GENETIC MARKERS LINKED TO DIFFERENCES IN WHITE MATTER MICROSTRUCTURE IN CORPUS CALLOSUM AND INFERIOR FRONTO-OCCIPITAL FASCICULUS IN 22q11.2 DELETION SYNDROME

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BACKGROUND

22q11.2 deletion syndrome (22q11.2DS, Velo-Cardio-Facial Syndrome (VCFS)) is a genetic disorder caused by a deletion of the q11.2 band of one copy of chromosome 22.

The syndrome is associated with a high prevalence of psychiatric disorders, including anxiety, autism spectrum disorder (ASD) and schizophrenia (SZ).

The prevalence of schizophrenia is about 30% in 22q11.2DS and young adults represent a high-risk population to develop SZ. White matter (WM) brain structure changes have been reported in patients with SZ or/and ASD.

Several genes of the 22q11.2 region have been reported in the literature to be associated with changes in WM development and in SZ.

The corpus callosum is a commissural fiber that plays an integral role in relaying sensory, motor and cognitive information from homologous regions in the two cerebral hemispheres.

The Inferior Fronto-Occipital Fasciculus (IFOF) is a long association fiber that connects the occipital, posterior temporal, and the orbito-frontal areas.

There is limited understanding of the relationship between genes at this locus that are implicated in SZ and WM changes in these tracts in adolescents with 22q11.2DS who might eventually develop SZ.

MATERIALS AND METHODS

51 adolescents with the syndrome (mean age 17.95, SD 2.27), participated in the study.

The subjects were genotyped on 17 SNPs of the genes PRODH, PIK4CA, SNAP29, and COMT, which are located at locus q11.2 and associated with SZ.

Diffusion weighted images were acquired on a 1.5 Tesla Philips Scanner. Images were post-processed to generate DTI images.

We utilized diffusion tensor imaging and white matter tractography to evaluate WM microstructure in the corpus callosum and in the IFOF.

Streamline tractography was based on manually drawn Regions of interest (ROIs) and performed using 3DSlicer software.

RESULTS

Between-group analyses comparing the different allele groups demonstrate a significant difference in the DTI measures.

We found that allelic variation in the SNAP29 gene was significantly associated with differences in axial diffusivity (AD) and radial diffusivity (RD) in the left IFOF.

Allelic variations in the PRODH gene were significantly associated with differences in: fractional anisotropy (FA) and RD in the CC, and FA bilaterally in the IFOF.

Allelic variations in the COMT gene were significantly associated with differences in: FA of the left IFOF, and RD in these tracts in adolescents with 22q11.2DS.

CONCLUSIONS

Several genes of the chromosomal region 22q11.2, which were previously reported as schizophrenia candidate genes, are also significantly associated with changes in WM microstructure in 22q11.2DS.

These preliminary results suggest that SNAP29, PRODH, and COMT may be markers for psychiatric disorders and exert their role through the disruption of inter-hemispheric and fronto-occipital connectivity in these youth.

Due to the small sample size and uncorrected p-values, larger, multi-site studies will be needed in the future in order to confirm these findings.

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