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Significant linkage and structural genomic variants at 12q24.21-q24.32 found in genetic isolate with aggregation of unspecific mental retardation

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Recent genome-wide association scans revealed associations between genomic variants on chromosome 12q24 and key brain structures related to cognition [1-4]. In an earlier genome-wide linkage scan of a genetic isolate from Dagestan (Northern Caucasus, Russia), we found evidence of linkage (LOD>3) between this locus and unspecific mental retardation (MRT) [5-7]. Here we report results from our recently completed expedition to update the pedigree, and our follow-up linkage results using the Weber panel of short tandem-repeats (STRs) and the Affymetrix 5.0 microarray of single nucleotide polymorphisms (SNPs). We used these methods to examine runs of homozygosity (ROHs) and copy-number variations (CNVs). The newly obtained results replicated our previous linkage findings with an even higher LOD = 3.87, peaking at 120 cM on chromosome 12, under a recessive model of inheritance. All 15 affected cases in the pedigree shared one founder allele, and 12 of the 15 affected subjects had homozygous genotypes, at markers D12S2070-D12S395-D12S2078.

The linked region contains more than 30 genes. Among them are some whose SNPs were found by large neuroimaging consortia to be associated with hippocampal and intracranial volume, which are key correlates of cognition and are implicated in many neuropsychiatric disorders [1, 3, 4]. For example, the intergenic marker rs7294919 is associated with expression levels of the positional candidate gene TESC in brain tissue [1, 3] and is within the linked region, as is the SBNO1 SNP rs7980687 that is associated with head circumference [4].

Eight affected MRT cases in our pedigree possessed CNVs involving FBXW8 and TESC SNPs (rs11609741, rs79667445 and rs4767490). In the

same intergenic region on 12q24.22 where rs7294919 maps, three of the most severely affected MRT cases demonstrated ROHs. We checked for loss of homozygosity among pedigree members in region 12q24.31 at the SBNO1 SNP rs7980687 implicated by meta-analysis as a determinant of head circumference in infancy [4], and 11 of 15 affected MR cases in the pedigree had ROHs at this locus.

Among five MRT cases in the pedigree, we found CNVs (deletions) involving the 12q14.3 gene, HMGA2, which was found by two groups to be associated with intracranial volume, and with intellectual performance in a large sample of healthy Australian twins [3, 4]. In addition, two heavily affected MRT cases in the pedigree had ROHs at this locus.

It is well known that the hippocampal formation is a crucial brain structure for many cognitive processes, especially learning and memory. Our work linking 12q24 variants to hippocampal structure on brain MRI – in over 20 cohorts from around the world – and to mental retardation in our pedigree are thus quite consistent. Interestingly, the regions of chromosome 12 we have found to be linked to MRT in our pedigree encompass SNPs that we recently reported to be significantly associated with volumetric differences in key brain structures for cognitive processing. These results from a highly isolated population of indigenous ethnic groups in Dagestan support these recent worldwide brain imaging association results, and validate them using a different method of genetic mapping (linkage analysis using STRs, and CNV and ROH analyses using SNPs). The linked mutations and structural genomic variants we observed here, in individuals affected with mental retardation in a highland genetic isolate, along with recent studies showing significant replicated association of SNPs with brain structure, firmly establish the importance and significance of chromosome 12q24 for cognition.

CONFLICT OF INTEREST

The authors report no biomedical financial interests or potential conflicts of interest.

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