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POP1-Skeletal Dysplasias : Description of Two New Families.

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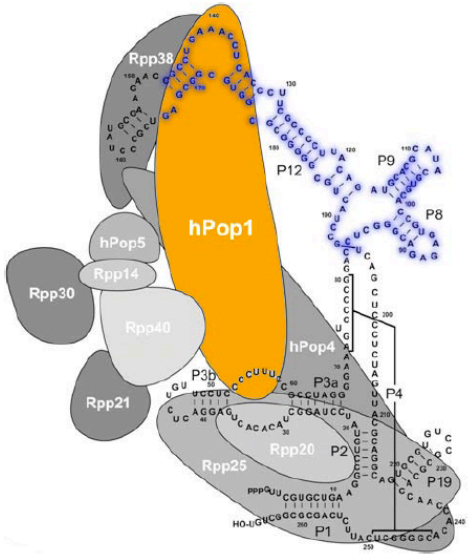
Background *POP1* mutations should be considered in anauxetic dysplasia (AD) patients without *RMRP* mutations but also in skeletal dysplasia (SD) of different severities. To date, only 5 patients were reported.

RMRP mutation
Cartilage Hair Hypoplasia
Metaphyseal chondrodysplasia (Mckusick type)

RMRP =
RNase MRP complex



POP1 mutation
Anauxetic Dysplasia 2
Spondyloepimetaphyseal dysplasia

Domains of RMRP RNA that have been implicated in anauxetic dysplasia

Citation: Glazov EA, Zankl A, Donskoi M, Kenna TJ, Thomas GP, et al. (2011) Whole-Exome Re-Sequencing in a Family Quartet Identifies *POP1* Mutations As the Cause of a Novel Skeletal Dysplasia. PLoS Genet 7(3): e1002027. doi:10.1371/journal.pgen.1002027

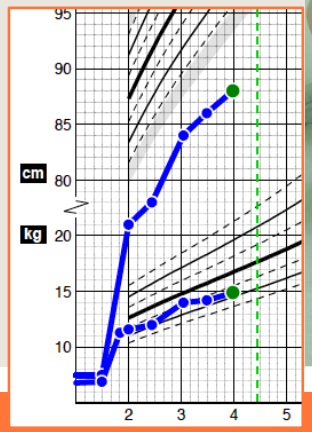
Welting, T.J., van Venrooij, W.J. & Pruijn, G.J. Mutual interactions between subunits of the human RNase MRP ribonucleoprotein complex. *Nucleic Acids Res* **32**, 2138-46 (2004).

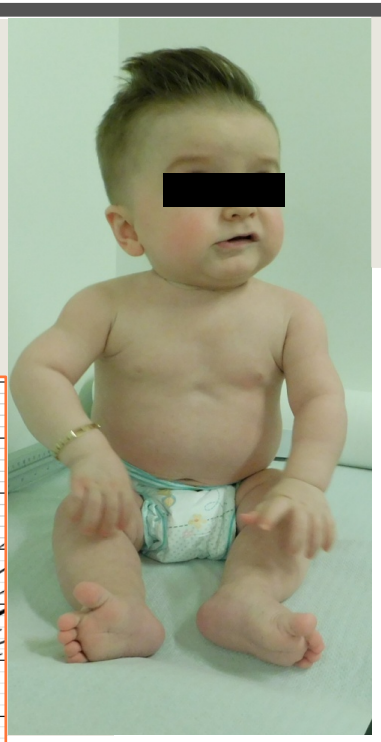
FAMILY 1 – A 4 years boy.

Personal history :
Normal delivery, at term.
BW 3845 gr (+1DS) – BH 47 cm (-2DS) - BHC 38 cm (P75)

Familial history:
Mother H : 170 cm. Father H : 174 cm
Turkish origin. Consanguinity.
Older sister with hypochondroplasia (diagnosis based on clinical criterias, GH treatment). Final Height 160 cm.

Clinical description:
Age 1 an et 5/12 ;
H 71 cm (-3,88DS)
W 9kg630 (-0,98DS)
HC 51 cm (+2,88 DS)
Normal psychomotor development.
Normal langage.

