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RAB3IP and DGCR8 as a potentially pathogenic novel candidate gene involving in growth disorders

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Introduction

The majority of children with short stature are classified as idiopathic short stature. Whole exome sequencing can help identify genetic causes of short stature.

Objectives

To identify the genetic aetiology of some idiopathic short stature by exome sequencing (WES).

Methods

DNA	Library Prep	WES	FASTQ	VCF	Sanger
6 patients and available relatives: 6 affected 5 unaffected	Agilent Sure Select XT All exonsV5	Illumina HiSeq2500 V3 and V4 (2x100)	Mean coverage: 170x	Freebayes ANNOVAR	Confirmation and segregation

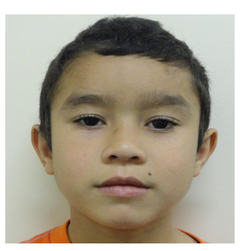
Our analysis focused on functional variants absent in controls (ExAC, ESP6500, 1000Genomes and 1,218 alleles from healthy ethnic matched individuals) that segregate in the families.

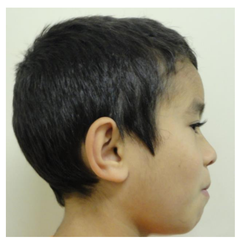
Results

The mean coverage of the captured regions was 170x (99.6% of target region with more than 10x). Each patient had an average of 64,490 allelic variants. All pedigrees suggested an autosomal dominant pattern of inheritance. We identified two novel candidate genes with loss of function (LoF) mutations.

Case 1

- Prenatal proportional short stature
- Neonatal hypomagnesemia and jaundice
- Mild neurodevelopment delay
- Echocardiogram: Pulmonary atresia
- Low IGF-1; normal GH peak
- Good response to rhGH therapy





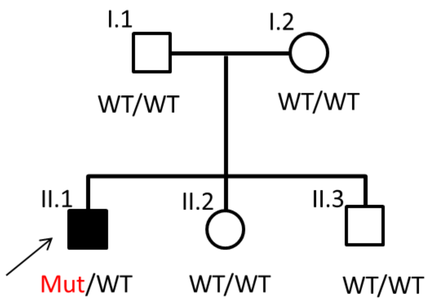


Table 1: Anthropometric measurements of family 1

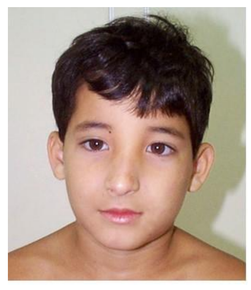
	I.1	I.2	II.1	II.2	II.3
Age (y)	Adult	Adult	3.6	12.2	2.9
Height (cm)	175.5	158.7	88	153.6	91
Height SDS	+0.12	-0.58	-2.5	+0.2	-0.8
SH:H SDS	-1		+1.3	-1.3	+0.2
Nowadays (age y)			9		
Height (cm)			122.7		
Height			-1.5		

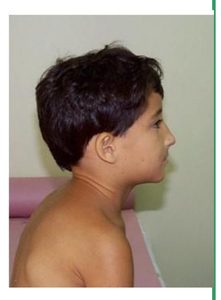
SDS: standard deviation score; SH:H: sitting height: height ratio

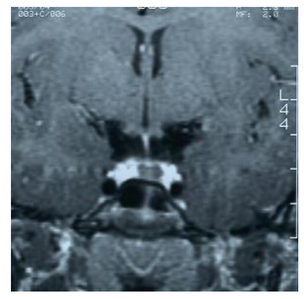
The patient has a de novo heterozygous variant in *DGCR8* gene (c.1321C>T/p.R441*). No phenotype was associated with *DGCR8* alteration in humans. This gene participates in microRNA biogenesis and it is extremely intolerant for LoF alterations. It was mapped in the chromosome 22q11.2 in a critical region of DiGeorge syndrome, which is associated with growth impairment. This patient was small for gestational age without catch-up growth and had a neonatal hypomagnesemia, mild delay in initial development and mild dysmorphic facial features.

Case 2

- Prenatal short stature
- Consanguineous family
- Microcephalic (normal intelligence)
- Seizure during the childhood
- Low IGF-1/IGFBP-3, normal GH peak
- MRI – small intrasellar rathke pouch cyst
- Elevated TSH, normal/mild elevated FT4
- Small testis (10mL), normal testosterone levels, elevated LH (36U/L), FSH (18.4U/L)
- Normal spermogram at the age of 24
- Normal karyotype and CGH-array







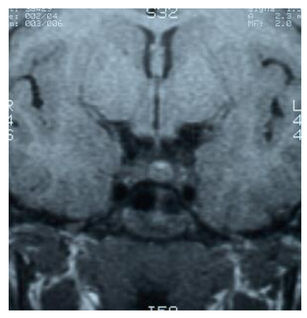
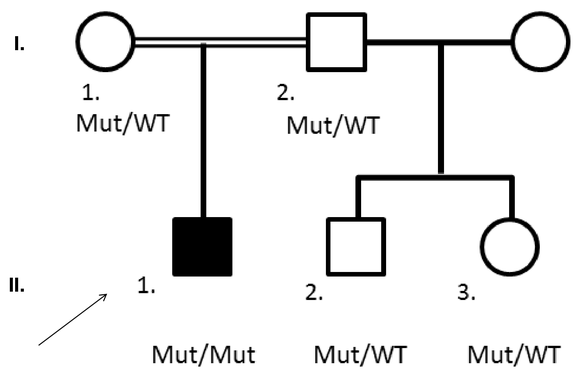


Table 2: Anthropometric measurements of the family 2

	I.1	I.2	II.1
Gestational age (ws)			39
Birth weight (kg)			2.68
Birth length (cm)			44
Age (y) at the 1st evaluation			4.2
Height (cm)			92.5
Height SDS			-2.8
Adult height (cm)	179	168	163.2*
Height SDS	-+0.8	+1.0	-1.7

SDS: standard deviation score; SH:H: sitting height: height ratio

* - after long term treatment with rhGH (6 year of rhGH 50µg/kg/d)



The patient has a homozygous nonsense allelic variant in *RAB3IP* (c.13A> T: p.K5*). The *RAB3IP* is an important factor for activation of specific proteins in the RAS family, known as RAB8A/B. These proteins participate in the ciliary and exocytosis process. This latter feature may be involved in hormone secretion. This patient has short stature with microcephaly, mild dysmorphic facial, mild disorder of sex development and a suggestive resistance hormonal profile with an important elevation of LH and FSH.

Conclusions

It is possible that *RAB3IP* and *DGCR8* genes have a relationship with a dysmorphic features and short stature in these patients. The identification of other patient with similar phenotype and genetic findings is important to prove this relationship.

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