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ORIGINAL RESEARCH

No Association Between General Cognitive Ability and Rare Copy Number Variation

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Abstract There is increasing evidence for the role of rare copy-number variation (CNV) in the development of neuropsychiatric disorders. It is likely that such variants also have an effect on the variation of cognition in what is considered the "normal" phenotypic range. The role of rare CNV (>20 KB in length; frequency <5 %) on general cognitive ability is investigated in a sample of 800 individuals (mean age = 16.5, SD = 1.2) using copy-number variants called from the Illumina 610K SNP genotyping array with the software QuantiSNP. We assessed three measures of CNV burden—total CNV length, number of CNV and average CNV length—for both deletions and duplications in combination and separately. No correlation was found between any of the measures of CNV burden and IQ, or when comparing the top and bottom 10 % of the sample for IQ, both on a genome-wide scale and at individual positions across the genome.

Keywords Intelligence · Copy-number variation · Genetic burden · Association

Introduction

Individual differences in intelligence in human populations have an impact on a number of life outcomes including health, education and socioeconomic status (Deary 2012). While a substantial portion of the variation in intelligence has been demonstrated to be due to genetic differences (Deary et al. 2009), thus far the search for the genetic variants underlying this variation has been unsuccessful. For example, a recent genome-wide association study using ~3,500 individuals found no genome-wide significant variants (Davies et al. 2011). However, Davies et al. did demonstrate that a large portion of the heritability of intelligence can be explained by common genetic variants, indicating that intelligence is highly polygenic with individual variants having small effects on the trait. This result does not exclude a role of rare genetic variants in the underlying genetics of intelligence.

Recently, the role of copy-number variants (CNVs) in the development of neuropsychiatric diseases has been highlighted. An elevated incidence of CNVs has been observed in schizophrenia (Stefansson et al. 2008; The International Schizophrenia Consortium 2008; Kirov et al. 2012), autism (Sebat et al. 2007; Gai et al. 2012), bipolar disorder (Zhang et al. 2009; Priebe et al. 2012), ADHD (Elia et al. 2012), mental retardation (Madrigal et al. 2007; Guilmatre et al. 2009; Vissers et al. 2010) and other intellectual disability (Cooper et al. 2011; Girirajan et al. 2011). Some of these studies have also linked CNVs from specific genomic locations to the disorders.

With this accumulation of evidence for the role of rare CNVs in neurological development, it is reasonable to hypothesise that a similar burden of rare CNVs could also be observed in normal range intelligence. Indeed, a recent study by Yeo et al. (2011) found a significant correlation between burden of rare deletions and IQ ($r = -0.30$, $p = 0.01$) in a small sample of individuals ($N = 74$) with alcohol dependence. While the results presented by Yeo et al. appear robust to issues related to population

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admixture and variation in the degree of alcohol dependence, it remains to be seen whether this result is applicable to the general population.

In this study, the effects of rare CNVs on intelligence was investigated in a sample of 800 individuals. Three measures of CNV burden are correlated with IQ and CNVs in individual regions of the genome were tested for their effect on IQ. To examine whether the effect of CNV burden is more prominent in those individuals with low IQ, we also tested for differences between individuals in the top and bottom 10 % of the sample for IQ.

Materials and methods

Participants

Full-scale IQ measurements and CNV calls (see below) were available for 1,785 adolescent twins and their singleton siblings from 800 families who had participated in the Genetics of Twin Cognition study (Wright et al. 2001). Of these families, 34 included one sibling (one co-twin or singleton), 570 had two, 174 three, 21 four, and 1 had five. A reduced dataset consisting of 800 unrelated individuals was created by selecting the individual with the most phenotypically extreme IQ (measured as deviation from the population mean) within each family. The approach of taking the individual with the most extreme IQ measurement simplifies the analysis by removing the need to account for relatedness between individuals while still capturing a large portion of the power of the complete sample. The ages of the set of unrelated individuals ranged from 15.7 to 28.9 years (mean = 16.5, SD = 1.2).

Families were recruited through mail-outs to schools in South East Queensland or through media appeals and word of mouth. Exclusion criteria were parental or self-report of head injury, neurological or psychiatric illness, substance abuse/dependence, or current use of psychoactive medication. Written informed consent was obtained from all participants and from a parent or guardian for those aged under 18 years. The studies were approved by the Human Research Ethics Committee at the Queensland Institute of Medical Research.

