Complexity and diversity of F8 genetic variations in the 1000 genomes. [1]

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BACKGROUND: Hemophilia A (HA) is an X-linked bleeding disorder caused by deleterious mutations in the coagulation factor VIII gene (F8). To date, F8 mutations have been documented predominantly in European subjects and in American subjects of European descent. Information on F8 variants in individuals of more diverse ethnic backgrounds is limited.

OBJECTIVES: To discover novel and rare F8 variants, and to characterize F8 variants in diverse population backgrounds.

PATIENTS/METHODS: We analyzed 2535 subjects, including 26 different ethnicities, whose data were available from the 1000 Genomes Project (1000G) phase 3 dataset, for F8 variants and their potential functional impact.

RESULTS: We identified 3030 single nucleotide variants, 31 short deletions and insertions (Indels) and a large, 497 kb, deletion. Among all variants, 86.4% were rare variants and 55.6% were novel. Eighteen variants previously associated with HA were found in our study. Most of these 'HA variants' were ethnic-specific with low allele frequency; however, one variant (p.M2257V) was present in 27% of African subjects. The p.E132D, p.T281A, p.A303V and p.D422H 'HA variants' were identified only in males. Twelve novel missense variants were predicted to be deleterious. The large deletion was discovered in eight female subjects without affecting F8 transcription and the transcription of genes on the X chromosome.

CONCLUSION: Characterizing F8 in the 1000G project highlighted the complexity of F8 variants and the importance of interrogating genetic variants on multiple ethnic backgrounds for associations with bleeding and thrombosis. The haplotype analysis and the orientation of duplicons that flank the large deletion suggested that the deletion was recurrent and originated by homologous recombination.

Abstract

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