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SMARCA2 COMMON VARIANT ASSOCIATION AND RARE VARIANT EXCESS IN SCHIZOPHRENIA PATIENTS FROM AN ALGERIAN TRIO COHORT

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Genome wide association studies (GWAS) of Schizophrenia (SZ) patients have identified common variants in ten genes including SMARCA2 (Koga et al., HMG, 2009). We found that the SZ-GWAS genes are part of an interacting network centered on SMARCA2 (Loe-Mie et al., HMG, 2010). Furthermore, SMARCA2 was found disrupted in SZ (Walsh et al., Science, 2008). SMARCA2 encodes the ATPase (BRM) of the SWI/SNF chromatin remodeling complex that is at the interface of genome and environmental adaptation.

Taking advantage of an Algerian trio cohort of one hundred SZ patients (Benmessaoud et al., BMC Psychiatry, 2008), we replicated the association of SNP rs2296212 localized in exon 33, already shown associated in Koga study and resulting in D1546E amino acid change in the SMARCA2 protein. We studied SMARCA2 codons and found that exon 33 displays a signature of positive evolution in the primate lineage.

Our working hypothesis is that the coding regions displaying positive selection are target of novel rare variants. To address this question, we sequenced two exons displaying positive evolution and one exon without evidence of positive evolution.

We found (i) that rare variants are significantly in excess in SZ-patients compared to their parents (p=0.038, Fisher test) and (ii) a higher proportion of rare variants in the primate-accelerated exons compared with the non-evolutionary exon in SZ-patients (p=0.032, Fisher test).

SMARCA2 exon sequencing and whole exome sequencing from patients harboring SNP rs2296212 common variant are under progress. Altogether, these results are expected to give new insights into the genetic architecture of SZ.

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