Altered Frequency of Sequence Variants in Growth Related Genes in Children with Short Stature

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Background

Idiopathic Short Stature (ISS) can be defined as a condition of short stature in which height is below −2 SD scores (SDS) for age, sex and the corresponding population, without evidence of a systemic disease, nutritional, psychological or chromosomal disorder, or overt hormonal abnormalities. Short children without a defined aetiology are classified as ISS where birth weight/length is >-2SD and as Small for Gestational Age (SGA) where birth weight/length is ≤-2SD

The EPIGROW study[1] was a cross sectional epidemiogenetic study designed to identify clinical, biological, and genetic characteristics in a large European cohort of ISS/SGA children. Next generation deep sequencing of 232 candidate genes was undertaken in 263 ISS/SGA children and 263 ethnically matched controls. Two Single Nucleotide Polymorphisms (SNPs) (one in *ZBTB38* and one in *NFKB1*) and one insertion/deletion (indel) in *IGF1* were identified as having a significantly different frequency between cases and controls.

Aim

The aim of this study was to to determine in the EPIGROW cohort if the frequency of SNPs or indels within each of the 232 candidate genes was different between cases and controls.

Methods

All SNs/indels were identified in patients and controls. Gene level SNP/ indel frequency was considered to be different where a Benjamini-Hochberg adjusted p-value from a chi square test was <0.05. SNP/indel frequency was assessed for both carriage of SNP/indel (homozygous plus heterozygous v wild type) and carriage of homozygous SNP/indel (homozygous v heterozygous plus wild type).

Results

SNPs

30 genes were identified where SNP carriage frequency was significantly different (see Table 1). In patients SNP frequency was increased for 12 genes and decreased for 18 genes. These included *IGFALS*(↓), *HRAS*(↑), *STAT5b*(↓) and *FANCA*(↓) which are associated with short stature conditions, *MAP2K1*(↑) and *SOCS1*(↑) associated with growth pathways and *SDR16A5*(↑) associated with adult height.

45 genes were identified where homozygous SNP carriage frequency was significantly different (see Table 2). In patients SNP frequency was increased for 11 genes and decreased for 34 genes.

Table 1 – Genes where SNP carriage frequency (homozygous plus heterozygous v. wild type) was significantly different (adjusted p-value <0.05) between cases and controls. Arrows indicate change in frequency in patients relative to control.

Gene		
Short Stature Disease	Growth Pathway	Adult Height
CEP63 (↑)	*MAP2K1* (↑)	*PPARD* (↑)
HRAS (↑)	*SOCS2* (↑)	*SDR16C5* (↑)
IGFALS (↓)	*SOCS1* (↑)	*ATXN3* (↑)
CUL7 (↓)	*SOS2* (↑)	*DOT1L* (↑)
FANCA (↓)	*LRP5* (↑)	*TEAD3* (↑)
FANCD2 (↓)	*RPS6KA1* (↓)	*BCAS3* (↓)
FANCM (↓)	*CSNK2A2* (↓)	*RNF135* (↓)
STAT5B (↓)	*A2M* (↓)	*PTCH1* (↓)
COL1A1 (↓)	*PRKCH* (↓)	*EFEMP1* (↓)
PEX2 (↓)		*ZBTB38* (↓)
BUB1B (↓)		

Table 2 – Genes where SNP carriage frequency (homozygous v. heterozygous plus wild type) was significantly different (adjusted p-value <0.05) between cases and controls. Arrows indicate change in frequency in patients relative to control.

Gene			
Stature Disorders		Growth Pathway	Adult Height
FANCA (↓)	*GHR* (↑)	*MAPK8* (↑)	*ADAMTS17* (↑)
FANCD2 (↓)	*CEP63* (↑)	*RPS6KA6* (↑)	*TRIP11* (↑)
FANCM (↓)	*LEPR* (↑)	*AKT2* (↓)	*DGKE* (↑)
NPR2 (↓)	*SMC3* (↑)	*IGFBP1* (↓)	*CDH13* (↑)
CUL7 (↓)		*STAT5A* (↓)	*NEDD4* (↑)
FANCL (↓)		*A2M* (↓)	*ZBTB38* (↓)
SOS1 (↓)		*PRKCH* (↓)	*RNF135* (↓)
COL1A1 (↓)		*PTPN6* (↓)	*ZFHX4* (↓)
NBN (↓)		*CEBPA* (↓)	*RBBP8* (↓)
NFKB1 (↓)		*BMP6* (↓)	*COIL* (↓)
KRAS (↓)		*PRKACB* (↓)	*TRIM25* (↓)
LBR (↓)		*RPS6KB2* (↓)	*SV2A* (↓)
CEP290 (↓)		*RPS6KA2* (↓)	*ADAP2* (↓)
ALPL (↓)			
MC4R (↓)			

10 genes (*A2M*, *CEP63*, *COL1A1*, *CUL7*, *FANCA*, *FANCD2*, *FANCM*, *PRKCH*, *RNF135* and *ZBTB38*) were significant both for carriage of SNP (homozygous and heterozygous) and carriage of homozygous SNP.

Indels

No genes were identified in which the frequency of carriage (homozygous plus heterozygous) of an indel significantly differed. For one gene, *RPS6KA6* (a protein kinase involved in growth factor signalling), carriage of homozygous indels were more common in patients (p=0.001).

Conclusions

There are growth related genes in which sequence variant frequency was significantly different between children with short stature and controls. Combinations of functional variants in these genes may contribute to growth impairment. The majority of the genes identified had a decrease in sequence variant frequency in patients implying a substantial number of sequence variants are associated with improved growth.

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References
1. Clayton P, Bonnemarie M, Duatilly P, Maisonobe P, Naudin L, Pham E, et al. Characterizing short stature by insulin-like growth factor axis status and genetic associations: results from the prospective, cross-sectional, epidemiogenetic EPIGROW study. J Clin Endocrinol Metab; 2013; 98(6)1122-30.