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Mendelian and polygenic inheritance of intelligence: A common set of causal genes? Using next-generation sequencing to examine the effects of 168 intellectual disability genes on normal-range intelligence

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ABSTRACT

Despite twin and family studies having demonstrated a substantial heritability of individual differences in intelligence, no genetic variants have been robustly associated with normal-range intelligence to date. This is largely ascribed to the high polygenicity of intelligence, i.e., to its being subject to the effects of a large number of genes of individually small effect. Intellectual disability, on the other hand, frequently involves large effects of single genetic mutations, many of which have been identified. The present paper aims to 1) introduce the reader to the current state of genetic intelligence research, including next-generation sequencing and the analysis of rare genetic variants, and 2) examine the possible effects of known disability genes on normal-range intelligence. The rationale for the latter rests on the fact that genetic variants affecting continuous, polygenic traits are often concentrated in the same areas of the genome as those underlying related monogenic phenotypes. Using an existing pool of known intellectual disability genes, we constructed a set of 168 candidate genes for normal-range intelligence, and tested their association with intelligence in 191 individuals (aged 5–18) sampled from the high and low ends of the IQ distribution. In particular, we 1) employed exon sequencing to examine the possible effects of rare genetic variants in the 168 genes, and 2) used polygenic prediction to examine the overall effect of common genetic variants in the candidate gene set in a larger sample (N = 2125, mean age 20.4, SD = 14.1). No significant association between the candidate gene set and intelligence was detected.

1. Introduction

Intelligence is one of the most frequently studied human behavioral traits and one of the strongest known predictors of major life outcomes such as educational attainment, occupational success, health, and longevity (Deary, Johnson, & Houlihan, 2009; Deary, Whiteman, Starr, Whalley, & Fox, 2004;

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Gottfredson, 1997b; Gottfredson & Deary, 2004; Neisser et al., 1996; Schmidt & Hunter, 2004). Over the past century it has motivated research across a diverse range of fields including not only the behavioral sciences, but also neurosciences, molecular biology, economics, and genetics. Interestingly, behavior genetic studies of intelligence frequently converge on two seemingly incompatible findings. On the one hand, twin and family studies have demonstrated 1) a substantial genetic component of individual differences in intelligence (e.g., Bouchard & McGue, 1981; Deary, Spinath, & Bates, 2006; Plomin, Defries, McClearn, & McGuffin, 2008; Plomin & Spinath, 2004), and 2) an increase in the relative magnitude of this component across development (from around 20% in infancy, to ~40–50% in middle childhood and ~60–80% in adulthood (e.g., Bartels, Rietveld, Van Baal, & Boomsma, 2002; Bishop et al., 2003; Boomsma & van Baal, 1998; Deary, Spinath, et al., 2006; Deary, Whalley, Batty, & Starr, 2006; Haworth et al., 2009; Hoekstra, Bartels, & Boomsma, 2007; McGue, Bouchard, Iacono, & Lykken, 1993; Petrill et al., 2004; Plomin, 1986; Polderman et al., 2006). On the other hand, genetic association studies aiming to identify the genetic variants contributing to the observed individual differences have cumulatively identified genetic variants that explain less than 1% of the observed variability (Benyamin et al., 2013; Chabris et al., 2012; Davies et al., 2011). This gap between the estimated heritability and the variance explained by known variants, frequently termed the 'missing heritability' (Maher, 2008), has been assigned a multitude of explanations. These include the insufficient statistical power to detect genetic variants of small effect size, the potential overestimation of heritability by twin studies, issues pertaining to the measurement and operationalization of intelligence, and the possibility of causal genetic variants not tagged on present genotyping platforms (including rare and structural variation) underlying the heritability (see, e.g., Dickson, Wang, Krantz, Hakonarson, & Goldstein, 2010; Eichler et al., 2010; Goldstein et al., 2013; Manolio et al., 2009; van der Sluis, Verhage, Posthuma, & Dolan, 2010; Zuk, Hechter, Sunyaev, & Lander, 2012). The largest genome-wide association (GWA) studies to date identified no genetic variants robustly associated with intelligence, and only one gene, FNBP1L, has been tentatively implicated in the etiology of normal-range intelligence to date (Benyamin et al., 2013; Davies et al., 2011).

Recent years have seen an increase in the use of several additional approaches to addressing the missing heritability issue. Firstly, the development of the methodology for the estimation of heritability using measured genetic information, implemented in the genome-wide complex trait analysis tool (GCTA; Yang, Lee, Goddard, & Visscher, 2011), has enabled the estimation of the proportion of the variance in intelligence explained by the total additive effects of common genetic variants tagged on the present genotyping platforms. Ranging from ~22 to ~46% in children and adolescents (Benyamin et al., 2013; Plomin, Haworth, Meaburn, Price, & Davis, 2013; Trzaskowski, Shakeshaft, & Plomin, 2013; Trzaskowski, Yang, Visscher, & Plomin, 2013; Trzaskowski et al., 2014) and from ~29 to ~51% in adults (Davies et al., 2011; Marioni et al., 2014), these estimates are substantially larger than the variance presently explained in the GWA studies. However, they remain lower than the (twin and family study-based) estimates of the total genetic variance of intelligence. In addition, while demonstrating that a substantial proportion of the variance in intelligence is attributable to the additive effects of common genetic variation, GCTA estimates provide no information on the specific genetic variants associated with intelligence. Secondly, the recent advent of the large-scale use of sequencing technologies, which enable the measurement of the complete nucleotide sequence of a genome, has opened a wealth of possibilities for the study of intellectual disability (much of which is monogenic, i.e., caused by a single genetic mutation), This led to the discoveries of many previously unknown genetic causes of cognitive impairment (e.g., Najmabadi et al., 2007; Najmabadi et al., 2011). For instance, sequencing has enabled the identification of genes underlying a range of sporadic, syndromic conditions involving intellectual disability (e.g. Schinzel–Giedion syndrome, Kabuki syndrome; Hoischen et al., 2010; Ng et al., 2010), as well as many sporadic and familial causes of non-syndromic intellectual disability (see Topper, Ober, & Das, 2011). However, sequencing technologies are seldom employed to study the genetics of normal-range intelligence. This is partly due to the highly polygenic nature of intelligence (i.e., its being subject to a large number of very small genetic effects), and the consequent need for (often prohibitively) large samples to achieve sufficient statistical power for the detection of individual causal variants.

