Copy number variations in patients with idiopathic short stature

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Introduction

Height is a highly heritable and classic polygenic trait. We performed genome-wide analysis for copy number variants (CNVs) in children with idiopathic short stature (ISS) using single nucleotide polymorphism (SNP) arrays, in an effort to identify novel rare variants that may influence height.

Conclusion

Whole genome SNP array analysis identified known pathogenic CNVs in 3.7% and potentially pathogenic CNVs in 23.5% of patients with ISS. GWAS and bioinformatic analysis identified 10 candidate genes.

Subjects and Methods

162 patients with a height of ≤ -2 SDS were analyzed with whole genome SNP arrays (Affymetrix GeneChip Human Mapping 250K or Illumina HumanHap300 BeadChip arrays).

The CNVs were classified into 4 groups

I known pathogenic CNVs
II potentially pathogenic CNVs, not described in the Database of Genomic Variants (DGV)
III CNVs not described in the DGV, but not containing any protein-coding genes
IV known polymorphic CNVs described in the DGV or observed in our in-house reference set, at least 3 individuals must have been reported with the same rearrangement

Type IV CNVs were not further evaluated. All type II CNVs were assessed with Ensembl and DECIPHER for gene and microRNA (miRNA) content and similar cases. If DNA from the parents was available, segregation analysis was performed.

Bioinformatic approach

All CNVs were checked whether they were located in one of the chromosomal regions associated with height in GWAS studies[1].
For genes in *de novo* CNVs 3 additional approaches were used:
1) The rodent homologues were checked for 3 criteria:
   - Higher expression in 1-wk-old mouse growth plate (GP) than in lung, kidney, and heart
   - Spatial regulation: significant difference between zones in the 1-wk-old rat GP
   - Temporal regulation: significant difference between 3 and 12 wks of age in the rat GP
2) Associations were investigated for mouse GP-related phenotypes
3) Associations with human GP-related phenotypes were investigated

Results

CNVs were found in 43 patients, 6 (3.7%) with type I, 38 (23.5%) with one or more type II, 1 (0.6%) with type III, and type IV or no CNVs were found in 119 patients (73.5%). The type I CNVs included 2 microdeletions and 2 microduplications containing *SHOX*, and two terminal 15q deletions containing *IGF1R* + a type II CNV.

Type II CNVs

47 potentially pathogenic CNVs were observed in 38 patients, of whom two also have a type I CNV. Segregation analysis in 28 patients (37 CNVs) led to 4 *de novo* CNVs and 13 CNVs segregating with short stature. There was no segregation with short stature in 20 CNVs.

Type II CNVs located near loci associated with height in GWAS

Five CNVs encountered in our study are close to loci associated with height in GWAS[1]: *ADAMTS17*, *PRKG2/BMP3*, *PAPPA*, *TULP4*, and *MKL2*.

Bioinformatic approach

Rodent homologues of 5 genes in *de novo* CNVs were associated with GP phenotypes:

- *Furin* is expressed higher in GP, and upregulated from proliferative to hypertrophic zone.
- *Fam3c* is expressed higher in GP, downregulated from resting to proliferative zone, and increased with age.
- The *de novo* deletion near *ADAMTS17* contained 3 genes of interest; *Aldh1a3* is expressed highly in hypertrophic zone compared to heart and lung; *Lrrk1* is expressed higher in GP, and upregulated from proliferative to hypertrophic zone; the expression of *Chsy1* is high in hypertrophic zone, and downregulated with age.

miRNA

None of the 6 identified miRNAs in type II CNVs could be linked to short stature.

References 1 Lango Allen H et al. Nature 2010; 467(7317):832-838.

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