiatric comorbidity in patients with IBD. We evaluated the
120 CNV burden and performed CNV-based gene set overrepresentation analysis of the candidate gene
121 sets of neurological and immunological relevance to identify cytokine signaling pathways
122 associated with IBD patients with PC.

123 ## 2. Materials and Methods

124 ### 2.1 Study participants

125 Individuals enrolled in The Manitoba IBD Cohort Study – a population-based study of persons
126 with IBD (within seven years after diagnosis) were followed prospectively to assess predictors of
127 outcomes. Diagnoses were confirmed on chart review. Participants were surveyed semiannually
128 and interviewed in person annually. A number of survey tools were used to assess ongoing
129 symptoms of depression and anxiety. Within one year of study enrolment all partcipants underwent
130 a Comprehensive International Diagnostic Interview developed by the World Health Organization
131 (Walker et al., 2008). The psychiatric disorder diagnosis process and criteria were described in
132 detail elsewhere (Walker et al., 2008). Blood samples for genotyping were obtained from a total
133 of 269 IBD patients, 104 of those had PC. The Manitoba IBD Cohort Study was approved by the

University of Manitoba Health Research Ethics Board, and participants provided written informed consent.

2.2 Microarray genotyping and quality control procedures

DNA was extracted from blood and genotyped using the Illumina Human Omni2.5M-8 microarray (San Diego, CA, USA) at The Centre for Applied Genomics (TCAG) in Toronto using established protocols (Scherer et al., 2007). SNPs were required to match several quality control criteria (**Figure 1**): minimal SNP call rate of 95% (propotion of the samples with the genotype calls for the given SNP), the SD (standard deviation) for the LRR (log R ratio) and BAF (B allele frequency) for an individual sample were required to be within the mean ± three times the SD for each of these criteria for an analysis batch (Noor et al., 2014; Pinto et al., 2010). Any samples outside this range were removed from further analysis.

2.3 Population stratification analysis

Population stratification and outlier detection were performed by multidimensional scaling analysis (MDS) as implemented in PLINK (Chang et al., 2015). MDS has been applied for identification of ethnicity outliers by comparing the SNP population frequencies in IBD patients to the SNP frequencies in the reference populations, while phase 3 data from 1000 Genomes Project was utilised as the reference (Auton et al., 2015). Only the samples with European ancestry were used for the study. Additionally, the individuals' sex was estimated based on X chromosome homozygosity rate, and samples relatedness was assessed by calculating the identity-by-state distance for each pair of individuals. Highly-related individuals and the individuals with the

inconsistencies between self-reported sex and X chromosome homozygosity rate were removed as well.

2.4 Allelic Association Test

Allelic association test was performed separately for each individual SNP. For the test, the observed frequencies of alternative alleles in two IBD groups (IBD+PC vs IBD) were represented as a contingency table. Under the null hypothesis of lack of association of minor allele frequency with the PC, we expect the allele frequencies to be the same in IBD+PC and IBD groups. Person's χ^2 with one degree of freedom was used for testing independence of the rows and columns of the contingency table in accordance with the protocol written by Clarke et al. (Clarke et al., 2011). The odds ratio (OR) and 95% confidence intervals (95% CI, a statistical measure of a range of measurements that we can be 95% certain contains the population mean) were calculated to assess the association between the alleles and the risk of IBD with PC.

2.5 CNVs detecting algorithms

Similarly to the methodology described before (Noor et al., 2014; Oskoui et al., 2015; Pinto et al., 2010), we applied three CNV calling algorithms, namely, iPattern (Pinto et al., 2011), PennCNV (Wang et al., 2007) and QuantiSNP (Colella et al., 2007), to obtain high-confidence calls from our IBD samples. The detected CNVs were first filtered based on their size (no less than 20 kilobase pairs (kbp), probe content (no less than five consecutive probes) and algorithm-specific quality score (see **Figure 1**). For maximal sensitivity and specificity of CNV detection, we required CNV calling by at least two algorithms, one of which had to be either iPattern or PennCNV. The CNVs detected by two or three algorithms were merged. In the case of position mismatch of the results received from different algorithms, outermost positions were used as stringent CNV positions (i.e., union of the CNVs) as described in Pinto *et al.* (Pinto et al., 2010). Further, we excluded CNVs

that: 1) overlapped the centromere (100kbp regions before and after centromeres) or the telomere (100 kb from the ends of the chromosome); 2) had > 70% of its length overlapping a segmental duplication using the entire segmental duplication dataset downloaded from the University of California, Santa Cruz (UCSC) Genome Browser website; 3) had >70% overlap with immunoglobulin region (Wang et al., 2007; Zarrei et al., 2015).

2.6 CNV burden and permutation test

For the analysis of CNV burden in two IBD groups, we divided the CNVs by their length into three groups: shorter than 100 kbp, from 100 to 500 kbp and larger than 500 kbp. We analysed the CNV burdens of deletions and duplications jointly and separately. For each type and size of CNVs we first calculated the number of CNVs in IBD+PC and IBD groups, then estimated the average number of CNVs per sample in each group (named as IBD+PC rate and IBD rate, respectively), and finally defined the ratio of IBD+PC rate / IBD rate as CNV burden risk. We applied a permutation test to evaluate the significance of the CNV burden risk. The permutation procedure randomly shuffled the samples between IBD+PC and IBD groups and recalculated the ratio of IBD+PC rate / IBD rate in each permutated data set. We defined the permutation p-value of the CNV burden risk as the proportion of ratio of IBD+PC rate / IBD rate observed in 10,000 permutated datasets larger than this ratio in the original data. Genic regions were ascertained by RefSeq annotation (UCSC, hg19). The global burden of CNVs overlapping genic regions was analysed similarly.

2.7 Gene-based CNV association test

The human genes positions (UCSC, hg19) were obtained from the UCSC Genome Browser website. All genes, overlapped with at least one nucleotide by at least one CNV in the tested groups, were selected for the gene-based CNV association test. For each gene, the number of

overlapping CNVs in IBD+PC samples was compared with the number of overlapping CNVs in IBD using two-tailed Fisher's exact test. The analysis was conducted separately for genes overlapped by deletions and by duplications separately.

2.8 Gene set overrepresentation analysis

The gene set overrepresentation analysis was conducted using the genes overlapped by at least one CNV in the tested groups as the background gene list. Four lists of genes overlapped by deletions and duplications in the IBD+PC and IBD samples were used to test the enrichment of functional gene sets using Fisher's exact test, respectively. The Gene Ontology (GO) and KEGG pathway-derived sets of neurobiological and immunological relevance were used for the definition of customised gene sets (GSs) functionally related to the immune and nervous system activity (**Table 1**). Assuming the substantial role of neurotransmitters, neuronal and synaptic plasticity, and cytokine signalling pathways, we designed four GSs by merging relevant GO terms and KEGG pathways. Similarly, we created separated GS out of all immune-related GO terms, which did not include "GO Cytokine Pathways". In addition, the GO terms related to nervous system development, and higher cognitive functions were included in the analysis as corresponding GSs. Finally, all GSs related to the immune and nervous system were combined and included in the analysis as two large GSs. The detailed list of GO terms and KEGG pathways included in each of GSs is presented in the **Supplementary Table 1**.

2.9 DNA motifs identification and analysis

We retrieved corresponding sequences from the upstream regulatory regions of the 44 genes overlapped by deletions in IBD+PC samples and significantly over represented in the gene set "Cytokine Pathways (GO+KEGG)", each spanning from 1000 bp upstream to 100 bp downstream

of the gene start position, using the "retrieve EnsEMBL sequence" algorithm from the RSAT suite (Regulatory Sequence Analysis Tools) (Nguyen et al., 2018). The repetitive elements in the obtained sequences were masked to reduce the risk to get false-positive results. We used three motif-based sequence analysis tools from the MEME suite to search and analyse the DNA motifs in the chosen DNA regions. The obtained sequences were subjected to the novel DNA motifs identification using MEME (Timothy et al., 1994) with Zero or One Occurrence per Sequence search option. DNA motifs identified by MEME were compared with JASPAR databases of known motifs (transcription factor families) using Tomtom algorithm (Shobhit et al., 2007; Khan et al., 2018).

3. Results

3.1 Sample descriptive statistics and quality control

During the quality control procedures, a total of 26 out of the 269 samples were removed from further analysis (see **Figure 1**). Of those, five samples were excluded due to insufficient call rate and/or exceeded SD of LRR and BAF related to poor sample quality and genotyping errors. Another 18 samples were removed as population outliers (See **Figure S1**) or due to sample relatedness or the inconsistency between self-reported and genotyped sex. Three samples were disqualified after CNVs calling and merging due to an exceeded number of detected CNVs. The remaining 243 IBD individuals were included in the study. Of the included IBD samples, 97 were from persons with PC and 146 were from persons without PC. The comparison of several clinical and social characteristics of IBD with and without PC was shown in **Table 2**. No significant difference of sex, age, martial status and subtypes of IBD between IBD+PC and IBD groups was observed, while there was a significant association with IBD+PC for the level of adversity (adjusted p-value = 0.05, odds ratio (OR)=2.04, 95% Confidence Interval (95% CI)=1.15-3.63).

3.2 Allelic association test

After the quality control procedures, we completed a genome-wide allelic association analysis of 1,267,826 SNPs in 97 IBD+PC and 146 IBD cases. Results of the allelic association test have been visualized by Manhattan plot and Q-Q plot as shown in **Figure S2** and **Figure S3**, respectively**.** We can see there is no obvious deviation for observed p-values distribution from expected p values distribution, and inflation factor λ_{gc} is 1.00, which indicates there is no systematic bias in association analysis and no potential subpopulation structure in the study data. We did not find SNPs with significant associations with the risk for PC in IBD at genome-wide significance level 5×10^{-8}. However, there were 14 SNPs identified at the suggestive significance level 1×10^{-5}(**Supplementary Table 2**). **Figure S2** showed that the SNPs on chromosomes 3, 8, 16 and 18 were enriched for the associations of the suggestive level of significance and SNPs on chromosome 8 exhibited the strongest signals. Among them, the strongest association was observed for two SNPs placed on chromosome 8 in the intron region of the RBPMS gene (**Figure S4**). This gene encoded a member of the RNA recognition motif family of RNA-binding proteins involved in the nucleotide binding process and was previously reported in association with numerous blood count traits, including lymphocyte and neutrophil percentage of white blood cells (Astle et al., 2016).

3.3 CNV burden

After CNVs quality control and merging the results of three CNV calling algorithms, 2,086 stringent CNVs were kept for the further analysis, which included 1,089 deletions and 997 duplications. Overall, 1,054 CNVs (97%) overlapped at least one gene and were analyzed as genic CNVs. Of those, 456 and 598 were found in the samples with and without PC, respectively. More than a half of the detected CNVs (62%) were less than 100 kbp in size. However, 199 samples (82%) contained at least one CNV with a size larger than 100 kbp and 42 samples (17%) contained

CNVs longer than 500 kbp. Of those, 19 large CNVs were observed in IBD+PC samples, and 25 such CNVs were detected in IBD samples, including 11 and 16 genic CNVs, correspondingly. The number of medium-sized (100-500 kbp) duplications observed in IBD+PC cases significantly exceeded their number found in IBD cases (permutation test p-values 0.048 and 0.049 for all CNVs and genic CNVs correspondingly). All other size groups were not significantly overrepresented in one of the two sample groups (see **Supplementary Table 3** for details).

3.4 Gene-based CNV association analysis

Overall, 1,149 genes were intersected by at least one CNV (deletion or duplication) in at least one analysed sample; 589 and 644 genes were overlapped by deletions and duplications, correspondingly. For each gene, we compared the number of overlapping CNVs in an IBD+PC population with the number of overlapping CNVs in IBD groups. This comparison was conducted separately for deletions and duplications. After the correction of p-values for multiple testing over 1,233 comparisons, no significant association was observed. Of all CNV-overlapped genes, HLA-DRB5 and FAM35DP reached the highest level of significance (Fisher's exact test p-value = 0.12). The HLA-DRB5 gene was overlapped by deletions in five IBD+PC and two IBD samples. Similarly, the FAM35DP gene was overlapped by five duplications in IBD+PC and two in IBD groups. The HLA-DRB5 gene belongs to the HLA class II beta chain paralogues, which plays a central role in the immune system by presenting extracellular peptides and polysaccharides. The FAM35DP is a pseudogene. Both regions are overlapped by common CNVs detected in numerous genome-wide CNV studies. Disorders associated with genomic variants in the HLA-DRB5 gene locus include IBD (Anderson et al., 2011; de Lange et al., 2017; Franke et al., 2010; McGovern et al., 2010; Yang et al., 2014), rheumatoid arthritis (Jiang et al., 2014; Okada et al., 2014; Padyukov

et al., 2011; Saxena et al., 2017) and schizophrenia (Anney et al., 2017; Ripke et al., 2013). The result of the gene-based CNV association analysis is presented in the **Supplementary Table 4**.

3.5 Gene set overrepresentation analysis

We analysed 12 customised gene sets (GS), related to immune or nervous systems for the enrichment of CNV in IBD+PC or IBD. For these analyses, duplications and deletions were considered separately. In general, all tested groups of CNV-overlapped genes were presented in each of GS by at least one gene. Genes, overlapped by deletions in the IBD+PC population were overrepresented in four GSs related to the immune system with a nominal p-value < 0.05. The overrepresentation in two GSs (GO Cytokine pathways, and Cytokine pathways included relevant GSs from KEGG and GO) survived the multiple testing correction ($P_{corr} < 0.05$). In turn, the enrichment of group of genes, overlapped by duplications in IBD reached nominal significance in two GSs of neurological relevance: GO NS Development, and combined GS contained all genes related to the nervous system functioning. The same gene group was significantly underrepresented in the GSs related to the immune system; the genes overlapped by duplication in IBD+PC were underrepresented in the immune-related GSs as well. The details of the gene set overrepresentation analysis are presented in the **Supplementary Table 5**.