In the present study, we utilize the existing knowledge on the genetics of monogenic (i.e., Mendelian) disorders to construct a plausible set of candidate genes for normal-range intelligence. The study is based on a simple rationale, namely the idea that the genetic variants giving rise to monogenic disorders may be localized in the same areas of the genome as those affecting continuous variation in related polygenic traits. Previous research has amply demonstrated the plausibility of this with respect to several other phenotypes. For instance, several genes causing monogenic forms of Parkinson's disease have been associated with the common, polygenic form of the disease (Gasser, 2009). Rare genetic variants in three candidate genes (ABCA1, APOA1, and LCAT), giving rise to pathogenically low levels of HDL-cholesterol in plasma, are also found in individuals with the common, polygenic version of the low-HDL-cholesterol trait (Cohen et al., 2004; Frikke-Schmidt, Nordestgaard, Jensen, & Tybjærg-Hansen, 2004). Other examples include height (Allen et al., 2010), body mass index (Loos et al., 2008), lipid levels (Hirschhorn & Gajdos, 2011), hemoglobin F levels (Hirschhorn & Gajdos, 2011), and type 2 diabetes (Sandhu et al., 2007).

Genes underlying monogenic disorders, in which protein functioning is severely altered, may therefore provide an opportunity to localize the genetic variation underlying a similar, polygenic phenotype. Utilizing this idea, we sequenced the exons (i.e., expressed regions) of 168 genes known to underlie intellectual disability, and examined their association with intelligence in a sample of 191 individuals. By design, we focused on the detection of the possible effects of rare genetic variation. This is in line with the assumption of inter-individual variability in intelligence being maintained by low-frequency, disruptive mutations of small effect size (e.g., Hsu, 2012; Marioni et al., 2014). Because selection on fitness-related traits, including intelligence, is expected to a) prevent mutations with large negative effects from becoming common in the population, and b) lead to an accumulation of mutations with large positive effects, resulting in their uniform presence in the

population (as monomorphisms, i.e., non-variable DNA sites), the genetic architecture of intelligence is expected to be marked by the absence of genetic variants of large effect sizes. Mutations of small negative effects, however, are expected to linger at a low frequency (e.g., Hsu, 2012), and the genetic architecture of high intelligence may potentially be conceptualized as the absence of a large number of these disruptive mutations (e.g., Hsu, 2012; Marioni, Penke, et al., 2014).

While the above argues in favor of rare deleterious variants, we also consider common variants, as these may be present in the form of effectively neutral mutations (subject to genetic drift), or as relatively positive mutations (subject to positive selection), which have yet to become fixed in the population. To this end, we examine whether polygenic scores (Purcell et al., 2007) summarizing the effects of common single-nucleotide polymorphisms (SNPs) in the 168 genes of interest are predictive of intelligence, in a larger random sample of 2125 individuals. More details on the polygenic score prediction, next-generation sequencing and the analysis of rare variants can be found in the Methods section.

2. Methods

2.1. Phenotype data

Data on psychometric intelligence were obtained from the Young Netherlands Twin Register (YNTR, Boomsma et al., 2006; van Beijsterveldt et al., 2013). YNTR is a population-based register of Dutch twins born after 1986, recruited at birth and measured longitudinally at ages 1 through 18. The sequenced sample consisted of 191 unrelated children and adolescents of Dutch ancestry (Abdellaoui et al., 2013), aged 5–18 at the time of measurement. 46% of the participants were male. Intelligence was assessed longitudinally, using the Revised Amsterdam Children Intelligence Test (RAKIT; Bleichrodt, Drenth, Zaal, & Resing, 1984), the Wechsler Intelligence Scale for Children (WISC; Sattler, 1992; Van Haasen et al., 1986; Wechsler et al., 2002), and the Wechsler Adult Intelligence Scale (WAIS; Stinissen, Willems, Coetsier, & Hulsman, 1970; Wechsler, 1997), the choice of instrument being partly dependent on the participants' age. IQ scores were derived based on the respective age- and sex-appropriate norms for RAKIT, WISC, or WAIS, and subsequently converted to z-scale within each measurement occasion (i.e., within each time point used for assessment), and averaged over measurement occasions (i.e., across the different time points, within each participant). A previous study employing the same dataset found a high temporal stability of the additive genetic effects on intelligence (with the correlations between the additive genetic factors at consecutive measurement occasions ranging from .8 to 1; Franić et al., 2014), implying that the same genetic factors are relevant to intelligence over the developmental period under study (5–18 years of age). In situations of high genetic stability, averaging over the measurement occasions has been shown to be a sensible approach from the perspective of statistical power (Minică, Boomsma, Van Der Sluis, & Dolan, 2010).

The scores of the 191 individuals belonged to the tails of the IQ distribution: individuals were selected into the study from an initial pool of 1387 children/adolescents. The inclusion criterion was either an IQ z-score exceeding .8 (~112 IQ points) or an IQ z-score below -.8 (~88 IQ points), but above–1.33 (~80 IQ points). The rationale for excluding the individuals with an IQ below 80 is the focus of the present study on non-monogenic inheritance, i.e., the fact that the genetic architecture underlying their intellectual (dis)ability may differ from that of individuals from the rest of the distribution. Several additional exclusion criteria were applied. Participants were excluded if their IQ scores displayed excessive variation across the different measurement points (SD > 1 on a z-scale), or differed excessively from the IQ scores of their family members ('excessive' being defined as a difference of ~18 and ~11 IQ points for monozygotic (MZ) and dizygotic (DZ) twins, respectively; these numbers correspond to a difference at least one standard deviation greater than the average twin difference in our sample). Additional exclusion criteria included low birth weight (under 1000 g), known genetic defects, and discordance between IQ and educational attainment scores (individuals in the low IQ group were not included into the study if their educational attainment score on the Dutch national test of educational attainment (CITO, 2002) exceeded 539, i.e., belonged to the top 40% of the distribution). The IQ scores were dichotomized ('high' and 'low'; N = 104 and N = 87, respectively) for the first set of the analyses (gene-based testing).

In the second set of the analyses (polygenic prediction), all individuals from the Netherlands Twin Register (NTR; Boomsma et al., 2006; Boomsma et al., 2002; Willemsen et al., 2013) with psychometric intelligence and SNP microarray data were included into the sample (N = 2125, 45.4% male). The age distribution of the participants at the time of measurement is given in Supplementary Fig. 1 (mean = 20.4, SD = 14.1). The testing and the computation of IQ scores were performed in the same way as above, with the exception of participants for whom only the scores on Raven's Progressive Matrices (Raven, Raven, & Court, 1998; Raven, 1960) were available; for these participants, a z-transformed number of correct answers, rather than a z-transformed IQ score, was analyzed. Unlike the sample used for exon sequencing (N = 191), the larger sample was unselected on phenotype, i.e., the intelligence scores followed the normal distribution.

