

Identification of genetic etiologies of pediatric short stature using whole exome sequencing

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Introduction

The majority of pediatric patients with short stature are diagnosed with idiopathic short stature (ISS). A subset of ISS patients with severe short stature have rare genetic causes that may be identified using genetic analyses such as whole exome sequencing (WES).

Hypothesis

The short stature of two selected pediatric ISS patients is attributed to rare genetic variants that will be identified using WES analysis.

Methods

Patient 1 is an adult male whose height is -3.4 SDS; his clinical presentation is otherwise unremarkable. His mother and half-sister are also short statured, suggesting a dominant inheritance pattern. Patient 2 is a 2.9-year-old male whose height is -6.7 SDS. He is of a consanguineous pedigree, suggesting a recessive inheritance pattern. His clinical presentation appears to be consistent with microcephalic primordial dwarfism.

DNA samples from Patient 1 and his mother and Patient 2 and his parents were obtained and WES was performed using next-generation sequencing at the core sequencing facility at CCHMC. Variants were filtered by genotype, minor allele frequency, and the synonymous/non-synonymous nature of the variants, to generate unbiased candidate variant lists. Gene database searches were conducted to find disease phenotypes associated with the candidate variants and bioinformatics tools were used to predict functional effects of the primary candidate variants.

Results

Analysis of WES data of Patient 1 and his mother identified 32 novel, non-synonymous, heterozygous variants common to both individuals, one of which is a missense variant in *HMG2*. An association between *HMG2* variants and human height has been revealed through genome-wide association studies. Further familial segregation studies are pending. Analysis of WES data of Patient 2 identified a homozygous 19-nucleotide deletion in exon 2 of *PCNT*. *PCNT* is associated with microcephalic osteodysplastic primordial dwarfism II, which is consistent with the patient's clinical presentation. Subsequent Sanger sequencing of patient and parental DNA confirmed that the variant is present in Patient 2 and that both parents are heterozygous for the variant.

Conclusion

WES is a powerful analytic tool that can aid in the identification of novel genetic variants associated with pediatric short stature.

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