Next-generation sequencing-based panel testing identifies heterogeneous genetic etiologies of short stature

Johanna Huusko, Alicia Scocchia, Kaisa Kyöstilä, Lilí Gallo Ramirez, Liisa Pelttari, Satu Valo, Riitta Lindström, Cindy Si, Kimberly Gall, Inka Saarinen, Mikko Muona, Tuuli Pietilä, Janica Djupsjöbacka, Massimiliano Gentile, Pertteli Salmenperä, Eija Seppälä, Sari Tuupanen, **Lotta Koskinen**, Tiia Kangas-Kontio, Jussi Paananen, Samuel Myllykangas, Juha Koskenvuo

Blueprint Genetics, Espoo, Finland

Background

Identifying the molecular etiology for short stature (defined as height 2 or more standard deviations below the mean for age and sex) can guide treatment, allow early screening and supportive therapy for associated features, and inform familial recurrence. We retrospectively assessed the utility of NGS multi-gene panel testing for individuals with short stature and provided an overview of the positive genetic findings identified in this population.

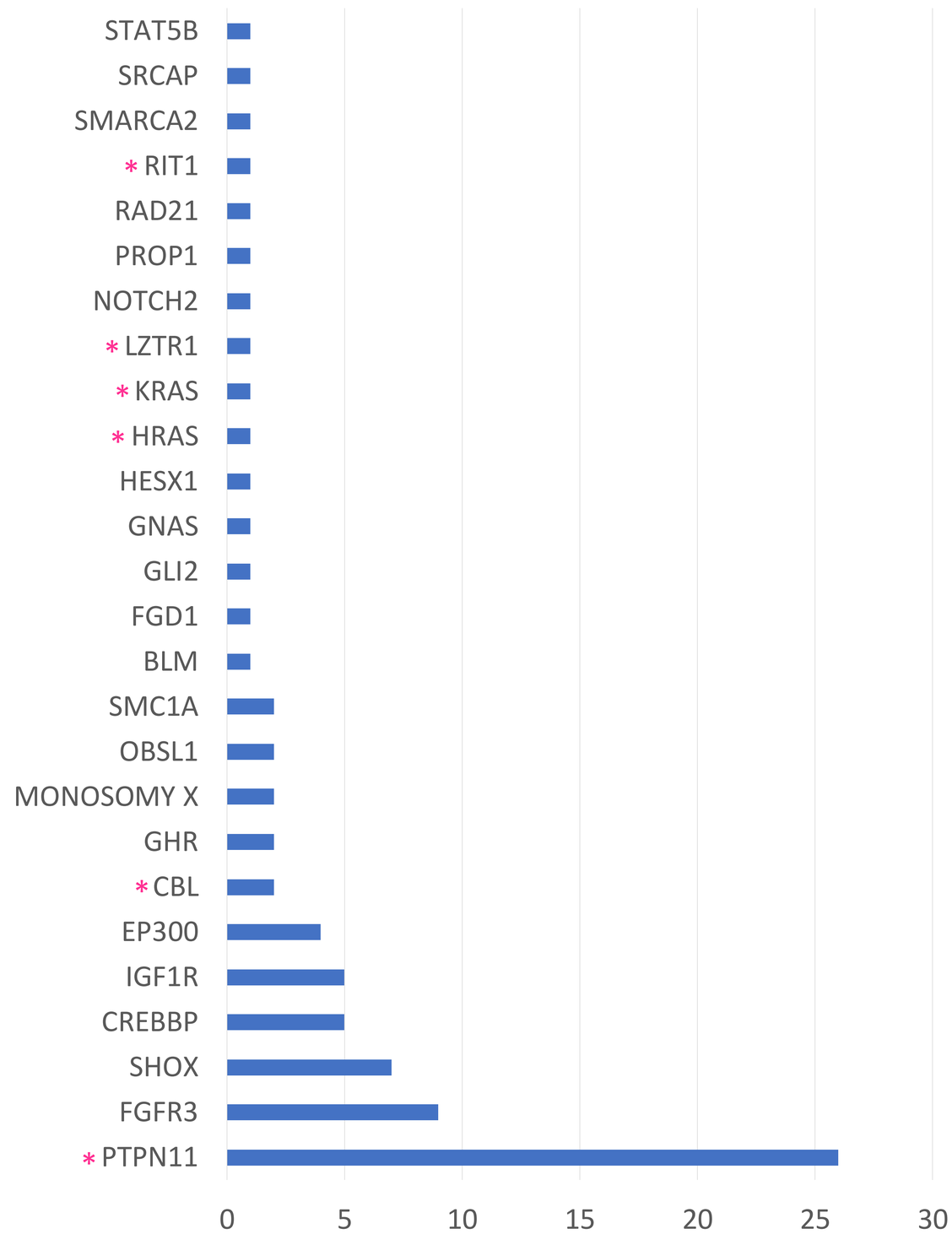
Methods

Clinical reports for 744 patients with an indication of short stature who underwent panel testing at Blueprint Genetics were examined (Table). Testing included both sequence and copy number variant (CNV) analyses of NGS data from validated clinical exome assays, including established non-coding variants. A positive result was defined as the identification of pathogenic or likely pathogenic variant(s) consistent with the patient's phenotype and known associated disease inheritance.

Results

A positive result was reported in 10.9% of patients (n= 81/744) in 27 genes. The most frequent (40%) positive results were associated with autosomal dominant RASopathies (*PTPN11*, *CBL*, *HRAS*, *KRAS*, *LZTR1*, *RIT1*) (n=32) and autosomal dominant *FGFR3*-related conditions (n=10) (Figure). CNVs accounted for 1.4% of the positive results, including five deletions involving the *SHOX* gene. One patient received a positive result through identification of a non-coding variant in the *GHR* gene.

Figure. Number of positive findings by gene. Positive findings were frequently identified in genes that encode protein components of the Ras/MAPK pathway(*).



Demographic	Number of individuals (n=744)	% of the cohort
Sex Female	394	53.0
Male sex	348	46.8
Sex not reported	2	0.3
Age range Fetus	2	0.3
0-2 years	162	21.8
3-10 years	357	48.0
11-18 years	197	26.5
19-40 years	22	3.0
41-64 years	4	0.5

Table. Patient demographics

Conclusions

Nearly 11% of patients in this cohort received a positive result, including a non-coding variant and CNVs.

This demonstrates the benefit of including robust CNV analysis and targeting disease-associated intronic variants in multi-gene panel testing for individuals with suspected monogenic short stature.

11% of patients received a positive test result

40% of positive findings were identified in genes that are associated with RASopathies

Usually genes involved in the RAS/MAPK pathway have been associated with Noonan syndrome, which presents with variable severity and manifestations. Some individuals carrying a pathogenic *PTPN11* variant only show short stature without other obvious clinical features typical for Noonan syndrome. Individuals with *PTPN11* pathogenic variants may have a degree of growth hormone resistance[1] and show positive response to growth hormone treatment with increase in growth velocity.

Reference: 1. Binder G *et al*. *PTPN11* mutations are associated with mild growth hormone resistance in individuals with Noonan syndrome. *J Clin Endocrinol Metab.* 2005;90(9):5377-5381.

Conflict of interest statement:
All authors are employed by Blueprint Genetics.

Blueprint Genetics