2.2. Next-generation sequencing

Nucleic acid sequencing is a set of methods used in the determination of the precise order of nucleotides in a nucleic acid molecule (see e.g. Grada & Weinbrecht, 2013 for a nontechnical overview). Initially accomplished through chain-termination methods (i.e., so-called Sanger or first-generation sequencing; Sanger, Nicklen, & Coulson, 1977), DNA sequencing is presently performed using a set of methodologies commonly denoted next-generation sequencing (e.g., Metzker, 2010; Rusk & Kiermer, 2008; Shendure & Ji, 2008). Next-generation sequencing is an umbrella term denoting a set of technologies (e.g., Illumina (Solexa) sequencing, Roche 454 sequencing, Ion torrent: Proton / PGM sequencing, SOLiD sequencing) that perform sequencing in a massively parallel fashion, sequencing millions of DNA fragments simultaneously. Unlike SNP microarrays that only measure common genetic variation (i.e., variants whose population frequency exceeds ~1%), sequencing technologies enable the interrogation of the entire nucleotide sequence of the genome, including rare and structural variation. The development of next-generation sequencing technologies was

accompanied by a rapid decline in the cost of DNA sequencing, resulting in a sharp increase in the accessibility of sequence data over the past decade. In addition, next-generation sequencing coupled with efficient DNA capture (i.e., the isolation of specific DNA targets) has facilitated the emergence of exome sequencing as a novel approach to the identification of rare variants underlying polygenic phenotypes, and a cost-efficient alternative to whole-genome sequencing (see Kiezun et al., 2012). Exome sequencing (i.e., targeted exome capture) denotes the sequencing of the entire set of expressed regions of the genome, while exon sequencing refers to the sequencing of a particular expressed region (i.e., exon) or a set of exons.

2.3. Genotype data

The genes examined in the present study were selected from the pool of genes presently known to underlie various forms of syndromic and non-syndromic intellectual disability (Najmabadi et al., 2011; Ropers, 2008, 2010). The selection of the genes was partially guided by practical considerations, e.g., by the limited target size allowed by the HaloPlex G9901B exon enrichment kit, which was used to selectively capture the genomic regions of interest from DNA samples prior to sequencing. 107 of the 168 genes were autosomal. Table 1 and Supplementary Data provide an overview of the genes and their function. Exon sequencing was performed using an Illumina HiSeq2000 sequencer with 100 bp paired-end reads. The raw reads were aligned to the NCBI37 human reference genome using the Stampy package (Lunter & Goodson, 2011). Variants were called using Platypus (Rimmer, Phan, Mathieson, Lunter, & McVean, 2013). The information on quality control and filtering of the genotype data can be found in Supplementary Methods. Mean sequencing depth (i.e., the mean number of times each nucleotide base was sequenced) was ~212x.

The second set of analyses (i.e., polygenic prediction) employed all common SNPs (i.e., SNPs with a minor allele frequency exceeding 1%) in the 168 genes that were both a) measured in the 2125 individuals, and b) analyzed in a recent meta-analysis of childhood intelligence (Benyamin et al., 2013). The reason for applying the latter criterion is our subsequent use of the effect size estimates from the meta-analysis as weights in the construction of a polygenic predictor (see Analyses). In total, this resulted in 8559 SNPs from 99 autosomal genes being used in the polygenic prediction (sex-linked genes, and 8 out of the 107 autosomal genes were not present in the meta-analysis dataset). Information on imputation and quality control of the SNP data can be found in Supplementary Methods.

2.4. Analyses

2.4.1. Association testing

To examine the association between intelligence and the rare genetic variants in the genes of interest, we applied a series of gene-based association tests implemented in the PLINK/SEQ tool (https://atgu.mgh.harvard.edu/plinkseq/). Gene-based as opposed to single-locus testing was used as a means of increasing statistical power (Kiezun et al., 2012; Purcell, Cherny, & Sham, 2003), seeing as the inherently small number of observations of rare variants limits the statistical power for their individual detection. Six gene-based association tests were employed: a burden test using adaptive permutation to test for excess of rare alleles in cases relative to controls (*–assoc* keyword in PLINK/SEQ), a test based on the count of case-unique rare alleles (*–uniq* command in PLINK/SEQ), a frequency-weighted test (see Madsen & Browning, 2009; *–fw* command), the variable threshold test (Price et al., 2010; *–vt* command in PLINK/SEQ), the c-alpha test (B. M. Neale et al., 2011; *–calpha*), and a sum of single-site statistics (*–sumstat*). Overall, the tests aim to assess the genetic burden due to the effects of rare genetic variants, working on the assumption that the phenotypic variation may be explained by the overall burden of rare deleterious mutations, while the individual causal variants may be heterogeneous and interchangeable.

The first test uses adaptive permutation to test for excess of rare alleles in the individuals in the low IQ group relative to those in the high IQ group. Permutation entails random re-allocation of genotypes over the phenotypes to generate an empirical distribution of p-values under the null-hypothesis, against which the p-value of interest can be compared. The permutation is adaptive in the sense that the variants that are highly unlikely to achieve statistical significance are dropped from the procedure. The second test is based on the count of alleles exclusive to the low end of the phenotypic distribution (i.e., low IQ). This strategy effectively eliminates common alleles from the test, because they would be present in individuals at both extremes unless they have a very large effect. The frequency-weighted test (similar to Madsen & Browning, 2009) scores each individual by a weighted sum of mutation counts within each gene. The weighing scheme assigns higher weights to variants that are rare in individuals from the high end of the phenotypic distribution (and thus presumably detrimental), effectively preventing common variants from dominating the test. Group counts (i.e., weighted sums in cases and controls) are compared, and permutation is used to evaluate the significance of the result. The variable threshold test (Price et al., 2010) is based on the regression of the phenotype on the genotype. The test assumes that there is an unknown threshold T, such that variants with a minor allele frequency below T are substantially more likely to have a functional effect than variants with a minor allele frequency above T. The test consists of computing a test statistic using only the variants that fall below a certain minor allele frequency cutoff, for the full range of cutoffs. The final test statistic is subsequently defined as the maximum of the test statistics across all the cutoffs. By optimizing the test statistic in this way, the test effectively gives higher weight to variants predicted to be functionally significant (i.e., to variants that fall below a minor allele frequency cutoff that resulted in the best test statistic). All of the aforementioned tests entail the assumption of rare variants within a given gene acting in the same direction (either increasing or decreasing intelligence). The c-alpha test (Neale et al., 2011) does not involve this assumption, i.e., it accommodates possible differences in the direction of effect across the measured variants. The test assesses the imbalance in the distribution of alleles over cases and controls, such that, e.g., the risk variants are more present in cases and protective variants more present in controls. Under the null hypothesis of no effect, the risk and the protective variants are expected to be distributed randomly over the cases and controls. An excess of, for instance, a risk allele in the cases, would result in an overdispersion in the distribution of this allele. C-alpha assesses

Table 1
List of the 168 genes included into the study, including gene description, chromosome (Chr), the base-pair positions of the start (Start (bp)) and the end (End (bp)) of the gene, length in base-pair units (Length (bp)), and the number of variants on each gene (Nvar). Supplementary Data provide detailed gene descriptions.

