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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