We analysed the CNV-overlapped genes related to the cytokines biosynthesis, production, and secretion, as well as cellular response to the cytokines stimulus (i.e., genes included in the "Cytokine pathways") comparing the genes overlapped by deletions and duplications in IBD+PC and IBD groups. It was found that most of the CNV-overlapped cytokine-related genes present in only one of the four tested gene groups. Some intersection were observed between groups of genes, overlapped by the same type of CNV (deletions or duplications) in IBD+PC and IBD, but not between groups of genes overlapped by a different type of CNVs in the same group of IBD

314 individuals (**Figure 3**). Thus, 34 genes were overlapped by deletions exclusively in the IBD
315 individuals with PC, 17 genes were overlapped by deletions in IBD group, and only seven genes
316 were overlapped by deletions in both groups. In turn, 10 and 13 genes were duplicated in IBD+PC
317 and IBD groups, correspondingly, while only three genes were overlapped by duplications in both
318 IBD+PC and IBD groups.

319 Of the 88 CNV-overlapped genes included in "Cytokine pathways", 46 were also included to one
320 or more neurological GSs. 26 genes were functionally related to the regulation of neuron
321 development and differentiation, neuron projection guidance and morphogenesis, response to the
322 neurotrophin, and, finally, to the neuron death. Of these genes, 15 were overlapped by deletions in
323 one or more IBD+PC individuals. In turn, 22 genes were also involved in the nervous system
324 development, and 10 of them were overlapped by deletions in IBD+PC. Similarly, eight genes
325 (three deleted in IBD+PC) were linked to the biosynthesis, metabolism or transport of
326 neurotransmitters, including dopamine, glutamate and nitric oxide. Nine genes, including three
327 deleted in IBD+PC, were associated with synaptic transmission and plasticity. Of seven genes
328 played a role in the higher cognitive functions, two were overlapped by deletions in IBD+PC.
329 Finally, ten genes (with five deleted in IBD+PC) were also included in "KEGG Neuronal System"
330 gene set (**Figure 4**).

331 ## 3.6 Identification of DNA motifs

332 We identified a motif overrepresented in the promoter regions of the 44 genes with an e-value of
333 2.8×10^{-8}, which was found in 29 of the 44 tested sequences (**Figure 5A**). This motif matched to
334 MA0528.1 (ZNF263) DNA motif from the JASPAR database belongs to the C2H2 zinc finger
335 factors class with q-value = 6.5×10^{-4} (**Figure 5B**). ZNF263 was described as a RNA polymerase
336 II-specific DNA-binding transcription factor, which has both positive and negative effects on the

337 wide range of target genes. The functional analysis of the target genes showed that ZNF263 may
338 play a critical role in maintaining cell structure and cell proliferation processes (Frietze et al.,
339 2009).

340 ## 4. Discussion

341 The prevalence of the middle size duplications was significantly enriched in the IBD+PC group,
342 but there was no difference of the smaller and larger duplications or deletions of any size between
343 the two IBD groups. Similarly, no significant association was observed in the gene-based CNV
344 association analysis. Although it is possible that that the individuals with IBD + PC had more
345 severe IBD or had longer duration IBD, which can potentially result in higher burden of median-
346 sized CNVs in IBD patients with PC, we analysed for PC in relation to IBD duration and also in
347 relation to the need for surgery or the need for infliximab usage as estimates of IBD severity. None
348 of these three measures (p-value=0.13 for IBD duration, p-value=0.47 for the need for surgery and
349 p-value=0.60 for the need for infliximab usage, respectively) demonstrated a significant
350 relationship with PC.

351 It should be taken into account that both inflammatory and psychiatric disorders are influenced
352 by many genetic variants with weak effect size, probably common, as well as interactions among
353 them. An aggregated effect of genes associated with the same biological pathway can be detected
354 using gene set overrepresentation analysis. Despite the low frequency of particular CNVs
355 overlapping cytokine-related genes in the analysed sample, the observed overrepresentation of
356 genes, overlapped by deletions in IBD+PC, in the cytokine-related gene set supported the
357 importance of cytokine signalling pathways in the development of PC in IBD. The disruption of
358 cytokine signalling pathways can be considered as a risk factor for the development of chronic
359 inflammation, related to both IBD and PC conditions. Moreover, baseline low-grade inflammation

360 in predisposed patients can initiate depression disorder that can trigger the IBD by the
361 hypothalamic pituitary adrenal axis.

362 Cytokines and growth factors play the essential role for the proper development and functioning
363 of the central and peripheral nervous systems, as well as survival and healing of traumatized or
364 diseased neurons, synapse plasticity and cognitive functions (Schwartz and Kipnis, 2011;
365 Woodruff et al., 2011; Ziv et al., 2006). One of the aspects of the cytokine influence to the nervous
366 system is in reducing the activity of neurotrophins, mainly the brain-derived neurotrophic factor
367 (BDNF), which plays the central role in the synapse and neuronal plasticity (Duclot and Kabbaj,
368 2015; Lotrich, 2015). Changes in the BDNF expression and activity were reported in the studies
369 related to the depressive disorders and antidepressant efficacy (Castrén, 2014). Likewise, BDNF
370 was proposed as the critical element in the pathogenesis of bipolar disorder, posttraumatic stress
371 disorder, schizophrenia and neurodevelopment disorders (Autry and Monteggia, 2012; Castrén,
372 2014; Mitchelmore and Gede, 2014). In the results presented here, more than half of the cytokine-
373 related genes overlapped by CNVs in the analysed cohort were included in one or more GSs of
374 neurological relevance. This intersection was observed in the groups of genes, overlapped by
375 deletions and duplications in both IBD+PC and IBD groups. Moreover, the analysis of cytokine-
376 related genes, overlapped by deletions in the IBD individuals with PC, demonstrated that their
377 possible neurological effect is mediated by their regulatory role in the neuronal plasticity and
378 nervous system development rather than influence to synapses, neurotransmitters and higher
379 cognitive functioning.

380 The PC in our study encompassed major depression to generalized anxiety disorder. Often these
381 diseases present on a spectrum where they overlap, and several subjects had both disorders. Due

to the small sample size and relative overlap of these conditions, we performed our genetic analysis using all PC together as one cohort. We acknowledge this is a limitation in the study.

For the IBD patients recruited in this study, we do not know the timing of the PC status in relation to IBD onset. This may be a potential confounding factor in our association analysis. This limitation can be overcome by comparing IBD patients who developed PC before or after the development of IBD in a prospective study. We will explore this issue in our future research.

Although it has been well-known that patients with IBD have elevated incidence rates of depression, anxiety disorder, bipolar disorder and schizophrenia, the role of genetic factors in the development of PC in IBD is considerably underexplored. Our work is one of the first efforts and the largest study to date to explore the potential association between the CNV variants and IBD with psychiatric disorder. We recognize that our sample size is not large enough to test the true associations at individual SNP level. Using the strict permutation-based test and the candidate gene set (pathway)-based approach, we found that the cytokine-related signaling pathways may be significantly associated with the psychiatric co-morbidity status of the patients by aggregating the CNV-specific genetic effect at gene set level. These findings may be helpful for developing targeted drug treatments for IBD patients with PC.

5. Conclusion

Overall our findings show a polygenic predisposition for PC in relation to IBD. This predisposition is most likely linked to cytokine-related pathways and their effect on the neuronal plasticity. Our results demonstrate that genetic studies related to both inflammatory and psychiatric diseases are

warranted, which can include extensive GWAS analysis as well as other study designs focused on cytokine-signalling pathways.

Competing interests

In the past four years, Dr Bernstein has consulted to or served on advisory boards of Abbvie Canada, Shire Canada, Takeda Canada, Pfizer Canada, Janssen Canada, Ferring Canada, Napo Pharmaceuticals and Mylan Pharmaceuticals. In addition, he has the educational grants from Abbvie Canada, Janssen Canada, Pfizer Canada. Shire Canada and Takeda Canada and has served on speakers' bureaus for Ferring Canada, Abbvie Canada, Janssen Canada and Medtronic Canada. Other authors declare no conflict of interest for this manuscript.

Authors' contributions

SF performed the data analysis and drafted the manuscript. MS and QK prepared the samples for microarray analysis. WJ preprocessed the data and performed the genetic association analysis. WX supervised part of the genetic association analysis. CN and PZ designed and supervised the study. All authors have reviewed and approved the manuscript.

Acknowledgement

The authors wish to acknowledge Dr. Sophia Rapoport, Dr. John Wei and Bhooma Thiruvahindrapuram for their useful help during the manuscript preparation. We also want to express our gratitude to Dr. John Wilkins for his great support.

Funding

This work was supported in part by Health Sciences Centre Foundation, Mitacs, Manitoba Research Health Council and the University of Manitoba.

Ethics approval

This study has been approved by the University of Manitoba Health Research Ethics Board.

Consent for Publication

Informed consent was obtained from all individual participants in the study.

Data Availability

The list of the stringent CNVs detected in this study is available in the NCBI dbVar database (id: nstd157).

Figures

Figure 1. Quality control and analysis workflow. The scheme is describing the main steps of the CNV detecting: microarray probes quality control, CNV calling, CNV quality control and stringent CNV merging. Quality control criteria and reasons for disqualification are provided for each step. SD: Standard deviation; LRR: Log R ratio; BAF: B allele frequency.

Figure 2. The results of gene set overrepresentation analysis. The gene set overrepresentation analysis was conducted by comparison of the lists o CNV-overlapped genes in two groups of individuals and lists of genes related to certain functional pathways (gene sets). We analysed the lists of genes overlapped by deletions and duplications in the group of individuals with Inflammatory Bowel Disease with and without psychiatric comorbidity (IBD+PC and IBD, correspondingly). The customised gene sets (GSs) contained genes functionally related to the immune and nervous system activity and were formed by merging Gene Ontology (GO) and KEGG pathway-derived sets of neurobiological and immunological relevance. The detailed list of GO terms and KEGG pathways included in each of GSs is presented in the **Supplementary Table 1**. Node shape legend: circle - functional gene sets; diamond - list of genes overlapped by

deletions; triangle - list of genes overlapped by duplications. Node colour legend: blue - list of genes overlapped by CNV in IBD patients with PC; white - list of genes overlapped by CNV in IBD patients without PC; green - gene sets functionally related to the immune system; orange - gene sets functionally related to the nervous system. Edge legend: edges width represents the number of genes in the intersection of the gene list and gene set (12-76 genes). The intersections between tested gene sets are removed. Pink edges connect gene list with significantly overrepresented gene set; blue edges connect gene lists with underrepresented gene sets; grey edges connect gene lists with gene sets, displayed not significant over- or underrepresentation. The odds ratio is provided only for the significant over- or underrepresentation ($P_{corr} < 0.05$).

Figure 3. The distribution of genes included in the "Cytokine Pathways" functional gene set in four lists of genes, overlapped by deletions or duplications in the samples from IBD patients with or without psychiatric comorbidity (IBD+PC and IBD, correspondingly). CNV-overlapped genes not included in the "Cytokine pathways" gene sets are not presented. Genes related to neurological functions are marked in bold. The significance of the overrepresentation was evaluated using Fisher's exact test. Benjamini-Hochberg method was used for multiple testing correction of p-values; p-value after correction (P_{corr}) is provided only for significantly overrepresented gene list.

Figure 4. Gene intersections between "Cytokine Pathways" and six gene sets of neurological relevance. Only CNV-overlapped genes included in the "Cytokine pathways" gene sets are presented.

Tables

Gene set	Gene group functions and source
GSs functionally related to the immune system	
KEGG Cytokine Pathways	Regulation of cytokine production, secretion, and signalling / KEGG pathways
GO Cytokine Pathways	Regulation of cytokine production, secretion, and signalling / GO database
GO Immune system	All immune and inflammatory processes not included in "GO Cytokine Pathways" / GO database
Cytokine Pathways (GO+KEGG)	Genes from the "KEGG Cytokine Pathways" and "GO Cytokine Pathways."
Immune System (GO+KEGG)	Genes from the "KEGG Cytokine Pathways," "GO Cytokine Pathways," and "GO Immune system."
GSs functionally related to the nervous system	
KEGG Neuronal Plasticity	Neuronal development, survival, and plasticity / KEGG pathways
GO Neuronal Plasticity	Neuronal development, survival, and plasticity / GO database
GO Neurotransmitters	Neurotransmitters secretion, transport, metabolism etc. / GO database
GO Synapse	Synapse organisation, maturation, plasticity, as well as synaptic potentiation and depression / GO database
GO NS Development	Central and peripheral nervous system development during the embryogenesis / GO database
GO Cognition	Behaviour, learning, memory, cognition / GO database

Nervous System (GO+KEGG)	All GSs functionally related to the nervous system combined

Table 1. Summary description of customised gene sets (GSs) functionally related to the immune and nervous system activity. The detailed list of GO terms and KEGG pathways included in each of GSs is presented in the Supplementary Table 1.

Clinical and social characteristics		IBD+PC	IBD	Fisher's exact test p-value (adjusted p-value**)
Sex	Male	35 (36.1%)	71 (48.6%)	0.06 (0.15)
	Female	62 (63.9%)	75 (51.4%)	
Age	16 years and under	4 (4.1%)	10 (6.8%)	0.51 (0.6)
	17 to 40 years	61 (62.9%)	82 (56.2%)	
	Over 40 years	32 (33.0%)	54 (37.0%)	
Marital status	Married, living common-law	66 (68.0%)	105 (71.9%)	0.57 (0.6)
	Single, divorced, widowed	31 (32.0%)	41 (28.1%)	
Level of adversity*	High	45 (48.9%)	45 (31.9%)	0.01, OR=2.04, 95%CI=1.15-3.63(0.05)
	Low	47 (51.1%)	96 (68.1%)	
IBD subtype	Crohn's disease	50 (51.5%)	69 (47.3%)	0.60 (0.6)

	Ulcerative colitis	47 (48.5%)	77 (52.7%)	

Table 2. Clinical and social characteristics of IBD individuals included in the analysis.