Gene	Description	Chr	Start (bp)	End (bp)	Length (bp)	Nvar
ACBD6	Acyl-CoA binding domain containing 6	1	180256351	180473022	216671	6
ACSL4	Acyl-CoA synthetase long-chain family member 4	X	108883563	108977621	94058	14
ADK	Adenosine kinase	10	75909942	76470061	560119	8
ADRA2B	Adrenoceptor alpha 2B	2	96777622	96782888	5266	3
AFF2	AF4/FMR2 family, member 2	X	147581138	148083193	502055	22
ALG6	Alpha-1,3-glucosyltransferase	1	63832260	63905233	72973	12
AP1S2	Adaptor-related protein complex 1, sigma 2 subunit	X	15842928	15874100	31172	2
AP4B1	Adaptor-related protein complex 4, beta 1 subunit	1	114436370	114448741	12371	12
AP4E1	Adaptor-related protein complex 4, epsilon 1 subunit	15	51199868	51299097	99229	24
AP4M1	Adaptor-related protein complex 4, mu 1 subunit	7	99698129	99705803	7674	19
AP4S1	Adaptor-related protein complex 4, sigma 1 subunit	14	31493311	31566656	73345	6
ARHGEF6	Rac/Cdc42 guanine nucleotide exchange factor (GEF) 6	X	135746711	135864503	117792	13
ARHGEF9	Cdc42 guanine nucleotide exchange factor (GEF) 9	X	62853847	63006426	152579	3
ARID1B	AT rich interactive domain 1B (SWI1-like)	6	157098063	157532913	434850	31
ARID5A	AT rich interactive domain 5A (MRF1-like)	2	97201463	97219371	17908	4
ARX	Aristaless related homeobox	X	25020812	25035065	14253	4
ASCL1	Achaete-scute complex homolog 1 (*Drosophila*)	12	103350451	103355294	4843	1
ASPM	Asp (abnormal spindle) homolog, microcephaly associated (*Drosophila*)	1	197052256	197116824	64568	44
ATRX	Alpha thalassemia/mental retardation syndrome X-linked	X	76759355	77042719	283364	12
AUTS2	Autism susceptibility candidate 2	7	69062904	70258885	1195981	31
BCOR	BCL6 corepressor	X	39909498	40037582	128084	18
BRWD3	Bromodomain and WD repeat domain containing 3	X	79923986	80066233	142247	13
C12orf57	Chromosome 12 open reading frame 57	12	7052202	7056165	3963	11
C9orf86	RAB, member RAS oncogene family-like 6	9	139701373	139736639	35266	30
CACNA1F	Calcium channel, voltage-dependent, L type, alpha 1F subunit	X	49060522	49090833	30311	23
CACNA1G	Calcium channel, voltage-dependent, T type, alpha 1G subunit	17	48637428	48705832	68404	60
CACNG2	Calcium channel, voltage-dependent, gamma subunit 2	22	36955915	37099690	143775	7
CASK	Calcium/calmodulin-dependent serine protein kinase (MAGUK family)	X	41373188	41783287	410099	5
CC2D1A	Coiled-coil and C2 domain containing 1A	19	14015955	14042693	26738	27
CCNA2	Cyclin A2	4	122736598	122746088	9490	11
CDK16	Cyclin-dependent kinase 16	X	47076527	47090394	13867	7
CDK5RAP2	CDK5 regulatory subunit associated protein 2	9	123150146	123343437	193291	65
CDKN2AIP	CDKN2A interacting protein	4	184364788	184370049	5261	11
CENPJ	Centromere protein J	13	25455411	25498085	42674	27
CLCN4	Chloride channel, voltage-sensitive 4	X	10123984	10206699	82715	9
CNKSR1	Connector enhancer of kinase suppressor of Ras 1	1	26502980	26517375	14395	24
CNKSR2	Connector enhancer of kinase suppressor of Ras 2	X	21391535	21673813	282278	15
CRBN	Cereblon	3	3190316	3222401	32085	20
CSTF2	Cleavage stimulation factor, 3′ pre-RNA, subunit 2, 64 kDa	X	100074347	100096923	22576	4
CUL4B	Cullin 4B	X	119657445	119710684	53239	10
DCX	Doublecortin	X	110536006	110656460	120454	6
DLG1	Discs, large homolog 1 (*Drosophila*)	3	196768430	197026447	258017	18
DLG3	Discs, large homolog 3 (*Drosophila*)	X	69663704	69726339	62635	22
DYRK1A	Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A	21	38738858	38888679	149821	11
EEF1B2	Eukaryotic translation elongation factor 1 beta 2	2	207023317	207028653	5336	4
EHMT1	Euchromatic histone-lysine N-methyltransferase 1	9	140512443	140731578	219135	49
EIF2AK3	Eukaryotic translation initiation factor 2-alpha kinase 3	2	88855258	88928094	72836	13
EIF2S3	Eukaryotic translation initiation factor 2, subunit 3 gamma, 52 kDa	X	24072064	24097927	25863	1
ELP2	Elongator acetyltransferase complex subunit 2	18	33708836	33755688	46852	29
ENTPD1	Ectonucleoside triphosphate diphosphohydrolase 1	10	97470535	97638023	167488	17
EPB41L1	Erythrocyte membrane protein band 4.1-like 1	20	34699347	34821721	122374	21
ERLIN2	ER lipid raft associated 2	8	37593096	37616319	23223	13
FASN	fatty acid synthase	17	80035213	80057106	21893	68
FGD1	FYVE, RhoGEF and PH domain containing 1	X	54470886	54523599	52713	17
FMR1	Fragile X mental retardation 1	X	146992468	147033647	41179	10
FOXG1	Forkhead box G1	14	29235286	29239871	4585	1
FOXP2	Forkhead box P2	7	113725364	114334827	609463	20
FRMPD4	FERM and PDZ domain containing 4	X	12155584	12743642	588058	29
GDI1	GDP dissociation inhibitor 1	X	153664258	153672814	8556	8
GFAP	Glial fibrillary acidic protein	17	42981993	42993920	11927	14
GPC3	Glypican 3	X	132668775	133120673	451898	5
GRIA3	Glutamate receptor, ionotropic, AMPA 3	X	122317095	122625766	308671	14
GRID1	Glutamate receptor, ionotropic, delta 1	10	87358311	88127250	768939	33
GRIK2	Glutamate receptor, ionotropic, kainate 2	6	101845860	102518958	673098	19
GRIN1	Glutamate receptor, ionotropic, N-methyl D-aspartate 1	9	140032608	140064214	31606	15
GRIN2A	Glutamate receptor, ionotropic, N-methyl D-aspartate 2A	16	9846264	10277611	431347	19
GRIN2B	Glutamate receptor, ionotropic, N-methyl D-aspartate 2B	12	13713409	14134022	420613	38
GRIP1	Glutamate receptor interacting protein 1	12	66740210	67073925	333715	43

