ACMG Annual Clinical Genetics Meeting, 14 Mar – 18 Mar, Salt Lake City, UT, USA
Abstract submission deadline: 18 Nov 2022, 11:59 pm PST

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

Tiziano Pramparo[1], Kimberly A. Chapman[2], Ying Chen[1], Can Ficicioglu[3], Harvey Levy[4], Janet Thomas[5], Sagar A. Vaidya[1], Steve Rodems[1], Ellen Crushell[6]

[1]Travere Therapeutics, San Diego, CA; [2]Children's National Medical Center, Washington, DC; [3]The Children's Hospital of Philadelphia, Philadelphia, PA; [4]Harvard Medical School, Boston, MA and Boston Children's Hospital, Boston, MA; [5]University of Colorado School of Medicine and The Children's Hospital of Colorado, Aurora, CO; [6]Children's Health Ireland at Temple St, Dublin, Ireland

ABSTRACT (277 words, excluding spaces/600 max)

Introduction: Classical homocystinuria (HCU) is a rare autosomal recessive disorder caused by pathogenic variants in the *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 Jul 15, 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. Fifty percent 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).

Conclusions: Most patients studied carried B6-nonresponsive alleles containing missense variants, with the Irish founder allele p.Gly307Ser being the 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.

DISCLOSURES

TP: Employee and stockholder, Travere Therapeutics, Inc.

KAC: Investigator for Travere Therapeutics, Inc.

YC: Employee and stockholder, Travere Therapeutics, Inc.

CF: Investigator for Travere Therapeutics, Inc.

HL: Investigator and consultant, Travere Therapeutics, Inc.

JT: Investigator for Travere Therapeutics, Inc.

SAV: Employee and stockholder, Travere Therapeutics, Inc.

SR: Employee and stockholder, Travere Therapeutics, Inc.

EC: Investigator for Travere Therapeutics, Inc.