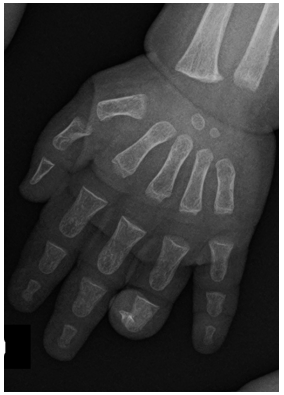


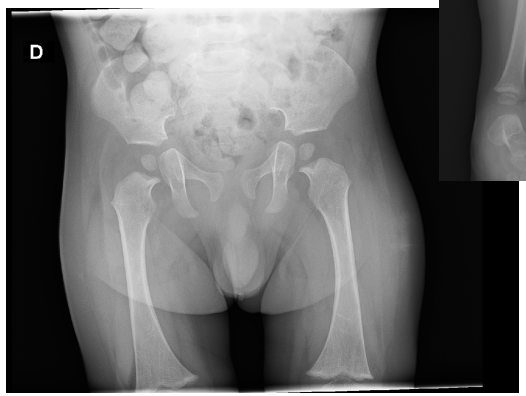


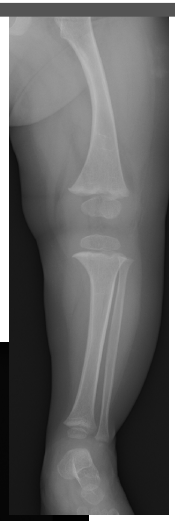
-Cervicocranial MRI : Normal

-Endocrinologic Work up : Normal

-Neuropediatric evaluation : Normal



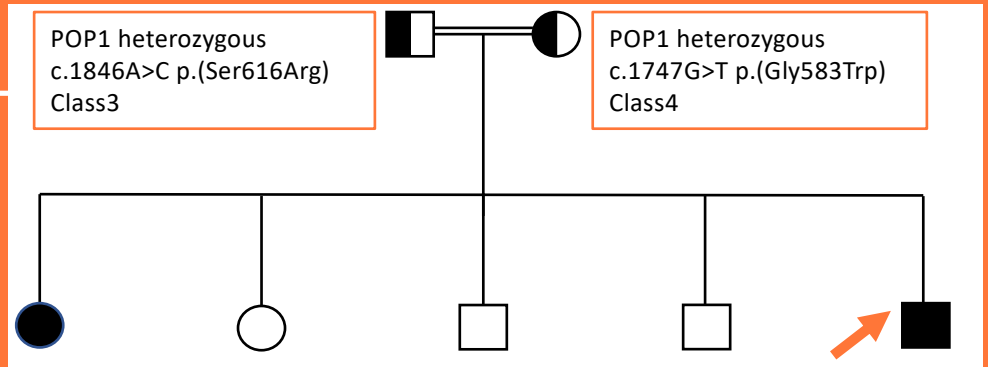




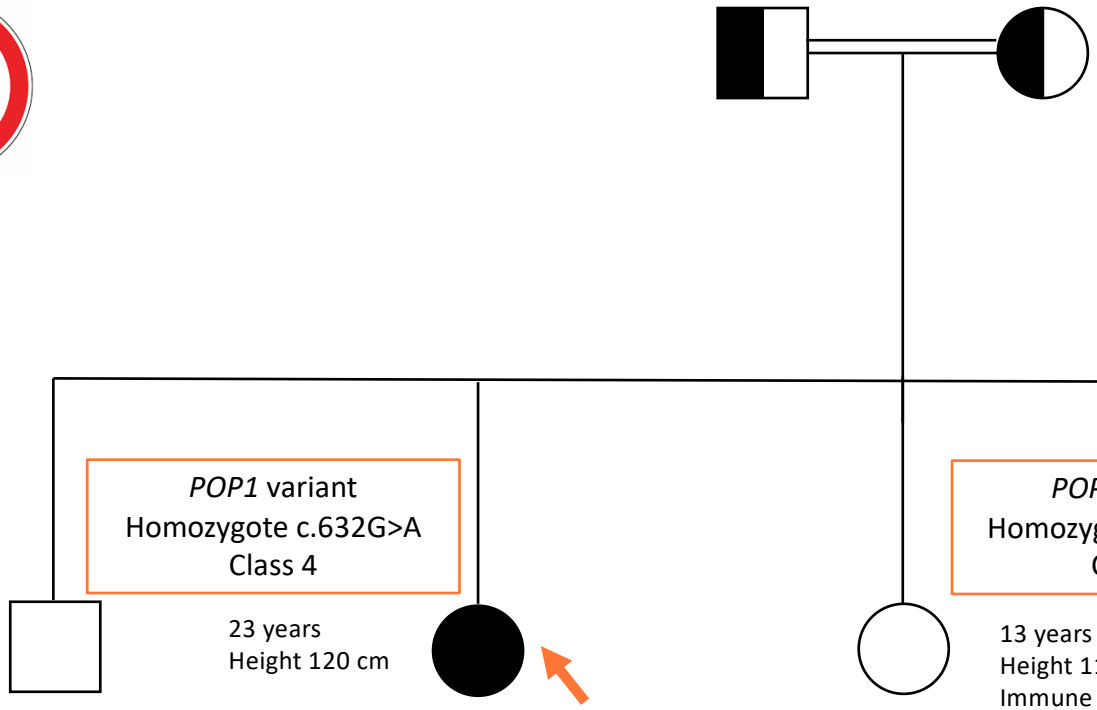
Genetics

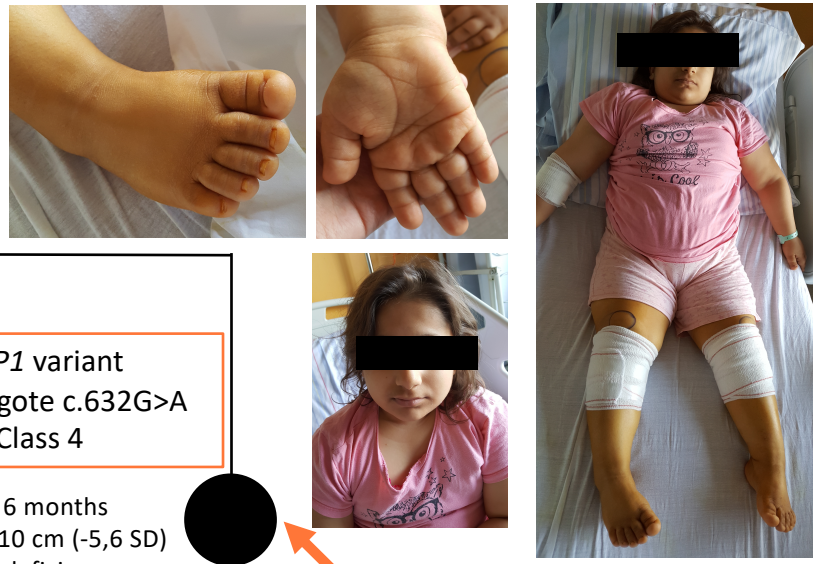
FGFR3 : negative
Standard Karyotype : normal
CGH array : 46, XY

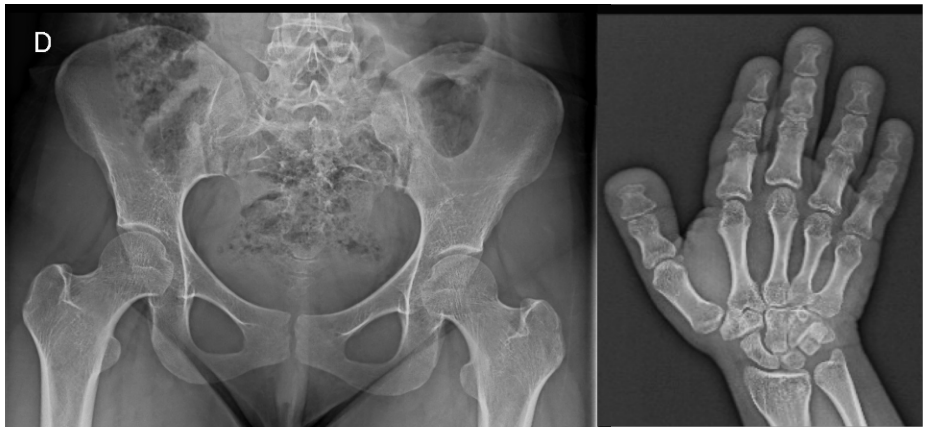
Mucopolyssacharides : normal

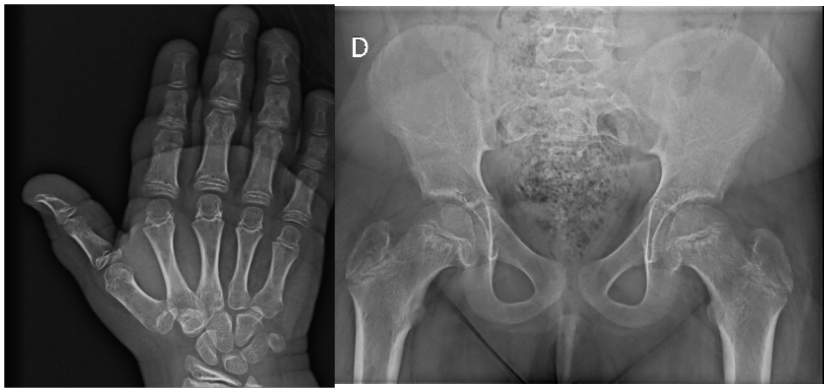


FAMILY 2 – Two sisters with severe short stature.