Table 1 *(continued)*

Gene	Description	Chr	Start (bp)	End (bp)	Length (bp)	Nvar
HCFC1	Host cell factor C1 (VP16-accessory protein)	X	153212007	153237819	25812	29
HDAC4	Histone deacetylase 4	2	239968863	240323643	354780	60
HFE2	Hemochromatosis type 2 (juvenile)	1	145412190	145418545	6355	3
HIST1H4B	Histone cluster 1, H4b	6	26026123	26028480	2357	9
HIST3H3	Histone cluster 3, H3	1	228611545	228614026	2481	4
INPP4A	Inositol polyphosphate-4-phosphatase, type I, 107 kDa	2	99060320	99208496	148176	24
IQSEC2	IQ motif and Sec7 domain 2	X	53261057	53351522	90465	12
KCNJ10	Potassium inwardly-rectifying channel, subfamily J, member 10	1	160006256	160041051	34795	6
KDM5A	Lysine (K)-specific demethylase 5A	12	388222	499620	111398	37
KDM5C	Lysine (K)-specific demethylase 5C	X	53219502	53255604	36102	14
KDM6B	Lysine (K)-specific demethylase 6B	17	7742234	7759118	16884	33
KIF1A	Kinesin family member 1A	2	241652180	241760725	108545	91
LARP7	La ribonucleoprotein domain family, member 7	4	113557119	113579742	22623	7
LAS1L	LAS1-like (*S. cerevisiae*)	X	64731461	64755686	24225	5
LMAN2L	Lectin, mannose-binding 2-like	2	97370666	97406813	36147	8
MAN1B1	Mannosidase, alpha, class 1B, member 1	9	139980378	140004639	24261	25
MAOA	Monoamine oxidase A	X	43514408	43607068	92660	15
MAPK10	Mitogen-activated protein kinase 10	4	86935275	87375283	440008	12
MBD5	Methyl-CpG binding domain protein 5	2	148777579	149272044	494465	10
MBTPS2	Membrane-bound transcription factor peptidase, site 2	X	21856655	21904541	47886	8
MCPH1	Microcephalin 1	8	6263112	6502140	239028	48
MECP2	Methyl CpG binding protein 2 (Rett syndrome)	X	153286263	153364188	77925	7
MED13L	Mediator complex subunit 13-like	12	116395380	116715991	320611	37
MEF2C	Myocyte enhancer factor 2C	5	88013057	88200922	187865	6
NCK2	NCK adaptor protein 2	2	106360519	106511730	151211	10
NDST1	N-Deacetylase/N-sulfotransferase (heparan glucosaminyl) 1	5	149886673	149938773	52100	24
NLGN4X	Neuroligin 4, X-linked	X	5807082	6147706	340624	8
NSDHL	NAD(P) dependent steroid dehydrogenase-like	X	151998510	152038907	40397	8
NSUN2	NOP2/Sun RNA methyltransferase family, member 2	5	6598351	6634473	36122	40
OPHN1	Oligophrenin 1	X	67261185	67654299	393114	22
PAFAH1B1	Platelet-activating factor acetylhydrolase 1b, regulatory subunit 1 (45 kDa)	17	2495922	2589909	93987	4
PAK3	p21 protein (Cdc42/Rac)-activated kinase 3	X	110186512	110465173	278661	8
PARP1	Poly (ADP-ribose) polymerase 1	1	226547391	226596801	49410	34
PECR	Peroxisomal trans-2-enoyl-CoA reductase	2	216902110	216947539	45429	10
PHF6	PHD finger protein 6	X	133506341	133563822	57481	4
PHF8	PHD finger protein 8	X	53962112	54072569	110457	14
POLR3B	Polymerase (RNA) III (DNA directed) polypeptide B	12	106750435	106904976	154541	22
PQBP1	polyglutamine binding protein 1	X	48754194	48761422	7228	5
PRMT10	Protein arginine methyltransferase 10 (putative)	4	148558533	148606280	47747	14
PRSS12	Protease, serine, 12 (neurotrypsin, motopsin)	4	119200192	119274922	74730	19
PTCH2	Patched 2	1	45284515	45309616	25101	18
PTCHD1	Patched domain containing 1	X	23351984	23415918	63934	9
RAI1	Retinoic acid induced 1	17	17583786	17715765	131979	12
RALGDS	ral guanine nucleotide dissociation stimulator	9	135972106	136025588	53482	36
RGS7	Regulator of G-protein signaling 7	1	240937816	241521478	583662	22
RLIM	Ring finger protein, LIM domain interacting	X	73801810	73835461	33651	5
RPL10	Ribosomal protein L10	X	153625570	153631680	6110	2
SARS	Seryl-tRNA synthetase	1	109755514	109781804	26290	13
SCAPER	S-phase cyclin A-associated protein in the ER	15	76639526	77177217	537691	30
SETBP1	SET binding protein 1	18	42259137	42649475	390338	21
SHANK2	SH3 and multiple ankyrin repeat domains 2	11	70312960	70936808	623848	44
SHANK3	SH3 and multiple ankyrin repeat domains 3	22	51112069	51172641	60572	43
SIM1	Single-minded homolog 1 (*Drosophila*)	6	100835749	100912551	76802	21
SLC16A2	Solute carrier family 16, member 2 (thyroid hormone transporter)	X	73640084	73754752	114668	9
SLC2A1	Solute carrier family 2 (facilitated glucose transporter), member 1	1	43390045	43425847	35802	10
SLC31A1	Solute carrier family 31 (copper transporter), member 1	9	115982807	116027772	44965	1
SLC6A8	Solute carrier family 6 (neurotransmitter transporter), member 8	X	152952751	152963048	10297	10
SLC9A6	Solute carrier family 9, subfamily A (NHE6, cation proton antiporter 6), member 6	X	135066582	135130428	63846	13
SNAP25	Synaptosomal-associated protein, 25 kDa	20	10198476	10289066	90590	9
SNAP29	Synaptosomal-associated protein, 29 kDa	22	21212291	21246501	34210	8
SNRPN	Small nuclear ribonucleoprotein polypeptide N	15	25067793	25224729	156936	5
SOX3	SRY (sex determining region Y)-box 3	X	139584151	139588225	4074	2
ST3GAL3	ST3 beta-galactoside alpha-2,3-sialyltransferase 3	1	44172217	44397831	225614	13
STIL	SCL/TAL1 interrupting locus	1	47714810	47780819	66009	27
STXBP1	Syntaxin binding protein 1	9	130373485	130455995	82510	22
SYN1	Synapsin I	X	47430299	47480256	49957	6
SYNGAP1	Synaptic Ras GTPase activating protein 1	6	33386846	33422466	35620	30
SYP	synaptophysin	X	49043264	49057661	14397	3
TAF2	TAF2 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 150 kDa	8	120742013	120846074	104061	35

(continued on next page)

