Homocystinuria Diagnosed by Whole Exome Sequencing in Siblings from an Isolated Central American Village

Poster
123

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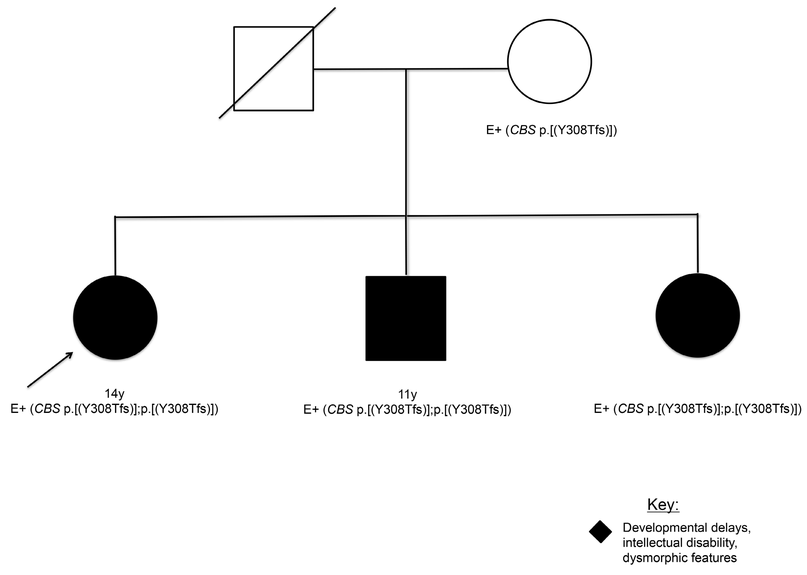
Case Report

A family from an isolated Central American village presented to medical care during a humanitarian visit by physicians from the Dartmouth-Hitchcock Medical Center. Examination revealed two children, similarly affected by developmental delays, intellectual disability, and dysmorphic features of unknown etiology (**FIGURE 1**). A younger sibling was beginning to display similar symptoms, but it was unclear whether this was related to the presentation of the older siblings. Access to previous laboratory work and medical records was limited.

FIGURE 1: Index Family Pedigree



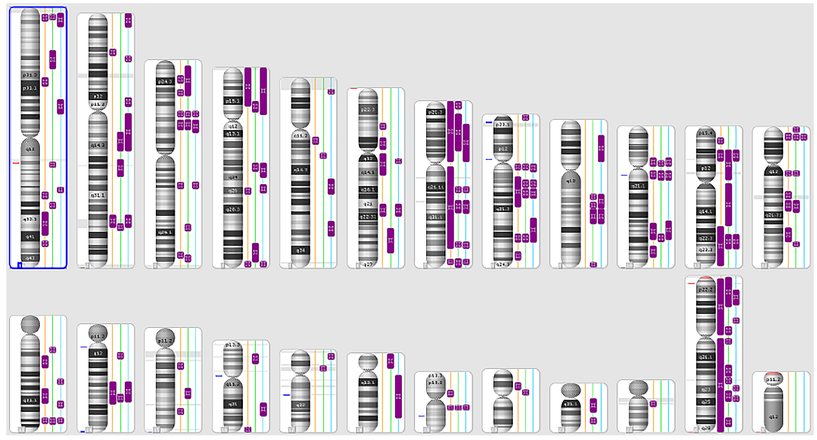
Case Evaluation

DNA samples were extracted from buccal swabs from the two eldest affected siblings and additional family members. Chromosomal microarray analysis (CMA) was performed using the CytoScan® HD Array (Affymetrix, Santa Clara, CA). Augmented whole exome sequencing (WES) was performed on DNA from the oldest sibling (ACE Exome, Personalis). Targeted confirmatory testing was performed by standard Sanger sequencing.

Case Results

Chromosomal microarray revealed no relevant copy number variation but identified multiple long contiguous stretches of homozygosity (LCSH) (**FIGURE 2**). More than 200 genes causative of autosomal recessive disease were contained within the homozygous stretches.

