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Low-frequency copy-number variants and general cognitive ability: No evidence of association

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ABSTRACT

Although twin, family, and adoption studies have shown that general cognitive ability (GCA) is substantially heritable, GWAS has not uncovered a genetic polymorphism replicably associated with this phenotype. However, most polymorphisms used in GWAS are common SNPs. The present study explores use of a different class of genetic variant, the copy-number variant (CNV), to predict GCA in a sample of 6199 participants, combined from two longitudinal family studies. We aggregated low-frequency (<5%) CNV calls into eight different mutational burden scores, each reflecting a different operationalization of mutational burden. We further conducted three genome-wide association scans, each of which utilized a different subset of identified low-frequency CNVs. Association signals from the burden analyses were generally small in effect size, and none were statistically significant after a careful Type I error correction was applied. No signal from the genome-wide scans significantly differed from zero at the adjusted Type I error rate. Thus, the present study provides no evidence that CNVs underlie heritable variance in GCA, though we cannot rule out the possibility of very rare or small-effect CNVs for this trait, which would require even larger samples to detect. We interpret these null results in light of recent breakthroughs that aggregate SNP effects to explain much, but not all, of the heritable variance in some quantitative traits.

1. Introduction

General cognitive ability (GCA) is the theoretical construct involved to some extent in every cognitively demanding task. Frequently identified with Spearman's (1904) general factor *g*, it is posited to contribute some part of the variance in scores on all mental-ability tests. GCA correlates appreciably with other variables in a striking variety of domains (Deary, 2012; Gottfredson, 2003; Herrnstein & Murray, 1996; Jensen, 1998). Decades of twin, adoption, and family studies have firmly established via biometric methods that general cognitive ability is substantially heritable (Bouchard & McGue, 2003; Deary, Johnson, & Houlihan, 2009), but genome-wide association studies (GWAS) for this trait (Benyamin et al., 2013; Butcher, Davis, Craig, & Plomin, 2008; Davies et al., 2011; Davis et al., 2010) have not uncovered a single-nucleotide polymorphism (SNP) replicably associated with it at genome-wide significance levels.

However, there are classes of genetic variation other than SNPs, which might instead more powerfully account for heritable variance in complex traits. One of these is the copy-number variant (CNV). According to Scherer et al. (2007) taxonomy of genomic variation, a CNV is a submicroscopic structural variant of at least 1000 base pairs that appears a different number of times in the genomes of different

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individuals. CNVs include deletions, in which case the individual will have fewer than the typical two copies of the DNA sequence, as well as duplications, where more than two copies are present.

Previous research has implicated CNVs in psychiatric diseases, including autism (Pinto et al., 2010; Sebat et al., 2007) and schizophrenia (The International Schizophrenia Consortium, 2008). Autism is highly comorbid with mental retardation (American Psychiatric Association, 1994), and the connection between schizophrenia and pre-morbid cognitive deficits is well-documented (Woodberry, Giuliano, & Seidman, 2008). This suggests the possibility that CNVs underlie part of the heritable variance of GCA. Indeed, large-scale, cytogenetically visible structural duplications and deletions of chromosomal material can cause syndromal forms of mental retardation, the textbook example being trisomy 21 (Down syndrome), caused by a redundant copy of an entire chromosome. CNVs (as defined here) are smaller-scale and submicroscopic, but recent technological advances have enabled identification of a growing list of specific deletions and duplications associated with syndromal intellectual disability (Mefford, Batshaw, & Hoffman, 2012), as well as neurodevelopmental disorders more generally (Coe, Girirajan, & Eichler, 2012; Glessner, Connolly, & Hakonarson, 2012). Thus, one research strategy would be to search for specific CNVs contributing to normal-range variation in cognitive functioning. However, if the same lessons learned from SNPs for quantitative phenotypes also hold for CNVs, the effect-sizes of relatively common deletions and duplications will be quite small. In fact, the effects of common CNVs have already been indirectly investigated by SNP GWAS, since most common CNVs are well tagged by common SNPs (Wellcome Trust Case Control Consortium, 2010). This is not to say that large-effect CNVs are unlikely to exist for GCA, but rather, that they are unlikely to be common mutations. The reliability of calls for low-baserate CNVs can be limited (Cooper & Mefford, 2011), and analyses of particularly rare variants will generally be underpowered unless the sample size is quite large. Therefore, another strategy is to aggregate CNVs from across the genome, into one or more mutational burden scores. Both The International Schizophrenia Consortium (2008) and Pinto et al. (2010) exploited this strategy, and report significant case-control burden differences. Further, a recent review of the role of CNVs in neurodevelopmental disorders (Coe et al., 2012) concluded that a greater burden of larger and/or more numerous small CNVs typically corresponds to greater phenotypic severity.

