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Association study of rare non-synonymous variants of *FTO* in bipolar disorder

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We carried out a weighted burden gene-wise association test comparing 99 whole genome sequenced UK bipolar subjects with 395 European subjects from the 1000 Genomes project (www.1000genomes.org), using the methods and samples already described (Curtis 2012; Fiorentino, O'Brien et al. 2014). Careful scrutiny of the output revealed that a few genes produced results which seemed to be clearly artefactual but that some might be showing real evidence for an excess of rare, functional variants among bipolar cases. Of these *FTO* had an uncorrected significance of $p=10^{-4}$ and ranked 31 out of 24204 genes. This result was mostly driven by the fact that three very rare non-synonymous variants were each found in two bipolar subjects, these being rs147561986, rs182784714 and rs144743617. These were seen in 1, 0 and 1 of the 1000 Genomes subjects and in ExAC European samples they have frequencies of 0.00064, 0.00052 and 0.0036 (Lek, Karczewski et al. 2015). Thus, one would not expect any of these variants to be observed by chance in a sample of only 99 subjects and it seemed remarkable that six subjects each had one of them. Inspection of the BAM files showed that the calls seemed unambiguous so we decided to attempt to validate them using Sanger sequencing. This confirmed the genotypes for rs182784714 and rs144743617 but not for rs147561986. There have been reports that *FTO* variants may influence weight and that this effect may be mediated, at least in part, through effects on cognitions and eating behaviour (Micali, Field et al. 2015). Given that appetite disturbances are a core feature of bipolar disorder we considered that it was possible that these variants were risk variants for affective disorder.

We genotyped rs182784714 and rs144743617 in samples of ethnically matched bipolar cases and controls with UK ancestry as previously described (Fiorentino, O'Brien et al. 2014). Among the successful genotypings, for rs182784714 there were 3 heterozygotes among 1099 cases and 1 among 731 controls (overall MAF=0.0011, $p=NS$) and for

rs144743617 there were 14 heterozygotes among 1293 cases and 10 among 899 controls (overall MAF=0.0055, p=NS).

Thus the results demonstrate no difference in allele frequencies between bipolar cases and controls and we conclude that there is no evidence that FTO variants affect susceptibility to affective disorder. The allele frequencies we observe for both cases and controls are higher than those reported by both 1000 Genomes and ExAC. We do not know if this is because these variants happen to be commoner in the UK population than in the wider European population or for some other reason. In any event, this study demonstrates that if one notes differences in allele frequency between case samples and large, published variant databases then one should follow this up by making direct comparisons using an ethnically matched set of controls genotyped using the same methods.

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