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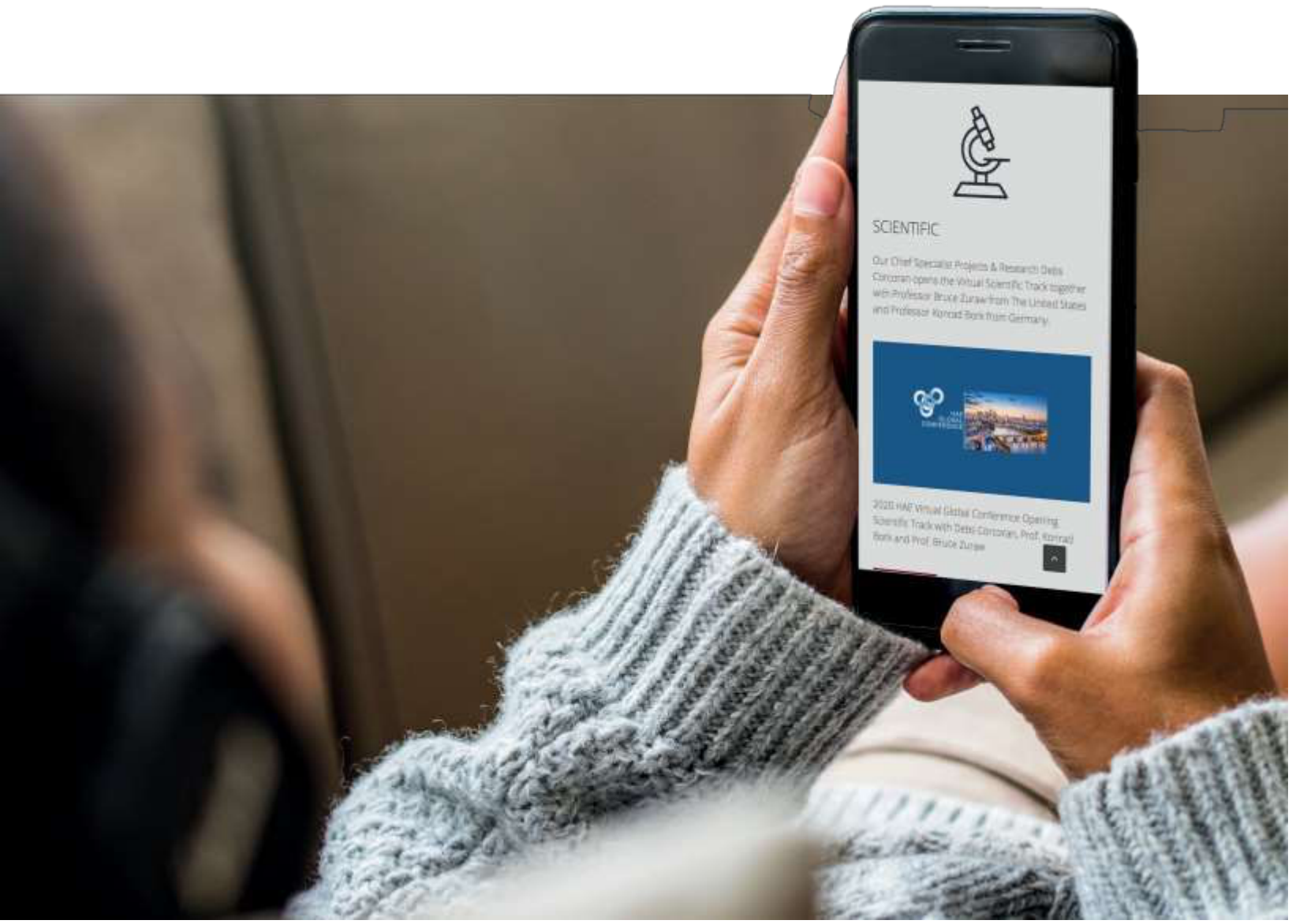
Scientific Track – Abstracts



Topic 1. Determining Better Pathways to Diagnosis and Management of HAE

Whole Exome Sequencing Identified Novel Candidate Genes Associated with Hereditary Angioedema of Unknown Origin

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Introduction: The prevalence of hereditary angioedema of unknown origin (U-HAE) is extremely low and accounts for about 1% of all cases of HAE. In the Next-Generation Sequencing (NGS) era, identifying genes whose changes can lead to edema has become more affordable. But the more we perform NGS for suspicious U-HAE, the more questions arise.

Methods: The study included 5 individuals from 2 unrelated families with clinical and laboratory characteristics of nC1NH-HAE, for whom we initially performed NGS for amplicons of 18 genes (including *FXII, PLG, ANGPT1, KNG1*) and the results were questionable. We thus performed Exome Sequencing (WES) using Nextera Exome Kit (Illumina). After variant calling, quality control and filtering (population frequency<1%) we identified some variants potentially disease associating. The uniqueness of variants was checked among other DNA samples and donors. All clinically significant variants were confirmed by Sanger sequencing.

Results: Analysis of WES in family 1 revealed one heterozygous change segregating with the phenotype in the CPA3 gene (NM_001870:c.509T>G;p.F170C), not previously described and with no data about population frequency. This gene encodes a member of the carboxypeptidase A family that is released by mast cells and is involved in the degradation of endogenous proteins. Among its related pathways are agents acting on the renin-angiotensin system. Analysis of NGS in family 2 revealed heterozygous changes common to the two affected members whose frequency in the general population is too high for them to be clear cut candidate to be causative variant. Among them a variant in the ANGPT1 gene (c.454-22T>C; rs200470101; AF_ALL 0.003), a gene already associated with nC1NH-HAE.

Conclusion: The next step in our work will be to examine all available symptomatic and asymptomatic relatives for these changes and to test the activity of the encoded proteins in plasma samples to validate their association with HAE.