Table 1 *(continued)*

Gene	Description	Chr	Start (bp)	End (bp)	Length (bp)	Nvar
TCF4	Transcription factor 4	18	52888561	53304188	415627	21
TMEM135	Transmembrane protein 135	11	86747885	87040876	292991	16
TRAPPC9	Trafficking protein particle complex 9	8	140741585	141469678	728093	44
TRMT1	tRNA methyltransferase 1 homolog (S. cerevisiae)	19	13214713	13228563	13850	14
TSPAN7	Tetraspanin 7	X	38419730	38549172	129442	3
TUBA1A	Tubulin, alpha 1a	12	49577582	49583861	6279	6
TUBA8	Tubulin, alpha 8	22	18592452	18615498	23046	15
TUSC3	Tumor suppressor candidate 3	8	15396595	15625158	228563	8
UBE2A	Ubiquitin-conjugating enzyme E2A	X	118707498	118719379	11881	4
UBE3A	Ubiquitin protein ligase E3A	15	25581395	25685175	103780	11
UBR7	Ubiquitin protein ligase E3 component n-recognin 7 (putative)	14	93672400	93696561	24161	13
UPF3B	UPF3 regulator of nonsense transcripts homolog B (yeast)	X	118966988	118987991	21003	12
WDR45L	WD repeat domain 45B	17	80571437	80607411	35974	20
WDR62	WD repeat domain 62	19	36544782	36597012	52230	68
WHSC1	Wolf–Hirschhorn syndrome candidate 1	4	1872122	1984934	112812	28
WHSC2	Negative elongation factor complex member A	4	1983440	2011962	28522	17
YWHAE	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon polypeptide	17	1246833	1304556	57723	6
ZBTB40	Zinc finger and BTB domain containing 40	1	22777343	22858650	81307	26
ZCCHC12	Zinc finger, CCHC domain containing 12	X	117956786	117961931	5145	3
ZCCHC8	Zinc finger, CCHC domain containing 8	12	122955145	122986543	31398	16
ZDHHC9	Zinc finger, DHHC-type containing 9	X	128936263	128978910	42647	2
ZNF526	Zinc finger protein 526	19	42723491	42733353	9862	6
ZNF621	Zinc finger protein 621	3	40565375	40582043	16668	5
ZNF711	Zinc finger protein 711	X	84497996	84529368	31372	3

this overdispersion, regardless of its origin (risk or protective), and is ideally suited for detecting a mixture of effects, such that some variants confer risk while others are neutral or protective. As evident, all of the six tests focus on the detection of the possible effects of rare genetic variants. This is consistent with our expectation of rare variants being enriched for functional alleles, and exhibiting stronger effect sizes than common genetic variants (e.g., Frazer, Murray, Schork, & Topol, 2009; Kryukov, Pennacchio, & Sunyaev, 2007; Pritchard, 2001).

Correction for multiple testing was performed by dividing the desired significance threshold (.05) by the total effective number of independent tests in the study. The estimate of the number of independent tests was based on the number of genes for which PLINK/SEQ's I-statistic (i.e., estimate of the minimal achievable p-value for a gene) was smaller than .05, as genes with an I-statistic greater than .05 are considered insufficiently powered and thus necessitate no correction (Kiezun et al., 2012). Bonferroni correction would be too stringent in the present context, as it assumes that each gene displays sufficient variation to achieve the asymptotic properties for the test statistic (Kiezun et al., 2012); an assumption that is not necessarily realistic in the context of rare variant data and the present sample size. For genes on the X chromosome, in addition to being performed on the entire sample, the analyses were performed for the males and the females separately.

2.4.2. Polygenic prediction

Subsequently, we examined whether continuous intelligence scores in the larger (N = 2125) sample can be predicted from a polygenic score constructed on the basis of the common SNPs in the candidate gene set. Here, the polygenic score is used as a means of summarization of genetic effects across the relevant genes: it is obtained as a weighted sum of the number of effect alleles within an individual, across all common SNPs in the candidate gene set. The weighing of the SNPs, and the determination of 'effect allele', were informed by prior knowledge: the weights were the effect size estimates for individual SNPs obtained in a large meta-analysis of GWA studies on childhood intelligence (Benyamin et al., 2013). The continuous intelligence scores were subsequently regressed on the polygenic scores. A significant regression coefficient would imply a genetic signal among the variants (see, e.g., Dudbridge, 2013).

The meta-analysis results were based on an analysis of six independent cohorts (combined N = 12,441): the Avon Longitudinal Study of Parents and Children, the Lothian Birth Cohorts, the Brisbane Adolescent Twin Study, the Western Australian Pregnancy Cohort Study, and the Twins Early Development Study (Benyamin et al., 2013). The polygenic scores were constructed by multiplying the number of effect alleles (0, 1, or 2) at a given locus in the present dataset by the meta-analysis regression coefficient for that locus, and summing the resulting scores over all relevant loci within an individual. The subsequent regression of intelligence on the polygenic scores was performed using generalized estimating equations ('gee' package in R; Carey, Lumley, & Ripley, 2012; Minică, Dolan, Kampert, Boomsma, & Vink, 2014; RCoreTeam, 2013) to control for the dependency in the data arising from the fact that some individuals in the sample are closely genetically related (e.g., twins, parents). To control for possible spurious association arising from population stratification (i.e., from any possible systematic differences in allele frequencies between the high and low IQ groups due to differences in ancestry; see, e.g., Cardon & Palmer, 2003; Freedman et al., 2004; Price et al., 2006), nine principal components reflective of the Dutch population structure (Abdellaoui et al., 2013) were included into the regression as covariates. As different populations frequently exhibit systematic differences in allele frequencies, principal components of a genome-wide covariance matrix of the individuals' allelic values frequently reflect variation in ancestry, and are known to efficiently control for

population stratification (e.g., Price et al., 2006). To remove any phenotypic variance associated with sex, sex was included as an additional covariate.

3. Results

The application of deep sequencing to the 168 genes of interest revealed 2900 point-mutations that passed quality control filters and differed from the reference dataset (Consortium, 2012) in at least one of the 191 DNA samples. Of these 2900 variants, 972 and 61 were observed only once and twice in the 191 samples, respectively. The estimated population frequencies of the 2900 variants are displayed in Fig. 1. Note that the estimated population frequencies may differ from the frequencies observed in our dataset. For instance, a mutation observed once in the present dataset will have a frequency of ~.5%; however, it could range from being a private mutation in a single individual in the world, to being common in the population (i.e., having a frequency exceeding 1%). As evident from Fig. 1, ~70% and ~76% of the variants have an estimated population frequency lower than 10% and 20%, respectively. Around 50% of the exonic variants were synonymous (i.e., base substitutions did not affect the produced amino acid sequence), with the remainder being non-synonymous. The distribution of the variants over the 168 genes is displayed in Fig. 2.