* The number of traumatic events, including sexual and physical violence, prior to the age of 17; "high level of adversity" status was given to individuals with more than two traumatic early childhood events.

**adjusted p-value was corrected by Benjamini & Hochberg approach (Benjamini and Hochberg, 1995)

Supplementary Figures

Figure S1: Multidimensional scaling (MDS) plot with four populations (CEU - Utah residents with Northern and Western European ancestry from the CEPH collection, CHB - Han Chinese in Beijing, JPT - Han Chinese in Beijing, YRI - Yoruba in Ibadan) for the merged dataset of IBD samples in this study and 1000 Genome samples. The red line in the picture is a cut-off threshold for detecting population outliers, which corresponds to 0.025, which means samples with MDS C2 <0.025 were excluded as population outliers.

Figure S2: Manhattan Plot of allelic association test with suggestive p-value 5×10^{-5} (Blue Line) and GWAS default significant p-value 5×10^{-8}: (Red Line). Suggestive significant SNPs are highlighted by green

Figure S3: Q-Q plot of allelic association test (Black Line: Observed p-value distribution, Red Line: Expected p-value distribution)

Figure S4: Regional association plot with the most significantly associated SNP - rs3779641 at chromosome 8 with Flank size: +/- 400KB (Genome Build / LD Population: hg19 / 1000 genome Nov 2014 EUR). The Corresponding gene annotation is RRPMS

Supplementary Tables

Supplementary Table 1: The detailed list of GO terms and KEGG pathways included in gene sets for the gene set overrepresentation test.

Supplementary Table 2:: SNPs with a p-value of association < 1×10^{-5} are presented with closest genes within 500kb upstream and downstream window. A1/A2, the two alleles at each SNP (minor/major); A1 alternative allele frequency was tested for association, and its OR (odds ratio) and 95% confidential interval (CI) are shown.

Supplementary Table 3: All CNVs and gene-overlapping CNVs of different lengths observed in the samples from IBD+PC and IBD groups. Summary data for all CNV types and separated data for deletions and duplications are provided. IBD+PC and IBD rate represents the average number of CNVs per sample. For each CNV type and length, a permutation test was applied to evaluate the significance of prevalence of CNVs in one of the tested groups; the permutation procedure randomly permuted the IBD+PC and IBD groups and recalculated the ratio of IBD+PC rate / IBD rate for 100,000 permutations.

Supplementary Table 4: The results of the gene-based CNV association analysis. For each gene, numbers of CNVs in IBD+PC and IBD cohort, the odds ratio with 95% confidence interval, Fisher's exact test p-value and corrected p-value are presented. Genes not overlapped by CNVs are not presented. Deletions and duplications are presented separately.

Supplementary Table 5: The details of the gene set overrepresentation analysis. For each tested gene list, number and list of genes also included in each of the tested gene sets, odds ratio with 95% confidence interval, Fisher's exact test p-value and corrected p-value are presented. Also, the table contains a number of genes from gene list not included in the gene set, number of genes in gene set not overlapped by CNVs and number of background genes not included neither in gene set nor in the tested gene list.

Reference

Abautret-Daly, Á., Dempsey, E., Parra-Blanco, A., Medina, C., Harkin, A., 2017. Gut–brain actions underlying comorbid anxiety and depression associated with inflammatory bowel disease. Acta Neuropsychiatr. 1–22. https://doi.org/10.1017/neu.2017.3

Ahola-Olli, A. V., Würtz, P., Havulinna, A.S., Aalto, K., Pitkänen, N., Lehtimäki, T., Kähönen, M., Lyytikäinen, L.P., Raitoharju, E., Seppälä, I., Sarin, A.P., Ripatti, S., Palotie, A., Perola, M., Viikari, J.S., Jalkanen, S., Maksimow, M., Salomaa, V., Salmi, M., Kettunen, J., Raitakari, O.T., 2017. Genome-wide Association Study Identifies 27 Loci Influencing Concentrations of Circulating Cytokines and Growth Factors. Am. J. Hum. Genet. 100, 40–50. https://doi.org/10.1016/j.ajhg.2016.11.007

572 Ananthakrishnan, A.N., 2015. Epidemiology and risk factors for IBD. Nat. Rev. Gastroenterol.
573 Hepatol. 12, 205–217. https://doi.org/10.1038/nrgastro.2015.34

574 Anderson, C.A., Boucher, G., Lees, C.W., Franke, A., D'Amato, M., Taylor, K.D., Lee, J.C.,
575 Goyette, P., Imielinski, M., Latiano, A., others, 2011. Meta-analysis identifies 29 additional
576 ulcerative colitis risk loci, increasing the number of confirmed associations to 47
577 Supplementary. Nat. Genet. 43, 246–252. https://doi.org/10.1038/ng.764

578 Andreoulakis, E., Hyphantis, T., Kandylis, D., Iacovides, A., 2012. Depression in diabetes
579 mellitus: a comprehensive review. Hippokratia 16, 205–14.

580 Anglin, R.E.S., Samaan, Z., Walter, S.D., McDonald, S.D., 2013. Vitamin D deficiency and
581 depression in adults: systematic review and meta-analysis. Br. J. Psychiatry 202, 100–107.
582 https://doi.org/10.1192/bjp.bp.111.106666

583 Anney, R.J.L., Ripke, S., Anttila, V., Consortium, A.S.D.W.G. of T.P.G., 2017. Meta-analysis of
584 GWAS of over 16,000 individuals with autism spectrum disorder highlights a novel locus at
585 10q24.32 and a significant overlap with schizophrenia. Mol. Autism 8, 21.
586 https://doi.org/10.1186/s13229-017-0137-9

587 Astle, W.J., Elding, H., Jiang, T., Allen, D., Ruklisa, D., Mann, A.L., Mead, D., Bouman, H.,
588 Riveros-Mckay, F., Kostadima, M.A., Lambourne, J.J., Sivapalaratnam, S., Downes, K.,
589 Kundu, K., Bomba, L., Berentsen, K., Bradley, J.R., Daugherty, L.C., Delaneau, O., Freson,
590 K., Garner, S.F., Grassi, L., Guerrero, J., Haimel, M., Janssen-Megens, E.M., Kaan, A.,
591 Kamat, M., Kim, B., Mandoli, A., Marchini, J., Martens, J.H.A., Meacham, S., Megy, K.,
592 O'Connell, J., Petersen, R., Sharifi, N., Sheard, S.M., Staley, J.R., Tuna, S., van der Ent, M.,
593 Walter, K., Wang, S.Y., Wheeler, E., Wilder, S.P., Iotchkova, V., Moore, C., Sambrook, J.,

Stunnenberg, H.G., Di Angelantonio, E., Kaptoge, S., Kuijpers, T.W., Carrillo-de-Santa-Pau, E., Juan, D., Rico, D., Valencia, A., Chen, L., Ge, B., Vasquez, L., Kwan, T., Garrido-Martín, D., Watt, S., Yang, Y., Guigo, R., Beck, S., Paul, D.S., Pastinen, T., Bujold, D., Bourque, G., Frontini, M., Danesh, J., Roberts, D.J., Ouwehand, W.H., Butterworth, A.S., Soranzo, N., 2016. The Allelic Landscape of Human Blood Cell Trait Variation and Links to Common Complex Disease. Cell 167, 1415–1429.e19. https://doi.org/10.1016/j.cell.2016.10.042

Auton, A., Abecasis, G.R., Altshuler, D.M., Durbin, R.M., Abecasis, G.R., Bentley, D.R., Chakravarti, A., Clark, A.G., Donnelly, P., Eichler, E.E., Flicek, P., Gabriel, S.B., Gibbs, R.A., Green, E.D., Hurles, M.E., Knoppers, B.M., Korbel, J.O., Lander, E.S., Lee, C., Lehrach, H., Mardis, E.R., Marth, G.T., McVean, G.A., Nickerson, D.A., Schmidt, J.P., Sherry, S.T., Wang, J., Wilson, R.K., Gibbs, R.A., Boerwinkle, E., Doddapaneni, H., Han, Y., Korchina, V., Kovar, C., Lee, S., Muzny, D., Reid, J.G., Zhu, Y., Wang, J., Chang, Y., Feng, Q., Fang, X., Guo, X., Jian, M., Jiang, H., Jin, X., Lan, T., Li, G., Li, J., Li, Y., Liu, S., Liu, X., Lu, Y., Ma, X., Tang, M., Wang, B., Wang, G., Wu, H., Wu, R., Xu, X., Yin, Y., Zhang, D., Zhang, W., Zhao, J., Zhao, M., Zheng, X., Lander, E.S., Altshuler, D.M., Gabriel, S.B., Gupta, N., Gharani, N., Toji, L.H., Gerry, N.P., Resch, A.M., Flicek, P., Barker, J., Clarke, L., Gil, L., Hunt, S.E., Kelman, G., Kulesha, E., Leinonen, R., McLaren, W.M., Radhakrishnan, R., Roa, A., Smirnov, D., Smith, R.E., Streeter, I., Thormann, A., Toneva, I., Vaughan, B., Zheng-Bradley, X., Bentley, D.R., Grocock, R., Humphray, S., James, T., Kingsbury, Z., Lehrach, H., Sudbrak, R., Albrecht, M.W., Amstislavskiy, V.S., Borodina, T.A., Lienhard, M., Mertes, F., Sultan, M., Timmermann, B., Yaspo, M.-L., Mardis, E.R., Wilson, R.K., Fulton, L., Fulton, R., Sherry, S.T., Ananiev, V., Belaia, Z., Beloslyudtsev, D., Bouk, N., Chen, C., Church, D., Cohen, R., Cook, C., Garner, J., Hefferon, T., Kimelman,

M., Liu, C., Lopez, J., Meric, P., O'Sullivan, C., Ostapchuk, Y., Phan, L., Ponomarov, S., Schneider, V., Shekhtman, E., Sirotkin, K., Slotta, D., Zhang, H., McVean, G.A., Durbin, R.M., Balasubramaniam, S., Burton, J., Danecek, P., Keane, T.M., Kolb-Kokocinski, A., McCarthy, S., Stalker, J., Quail, M., Schmidt, J.P., Davies, C.J., Gollub, J., Webster, T., Wong, B., Zhan, Y., Auton, A., Campbell, C.L., Kong, Y., Marcketta, A., Gibbs, R.A., Yu, F., Antunes, L., Bainbridge, M., Muzny, D., Sabo, A., Huang, Z., Wang, J., Coin, L.J.M., Fang, L., Guo, X., Jin, X., Li, G., Li, Q., Li, Y., Li, Z., Lin, H., Liu, B., Luo, R., Shao, H., Xie, Y., Ye, C., Yu, C., Zhang, F., Zheng, H., Zhu, H., Alkan, C., Dal, E., Kahveci, F., Marth, G.T., Garrison, E.P., Kural, D., Lee, W.-P., Fung Leong, W., Stromberg, M., Ward, A.N., Wu, J., Zhang, M., Daly, M.J., DePristo, M.A., Handsaker, R.E., Altshuler, D.M., Banks, E., Bhatia, G., del Angel, G., Gabriel, S.B., Genovese, G., Gupta, N., Li, H., Kashin, S., Lander, E.S., McCarroll, S.A., Nemesh, J.C., Poplin, R.E., Yoon, S.C., Lihm, J., Makarov, V., Clark, A.G., Gottipati, S., Keinan, A., Rodriguez-Flores, J.L., Korbel, J.O., Rausch, T., Fritz, M.H., Stütz, A.M., Flicek, P., Beal, K., Clarke, L., Datta, A., Herrero, J., McLaren, W.M., Ritchie, G.R.S., Smith, R.E., Zerbino, D., Zheng-Bradley, X., Sabeti, P.C., Shlyakhter, I., Schaffner, S.F., Vitti, J., Cooper, D.N., Ball, E. V., Stenson, P.D., Bentley, D.R., Barnes, B., Bauer, M., Keira Cheetham, R., Cox, A., Eberle, M., Humphray, S., Kahn, S., Murray, L., Peden, J., Shaw, R., Kenny, E.E., Batzer, M.A., Konkel, M.K., Walker, J.A., MacArthur, D.G., Lek, M., Sudbrak, R., Amstislavskiy, V.S., Herwig, R., Mardis, E.R., Ding, L., Koboldt, D.C., Larson, D., Ye, K., Gravel, S., Swaroop, A., Chew, E., Lappalainen, T., Erlich, Y., Gymrek, M., Frederick Willems, T., Simpson, J.T., Shriver, M.D., Rosenfeld, J.A., Bustamante, C.D., Montgomery, S.B., De La Vega, F.M., Byrnes, J.K., Carroll, A.W., DeGorter, M.K., Lacroute, P., Maples, B.K., Martin, A.R., Moreno-Estrada, A., Shringarpure, S.S., Zakharia,

