A GENOME WIDE ASSOCIATION STUDY IN PATIENTS WITH INTRACRANIAL AND EXTRACRANIAL ATHEROSCLEROSIS

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Background and Aims

Large-artery intracranial/extracranial atherosclerosis (ICAs/ECAs, respectively) are a major cause of stroke worldwide. Genome-Wide Association studies (GWAs) identified genes associated with Atherothrombotic stroke, such as *HDAC9* or *TSPAN2*. However, ICAs and ECAs have not been directly analyzed by GWAs using risk scores.

Methods

We studied 509 Caucasian subjects: 195 patients with ICAs and/or ECAs (94.6% symptomatic), and 315 population-based controls. We performed two analyses:

- Analysis 1. Patients with ICAs vs. controls
- Analysis 2. Use of scores:
 - Score1: number of ICAs measured with arteriography
 - Score2: number and severity of ICAs. For the severity:
 - Mild (<50%): 1 point
 - Moderate or severe (>50%): 2 points
 - Score3: number and severity of ICAs + number and severity of ECAs (measured with Doppler). Severity measured as score 2.

Genetic analyses were performed using Human Core Exome (Illumina). For quality controls, 1000G imputation and association analysis we used PLINK, R, IMPUTE2 and SNPTTEST software following previous recommendations. We used as covariates sex, age and principal components.

Results

After quality controls 8,047,349 SNPs, 173 patients and 315 controls were analyzed. None SNP in *HDAC9* nor *TSPAN2* was significantly associated with ICAs or ECAs using our scores.

ICAs vs. controls: One locus at 3p14 was genome-wide associated ($P < 10E-08$) with ICAs presence.

Score 1 and 2: Two loci, one at 7p21 and the other at 16p12 were genome-wide associated with these scores.

Score 3: One locus at 18q21 was genome-wide associated with score 3.

**Gene related with corticoids effect and also elevations in blood pressure.
*** Gene related with severity of pseudoxanthoma elasticum and sodium concentrations in arteries.

* Gene associated with β -amyloid in a GWAs with Alzheimer patients.

**** Nearest gene associated with calcified aortic stenosis in mi-RNA expression studies.

Conclusions

A GWAs in ICAs and ECAs patients has revealed potential genes associated with ICAs presence and with combination of ICAs and ECAs severity. These findings need to be replicated in other independent cohorts to confirm these results.