The QQ plots of the gene-based p-values obtained using the six association tests in Plink/SEQ are shown in Fig. 3. An inflation of the QQ plot, i.e., an excess of low p-values relative to the uniform expectation, would indicate a possible genetic signal in the candidate set of genes. As visible in the Figure, no inflation was observed for any of the six gene-based tests. After correction for multiple testing, none of the individual genes displayed a significant association with intelligence. Sex-stratified analysis confirmed the absence of a detectable association for the genes on the X chromosome. In addition, the polygenic score was not predictive of intelligence ($p = .69$).

4. Discussion

Utilizing existing knowledge on the genetics of monogenic disorders, the present study sought to examine the association of 168 genes implicated in genetics of intellectual disability with normal-range intelligence. Using exon sequencing and focusing primarily on rare genetic variation, we addressed this question in a sample of 191 individuals sampled from the ends of the IQ distribution (>112, <88 and >80). Several different methods of gene-based testing, implemented in the PLINK/SEQ tool, indicated the absence of a detectable association at the present sample size. Additionally, we employed polygenic prediction to examine the overall effect of common genetic variation in the candidate gene set, and found no significant prediction.

The first set of analyses focused on the detection of the possible effects of rare genetic variation, in line with the assumption of the inter-individual variability in intelligence being maintained by low-frequency, disruptive mutations of small effect size. Two findings in combination support the notion that the existing genetic variation in intelligence is likely to be retained through mutation–selection balance, i.e., a balance between the rate of occurrence of new, mostly deleterious mutations, and the rate of their removal by selection (Falconer & Mackay, 1996; Marioni, Penke, et al., 2014). The first is the consistent positive associations between intelligence and fitness components across the life span (Arden, Gottfredson, Miller, & Pierce, 2009; Banks, Batchelor, & McDaniel, 2010; Batty, Deary, & Gottfredson, 2007; Deary, Strand, Smith, & Fernandes, 2007; Deary, Whalley, Batty, & Starr, 2006; Gale, Batty, Tynelius, Deary, & Rasmussen, 2010; Silventoinen, Posthuma, Van Beijsterveldt, Bartels, & Boomsma, 2006; Strenze, 2007; Van Dongen & Gangestad, 2011). The second is the absence of the consequently expected depletion of the underlying genetic variation. Because selection will quickly eliminate mutations of strong deleterious effect on fitness-related traits, this mechanism suggests a genetic architecture

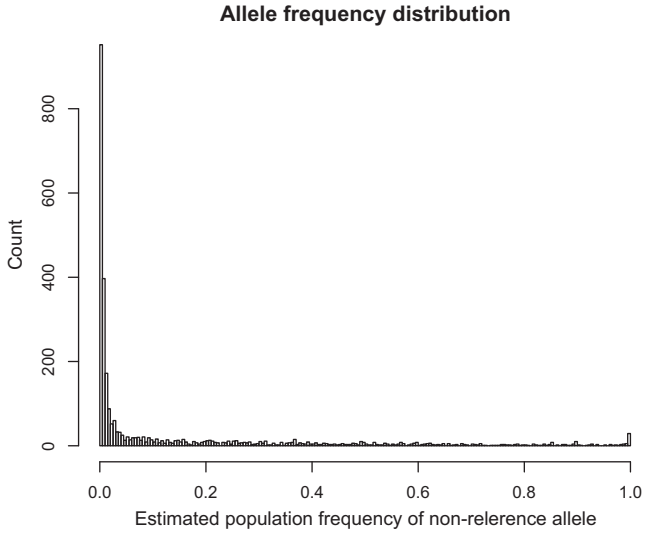

Fig. 1. Polymorphic sites in a DNA sequence can be described by the frequency of one of their alleles. The figure shows the distribution of these frequencies for all diallelic sites (i.e., all sites displaying two alternate forms) in the present dataset. 97.25% sites in the present dataset were diallelic. X-axis: estimated population frequency of the non-reference allele; y-axis: frequency count in the present sample.

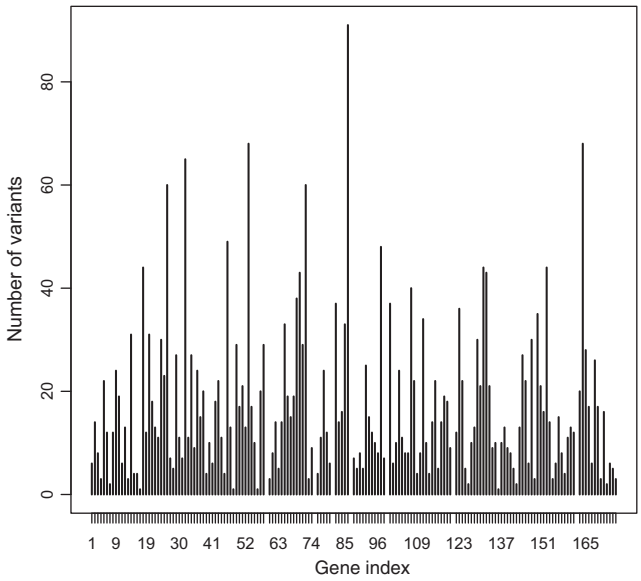

Fig. 2. Distribution of the 2900 variants over the 168 genes. x-axis: gene index, y-axis: number of variants on the gene.

that lacks common genetic variants of large effect size (Gibson, 2012; Marioni, Penke, et al., 2014); an expectation consistent with the lack of replicable findings from candidate gene and GWA studies (e.g., Benyamin et al., 2013; Chabris et al., 2012; Davies et al., 2011).

Utilizing the same rationale, Marioni et al. (Marioni, Penke, et al., 2014) recently examined the relationship between the genome-wide count of rare exonic variants and cognitive ability in childhood and old age (N = 1596), and detected no significant association. Yeo et al. (Yeo, Gangestad, Liu, Calhoun, & Hutchison, 2011) found a negative association between the genome-wide burden of rare copy number variants and psychometric intelligence in a sample of 74 individuals. However, subsequent studies using larger samples were unable to replicate this finding (Bagshaw et al., 2013; MacLeod et al., 2012; McRae, Wright, Hansell, Montgomery, & Martin, 2013).