F., Halperin, E., Baran, Y., Lee, C., Cerveira, E., Hwang, J., Malhotra, A., Plewczynski, D., Radew, K., Romanovitch, M., Zhang, C., Hyland, F.C.L., Craig, D.W., Christoforides, A., Homer, N., Izatt, T., Kurdoglu, A.A., Sinari, S.A., Squire, K., Sherry, S.T., Xiao, C., Sebat, J., Antaki, D., Gujral, M., Noor, A., Ye, K., Burchard, E.G., Hernandez, R.D., Gignoux, C.R., Haussler, D., Katzman, S.J., James Kent, W., Howie, B., Ruiz-Linares, A., Dermitzakis, E.T., Devine, S.E., Abecasis, G.R., Min Kang, H., Kidd, J.M., Blackwell, T., Caron, S., Chen, W., Emery, S., Fritsche, L., Fuchsberger, C., Jun, G., Li, B., Lyons, R., Scheller, C., Sidore, C., Song, S., Sliwerska, E., Taliun, D., Tan, A., Welch, R., Kate Wing, M., Zhan, X., Awadalla, P., Hodgkinson, A., Li, Y., Shi, X., Quitadamo, A., Lunter, G., McVean, G.A., Marchini, J.L., Myers, S., Churchhouse, C., Delaneau, O., Gupta-Hinch, A., Kretzschmar, W., Iqbal, Z., Mathieson, I., Menelaou, A., Rimmer, A., Xifara, D.K., Oleksyk, T.K., Fu, Y., Liu, X., Xiong, M., Jorde, L., Witherspoon, D., Xing, J., Eichler, E.E., Browning, B.L., Browning, S.R., Hormozdiari, F., Sudmant, P.H., Khurana, E., Durbin, R.M., Hurles, M.E., Tyler-Smith, C., Albers, C.A., Ayub, Q., Balasubramaniam, S., Chen, Y., Colonna, V., Danecek, P., Jostins, L., Keane, T.M., McCarthy, S., Walter, K., Xue, Y., Gerstein, M.B., Abyzov, A., Balasubramanian, S., Chen, J., Clarke, D., Fu, Y., Harmanci, A.O., Jin, M., Lee, D., Liu, J., Jasmine Mu, X., Zhang, J., Zhang, Y., Li, Y., Luo, R., Zhu, H., Alkan, C., Dal, E., Kahveci, F., Marth, G.T., Garrison, E.P., Kural, D., Lee, W.-P., Ward, A.N., Wu, J., Zhang, M., McCarroll, S.A., Handsaker, R.E., Altshuler, D.M., Banks, E., del Angel, G., Genovese, G., Hartl, C., Li, H., Kashin, S., Nemesh, J.C., Shakir, K., Yoon, S.C., Lihm, J., Makarov, V., Degenhardt, J., Korbel, J.O., Fritz, M.H., Meiers, S., Raeder, B., Rausch, T., Stütz, A.M., Flicek, P., Paolo Casale, F., Clarke, L., Smith, R.E., Stegle, O., Zheng-Bradley, X., Bentley, D.R., Barnes, B., Keira Cheetham, R., Eberle, M., Humphray, S., Kahn, S., Murray, L., Shaw,

663 R., Lameijer, E.-W., Batzer, M.A., Konkel, M.K., Walker, J.A., Ding, L., Hall, I., Ye, K.,
664 Lacroute, P., Lee, C., Cerveira, E., Malhotra, A., Hwang, J., Plewczynski, D., Radew, K.,
665 Romanovitch, M., Zhang, C., Craig, D.W., Homer, N., Church, D., Xiao, C., Sebat, J., Antaki,
666 D., Bafna, V., Michaelson, J., Ye, K., Devine, S.E., Gardner, E.J., Abecasis, G.R., Kidd, J.M.,
667 Mills, R.E., Dayama, G., Emery, S., Jun, G., Shi, X., Quitadamo, A., Lunter, G., McVean,
668 G.A., Chen, K., Fan, X., Chong, Z., Chen, T., Witherspoon, D., Xing, J., Eichler, E.E.,
669 Chaisson, M.J., Hormozdiari, F., Huddleston, J., Malig, M., Nelson, B.J., Sudmant, P.H.,
670 Parrish, N.F., Khurana, E., Hurles, M.E., Blackburne, B., Lindsay, S.J., Ning, Z., Walter, K.,
671 Zhang, Y., Gerstein, M.B., Abyzov, A., Chen, J., Clarke, D., Lam, H., Jasmine Mu, X., Sisu,
672 C., Zhang, J., Zhang, Y., Gibbs, R.A., Yu, F., Bainbridge, M., Challis, D., Evani, U.S., Kovar,
673 C., Lu, J., Muzny, D., Nagaswamy, U., Reid, J.G., Sabo, A., Yu, J., Guo, X., Li, W., Li, Y.,
674 Wu, R., Marth, G.T., Garrison, E.P., Fung Leong, W., Ward, A.N., del Angel, G., DePristo,
675 M.A., Gabriel, S.B., Gupta, N., Hartl, C., Poplin, R.E., Clark, A.G., Rodriguez-Flores, J.L.,
676 Flicek, P., Clarke, L., Smith, R.E., Zheng-Bradley, X., MacArthur, D.G., Mardis, E.R.,
677 Fulton, R., Koboldt, D.C., Gravel, S., Bustamante, C.D., Craig, D.W., Christoforides, A.,
678 Homer, N., Izatt, T., Sherry, S.T., Xiao, C., Dermitzakis, E.T., Abecasis, G.R., Min Kang, H.,
679 McVean, G.A., Gerstein, M.B., Balasubramanian, S., Habegger, L., Yu, H., Flicek, P., Clarke,
680 L., Cunningham, F., Dunham, I., Zerbino, D., Zheng-Bradley, X., Lage, K., Berg Jespersen,
681 J., Horn, H., Montgomery, S.B., DeGorter, M.K., Khurana, E., Tyler-Smith, C., Chen, Y.,
682 Colonna, V., Xue, Y., Gerstein, M.B., Balasubramanian, S., Fu, Y., Kim, D., Auton, A.,
683 Marcketta, A., Desalle, R., Narechania, A., Wilson Sayres, M.A., Garrison, E.P., Handsaker,
684 R.E., Kashin, S., McCarroll, S.A., Rodriguez-Flores, J.L., Flicek, P., Clarke, L., Zheng-
685 Bradley, X., Erlich, Y., Gymrek, M., Frederick Willems, T., Bustamante, C.D., Mendez, F.L.,

David Poznik, G., Underhill, P.A., Lee, C., Cerveira, E., Malhotra, A., Romanovitch, M., Zhang, C., Abecasis, G.R., Coin, L., Shao, H., Mittelman, D., Tyler-Smith, C., Ayub, Q., Banerjee, R., Cerezo, M., Chen, Y., Fitzgerald, T.W., Louzada, S., Massaia, A., McCarthy, S., Ritchie, G.R., Xue, Y., Yang, F., Gibbs, R.A., Kovar, C., Kalra, D., Hale, W., Muzny, D., Reid, J.G., Wang, J., Dan, X., Guo, X., Li, G., Li, Y., Ye, C., Zheng, X., Altshuler, D.M., Flicek, P., Clarke, L., Zheng-Bradley, X., Bentley, D.R., Cox, A., Humphray, S., Kahn, S., Sudbrak, R., Albrecht, M.W., Lienhard, M., Larson, D., Craig, D.W., Izatt, T., Kurdoglu, A.A., Sherry, S.T., Xiao, C., Haussler, D., Abecasis, G.R., McVean, G.A., Durbin, R.M., Balasubramaniam, S., Keane, T.M., McCarthy, S., Stalker, J., Chakravarti, A., Knoppers, B.M., Abecasis, G.R., Barnes, K.C., Beiswanger, C., Burchard, E.G., Bustamante, C.D., Cai, H., Cao, H., Durbin, R.M., Gerry, N.P., Gharani, N., Gibbs, R.A., Gignoux, C.R., Gravel, S., Henn, B., Jones, D., Jorde, L., Kaye, J.S., Keinan, A., Kent, A., Kerasidou, A., Li, Y., Mathias, R., McVean, G.A., Moreno-Estrada, A., Ossorio, P.N., Parker, M., Resch, A.M., Rotimi, C.N., Royal, C.D., Sandoval, K., Su, Y., Sudbrak, R., Tian, Z., Tishkoff, S., Toji, L.H., Tyler-Smith, C., Via, M., Wang, Y., Yang, H., Yang, L., Zhu, J., Bodmer, W., Bedoya, G., Ruiz-Linares, A., Cai, Z., Gao, Y., Chu, J., Peltonen, L., Garcia-Montero, A., Orfao, A., Dutil, J., Martinez-Cruzado, J.C., Oleksyk, T.K., Barnes, K.C., Mathias, R.A., Hennis, A., Watson, H., McKenzie, C., Qadri, F., LaRocque, R., Sabeti, P.C., Zhu, J., Deng, X., Sabeti, P.C., Asogun, D., Folarin, O., Happi, C., Omoniwa, O., Stremlau, M., Tariyal, R., Jallow, M., Sisay Joof, F., Corrah, T., Rockett, K., Kwiatkowski, D., Kooner, J., Tịnh Hiê`n, T., Dunstan, S.J., Thuy Hang, N., Fonnie, R., Garry, R., Kanneh, L., Moses, L., Sabeti, P.C., Schieffelin, J., Grant, D.S., Gallo, C., Poletti, G., Saleheen, D., Rasheed, A., Brooks, L.D., Felsenfeld, A.L., McEwen, J.E., Vaydylevich, Y., Green, E.D., Duncanson, A., Dunn, M., Schloss, J.A.,

Wang, J., Yang, H., Auton, A., Brooks, L.D., Durbin, R.M., Garrison, E.P., Min Kang, H., Korbel, J.O., Marchini, J.L., McCarthy, S., McVean, G.A., Abecasis, G.R., 2015. A global reference for human genetic variation. Nature 526, 68–74. https://doi.org/10.1038/nature15393

Autry, A.E., Monteggia, L.M., 2012. Brain-derived neurotrophic factor and neuropsychiatric disorders. Pharmacol Rev 64, 238–258. https://doi.org/10.1124/pr.111.005108

Benjamini, Y., and Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. Journal of the Royal Statistical Society Series B 57, 289–300.

Berk, M., Williams, L.J., Jacka, F.N., Neil, A.O., Pasco, J.A., Moylan, S., Allen, N.B., Stuart, A.L., Hayley, A.C., Byrne, M.L., Maes, M., 2013. So depression is an inflammatory disease, but where does the inflammation c...: EBSCOhost 1–16.

Bernstein, C.N., Hitchon, C.A., Walld, R., Bolton, J.M., Sareen, J., Walker, J.R., Graff, L.A., Patten, S.B., Singer, A., Lix, L.M., El-Gabalawy, R., Katz, A., Fisk, J.D., Marrie, R.A., 2018. Increased Burden of Psychiatric Disorders in Inflammatory Bowel Disease. Inflamm. Bowel Dis. https://doi.org/10.1093/ibd/izy235

Bodian, D.L., McCutcheon, J.N., Kothiyal, P., Huddleston, K.C., Iyer, R.K., Vockley, J.G., Niederhuber, J.E., 2014. Germline variation in cancer-susceptibility genes in a healthy, ancestrally diverse cohort: Implications for individual genome sequencing. PLoS One 9. https://doi.org/10.1371/journal.pone.0094554

Bonaz, B.L., Bernstein, C.N., 2013. Brain-gut interactions in inflammatory bowel disease.

730 Gastroenterology 144, 36–49. https://doi.org/10.1053/j.gastro.2012.10.003

731 Castrén, E., 2014. Neurotrophins and Psychiatric Disorders. pp. 461–479.
732 https://doi.org/10.1007/978-3-642-45106-5_17

733 Cawthorpe, D., 2015. Temporal Comorbidity of Mental Disorder and Ulcerative Colitis. Perm. J.
734 19, 52–57. https://doi.org/10.7812/TPP/14-120

735 Chang, C.C., Chow, C.C., Tellier, L.C., Vattikuti, S., Purcell, S.M., Lee, J.J., Purcell, S., Neale,
736 B., Todd-Brown, K., Thomas, L., Ferreira, M., Bender, D., Browning, B., Browning, S.,
737 Howie, B., Donnelly, P., Marchini, J., McKenna, A., Hanna, M., Banks, E., Sivachenko, A.,
738 Cibulskis, K., Kernytsky, A., Danecek, P., Auton, A., Abecasis, G., Albers, C., Banks, E.,
739 DePristo, M., Li, H., Handsaker, B., Wysoker, A., Fennell, T., Ruan, J., Homer, N., Yang, J.,
740 Lee, S., Goddard, M., Visscher, P., Lee, V., Kim, C., Chhugani, J., Deisher, M., Kim, D.,
741 Nguyen, A., Haque, I., Pande, V., Walters, W., Hardy, H., Wigginton, J., Cutler, D., Abecasis,
742 G., Guo, S., Thompson, E., Mehta, C., Patel, N., Clarkson, D., Fan, Y., Joe, H., Requena, F.,
743 Ciudad, N.M., Lydersen, S., Fagerland, M., Laake, P., Graffelman, J., Moreno, V., Wall, J.,
744 Pritchard, J., Gabriel, S., Schaffner, S., Nguyen, H., Moore, J., Roy, J., Blumenstiel, B.,
745 Barrett, J., Fry, B., Maller, J., Daly, M., Hill, W., Gaunt, T., Rodríguez, S., Day, I., Taliun,
746 D., Gamper, J., Pattaro, C., Friedman, J., Hastie, T., Höfling, H., Tibshirani, R., Vattikuti, S.,
747 Lee, J., Chang, C., Hsu, S., Chow, C., Steiß, V., Letschert, T., Schäfer, H., Pahl, R., Wan, X.,
748 Yang, C., Yang, Q., Xue, H., Fan, X., Tang, N., Ueki, M., Cordell, H., Abecasis, G., Cardon,
749 L., Cookson, W., Ewens, W., Li, M., Spielman, R., Su, Z., Marchini, J., Donnelly, P., Xu, Y.,
750 Wu, Y., Song, C., Zhang, H., Defays, D., Browning, B., Browning, S., Browning, B., Loh,
751 P., Baym, M., Berger, B., Sambo, F., Camillo, B. Di, Toffolo, G., Cobelli, C., 2015. Second-

752 generation PLINK: rising to the challenge of larger and richer datasets. Gigascience 4, 7.
753 https://doi.org/10.1186/s13742-015-0047-8

754 Clarke, G.M., Anderson, C. a, Pettersson, F.H., Cardon, L.R., Morris, A.P., Zondervan, K.T., 2011.
755 Basic statistical analysis in genetic case-control studies. Nat. Protoc. 6, 121–133.
756 https://doi.org/10.1038/nprot.2010.182