IQ measurement

General cognitive ability was assessed using a shortened version of the computerised multidimensional aptitude battery (Jackson 1998). This included three verbal subtests (information, arithmetic, vocabulary) and two performance subtests (spatial, object assembly), which provided scaled a score for full-scale IQ. Details of the IQ assessment procedures has been described previously (Luciano et al. 2004). Months of schooling has typically been included as a covariate for this sample as the large majority are tested close to their 16th birthday and consequently pairs differ in the amount of schooling received at time of testing (Luciano et al. 2004). The set of 800 unrelated individuals had a mean IQ of 112 (range 79–153).

Calling of copy-number variation

DNA samples were genotyped on Illumina 610K Quad SNP array and were subject to standard quality control measures as detailed elsewhere (Medland et al. 2009, see Project 5 in their Table 2). CNV calls were generated using the software QuantiSNP (v1.1; Colella et al. 2007). The default program settings were used in addition to using a maximum copy number of four and performing a GC correction. A small number of individuals showed total numbers of CNV calls that were extreme outliers from the population distribution (>5 SDs from the mean) and were removed from the dataset prior to selecting the 800 unrelated individuals as this likely reflects a lower quality of their genotyping array data rather than true biological variation. To minimise the inclusion of false positive CNV calls, only CNV that were both >20 KB in length and called with a high confidence measure (log Bayes' factor >10) were considered. Given that the genome-wide burden of CNVs is dominated by the largest CNVs an individual is carrying, measures of CNV burden with different size thresholds are highly correlated and thus the choice of size threshold makes little difference to the final result. As common CNVs are well tagged by current SNP arrays (Wellcome Trust Case Control Consortium 2010), the influence of common CNV on IQ has already been indirectly assessed through GWAS studies. GWAS results show that any effect of common variation is very small and essentially undetectable with the sample size used in this study. Also, CNV burden measures would be dominated by the common copy-number variation. Thus, it was chosen to remove CNV with frequency >5 % and focus on the burden of rare CNV.

CNV burden analysis

The correlation between IQ and several measures of rare CNV burden (total CNV length, number of CNV and average CNV length) was tested using all CNV as well as separately for deletions and duplications. The analysis of the X chromosome was performed separately from the autosomes and for males and females due to potential for differential effects between the sexes in addition to the well documented role of the X chromosome in mental disorders (Ropers and Hamel 2005).

The effect of rare CNV burden may a priori be expected to be greatest in the population extremes, in particular at the lower end of the distribution of IQ, given the evidence for CNV burden in mental retardation. This effect may be masked in the analysis of the whole population due to lack of effect through the majority of the distribution of IQ values. To address this possibility, an additional analysis was performed testing the difference between individuals in the top and bottom 10 % of the distribution. Significance of the difference in average CNV burden values between the two extremes was tested using 10,000 permutations.

Locus specific CNV analysis

The effect of rare CNV frequency at specific points along the genome on IQ was tested using PLINK (Purcell et al. 2007). This is equivalent to genome-wide SNP analysis, except that the much smaller number of CNV variants tested results in a greatly reduced multiple testing burden. Significance was estimated through the use of 10,000 permutations. The analysis was performed using all CNV as well as separately for deletions and duplications.

Results

Table 1 summarises the called CNV in the 800 individuals. On average, each individual had 11 CNVs of >20 KB in length identified. Deletions occurred at three times the frequency of duplications, although duplications were on average approximately 2.3 times the length of deletions.

No significant correlations were observed between the measures of total autosomal CNV burden and IQ for all CNVs and both deletions and duplications separately (Table 2) and on the X chromosome in either males or females (Table 3). Separate analysis of deletions and duplications on the X chromosome similarly shows no significant correlations (data not shown).

A priori we might expect copy-number variation to have the largest effect in the lower tail of IQ measurements. This might be masked in an analysis using the entire distribution of IQ scores if there is no (or a minimal) effect across the rest of the distribution. To investigate this possibility, the CNV burden in individuals falling within the 10 % tails of the distribution were compared. As with the test using the entire distribution of IQ values, no significant difference in CNV burden was observed between individuals with the top and bottom 10 % IQ scores for either the autosomes or X chromosome (Tables 4, 5).

The genome-wide association of CNV frequency across the genome found no region of the genome with a significant correlation between CNV presence and IQ at the 5 % genome-wide level (Fig. 1). Similarly, no significant association was observed when analysing deletion and duplications separately (data not shown).

