SSIEM 2022 Annual Symposium, 30 August – 2 September, Freiburg, Germany
Abstract submission deadline: 19 April, 23:59:59 CEST

HCU Genotypes Abstract

Insights from the First Genetic Evaluation of a Longitudinal Natural History Study in Classical Homocystinuria (HCU)

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ABSTRACT (1,980/2,000 characters, including spaces)

Background: Classical homocystinuria (HCU) is a rare autosomal recessive disorder caused by mutations in cystathionine beta-synthase (CBS) gene, resulting in markedly elevated levels of plasma total homocysteine (tHcy). The relationship between genotype and tHcy levels is not well-understood. Here we describe the initial results of a genetic analysis in a cohort of HCU patients and the association of pathogenic variants with tHcy levels.

Methods: A prospective, longitudinal, multicenter, multinational natural history study in patients with HCU aged 5-65, conducted at 8 sites across the US, UK, and Ireland.

Results: Sixty-two patients were enrolled as of 15 JUL 2021 (52% male; age range 5-53 years; 94% white). Of these, 89% had baseline tHcy levels measured (mean=109.6, SD=90.6), 82% had a CBS genotype available; and 76% had both. Of the 51 genotypes analyzed, 20 carried homozygous CBS variants, and 2 lacked bi-allelic genetic confirmation of HCU. 50% of homozygous patients carried the Irish allele c.919G>A (p.Gly307Ser), which was the most prevalent (29% [n=30]), followed by the missense variants c.325T>C (p.Cys109Arg) and c.833T>C (p.Ile278Thr). Missense variants accounted for 74% of genotypes. Three B6 responsive alleles were identified: c.833T>C (p.Ile278Thr), c.1058C>T (p.Thr353Met) and c.1152G>C (p.Lys384Asn). Among patients with the same homozygous p.Gly307Ser genotype, high variability in tHcy levels was observed (ranging from 21-192 µmol/L). Heterozygosity for the B6 responsive allele p.Ile278Thr was associated with a lower tHcy level (p=0.0006).

Discussion: Most patients studied carried B6 non-responsive alleles containing missense variants, with the Irish founder allele p.Gly307Ser being most common. We observed high variability in tHcy levels for common CBS variants, suggesting that factors other than the genotype likely influence tHcy levels. Heterozygosity for the B6 responsive allele p.Ile278Thr was associated with lower tHcy levels.

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Questions asked during submission:

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Proposed key words: Homocystinuria, genotypes, total homocysteine concentration, natural history

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