757 Colella, S., Yau, C., Taylor, J.M., Mirza, G., Butler, H., Clouston, P., Bassett, A.S., Seller, A.,
758 Holmes, C.C., Ragoussis, J., 2007. QuantiSNP: an Objective Bayes Hidden-Markov Model
759 to detect and accurately map copy number variation using SNP genotyping data. Nucleic
760 Acids Res. 35, 2013–2025. https://doi.org/10.1093/nar/gkm076

761 de Lange, K.M., Moutsianas, L., James C. Lee, Lamb, C.A., Luo, Y., Kennedy, N.A., Jostins, L.,
762 Rice, D.L., Gutierrez-Achury, J., Ji, S.-G., Heap, G., Nimmo, E.R., Edwards, C., Henderson,
763 P., Mowat, C., Sanderson, J., Satsangi, J., Simmons, A., Wilson, D.C., Tremelling, M., Hart,
764 A., Mathew, C.G., Newman, W., Parkes, M., Lees, C.W., Uhlig, H., Hawkey, C., Prescott,
765 N.J., Ahmad, T., Mansfield, J.C., Anderson, C.A., Barrett, J.C., 2017. Genome-wide
766 association study implicates immune activation of multiple integrin genes in inflammatory
767 bowel disease. Nat. Genet. 49, 256–261. https://doi.org/10.1038/ng.3760

768 Duclot, F., Kabbaj, M., 2015. Epigenetic mechanisms underlying the role of brain-derived
769 neurotrophic factor in depression and response to antidepressants. J. Exp. Biol. 218, 21–31.
770 https://doi.org/10.1242/jeb.107086

771 Enns, M.W., Bernstein, C.N., Kroeker, K., Graff, L., Walker, J.R., Lix, L.M., Hitchon, C.A., El-
772 Gabalawy, R., Fisk, J.D., Marrie, R.A., CIHR Team in Defining the Burden and Managing
773 the Effects of Psychiatric Comorbidity in Chronic Immunoinflammatory Disease, 2018. The

774 association of fatigue, pain, depression and anxiety with work and activity impairment in
775 immune mediated inflammatory diseases. PLoS One 13, e0198975.
776 https://doi.org/10.1371/journal.pone.0198975

777 Fan, Q., Guo, X., Tideman, J.W.L., Williams, K.M., Yazar, S., Hosseini, S.M., Howe, L.D.,
778 Pourcain, B.S., Evans, D.M., Timpson, N.J., McMahon, G., Hysi, P.G., Krapohl, E., Wang,
779 Y.X., Jonas, J.B., Baird, P.N., Wang, J.J., Cheng, C.Y., Teo, Y.Y., Wong, T.Y., Ding, X.,
780 Wojciechowski, R., Young, T.L., Pärssinen, O., Oexle, K., Pfeiffer, N., Bailey-Wilson, J.E.,
781 Paterson, A.D., Klaver, C.C.W., Plomin, R., Hammond, C.J., He, M., Saw, S.M.,
782 Guggenheim, J.A., Meguro, A., Wright, A.F., Hewitt, A.W., Young, A.L., Veluchamy, A.B.,
783 Metspalu, A., Döring, A., Khawaja, A.P., Klein, B.E., St Pourcain, B., Fleck, B., Klaver,
784 C.C.W., Hayward, C., Williams, C., Delcourt, C., Pang, C.P., Khor, C.C., Gieger, C.,
785 Simpson, C.L., Van Duijn, C.M., Mackey, D.A., Stambolian, D., Chew, E., Tai, E.S.,
786 Mihailov, E., Smith, G.D., Biino, G., Campbell, H., Rudan, I., Seppälä, I., Kaprio, J., Wilson,
787 J.F., Craig, J.E., Ried, J.S., Korobelnik, J.F., Fondran, J.R., Liao, J., Zhao, J.H., Xie, J., Kemp,
788 J.P., Lass, J.H., Rahi, J.S., Wedenoja, J., Mäkelä, K.M., Burdon, K.P., Khaw, K.T.,
789 Yamashiro, K., Chen, L.J., Xu, L., Farrer, L., Ikram, M.K., Deangelis, M.M., Morrison, M.,
790 Schache, M., Pirastu, M., Miyake, M., Yap, M.K.H., Fossarello, M., Kähönen, M., Tedja,
791 M.S., Yoshimura, N., Martin, N.G., Wareham, N.J., Mizuki, N., Raitakari, O., Polasek, O.,
792 Tam, P.O., Foster, P.J., Mitchell, P., Chen, P., Cumberland, P., Gharahkhani, P., Höhn, R.,
793 Fogarty, R.D., Luben, R.N., Igo, R.P., Klein, R., Janmahasatian, S., Yip, S.P., Feng, S.,
794 Vaccargiu, S., Panda-Jonas, S., MacGregor, S., Iyengar, S.K., Rantanen, T., Lehtimäki, T.,
795 Meitinger, T., Aung, T., Haller, T., Vitart, V., Nangia, V., Verhoeven, V.J.M., Jhanji, V.,
796 Zhao, W., Chen, W., Zhou, X., Lu, Y., Vatavuk, Z., 2016. Childhood gene-environment

interactions and age-dependent effects of genetic variants associated with refractive error and myopia: The CREAM Consortium. Sci. Rep. 6, 1–14. https://doi.org/10.1038/srep25853

Felger, J.C., Lotrich, F.E., 2013. Inflammatory cytokines in depression: Neurobiological mechanisms and therapeutic implications. Neuroscience 246, 199–229. https://doi.org/10.1016/j.neuroscience.2013.04.060

Filiano, A.J., Gadani, S.P., Kipnis, J., 2015. Interactions of innate and adaptive immunity in brain development and function. Brain Res. 1617, 18–27. https://doi.org/10.1016/j.brainres.2014.07.050

Foster, J.A., Rinaman, L., Cryan, J.F., 2017. Stress & the gut-brain axis: Regulation by the microbiome. Neurobiol. Stress 7, 124–136. https://doi.org/10.1016/j.ynstr.2017.03.001

Frank, B., Hoffmeister, M., Klopp, N., Illig, T., Chang-Claude, J., Brenner, H., 2010. Colorectal cancer and polymorphisms in DNA repair genes WRN, RMI1 and BLM. Carcinogenesis 31, 442–445. https://doi.org/10.1093/carcin/bgp293

Franke, a, McGovern, D., Barrett, J., Wang, K., Radford-Smith, G., Ahmad, T., Lees, C., Balschun, T., Lee, J., Roberts, R., Anderson, C., 2010. Meta-Analysis Increases to 71 the Tally of confirmed {C}rohn's Disease Susceptibility Loci. Nat. Genet. 42, 1118–1125. https://doi.org/10.1038/ng.717.Meta-Analysis

Franzen, P.L., Buysse, D.J., 2008. Sleep disturbances and depression: Risk relationships for subsequent depression and therapeutic implications. Dialogues Clin. Neurosci. 10, 473–481.

816 Frietze, S., Lan, X., Jin, V.X., Farnham, P.J., 2009. Genomic targets of the KRAB and SCAN
817 domain-containing zinc finger protein 263. *J Biol Chem*. 285(2), 1393–1403.
818 doi:10.1074/jbc.M109.063032

819 Graff, L.A., Vincent, N., Walker, J.R., Clara, I., Carr, R., Ediger, J., Miller, N., Rogala, L.,
820 Rawsthorne, P., Lix, L., Bernstein, C.N., 2011. A population-based study of fatigue and sleep
821 difficulties in inflammatory bowel disease. Inflamm. Bowel Dis. 17, 1882–1889.
822 https://doi.org/10.1002/ibd.21580

823 Grassmann, F., Kiel, C., Zimmermann, M.E., Gorski, M., Grassmann, V., Stark, K., Heid, I.M.,
824 Weber, B.H.F., Fritsche, L.G., Igl, W., Bailey, J.N.C., Sengupta, S., Bragg-Gresham, J.L.,
825 Burdon, K.P., Hebbring, S.J., Wen, C., Kim, I.K., Cho, D., Zack, D., Souied, E., Scholl,
826 H.P.N., Bala, E., Lee, K.E., Hunter, D.J., Sardell, R.J., Mitchell, P., Merriam, J.E., Cipriani,
827 V., Hoffman, J.D., Schick, T., Lechanteur, Y.T.E., Guymer, R.H., Johnson, M.P., Jiang, Y.,
828 Stanton, C.M., Buitendijk, G.H.S., Zhan, X., Kwong, A.M., Boleda, A., Brooks, M., Gieser,
829 L., Ratnapriya, R., Branham, K.E., Foerster, J.R., Heckenlively, J.R., Othman, M.I., Vote,
830 B.J., Liang, H.H., Souzeau, E., McAllister, I.L., Isaacs, T., Hall, J., Lake, S., Mackey, D.A.,
831 Constable, I.J., Craig, J.E., Kitchner, T.E., Yang, Z., Su, Z., Luo, H., Chen, D., Ouyang, H.,
832 Flagg, K., Lin, D., Mao, G., Ferreyra, H., von Strachwitz, C.N., Wolf, A., Brandl, C.,
833 Rudolph, G., Olden, M., Morrison, M.A., Morgan, D.J., Schu, M., Ahn, J., Silvestri, G.,
834 Tsironi, E.E., Park, K.H., Farrer, L.A., Orlin, A., Brucker, A., Li, M., Curcio, C.A., Mohand-
835 Saïd, S., Sahel, J.A., Audo, I., Benchaboune, M., Cree, A.J., Rennie, C.A., Goverdhan, S. V.,
836 Grunin, M., Hagbi-Levi, S., Campochiaro, P., Katsanis, N., Holz, F.G., Blond, F., Blanché,
837 H., Deleuze, J.F., Igo, R.P., Truitt, B., Peachey, N.S., Meuer, S.M., Myers, C.E., Moore, E.L.,
838 Klein, R., Hauser, M.A., Postel, E.A., Courtenay, M.D., Schwartz, S.G., Kovach, J.L., Scott,

W.K., Liew, G., Tan, A.G., Gopinath, B., Merriam, J.C., Smith, R.T., Khan, J.C., Shahid, H., Moore, A.T., McGrath, J.A., Laux, R., Brantley, M.A., Agarwal, A., Ersoy, L., Caramoy, A., Langmann, T., Saksens, N.T.M., de Jong, E.K., Hoyng, C.B., Cain, M.S., Richardson, A.J., Martin, T.M., Blangero, J., Weeks, D.E., Dhillon, B., van Duijn, C.M., Doheny, K.F., Romm, J., Klaver, C.C.W., Hayward, C., Gorin, M.B., Klein, M.L., Baird, P.N., den Hollander, A.I., Fauser, S., Yates, J.R.W., Allikmets, R., Wang, J.J., Schaumberg, D.A., Klein, B.E.K., Hagstrom, S.A., Chowers, I., Lotery, A.J., Léveillard, T., Zhang, K., Brilliant, M.H., Hewitt, A.W., Swaroop, A., Chew, E.Y., Pericak-Vance, M.A., DeAngelis, M., Stambolian, D., Haines, J.L., Iyengar, S.K., Abecasis, G.R., 2017. Genetic pleiotropy between age-related macular degeneration and 16 complex diseases and traits. Genome Med. 9, 1–13. https://doi.org/10.1186/s13073-017-0418-0

Gratten, J., Wray, N.R., Keller, M.C., Visscher, P.M., 2014. Large-scale genomics unveils the genetic architecture of psychiatric disorders. Nat. Neurosci. 17, 782–790. https://doi.org/10.1038/nn.3708

Green, E.K., Rees, E., Walters, J.T.R., Smith, K.-G., Forty, L., Grozeva, D., Moran, J.L., Sklar, P., Ripke, S., Chambert, K.D., Genovese, G., McCarroll, S.A., Jones, I., Jones, L., Owen, M.J., O'Donovan, M.C., Craddock, N., Kirov, G., 2016. Copy number variation in bipolar disorder. Mol. Psychiatry 21, 89–93. https://doi.org/10.1038/mp.2014.174

Guyatt, A.L., Stergiakouli, E., Martin, J., Walters, J., O'Donovan, M., Owen, M., Thapar, A., Kirov, G., Rodriguez, S., Rai, D., Zammit, S., Gaunt, T.R., 2018. Association of copy number variation across the genome with neuropsychiatric traits in the general population. Am. J. Med. Genet. Part B Neuropsychiatr. Genet. 1–14. https://doi.org/10.1002/ajmg.b.32637

Hare, D.L., Toukhsati, S.R., Johansson, P., Jaarsma, T., 2014. Depression and cardiovascular disease: A clinical review. Eur. Heart J. 35, 1365–1372. https://doi.org/10.1093/eurheartj/eht462

Hyde, C.L., Nagle, M.W., Tian, C., Chen, X., Paciga, S.A., Wendland, J.R., Tung, J.Y., Hinds, D.A., Perlis, R.H., Winslow, A.R., 2016. Identification of 15 genetic loci associated with risk of major depression in individuals of European descent. Nat. Genet. https://doi.org/10.1038/ng.3623

Jiang, L., Yin, J., Ye, L., Yang, J., Hemani, G., Liu, A.J., Zou, H., He, D., Sun, L., Zeng, X., Li, Z., Zheng, Y., Lin, Y., Liu, Y., Fang, Y., Xu, J., Li, Y., Dai, S., Guan, J., Jiang, L., Wei, Q., Wang, Y., Li, Y., Huang, C., Zuo, X., Liu, Y., Wu, X., Zhang, L., Zhou, L., Zhang, Q., Li, T., Chen, L., Xu, Z., Yang, X., Qian, F., Xie, W., Liu, W., Guo, Q., Huang, S., Zhao, J., Li, M., Jin, Y., Gao, J., Lv, Y., Wang, Y., Lin, L., Guo, A., Danoy, P., Willner, D., Cremin, C., Hadler, J., Zhang, F., Zhao, Y., Li, M., Yue, T., Fan, X., Guo, J., Mu, R., Li, J., Wu, C., Zeng, M., Wang, J., Li, S., Jin, L., Wang, B., Wang, J., Ma, X., Sun, L., Zhang, X., Brown, M.A., Visscher, P.M., Su, D.F., Xu, H., 2014. Novel risk loci for rheumatoid arthritis in han chinese and congruence with risk variants in europeans. Arthritis Rheumatol. 66, 1121–1132. https://doi.org/10.1002/art.38353

