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Searching for genetic biomarkers for hereditary angioedema due to C1-inhibitor deficiency (C1-INH-HAE)

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Abstract

Biological parameters modifying patients' phenotype and/or the effectiveness of various treatments might result in optimization of hereditary angioedema management. Our aim was to detect genetic alterations that could be used as prognostic biomarkers of the severity of C1-INH-HAE. Using a custom NGS platform (Thermo Scientific) we investigated the presence of 18 functional SNPs (MAF≥1%) in 233 C1-INH-HAE patients (113 Hungarian, 47 Polish, 31 Greek, 23 German, 19 Bulgarian) from 144 different families. Disease severity was estimated by CALS severity score (sum of cutaneous, duplicated abdominal and triplicated laryngeal attacks during the last year). Multivariate analysis was implemented with dependent variables the age at disease onset, the long-term prophylaxis (LTP) or the CALS, and with those of the polymorphisms presenting with significant associations in univariate analysis fitted as independent variables. A generalized estimating equations model was also performed. Regardless of *SERPING1* mutational

status, heterozygous and homozygous carriers of *F12* c.-4T>C presented CALS increased by 18.69 (p=0.002) and 28.21 (p<0.001), respectively; the *SERPING1* c.-21T>C polymorphism was associated with a 2.5-fold increase of the need for LTP (p=0.012); *SERPING1* c.1438G>A carriers exhibited a delayed disease onset by 3.6 (heterozygous, p=0.018) and 6.3 (homozygous, p=0.058) years; heterozygous carriers of *F13B* c.344G>A were presented with decreased CALS by 11.84 (p=0.024); *PLAU* c.422T>C homozygosity was associated with decreased CALS by 13.67 (p=0.004); presence of the A allele of *SERPINA1* c.1096G>A was significantly associated with increased CALS by 80.16 (p=0.003). In carriers of missense *SERPING1* mutations, *F12* c.-4T>C carriers were presented with increased CALS by 13.88 (heterozygous, p=0.003) and 25.48 (homozygous, p=0.002); the *SERPING1* c.-21T>C polymorphism was associated with a 4.2-fold increase of the need for LTP (p=0.02); heterozygous carriers of *SERPINA1* c.863A>T exhibited an earlier disease onset by 8 years (p<0.001); homozygous carriers of *SERPINE1* c.43G>A exhibited a delayed disease onset by 8.4 years (p=0.009); homozygous carriers of *KLKB1* c.428G>A exhibited an earlier disease onset by 7 years (p=0.029) along with increased CALS by 30.45 (p=0.001); heterozygous carriers of *KLK1* c.230G>A exhibited a delayed disease onset by 8.95 years (p=0.05) along with decreased CALS by 16.79 (p=0.029); heterozygosity for *CPN1* c.533G>A was independently associated with a decreased need for LTP by 98% (p=0.017); heterozygosity for *F2* c.*97G>A was significantly associated with decreased CALS by 25.97 (p=0.017). It is concluded that variants other than those of *SERPING1* act as independent modifiers of C1-INH-HAE severity and thus they could be tested as possible prognostic biomarkers of the disease.