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# Magnitude of the founder effect for migraine in exomes of the Mennonite population

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The Mennonite population has been genetically isolated for about 500 years since the Anabaptist movement. Due to political-religious conflicts, the population has experienced three significant reductions in size (bottleneck events), leading to increased inbreeding, a small number of couples contributing to the next generation (founder effect), and susceptibility to chronic diseases such as migraine. In this study, we screened 325 exomes of South Brazilian Mennonites (SBM: 131 from Curitiba - PR and 194 from Colônia Nova - RS) for variants previously associated with migraine in genome-wide association studies (GWAS database). Among 244 headache-associated variants, we found 9 in SBM. We further compared their frequencies with those of the non-Finnish European population (EURO, N=589,961), the Amish (N=456), and the Brazilian population (BR, N=1,171), using the gnomAD v4.1.0 and ABraOM databases, correcting p-values for multiple testing using the False Discovery Rate method and evaluating possible associations with gene expression using GTEx portal. The nine variants occur in the HJURP, ANAPC4, IRAG1, CHRM4, and AMN genes, with four occurring in the RNF213 gene. The frequencies of three polymorphisms differed between SBM vs. EURO (founder effect), eight between SBM and Amish (genetic drift effect), and seven between SBM and BR (possible epidemiological relevance). The only protective variant was a benign aminoacid substitution (p.Arg465Gln), associated with lower expression of the ANAPC4 gene in several brain regions. Three RNF213 variants form a susceptibility haplotype, found more frequently in SBM than in Amish and BR (p=0.045). The benign p.Ser2383Asn (rs9674961) variant is among them, being also associated with lower RNF213 expression in the frontal cortex (p=0,03). Mutations in this gene further cause progressive cerebral angiopathy in the Moyamoya syndrome. In conclusion, we observed a founder and genetic drift effect for headache-associated variants among the Mennonite population. Further studies are needed to validate these genes' actions and the potential impact of these variants on migraine development.