Jostins, L., Ripke, S., Weersma, R.K., Duerr, R.H., McGovern, D.P., Hui, K.Y., Lee, J.C., Philip Schumm, L., Sharma, Y., Anderson, C.A., Essers, J., Mitrovic, M., Ning, K., Cleynen, I., Theatre, E., Spain, S.L., Raychaudhuri, S., Goyette, P., Wei, Z., Abraham, C., Achkar, J.-P., Ahmad, T., Amininejad, L., Ananthakrishnan, A.N., Andersen, V., Andrews, J.M., Baidoo, L., Balschun, T., Bampton, P.A., Bitton, A., Boucher, G., Brand, S., Büning, C., Cohain, A.,

Cichon, S., D'Amato, M., De Jong, D., Devaney, K.L., Dubinsky, M., Edwards, C., Ellinghaus, D., Ferguson, L.R., Franchimont, D., Fransen, K., Gearry, R., Georges, M., Gieger, C., Glas, J., Haritunians, T., Hart, A., Hawkey, C., Hedl, M., Hu, X., Karlsen, T.H., Kupcinskas, L., Kugathasan, S., Latiano, A., Laukens, D., Lawrance, I.C., Lees, C.W., Louis, E., Mahy, G., Mansfield, J., Morgan, A.R., Mowat, C., Newman, W., Palmieri, O., Ponsioen, C.Y., Potocnik, U., Prescott, N.J., Regueiro, M., Rotter, J.I., Russell, R.K., Sanderson, J.D., Sans, M., Satsangi, J., Schreiber, S., Simms, L.A., Sventoraityte, J., Targan, S.R., Taylor, K.D., Tremelling, M., Verspaget, H.W., De Vos, M., Wijmenga, C., Wilson, D.C., Winkelmann, J., Xavier, R.J., Zeissig, S., Zhang, B., Zhang, C.K., Zhao, H., Silverberg, M.S., Annese, V., Hakonarson, H., Brant, S.R., Radford-Smith, G., Mathew, C.G., Rioux, J.D., Schadt, E.E., Daly, M.J., Franke, A., Parkes, M., Vermeire, S., Barrett, J.C., Cho, J.H., 2012. Host–microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature 491, 119–124. https://doi.org/10.1038/nature11582

Keeton, R.L., Mikocka-Walus, A., Andrews, J.M., 2015. Concerns and worries in people living with inflammatory bowel disease (IBD): A mixed methods study. J. Psychosom. Res. 78, 573–578. https://doi.org/10.1016/j.jpsychores.2014.12.004

Khan, A., Fornes, O., Stigliani, A., Gheorghe, M., Castro-Mondragon, J.A., van der Lee, R., Bessy, A., Chèneby, J., Kulkarni, S.R., Tan, G., Baranasic, D., Arenillas, D.J., Sandelin, A., Vandepoele, K., Lenhard, B., Ballester, B., Wasserman, W.W., Parcy, F., Mathelier, A.. 2018. JASPAR 2018: update of the open-access database of transcription factor binding profiles and its web framework. Nucleic Acids Res. 46, D260–D266, doi: 10.1093/nar/gkx1126

Kiefer, A.K., Tung, J.Y., Do, C.B., Hinds, D.A., Mountain, J.L., Francke, U., Eriksson, N., 2013.

905 Genome-Wide Analysis Points to Roles for Extracellular Matrix Remodeling, the Visual
906 Cycle, and Neuronal Development in Myopia. PLoS Genet. 9.
907 https://doi.org/10.1371/journal.pgen.1003299

908 Kim, Y.K., Na, K.S., Myint, A.M., Leonard, B.E., 2016. The role of pro-inflammatory cytokines
909 in neuroinflammation, neurogenesis and the neuroendocrine system in major depression.
910 Prog. Neuro-Psychopharmacology Biol. Psychiatry 64, 277–284.
911 https://doi.org/10.1016/j.pnpbp.2015.06.008

912 Kostic, A.D., Xavier, R.J., Gevers, D., 2014. The Microbiome in Inflammatory Bowel Disease:
913 Current Status and the Future Ahead. Gastroenterology 146, 1489–1499.
914 https://doi.org/10.1053/j.gastro.2014.02.009

915 Kronfol, Z., 2000. Cytokines and the Brain: Implications for Clinical Psychiatry. Am. J. Psychiatry
916 157, 683–694. https://doi.org/10.1176/appi.ajp.157.5.683

917 Liu, J.Z., van Sommeren, S., Huang, H., Ng, S.C., Alberts, R., Takahashi, A., Ripke, S., Lee, J.C.,
918 Jostins, L., Shah, T., Abedian, S., Cheon, J.H., Cho, J., Daryani, N.E., Franke, L., Fuyuno,
919 Y., Hart, A., Juyal, R.C., Juyal, G., Kim, W.H., Morris, A.P., Poustchi, H., Newman, W.G.,
920 Midha, V., Orchard, T.R., Vahedi, H., Sood, A., Sung, J.J.Y., Malekzadeh, R., Westra, H.-J.,
921 Yamazaki, K., Yang, S.-K., Barrett, J.C., Franke, A., Alizadeh, B.Z., Parkes, M., B K, T.,
922 Daly, M.J., Kubo, M., Anderson, C. a, Weersma, R.K., 2015. Association analyses identify
923 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across
924 populations. Nat. Genet. 47, 979–989. https://doi.org/10.1038/ng.3359

925 Lix, L.M., Graff, L.A., Walker, J.R., Clara, I., Rawsthorne, P., Rogala, L., Miller, N., Ediger, J.,
926 Pretorius, T., Bernstein, C.N., Rogala, P.L., Miller, P.N., Ediger, P.J., Pretorius, T., Bernstein,

C.N., 2008. Longitudinal Study of Quality of Life and Psychological Functioning for Active , Fluctuating , and Inactive Disease Patterns in Inflammatory Bowel Disease. Inflamm. Bowel Dis. 14, 1575–1584. https://doi.org/10.1002/ibd.20511

Long, M.D., Kappelman, M.D., Martin, C.F., Chen, W., Anton, K., Sandler, R.S., 2014. Risk factors for depression in the elderly inflammatory bowel disease population. J. Crohn's Colitis 8, 113–119. https://doi.org/10.1016/j.crohns.2013.07.002

Lotrich, F.E., 2015. Inflammatory cytokine-associated depression. Brain Res. 1617, 113–125. https://doi.org/10.1016/j.brainres.2014.06.032

Lotrich, F.E., 2009. Major depression during interferon-alpha treatment: vulnerability and prevention. Dialogues Clin. Neurosci. 11, 417–25.

Margaretten, M., Julian, L., Katz, P., Yelin, E., 2011. Depression in patients with rheumatoid arthritis: description, causes and mechanisms. Int. J. Clin. Rheumtol. 6, 617–623. https://doi.org/10.2217/ijr.11.62

Marrie, R.A., Walld, R., Bolton, J.M., Sareen, J., Walker, J.R., Patten, S.B., Singer, A., Lix, L.M., Hitchon, C.A., El-Gabalawy, R., Katz, A., Fisk, J.D., Bernstein, C.N., 2017. Increased incidence of psychiatric disorders in immune-mediated inflammatory disease. J. Psychosom. Res. 101, 17–23. https://doi.org/10.1016/j.jpsychores.2017.07.015

Marrie, R.A., Walld, R., Bolton, J.M., Sareen, J., Walker, J.R., Patten, S.B., Singer, A., Lix, L.M., Hitchon, C.A., El-Gabalawy, R., Katz, A., Fisk, J.D., Bernstein, C.N., 2017. Rising incidence of psychiatric disorders before diagnosis of immune-mediated inflammatory disease. Epidemiol. Psychiatr. Sci. 1–10. https://doi.org/10.1017/S2045796017000579

948 Marshall, C.R., Howrigan, D.P., Merico, D., Thiruvahindrapuram, B., Wu, W., Greer, D.S.,
949 Antaki, D., Shetty, A., Holmans, P.A., Pinto, D., Gujral, M., Brandler, W.M., Malhotra, D.,
950 Wang, Z., Fajarado, K.V.F., Maile, M.S., Ripke, S., Agartz, I., Albus, M., Alexander, M.,
951 Amin, F., Atkins, J., Bacanu, S.A., Belliveau, R.A., Bergen, S.E., Bertalan, M., Bevilacqua,
952 E., Bigdeli, T.B., Black, D.W., Bruggeman, R., Buccola, N.G., Buckner, R.L., Bulik-
953 Sullivan, B., Byerley, W., Cahn, W., Cai, G., Cairns, M.J., Campion, D., Cantor, R.M., Carr,
954 V.J., Carrera, N., Catts, S. V, Chambert, K.D., Cheng, W., Cloninger, C.R., Cohen, D.,
955 Cormican, P., Craddock, N., Crespo-Facorro, B., Crowley, J.J., Curtis, D., Davidson, M.,
956 Davis, K.L., Degenhardt, F., Del Favero, J., DeLisi, L.E., Dikeos, D., Dinan, T., Djurovic, S.,
957 Donohoe, G., Drapeau, E., Duan, J., Dudbridge, F., Eichhammer, P., Eriksson, J., Escott-
958 Price, V., Essioux, L., Fanous, A.H., Farh, K.-H., Farrell, M.S., Frank, J., Franke, L.,
959 Freedman, R., Freimer, N.B., Friedman, J.I., Forstner, A.J., Fromer, M., Genovese, G.,
960 Georgieva, L., Gershon, E.S., Giegling, I., Giusti-Rodríguez, P., Godard, S., Goldstein, J.I.,
961 Gratten, J., de Haan, L., Hamshere, M.L., Hansen, M., Hansen, T., Haroutunian, V.,
962 Hartmann, A.M., Henskens, F.A., Herms, S., Hirschhorn, J.N., Hoffmann, P., Hofman, A.,
963 Huang, H., Ikeda, M., Joa, I., Kähler, A.K., Kahn, R.S., Kalaydjieva, L., Karjalainen, J.,
964 Kavanagh, D., Keller, M.C., Kelly, B.J., Kennedy, J.L., Kim, Y., Knowles, J.A., Konte, B.,
965 Laurent, C., Lee, P., Lee, S.H., Legge, S.E., Lerer, B., Levy, D.L., Liang, K.-Y., Lieberman,
966 J., Lönnqvist, J., Loughland, C.M., Magnusson, P.K.E., Maher, B.S., Maier, W., Mallet, J.,
967 Mattheisen, M., Mattingsdal, M., McCarley, R.W., McDonald, C., McIntosh, A.M., Meier,
968 S., Meijer, C.J., Melle, I., Mesholam-Gately, R.I., Metspalu, A., Michie, P.T., Milani, L.,
969 Milanova, V., Mokrab, Y., Morris, D.W., Müller-Myhsok, B., Murphy, K.C., Murray, R.M.,
970 Myin-Germeys, I., Nenadic, I., Nertney, D.A., Nestadt, G., Nicodemus, K.K., Nisenbaum, L.,

971 Nordin, A., O'Callaghan, E., O'Dushlaine, C., Oh, S.-Y., Olincy, A., Olsen, L., O'Neill, F.A.,
972 Van Os, J., Pantelis, C., Papadimitriou, G.N., Parkhomenko, E., Pato, M.T., Paunio, T.,
973 Perkins, D.O., Pers, T.H., Pietiläinen, O., Pimm, J., Pocklington, A.J., Powell, J., Price, A.,
974 Pulver, A.E., Purcell, S.M., Quested, D., Rasmussen, H.B., Reichenberg, A., Reimers, M.A.,
975 Richards, A.L., Roffman, J.L., Roussos, P., Ruderfer, D.M., Salomaa, V., Sanders, A.R.,
976 Savitz, A., Schall, U., Schulze, T.G., Schwab, S.G., Scolnick, E.M., Scott, R.J., Seidman,
977 L.J., Shi, J., Silverman, J.M., Smoller, J.W., Söderman, E., Spencer, C.C.A., Stahl, E.A.,
978 Strengman, E., Strohmaier, J., Stroup, T.S., Suvisaari, J., Svrakic, D.M., Szatkiewicz, J.P.,
979 Thirumalai, S., Tooney, P.A., Veijola, J., Visscher, P.M., Waddington, J., Walsh, D., Webb,
980 B.T., Weiser, M., Wildenauer, D.B., Williams, N.M., Williams, S., Witt, S.H., Wolen, A.R.,
981 Wormley, B.K., Wray, N.R., Wu, J.Q., Zai, C.C., Adolfsson, R., Andreassen, O.A.,
982 Blackwood, D.H.R., Bramon, E., Buxbaum, J.D., Cichon, S., Collier, D.A., Corvin, A., Daly,
983 M.J., Darvasi, A., Domenici, E., Esko, T., Gejman, P. V, Gill, M., Gurling, H., Hultman,
984 C.M., Iwata, N., Jablensky, A. V, Jönsson, E.G., Kendler, K.S., Kirov, G., Knight, J.,
985 Levinson, D.F., Li, Q.S., McCarroll, S.A., McQuillin, A., Moran, J.L., Mowry, B.J., Nöthen,
986 M.M., Ophoff, R.A., Owen, M.J., Palotie, A., Pato, C.N., Petryshen, T.L., Posthuma, D.,
987 Rietschel, M., Riley, B.P., Rujescu, D., Sklar, P., St Clair, D., Walters, J.T.R., Werge, T.,
988 Sullivan, P.F., O'Donovan, M.C., Scherer, S.W., Neale, B.M., Sebat, J., 2017. Contribution
989 of copy number variants to schizophrenia from a genome-wide study of 41,321 subjects. Nat.
990 Genet. 49, 27–35. https://doi.org/10.1038/ng.3725

