**Copy number variations analysis in Brazilian and Italian patients with Hemorrhagic Stroke**

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**Introduction:** Stroke is a heterogeneous and multifactorial condition, responsible for blockage in blood flow to the brain. Several studies have demonstrated evidence of genetic factors influencing stroke. However, due to its low population frequency and higher mortality rate, hemorrhagic stroke has been less studied. Copy number variations (CNVs) are common structural mutations, which have been identified as causing changes in gene expression, thus leading to disease. The main objective of this study is to study copy number variations in patients with hemorrhagic stroke, looking for possible functional correlates with genes affected.

**Materials and Methods:** We used DNA samples from 45 patients with hemorrhagic stroke and 41 controls without stroke from the Stroke Biobank in Joinville/SC. In addition, we validated the results in a group of 18 Italian patients with hemorrhagic stroke. In order to evaluate if Brazilian and Italian sample have similar genetic structure, we performed a principal component analysis (PCA), using R software and the *mahalanobisDist-package*, developed in our laboratory. Only CNVs present exclusively in patients were recorded in our results. We used microarray chips based on SNPs (*Genome-Wide Human SNP Array* 6.0; Affymetrix Inc.) for CNV identification. The results were evaluated by Genotyping Console® Software (Affymetrix Inc.). We analyzed biological pathways containing genes with CNVs using the METACORE Software. The genes selected by this software were further analyzed at DGV and DECIPHER databases as well.

**Results:** Our PCA showed that Brazilian and Italian patients present similar genetic structure (p-value = 0.1639). We identified 384 CNVs present only in Brazilian patients with hemorrhagic stroke. These CNVs were present in19 genes potentially related to stroke, with function related to angiogenesis, coagulation, immunology, tissue development and lipid metabolism process. According to DGV database, 4 of these genes (*CDH13*, *FNTA*, *MACROD2* e *NAALADL2*) had no common CNVs reported in the normal population. In addition, 8 of these genes (*CYP2E1*, *DEFB4B*, *MACROD2*, *NOMO1*, *NSF*, *PRODH*, *RAF1* e *RB1CC1*) have been described with relation to cardiovascular and neurological processes. The validation study identified two genes in Italian patients that were also present in Brazilian patients: *MACROD2* and *NSF*.

**Discussion:** The genes identified in the present study are good candidates for further analysis, such as *NFS,* which is related to vascular repair and neurological process and*MACROD2*which is related to cardiac and neurological development as well as cardiomyopathy.

**Conclusion:** We have demonstrated for the first time that CNVs in *NSF* and *MACROD2*genes may influence the risk for hemorrhagic stroke. In addition, our findings were confirmed in two independent samples of patients with hemorrhagic stroke.

**References:** [1] Traylor M. et al., Lancet Neurol, 2012. **11**(11): 951-62; [2] Bae J.S. et al., J Hum Genet, 2010. **55**(11): 726-30; [3] Jahanshad, N., et al., Proc Natl Acad Sci USA, 2013. **110**(12): 4768-73; [4] Liu, C. and B. Hu, Neuroscience, 2004. **128**(4): 767-74.

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