Discussion

The results presented here find no significant relationship between rare copy-number variation and IQ, both when

Table 2 Correlation between three CNV burden measures and IQ for autosomal chromosomes

CNV burden measurement	All CNVs	Deletions only	Duplications only
Total CNV length	−0.0016 (0.96)[a]	−0.00020 (1.0)	−0.0019 (0.96)
Number of CNV	−0.0064 (0.86)	−0.0035 (0.92)	−0.0090 (0.80)
Average CNV length	0.011 (0.77)	0.016 (0.65)	−0.0012 (0.97)

No significant correlation is observed between IQ and any of the CNV burden measures

[a] Correlation (two-sided test p value)

Table 1 Summary of copy-number data from 800 unrelated individuals after filtering CNV to have length >20 KB and population frequency less than 5 %

Copy-number	Autosomes		X chromosome, female		X chromosome, male	
	Count	Length in KB Mean (SD)	Count	Length in KB Mean (SD)	Count	Length in KB Mean (SD)
0	2,638	70 (119)	62	151 (73)	113	96 (57)
1	3,892	74 (273)	33	313 (763)	–	
2	–		–		44	225 (350)
3	1,875	181 (592)	105	260 (267)	–	
4+	251	171 (866)	10	168 (104)	–	

For autosomes and female X chromosomes a copy-number state of 0 corresponds to a homozygous deletion, 1 is a heterozygous deletion, 2 is normal copy number, 3 is a duplication and 4+ indicates multiple duplications

Table 3 Correlation between CNV burden measures and IQ for the X chromosome (combined deletions and duplications)

CNV burden measurement	Males	Females
Total CNV length	0.029 (0.57)	0.0049 (0.92)
Number of CNV	−0.0059 (0.91)	0.029 (0.55)
Average CNV length	0.037 (0.47)	0.019 (0.69)

No significant correlation is observed between IQ and any of the CNV burden measures. Separately analysing deletions and duplications also gave no significant correlation (data not shown)

Table 5 Average CNV burden measures for the individuals with the extreme 10 % of IQ measures for the X chromosome (combined deletions and duplications)

CNV burden measurement	Males	Females
Total CNV length	34.9, 59.5 (0.52)	181, 91 (0.34)
Number of CNV	0.34, 0.47 (0.72)	0.83, 0.60 (0.46)
Average CNV length	10.5, 18.8 (0.40)	115, 58 (0.77)

No significant correlation is observed between IQ and any of the CNV burden measures. Separately analysing deletions and duplications also gave no significant correlation (data not shown)

using individuals from the full range of IQ and when comparing the extreme 10 % of the distribution. Also no specific region of the genome was demonstrated to harbour rare copy-number variation that affected IQ.

While no significant correlation is found between IQ and rare copy-number variation in this study, this does not rule out a relationship between CNVs and IQ. Firstly, the methodologies used in recruitment and measurement of the individuals in this dataset essentially excludes, or at least greatly reduces participation probability, of individuals with extremely low IQ levels. Given much of the prior evidence of the role on copy-number variation in determining IQ comes from individuals with mental retardation, such large effects may not be seen in "normal" range IQ. Secondly, given our current understanding of the genetics of IQ from genome-wide association studies, the effects of CNV on IQ in individuals without mental retardation are likely to be small in size. This would indicate that the required sample size to detect these effects would be at least an order or two magnitude greater than what is used in this study. While the power of this study could be increased through the use of all individuals rather than an unrelated subset, this can not result in the observation of significant correlations between CNV and IQ. This is due to the combination of most of the power in the dataset being captured through the use of the most phenotypically extreme individual from each family and the fact that none of the correlations tested in this study approached significance. Obtaining a significant result in the analysis of the combined data-set would require a highly significant difference in the relationship between IQ and CNV burden between the sets of individuals who were included and excluded from the analysis. Given the inclusion criterion was based solely on IQ and not CNV burden, such a difference is a statistical impossibility.

Finally there are limitations in calling CNV using SNP arrays, both in accuracy of the variant calling and in the minimum size of CNV that can be detected. Manual inspection of the called CNV suggests that the minimum CNV confidence score imposed in this study served to minimise the number of false positive CNV calls. Also, from examining transmission of CNV in families, it is seen that the use of a minimum length of CNV served to reduce the number of false negative calls. Adjusting these parameters to allow smaller CNVs called with lower confidence was seen to increase the false negative and false positive rates respectively, but had no effect on the final results (data not shown). Another approach to improving CNV calling is to combine the output from multiple software packages. However, different CNV calling algorithms are usually consistent in their calls of large CNVs and these form the majority of the CNV burden measure, indicating that the result would not be altered by performing this addition step.