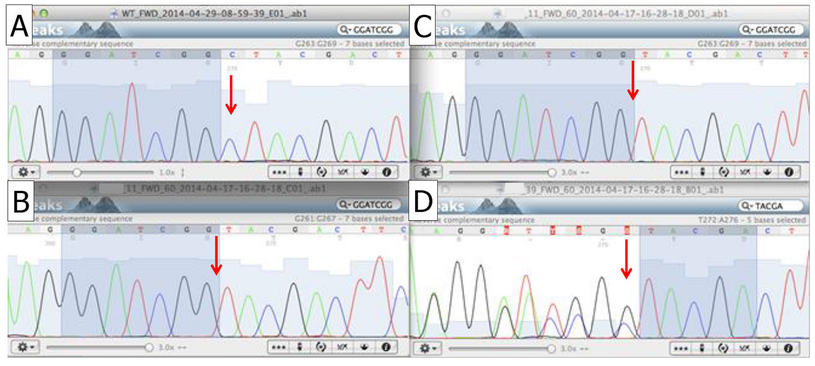
FIGURE 2: CMA Results



Extensive regions of homozygosity (purple boxes) **detected in two affected siblings** (orange and blue lines) **and mother** (green line).

ACE Exome sequencing recapitulated the CMA finding, again identifying multiple LCSHs. A novel, homozygous, single base pair deletion in *CBS* was identified as the most likely disease-causing candidate. The variant, p.Tyr308Thrfs (c.921delC), was confirmed by capillary electrophoresis in the proband, and also detected in the homozygous state in the affected brother and the youngest sibling. The unaffected mother was confirmed to be heterozygous for the variant (**FIGURE 3**).

FIGURE 3: Confirmation by Capillary Electrophoresis



Electropherograms depicting a normal control (A), proband (B), sibling (C), and mother (D).

Diagnosis

Homocystinuria is an autosomal recessive metabolic condition caused by deficiency of cystathionine β-synthase (*CBS*). Markedly elevated concentrations of methionine and homocysteine are detected in affected individuals, resulting from the inability to convert homocysteine to cysteine in the absence of functioning CBS protein. The presenting features of the disorder are variable but generally include developmental delay, intellectual disability, skeletal abnormalities, ocular defects, osteoporosis, and thromboembolism.

A diagnosis of homocystinuria was confirmed in the index patient by detection of an elevated blood homocysteine concentration.

Discussion

This case report of undiagnosed homocystinuria serves as a learning tool for genetic counselors. When working with international patients, we face many cultural, social and language barriers. Increasing this challenge, is the fact that we rarely have access to medical records and evaluations previously performed.

Although screening for homocystinuria occurs routinely in the United States, newborn screening programs vary dramatically in other countries with many countries lacking access to newborn screening programs altogether. It is therefore important that these diseases not be overlooked when counseling patients, especially in patients without access to standard US medical services.

Further Information

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Booth
205

- **The ACE Clinical Exome Test: Advanced Diagnostic Test for Genetic Disease**
  Thursday, 9/18 @ 11:30 AM in VSP Pavilion, Exhibitor Suite, Hall B
- **Application of an Enhanced Exome in the Diagnosis of Rare Genetic Diseases**
  Friday, 9/19 @ 7:00 AM (CEU-approved) in Great Hall B & C
- **Gemma Chandratillake**: *"Revised Diagnosis Through Exome Sequencing of an Infant With Congenital Cataracts Expands Phenotypic Spectrum of COL4A1-associated Disorders"* **Concurrent Session: Genetic Testing I, Friday 8.15 AM**
- **Jeanie Tirch** *et al.*, *"Successful Utilization of Enhanced Exome Sequencing to Identify the Genetic Cause of Retinal Disorders in a Case Series"* **Poster #148**
- **Gemma Chandratillake** *et al.*, *"A Negative Result on Exome Sequencing: What a Genetic Counselor Should Know"* **Poster #119**
- **Sarah Garcia** *et al.*, *"Use of an Enhanced Exome with Genome-wide Structural Variant Detection for the Diagnosis of Mendelian Disease"* **Poster #124**