Contemporary neurobiological theory of general intelligence recognizes the key role of a distributed network of frontal and parietal brain structures (Gläscher et al., 2010; Jung & Haier, 2007), and much evidence supports the hypothesis that the brains of more-intelligent individuals function more efficiently, in terms of energy consumption during a cognitively demanding task (Neubauer & Fink, 2009). GCA seemingly depends upon the efficient functioning and coordinated directed effort of a distributed array of neural structures, and the functioning of such a system is far easier to disturb than enhance. Approximately 84% of human genes are expressed in the brain (Hawrylycz et al., 2012), and in light of CNVs' role in pathological cognitive deficits, it seems reasonable to hypothesize that they could contribute to normal-range variation as well. Specifically, individuals whose genomes show greater deviation from "typical" reference copy-number states would more likely to harbor detrimental trait-relevant mutations, and have correspondingly lower cognitive ability scores.

An organism's total load of mutations relative to the "typical" reference genome could reflect developmental instability, particularly if the mutations in question are rare. In turn, developmental instability is frequently operationalized as fluctuating asymmetry (deviation from morphological bilateral symmetry; Gangestad & Thornhill, 1999), which correlates negatively with GCA (Banks, Batchelor, & McDaniel, 2010). Therefore, one might hypothesize that mutational burden would also associate negatively with GCA. This evolutionary-biological hypothesis motivated a small-sample study of CNVs and IQ, by Yeo, Gangestad, Liu, Calhoun, and Hutchinson (2011). The study participants entered into analysis were $N = 74$ adults diagnosed with alcohol dependence, who had been assessed with the Wechsler Abbreviated Scale of Intelligence. From DNA samples, Yeo et al. detected a total of 13,557 low-frequency (<5%) CNVs, 7249 of which were deletions, and 6308 of which were duplications. Detected copy-number deletions in the sample ranged from ~8 kb to ~626 kb in length; the average copy-number deletion was ~210 kb long ($SD \approx 14$ kb). The length (in kilobases) of the copy-number deletion participants carried correlated negatively with their full-scale IQ (FSIQ) scores ($r = -0.30$, $p = 0.01$). In contrast, participants' counts of deletions carried correlated *positively* with FSIQ, though not significantly so ($r = 0.21$, $p = 0.08$). The number of deletions carried ranged from 1 to 25 in the sample, with an average of 10.95 ($SD = 5.48$). Neither the length nor the count of copy-number duplications correlated significantly with FSIQ, and both correlations were less than 0.10 in absolute magnitude. Yeo et al. (2011) interpret their result for copy-deletion length as consistent with the hypothesis that individual differences in cognitive ability result partly from individual variation in the total burden of detrimental mutations carried.

Three recent studies with larger samples have attempted to replicate Yeo et al. (2011). One of these (MacLeod et al., 2012) was a study of both fluid and crystallized intelligence in a sample of over 3000 older British adults genotyped on the Illumina 610-Quadv1 chip. MacLeod et al. called CNVs using both *PennCNV* (Wang et al., 2007) and *QuantiSNP* (Colella et al., 2007), retaining only those calls produced by both. No association was observed with rare-CNV (<1%) burden. Suggestive evidence of association with fluid intelligence was observed for a specific CNV overlapping with *SHANK3* (permutation-corrected $p = 0.01$). But, of the three mutant carriers in the sample, two had duplications and one had a deletion, which MacLeod et al. regard as counter-intuitive.

Bagshaw et al. (2013) reported a study of IQ and academic achievement conducted in a sample of 717 participants from the longitudinal Christchurch Health and Development Study in New Zealand. These participants were genotyped on the Illumina 660 W-Quad chip. Bagshaw et al. called CNVs with *PennCNV*, and conducted a rare-CNV burden analysis and a genome-wide scan of common CNVs. They observed no strong evidence of association, and the only suggestive association signals were for academic achievement, and not IQ, which we regard as a superior measure of the GCA construct.

The third recent study of interest is McRae, Wright, Hanselle, Montgomery, and Martin (2013), which was conducted in a sample of 800 Australian adolescents, who were IQ-tested around age 16, and genotyped on the Illumina