The results presented here contrast with those in Yeo et al. (2011), who find a substantial correlation between intelligence and rare copy number deletions in their sample ($r = -0.30$, $p = 0.01$). Their sample had CNV calls made using a more dense genotyping platform (Illumina Human 1 M)

Table 4 Average CNV burden measures for the individuals with the extreme 10 % of IQ measures for autosomal chromosomes

CNV burden measurement	All CNVs	Deletions only	Duplications only
Total CNV length (KB)	1,042, 1,122 (0.82)[a]	590, 411 (0.06)	452, 711 (0.35)
Number of CNV	9.89, 10.05 (0.86)	7.6,0 7.45 (0.85)	2.29, 2.60 (0.37)
Average CNV length (KB)	106.2, 104.6 (0.94)	73.0, 54.3 (0.09)	147.3, 181.6 (0.56)

While the burden of deletions approaches a nominally significant association with IQ with a two-sided test, it is in the opposite direction of what is a priori expected

[a] High 10 % mean, low 10 % mean (two-sided test p value)

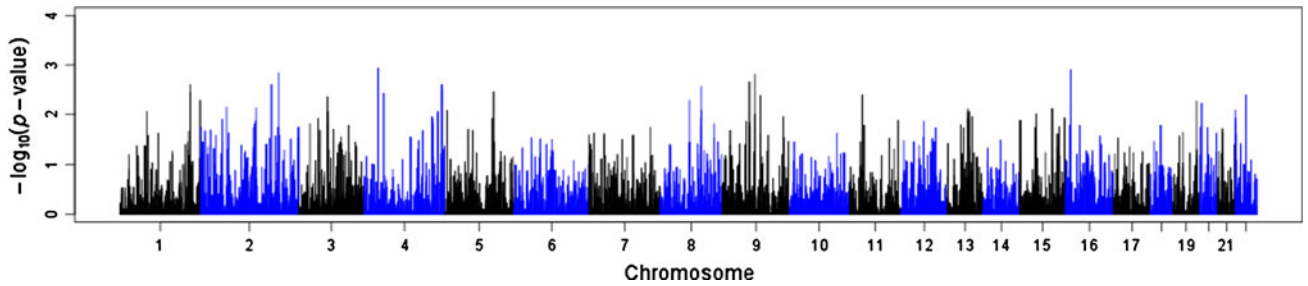

Fig. 1 Genome-wide association between copy-number variation and full-scale IQ. Each region across the genome was tested for association between the presence of rare CNV and IQ using the software PLINK. No region reached the 5 % genome-wide significance threshold ($-\log_{10}(p)$ of 3.5)

and a combination of two different CNV calling algorithms. Although Yeo et al. did not filter CNV on length, this would likely make little difference to the results as the total rare deletion length is dominated by larger CNVs. Given the manual checking of CNV calls in this study indicated a low rate of both false positive and false negative calls, it is unlikely these differences in CNV calling directly result in either a false negative result in this study or a false positive correlation for Yeo et al.

One potentially major difference between the present study and Yeo et al. is the population used. Yeo et al. use 74 individuals, of mixed ethnicity, aged between 21 and 55, who met the DSM IV criteria for alcohol dependence. Although low intelligence in childhood is associated with alcohol abuse later in life (Gale et al. 2010), the average IQ in this sample was only slightly below the mean level for the general population. Also, their findings were not driven by an association between full-scale IQ and severity of alcohol dependence. The mixed ethnicity of the samples was also demonstrated to not be causing the correlation as the relationship between IQ and total rare deletion length increased when only the individuals who identified themselves as "Anglo/white" were considered. However, the age difference between the two study samples is a potential explanatory factor for the difference in results. Indeed, an interaction between age and deletion length was observed by Yeo et al. to have an effect on IQ, indicating that the effect of rare deletions increases with age via an unknown mechanism. If this is the case, the effect of rare deletions on IQ may be negligible in the individuals used in our study, who were primarily adolescents, due to their younger age.

Overall, the results presented here indicate that rare copy-number variation does not explain much, or any, of the genetic basis of variation in adolescent IQ. Whether the effect of rare copy-number variants on IQ increases with age warrants further investigation in a large sample, as does copy-number variation in individuals with low IQ but in the normal range.

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