The present study focused on a smaller part of the genome, in line with the hypothesis that the genetic variation affecting continuous variation in quantitative traits may be concentrated in the same areas of the genome as that underlying similar monogenic phenotypes. The lack of detectable association is consistent with the aforementioned studies, and provides evidence against this hypothesis. Indeed, the opposite hypothesis may conceivably hold, i.e., exomes that display monogenic effects may be less likely to contribute to heritability of normal variability — a notion supported by the fact that a substantial number of replicated association from GWA studies are located outside of genes. However, a larger study may still be advisable to minimize the probability of the finding reflecting a power issue. In addition, considering the diverse nature of intellectual abilities, as well as the pervasive disagreement between intelligence researchers on the existence and causal relevance of general intelligence (e.g., Gottfredson, 1997a; Neisser et al., 1996), future studies may also employ a finer-grained definition of the phenotype (e.g., verbal and nonverbal intelligence, specific subscale scores, or additive genetic factor(s) derived through the application of genetic covariance structure modeling to twin data; e.g., Franić, Dolan, Borsboom, & Boomsma, 2012; M. C. Neale & Cardon, 1992). A substantial heterogeneity in the genetic etiology of intelligence has been demonstrated by previous studies (e.g., Johnson et al., 2007; Luo, Petrill, & Thompson, 1994; Rijsdijk, Vernon, & Boomsma, 2002), which typically show significant additive genetic influences specific to distinct cognitive abilities (e.g., verbal, special, perceptual, arithmetic, etc.), in addition to a genetic *g* factor. Provided that such subscale-specific influences are a significant contributor to the genetic etiology of intelligence, future studies may consider their explicit modeling (using, for instance, a multivariate approach). More fundamentally, the question of the ontological and biological reality of the *g* factor has been widely debated (Jensen, 1998; van der Maas, Kan, & Borsboom, 2014; van der Maas et al., 2006); if *g* is a causal entity generating the observed covariation between distinct cognitive abilities, as assumed throughout much of the literature, the search for genes for *g* is sensible both from a substantive perspective and the perspective of statistical power. However, if *g* is simply an index variable summarizing the covariation between different cognitive abilities without playing a causal role, then seeking genetic influences at the level of *g* will diminish the statistical power to detect the effects of measured genetic variants, relative to seeking genetic influences at the level of its constituent abilities. Genetically informed item-level analyses that assess the mediatory role of intelligence with respect to genetic and environmental effects (Franić et al., 2013) can be used to address this issue.

The rationale behind the present study, namely the supposition of the relevance of genes involved in intellectual disability to normal-range intelligence, is based on ample similar examples from the literature, including height (Allen et al., 2010), body mass index (Loos et al., 2008), lipid levels (Hirschhorn & Gajdos, 2011 review), hemoglobin F levels (Hirschhorn & Gajdos, 2011), type 2 diabetes (Sandhu et al., 2007), Parkinson's disease (Gasser, 2009; Lesage & Brice, 2009), and others. A recent study by Blair et al. (2013) identified

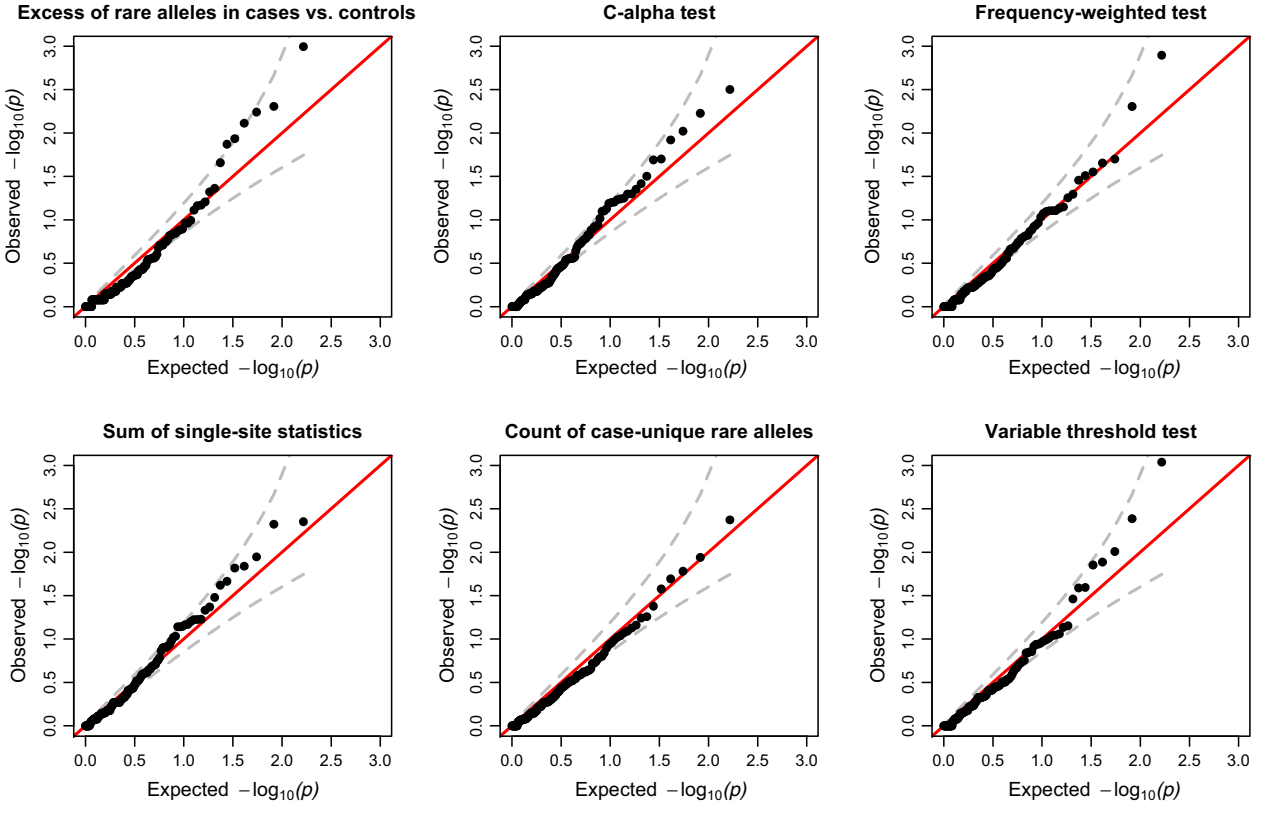

Fig. 3. QQ plots of the gene-based p-values obtained using six different association tests in PLINK/SEQ. Gray lines represent 95% confidence intervals.

nearly 3000 comorbidities between Mendelian disorders and complex diseases present in the electronic medical records in the United States and Denmark. They found that each complex disease displayed an association with a unique set of Mendelian disorders, implying a sharing of the causal pathways between the Mendelian and the polygenic phenotypes. Consistent with this, we recently demonstrated an enrichment of 43 genes underlying Mendelian disorders of intellectual functioning (39 of which were included in the present study) for common polymorphisms associated with intelligence (Franić et al., in press). The present study aimed to extend this work to a larger set of genes and examine the role of rare variants, in addition to common genetic variation. The absence of a detectable association at the present sample size may be considered a (partial) non-replication, although, as mentioned, a larger sample size may be advisable. Other improvements to the present study may include the examination of structural variation (including, for instance, copy-number variants; Redon et al., 2006), gene-by-gene interactions, heterogeneity of genetic effects across different environments, or the intronic regions of the genome. The increasing availability of next-generation sequencing technologies is expected to facilitate a more detailed study into some of the above issues.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.intell.2014.12.001.

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