991 McGovern, D.P.B., Gardet, A., Törkvist, L., Goyette, P., Essers, J., Taylor, K.D., Neale, B.M.,
992 Ong, R.T.H., Lagacé, C., Li, C., Green, T., Stevens, C.R., Beauchamp, C., Fleshner, P.R.,
993 Carlson, M., D'Amato, M., Halfvarson, J., Hibberd, M.L., Lördal, M., Padyukov, L.,

994 Andriulli, A., Colombo, E., Latiano, A., Palmieri, O., Bernard, E.-J., Deslandres, C.,
995 Hommes, D.W., de Jong, D.J., Stokkers, P.C., Weersma, R.K., Sharma, Y., Silverberg, M.S.,
996 Cho, J.H., Wu, J., Roeder, K., Brant, S.R., Schumm, L.P., Duerr, R.H., Dubinsky, M.C.,
997 Glazer, N.L., Haritunians, T., Ippoliti, A., Melmed, G.Y., Siscovick, D.S., Vasiliauskas, E.A.,
998 Targan, S.R., Annese, V., Wijmenga, C., Pettersson, S., Rotter, J.I., Xavier, R.J., Daly, M.J.,
999 Rioux, J.D., Seielstad, M., 2010. Genome-wide association identifies multiple ulcerative
1000 colitis susceptibility loci. Nat. Genet. 42, 332–337. https://doi.org/10.1038/ng.549

1001 McIlhatton, M.A., Boivin, G.P., Groden, J., 2016. Manipulation of DNA repair proficiency in
1002 mouse models of colorectal cancer. Biomed Res. Int. 2016.
1003 https://doi.org/10.1155/2016/1414383

1004 Mitchelmore, C., Gede, L., 2014. Brain derived neurotrophic factor: Epigenetic regulation in
1005 psychiatric disorders. Brain Res. 1586, 162–172.
1006 https://doi.org/10.1016/j.brainres.2014.06.037

1007 Ng, S.C., Shi, H.Y., Hamidi, N., Underwood, F.E., Tang, W., Benchimol, E.I., Panaccione, R.,
1008 Ghosh, S., Wu, J.C.Y., Chan, F.K.L., Sung, J.J.Y., Kaplan, G.G., 2017. Worldwide incidence
1009 and prevalence of inflammatory bowel disease in the 21st century: a systematic review of
1010 population-based studies. Lancet 390, 2769–2778. https://doi.org/10.1016/S0140-
1011 6736(17)32448-0

1012 Nguyen, N.T.T., Contreras-Moreira, B., Castro-Mondragon, J.A., Santana-Garcia, W., Ossio, R.,
1013 Robles-Espinoza, C.D., Bahin, M., Collombet, S., Vincens, P., Thieffry, D., van Helden, J.,
1014 Medina-Rivera, A., Thomas-Chollier, M., 2018. RSAT 2018: regulatory sequence analysis tools
1015 20th anniversary. Nucleic Acids Research, gky317, doi:10.1093/nar/gky317.

1016 Noor, A., Lionel, A.C., Cohen-Woods, S., Moghimi, N., Rucker, J., Fennell, A.,
1017 Thiruvahindrapuram, B., Kaufman, L., Degagne, B., Wei, J., Parikh, S. V., Muglia, P., Forte,
1018 J., Scherer, S.W., Kennedy, J.L., Xu, W., Mcguffin, P., Farmer, A., Strauss, J., Vincent, J.B.,
1019 2014. Copy number variant study of bipolar disorder in Canadian and UK populations
1020 implicates synaptic genes. Am. J. Med. Genet. Part B Neuropsychiatr. Genet. 165, 303–313.
1021 https://doi.org/10.1002/ajmg.b.32232

1022 O'Dushlaine, C., Ripke, S., Ruderfer, D.M., Hamilton, S.P., Fava, M., Iosifescu, D. V., Kohane,
1023 I.S., Churchill, S.E., Castro, V.M., Clements, C.C., Blumenthal, S.R., Murphy, S.N., Smoller,
1024 J.W., Perlis, R.H., 2014. Rare Copy Number Variation in Treatment-Resistant Major
1025 Depressive Disorder. Biol. Psychiatry 76, 536–541.
1026 https://doi.org/10.1016/j.biopsych.2013.10.028

1027 Okada, Y., Wu, D., Trynka, G., Raj, T., Terao, C., Ikari, K., Kochi, Y., Ohmura, K., Suzuki, A.,
1028 Yoshida, S., Graham, R.R., Manoharan, A., Ortmann, W., Bhangale, T., Denny, J.C., Carroll,
1029 R.J., Eyler, A.E., Greenberg, J.D., Kremer, J.M., Pappas, D.A., Jiang, L., Yin, J., Ye, L., Su,
1030 D.-F., Yang, J., Xie, G., Keystone, E., Westra, H.-J., Esko, T., Metspalu, A., Zhou, X., Gupta,
1031 N., Mirel, D., Stahl, E.A., Diogo, D., Cui, J., Liao, K., Guo, M.H., Myouzen, K., Kawaguchi,
1032 T., Coenen, M.J.H., van Riel, P.L.C.M., van de Laar, M.A.F.J., Guchelaar, H.-J., Huizinga,
1033 T.W.J., Dieudé, P., Mariette, X., Louis Bridges Jr, S., Zhernakova, A., Toes, R.E.M., Tak,
1034 P.P., Miceli-Richard, C., Bang, S.-Y., Lee, H.-S., Martin, J., Gonzalez-Gay, M.A.,
1035 Rodriguez-Rodriguez, L., Rantapää-Dahlqvist, S., Ärlestig, L., Choi, H.K., Kamatani, Y.,
1036 Galan, P., Lathrop, M., Eyre, S., Bowes, J., Barton, A., de Vries, N., Moreland, L.W.,
1037 Criswell, L.A., Karlson, E.W., Taniguchi, A., Yamada, R., Kubo, M., Liu, J.S., Bae, S.-C.,
1038 Worthington, J., Padyukov, L., Klareskog, L., Gregersen, P.K., Raychaudhuri, S., Stranger,

1039 B.E., De Jager, P.L., Franke, L., Visscher, P.M., Brown, M.A., Yamanaka, H., Mimori, T.,
1040 Takahashi, A., Xu, H., Behrens, T.W., Siminovitch, K.A., Momohara, S., Matsuda, F.,
1041 Yamamoto, K., Plenge, R.M., 2014. Genetics of rheumatoid arthritis contributes to biology
1042 and drug discovery. Nature 506, 376–381. https://doi.org/10.1038/nature12873

1043 Oskoui, M., Gazzellone, M.J., Thiruvahindrapuram, B., Zarrei, M., Andersen, J., Wei, J., Wang,
1044 Z., Wintle, R.F., Marshall, C.R., Cohn, R.D., Weksberg, R., Stavropoulos, D.J., Fehlings, D.,
1045 Shevell, M.I., Scherer, S.W., 2015. Clinically relevant copy number variations detected in
1046 cerebral palsy. Nat Commun 6, 7949. https://doi.org/10.1038/ncomms8949

1047 Padyukov, L., Seielstad, M., Ong, R.T.H., Ding, B., Rönnelid, J., Seddighzadeh, M., Alfredsson,
1048 L., Klareskog, L., 2011. A genome-wide association study suggests contrasting associations
1049 in ACPA-positive versus ACPA-negative rheumatoid arthritis. Ann. Rheum. Dis. 70, 259–
1050 265. https://doi.org/10.1136/ard.2009.126821

1051 Perlis, R.H., Ruderfer, D., Hamilton, S.P., Ernst, C., 2012. Copy Number Variation in Subjects
1052 with Major Depressive Disorder Who Attempted Suicide. PLoS One 7, 7–10.
1053 https://doi.org/10.1371/journal.pone.0046315

1054 Persoons, P., Vermeire, S., Demyttenaere, K., Fischler, B., Vandenberghe, J., Van Oudenhove, L.,
1055 Pierik, M., Hlavaty, T., Van Assche, G., Noman, M., Rutgeerts, P., 2005. The impact of major
1056 depressive disorder on the short- and long-term outcome of Crohn's disease treatment with
1057 infliximab. Aliment. Pharmacol. Ther. 22, 101–110. https://doi.org/10.1111/j.1365-
1058 2036.2005.02535.x

1059 Pinto, D., Darvishi, K., Shi, X., Rajan, D., Rigler, D., Fitzgerald, T., Lionel, A.C.,
1060 Thiruvahindrapuram, B., Macdonald, J.R., Mills, R., Prasad, A., Noonan, K., Gribble, S.,

1061 Prigmore, E., Donahoe, P.K., Smith, R.S., Park, J.H., Hurles, M.E., Carter, N.P., Lee, C.,
1062 Scherer, S.W., Feuk, L., 2011. Comprehensive assessment of array-based platforms and
1063 calling algorithms for detection of copy number variants. Nat. Biotechnol. 29, 512–20.
1064 https://doi.org/10.1038/nbt.1852

1065 Pinto, D., Pagnamenta, A.T., Klei, L., Anney, R., Merico, D., Regan, R., Conroy, J., Magalhaes,
1066 T.R., Correia, C., Abrahams, B.S., Almeida, J., Bacchelli, E., Bader, G.D., Bailey, A.J., Baird,
1067 G., Battaglia, A., Berney, T., Bolshakova, N., Bölte, S., Bolton, P.F., Bourgeron, T., Brennan,
1068 S., Brian, J., Bryson, S.E., Carson, A.R., Casallo, G., Casey, J., Chung, B.H.Y., Cochrane, L.,
1069 Corsello, C., Crawford, E.L., Crossett, A., Cytrynbaum, C., Dawson, G., de Jonge, M.,
1070 Delorme, R., Drmic, I., Duketis, E., Duque, F., Estes, A., Farrar, P., Fernandez, B.A., Folstein,
1071 S.E., Fombonne, E., Freitag, C.M., Gilbert, J., Gillberg, C., Glessner, J.T., Goldberg, J.,
1072 Green, A., Green, J., Guter, S.J., Hakonarson, H., Heron, E.A., Hill, M., Holt, R., Howe, J.L.,
1073 Hughes, G., Hus, V., Igliozzi, R., Kim, C., Klauck, S.M., Kolevzon, A., Korvatska, O.,
1074 Kustanovich, V., Lajonchere, C.M., Lamb, J.A., Laskawiec, M., Leboyer, M., Le Couteur,
1075 A., Leventhal, B.L., Lionel, A.C., Liu, X.-Q., Lord, C., Lotspeich, L., Lund, S.C., Maestrini,
1076 E., Mahoney, W., Mantoulan, C., Marshall, C.R., McConachie, H., McDougle, C.J.,
1077 McGrath, J., McMahon, W.M., Merikangas, A., Migita, O., Minshew, N.J., Mirza, G.K.,
1078 Munson, J., Nelson, S.F., Noakes, C., Noor, A., Nygren, G., Oliveira, G., Papanikolaou, K.,
1079 Parr, J.R., Parrini, B., Paton, T., Pickles, A., Pilorge, M., Piven, J., Ponting, C.P., Posey, D.J.,
1080 Poustka, A., Poustka, F., Prasad, A., Ragoussis, J., Renshaw, K., Rickaby, J., Roberts, W.,
1081 Roeder, K., Roge, B., Rutter, M.L., Bierut, L.J., Rice, J.P., Salt, J., Sansom, K., Sato, D.,
1082 Segurado, R., Sequeira, A.F., Senman, L., Shah, N., Sheffield, V.C., Soorya, L., Sousa, I.,
1083 Stein, O., Sykes, N., Stoppioni, V., Strawbridge, C., Tancredi, R., Tansey, K.,

1084 Thiruvahindrapduram, B., Thompson, A.P., Thomson, S., Tryfon, A., Tsiantis, J., Van
1085 Engeland, H., Vincent, J.B., Volkmar, F., Wallace, S., Wang, K., Wang, Z., Wassink, T.H.,
1086 Webber, C., Weksberg, R., Wing, K., Wittemeyer, K., Wood, S., Wu, J., Yaspan, B.L.,
1087 Zurawiecki, D., Zwaigenbaum, L., Buxbaum, J.D., Cantor, R.M., Cook, E.H., Coon, H.,
1088 Cuccaro, M.L., Devlin, B., Ennis, S., Gallagher, L., Geschwind, D.H., Gill, M., Haines, J.L.,
1089 Hallmayer, J., Miller, J., Monaco, A.P., Nurnberger Jr, J.I., Paterson, A.D., Pericak-Vance,
1090 M.A., Schellenberg, G.D., Szatmari, P., Vicente, A.M., Vieland, V.J., Wijsman, E.M.,
1091 Scherer, S.W., Sutcliffe, J.S., Betancur, C., 2010. Functional impact of global rare copy
1092 number variation in autism spectrum disorders. Nature 466, 368–372.
1093 https://doi.org/10.1038/nature09146

1094 Ripke, S., O'Dushlaine, C., Chambert, K., Moran, J.L., Kähler, A.K., Akterin, S., Bergen, S.E.,
1095 Collins, A.L., Crowley, J.J., Fromer, M., Kim, Y., Lee, S.H., Magnusson, P.K.E., Sanchez,
1096 N., Stahl, E.A., Williams, S., Wray, N.R., Xia, K., Bettella, F., Borglum, A.D., Bulik-
1097 Sullivan, B.K., Cormican, P., Craddock, N., de Leeuw, C., Durmishi, N., Gill, M., Golimbet,
1098 V., Hamshere, M.L., Holmans, P., Hougaard, D.M., Kendler, K.S., Lin, K., Morris, D.W.,
1099 Mors, O., Mortensen, P.B., Neale, B.M., O'Neill, F.A., Owen, M.J., Milovancevic, M.P.,
1100 Posthuma, D., Powell, J., Richards, A.L., Riley, B.P., Ruderfer, D., Rujescu, D., Sigurdsson,
1101 E., Silagadze, T., Smit, A.B., Stefansson, H., Steinberg, S., Suvisaari, J., Tosato, S., Verhage,
1102 M., Walters, J.T., Bramon, E., Corvin, A.P., O'Donovan, M.C., Stefansson, K., Scolnick, E.,
1103 Purcell, S., McCarroll, S.A., Sklar, P., Hultman, C.M., Sullivan, P.F., 2013. Genome-wide
1104 association analysis identifies 13 new risk loci for schizophrenia. Nat. Genet. 45, 1150–1159.
1105 https://doi.org/10.1038/ng.2742

1106 Sardell, R.J., Bailey, J.N.C., Courtenay, M.D., Whitehead, P., Laux, R., Adams, L.D., Fortun, J.A.,

1107 Brantley, M.A., Kovach, J.L., Schwartz, S.G., Agarwal, A., Williams, S.M., Haines, J.L.,
1108 Pericak-Vance, M.A., 2016. Whole exome sequencing of extreme age-related macular
1109 degeneration phenotypes. Mol. Vis. 22, 1062–1076.

