A quest for copy number variations causing extreme tall stature

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Introduction

Height is a highly heritable and classic polygenic trait. In the majority of individuals with extreme tall stature (ETS) no genetic cause is known. We performed genome-wide analysis for copy number variants (CNVs) in people with ETS using single nucleotide polymorphism (SNP) arrays, in an effort to identify novel rare variants that may influence height.

Subjects and Methods

Clinical and family history of 18 adults with ETS were obtained and whole genome SNP array (Affymetrix 262K NspI arrays) analysis was performed. All potentially pathogenic CNVs were assessed with Ensembl and DECIPHER for gene content and similar cases.
If possible, segregation analysis was performed.

Conclusion

Whole genome SNP array and segregation analysis identified potentially pathogenic CNVs in 2 cases (11%). The 1p34.1 duplication, although of interest because it contains part of *PIK3R3*, is probably not the cause of ETS. The extra Y chromosome in the other case is known to contribute to increased height, but the role of the 13q33.1 deletion still remains unclear.

Clinical results

	Height		Head Circumference	
	cm	SDS	cm	SDS
Men (11)	201.9 – 212.4	+2.5 – +4.0	55.7 – 62.0	-1.2 – +2.4
Women (7)	185.9 – 198.9	+2.4 – +4.4	54.5 – 58.8	-0.5 – +2.1

Table 1. Height and head circumference range (in cm and SDS) of the 18 adults with ETS.

Results

In 4 cases (3 males) potentially pathogenic CNVs were identified and further analyzed. There was no segregation in 2 cases.

In a 204.2 cm (+2.9 SDS) tall male, a 1p34.1 duplication (Fig. 1) containing part of *MAST2* and *PIK3R3* (Fig. 2) was observed. The duplication was in tandem, i.e. one copy following the other in the same orientation (Fig. 3). *In silico* analysis showed that PIK3R3 binds the intracellular part of the IGF1R. The duplication segregated with tall stature (+1.9 and +1.8 SDS). A similar duplication was identified in our in-house reference set, but without tall stature. *PIK3R3* sequencing in 152 tall and 80 short stature patients identified an intronic duplication (c.764+2dup) in 4 patients with tall stature. However, the same duplication was also present in an in-house exome dataset suggesting that it is a rare polymorphism.

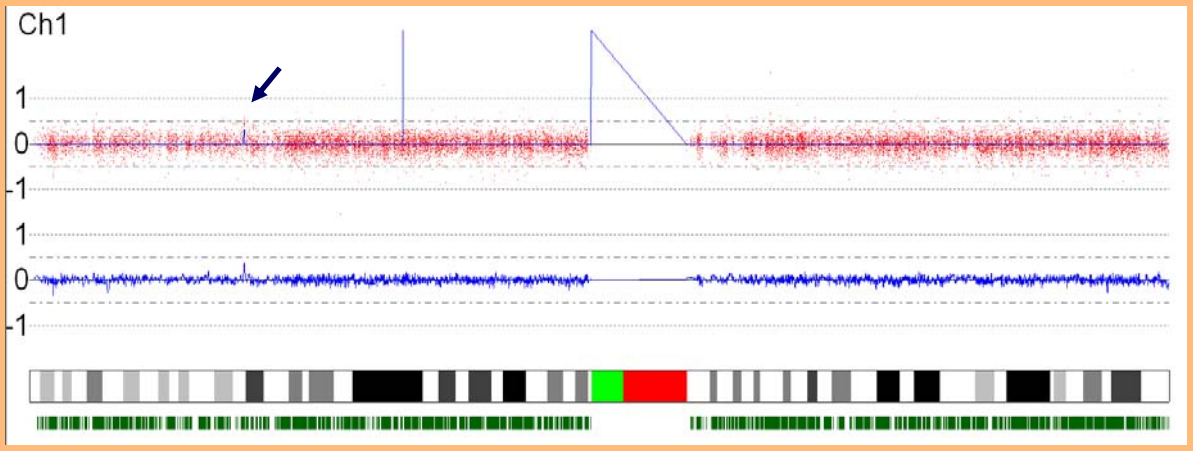

Fig. 1. Affymetrix SNP array results.

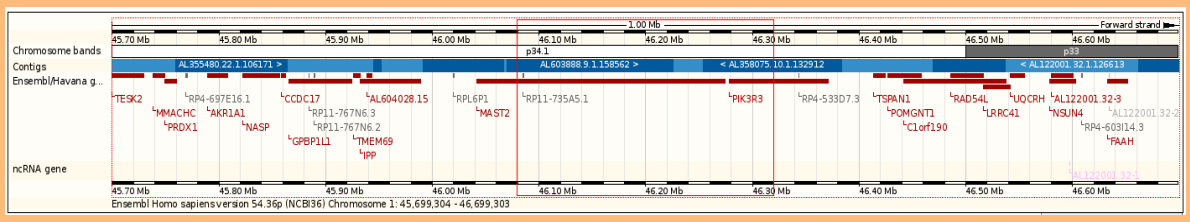

Fig. 2. Ensembl output of the duplicated area, containing part of *MAST2* and *PIK3R3*.

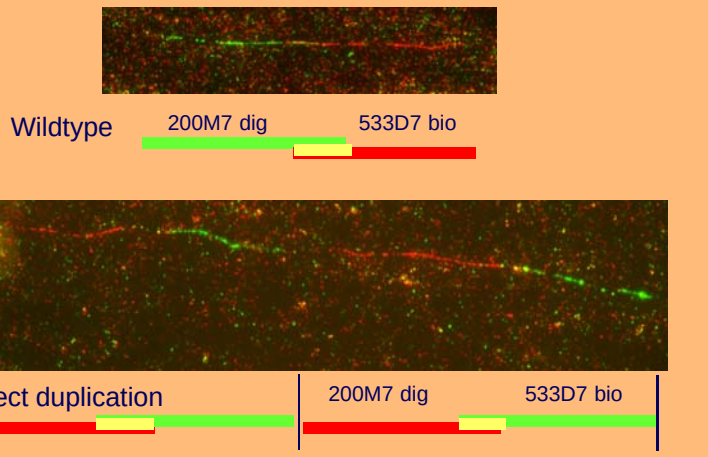

Fig. 3. Fiber FISH to identify the location and orientation of the 1p34.1 duplication.

In a male with a height of 201.9 cm (+2.5 SDS) 3 aberrations were detected; a duplication of 12q21.1 not segregating with tall stature, a 13q33.1 deletion without any genes and an extra copy of the Y chromosome (47,XYY).

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