1110 Saxena, R., Plenge, R.M., Bjonnes, A.C., Dashti, H.S., Okada, Y., Gad El Haq, W., Hammoudeh,
1111 M., Al Emadi, S., Masri, B.K., Halabi, H., Badsha, H., Uthman, I.W., Margolin, L., Gupta,
1112 N., Mahfoud, Z.R., Kapiri, M., Dargham, S.R., Aranki, G., Kazkaz, L.A., Arayssi, T., 2017.
1113 A Multinational Arab Genome-Wide Association Study Identifies New Genetic Associations
1114 for Rheumatoid Arthritis. Arthritis Rheumatol. 69, 976–985.
1115 https://doi.org/10.1002/art.40051

1116 Scherer, S.W., Lee, C., Birney, E., Altshuler, D.M., Eichler, E.E., Carter, N.P., Hurles, M.E., Feuk,
1117 L., 2007. Challenges and standards in integrating surveys of structural variation. Nat. Genet.
1118 39, S7–S15. https://doi.org/10.1038/ng2093

1119 Schuetz, J.M., MacArthur, A.C., Leach, S., Lai, A.S., Gallagher, R.P., Connors, J.M., Gascoyne,
1120 R.D., Spinelli, J.J., Brooks-Wilson, A.R., 2009. Genetic variation in the NBS1, MRE11,
1121 RAD50 and BLM genes and susceptibility to non-Hodgkin lymphoma. BMC Med. Genet.
1122 10, 1–10. https://doi.org/10.1186/1471-2350-10-117

1123 Schwartz, M., Kipnis, J., 2011. A conceptual revolution in the relationships between the brain and
1124 immunity. Brain. Behav. Immun. 25, 817–819. https://doi.org/10.1016/j.bbi.2010.12.015

1125 Gupta, S., Stamatoyannopolous, J.A., Bailey, T., Noble, W.S., 2007. Quantifying similarity
1126 between motifs. Genome Biology 8(2), R24.

1127 Shastri, V.M., Schmidt, K.H., 2016. Cellular defects caused by hypomorphic variants of the Bloom

syndrome helicase gene *BLM*. Mol. Genet. Genomic Med. 4, 106–119. https://doi.org/10.1002/mgg3.188

Shriner, D., Adeyemo, A., Gerry, N.P., Herbert, A., Chen, G., Doumatey, A., Huang, H., Zhou, J., Christman, M.F., Rotimi, C.N., 2009. Transferability and fine-mapping of genome-wide associated loci for adult height across human populations. PLoS One 4. https://doi.org/10.1371/journal.pone.0008398

Thompson, E.R., Doyle, M.A., Ryland, G.L., Rowley, S.M., Choong, D.Y.H., Tothill, R.W., Thorne, H., Barnes, D.R., Li, J., Ellul, J., Philip, G.K., Antill, Y.C., James, P.A., Trainer, A.H., Mitchell, G., Campbell, I.G., 2012. Exome Sequencing Identifies Rare Deleterious Mutations in DNA Repair Genes FANCC and BLM as Potential Breast Cancer Susceptibility Alleles. PLoS Genet. 8. https://doi.org/10.1371/journal.pgen.1002894

Timothy, L.B., and Elkan, C., 1994. Fitting a mixture model by expectation maximization to discover motifs in biopolymers. Proceedings of the Second International Conference on Intelligent Systems for Molecular Biology, pp. 28-36, AAAI Press, Menlo Park, California.

Tyring, S., Gottlieb, A., Papp, K., Gordon, K., Leonardi, C., Wang, A., Lalla, D., Woolley, M., Jahreis, A., Zitnik, R., Cella, D., Krishnan, R., 2006. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: Double-blind placebo-controlled randomised phase III trial. Lancet 367, 29–35. https://doi.org/10.1016/S0140-6736(05)67763-X

Uçar, H.N., Eray, Ş., Murat, D., 2018. Simple peripheral markers for inflammation in adolescents with major depressive disorder. Psychiatry Clin. Psychopharmacol. 0573, 1–7.

https://doi.org/10.1080/24750573.2018.1423769

Vidal, A., Gomez-Gil, E., Sans, M., Portella, M.J., Salamero, M., Piqué, J.M., Panés, J., 2008. Health-related quality of life in inflammatory bowel disease patients: The role of psychopathology and personality. Inflamm. Bowel Dis. 14, 977–983. https://doi.org/10.1002/ibd.20388

Walker, J.R., Ediger, J.P., Graff, L.A., Greenfeld, J.M., Clara, I., Lix, L., Rawsthorne, P., Miller, N., Rogala, L., McPhail, C.M., Bernstein, C.N., 2008. The Manitoba IBD Cohort Study: A Population-Based Study of the Prevalence of Lifetime and 12-Month Anxiety and Mood Disorders. Am. J. Gastroenterol. 103, 1989–1997. https://doi.org/10.1111/j.1572-0241.2008.01980.x

Wang, K., Li, M., Hadley, D., Liu, R., Glessner, J., Grant, S.F.A., Hakonarson, H., Bucan, M., 2007. PennCNV: An integrated hidden Markov model designed for high-resolution copy number variation detection in whole-genome SNP genotyping data. Genome Res. 17, 1665–1674. https://doi.org/10.1101/gr.6861907

Westover, A.N., Marangell, L.B., 2002. A cross-national relationship between sugar consumption and major depression? Depress. Anxiety 16, 118–120. https://doi.org/10.1002/da.10054

Wirtenberger, M., Frank, B., Hemminki, K., Klaes, R., Schmutzler, R.K., Wappenschmidt, B., Meindl, A., Kiechle, M., Arnold, N., Weber, B.H.F., Niederacher, D., Bartram, C.R., Burwinkel, B., 2006. Interaction of Werner and Bloom syndrome genes with p53 in familial breast cancer. Carcinogenesis 27, 1655–1660. https://doi.org/10.1093/carcin/bgi374

Woodruff, R.T., Schorpp, K.M., Lawrenczyk, A.J., Chakraborty, T., Kusnecov, A.W., 2011.

1170 Effects of acute and repeated administration of Staphylococcal enterotoxin A on Morris water
1171 maze learning, corticosterone and hippocampal IL-1β and TNFα. Brain. Behav. Immun. 25,
1172 938–946. https://doi.org/10.1016/j.bbi.2010.10.005

1173 Wray, N.R., Ripke, S., Mattheisen, M., Trzaskowski, M., Byrne, E.M., Abdellaoui, A., Adams,
1174 M.J., Agerbo, E., Air, T.M., Andlauer, T.M.F., Bacanu, S.-A., Bækvad-Hansen, M.,
1175 Beekman, A.F.T., Bigdeli, T.B., Binder, E.B., Blackwood, D.R.H., Bryois, J., Buttenschøn,
1176 H.N., Bybjerg-Grauholm, J., Cai, N., Castelao, E., Christensen, J.H., Clarke, T.-K., Coleman,
1177 J.I.R., Colodro-Conde, L., Couvy-Duchesne, B., Craddock, N., Crawford, G.E., Crowley,
1178 C.A., Dashti, H.S., Davies, G., Deary, I.J., Degenhardt, F., Derks, E.M., Direk, N., Dolan, C.
1179 V., Dunn, E.C., Eley, T.C., Eriksson, N., Escott-Price, V., Kiadeh, F.H.F., Finucane, H.K.,
1180 Forstner, A.J., Frank, J., Gaspar, H.A., Gill, M., Giusti-Rodríguez, P., Goes, F.S., Gordon,
1181 S.D., Grove, J., Hall, L.S., Hannon, E., Hansen, C.S., Hansen, T.F., Herms, S., Hickie, I.B.,
1182 Hoffmann, P., Homuth, G., Horn, C., Hottenga, J.-J., Hougaard, D.M., Hu, M., Hyde, C.L.,
1183 Ising, M., Jansen, R., Jin, F., Jorgenson, E., Knowles, J.A., Kohane, I.S., Kraft, J.,
1184 Kretzschmar, W.W., Krogh, J., Kutalik, Z., Lane, J.M., Li, Y., Li, Y., Lind, P.A., Liu, X., Lu,
1185 L., MacIntyre, D.J., MacKinnon, D.F., Maier, R.M., Maier, W., Marchini, J., Mbarek, H.,
1186 McGrath, P., McGuffin, P., Medland, S.E., Mehta, D., Middeldorp, C.M., Mihailov, E.,
1187 Milaneschi, Y., Milani, L., Mill, J., Mondimore, F.M., Montgomery, G.W., Mostafavi, S.,
1188 Mullins, N., Nauck, M., Ng, B., Nivard, M.G., Nyholt, D.R., O'Reilly, P.F., Oskarsson, H.,
1189 Owen, M.J., Painter, J.N., Pedersen, C.B., Pedersen, M.G., Peterson, R.E., Pettersson, E.,
1190 Peyrot, W.J., Pistis, G., Posthuma, D., Purcell, S.M., Quiroz, J.A., Qvist, P., Rice, J.P., Riley,
1191 B.P., Rivera, M., Saeed Mirza, S., Saxena, R., Schoevers, R., Schulte, E.C., Shen, L., Shi, J.,
1192 Shyn, S.I., Sigurdsson, E., Sinnamon, G.B.C., Smit, J.H., Smith, D.J., Stefansson, H.,

Steinberg, S., Stockmeier, C.A., Streit, F., Strohmaier, J., Tansey, K.E., Teismann, H., Teumer, A., Thompson, W., Thomson, P.A., Thorgeirsson, T.E., Tian, C., Traylor, M., Treutlein, J., Trubetskoy, V., Uitterlinden, A.G., Umbricht, D., Van der Auwera, S., van Hemert, A.M., Viktorin, A., Visscher, P.M., Wang, Y., Webb, B.T., Weinsheimer, S.M., Wellmann, J., Willemsen, G., Witt, S.H., Wu, Y., Xi, H.S., Yang, J., Zhang, F., Arolt, V., Baune, B.T., Berger, K., Boomsma, D.I., Cichon, S., Dannlowski, U., de Geus, E.C.J., DePaulo, J.R., Domenici, E., Domschke, K., Esko, T., Grabe, H.J., Hamilton, S.P., Hayward, C., Heath, A.C., Hinds, D.A., Kendler, K.S., Kloiber, S., Lewis, G., Li, Q.S., Lucae, S., Madden, P.F.A., Magnusson, P.K., Martin, N.G., McIntosh, A.M., Metspalu, A., Mors, O., Mortensen, P.B., Müller-Myhsok, B., Nordentoft, M., Nöthen, M.M., O'Donovan, M.C., Paciga, S.A., Pedersen, N.L., Penninx, B.W.J.H., Perlis, R.H., Porteous, D.J., Potash, J.B., Preisig, M., Rietschel, M., Schaefer, C., Schulze, T.G., Smoller, J.W., Stefansson, K., Tiemeier, H., Uher, R., Völzke, H., Weissman, M.M., Werge, T., Winslow, A.R., Lewis, C.M., Levinson, D.F., Breen, G., Børglum, A.D., Sullivan, P.F., 2018. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nat. Genet. 50, 668–681. https://doi.org/10.1038/s41588-018-0090-3

Yang, S.K., Hong, M., Zhao, W., Jung, Y., Baek, J., Tayebi, N., Kim, K.M., Ye, B.D., Kim, K.J., Park, S.H., Lee, I., Lee, E.J., Kim, W.H., Cheon, J.H., Kim, Y.H., Jang, B.I., Kim, H.S., Choi, J.H., Koo, J.S., Lee, J.H., Jung, S.A., Lee, Y.J., Jang, J.Y., Shin, H.D., Kang, D., Youn, H.S., Liu, J., Song, K., 2014. Genome-wide association study of Crohn's disease in Koreans revealed three new susceptibility loci and common attributes of genetic susceptibility across ethnic populations. Gut 63, 80–87. https://doi.org/10.1136/gutjnl-2013-305193

Zarrei, M., MacDonald, J.R., Merico, D., Scherer, S.W., 2015. A copy number variation map of

the human genome. Nat. Rev. Genet. 16, 172–183. https://doi.org/10.1038/nrg3871

Ziv, Y., Ron, N., Butovsky, O., Landa, G., Sudai, E., Greenberg, N., Cohen, H., Kipnis, J., Schwartz, M., 2006. Immune cells contribute to the maintenance of neurogenesis and spatial learning abilities in adulthood. Nat. Neurosci. 9, 268–275. https://doi.org/10.1038/nn1629