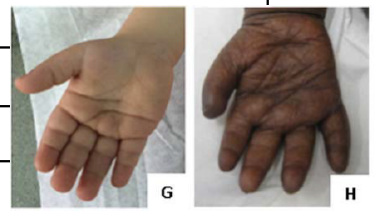






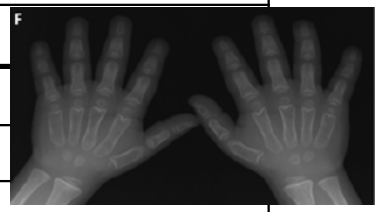
DISCUSSION - Litterature review : 5 published patients with *POP1* mutation.

	1	2	3	4	5	CLINICAL OBSERVATIONS
Sex	F	M	F	F	M	
Age	4,6	6	1		5	
Height (SDS)	-5,5	-10,2			-7,1	
Dysmorphism						1/3 Midface Hypoplasia – 1/3 Hypopigmented hair
Hands and Feet						3/3 Brachydactylia
Psychomotor dev.						1/3 Cognitive Delay
Other findings						1/2 Deficiency of Complex I of the respiratory chain
Diagnosis Hypothesis	SD	CHH/AD	AD	AD	AD	



Barrazza *et al*, 2017

	1	2	3	4	5	RADIOLOGICAL OBSERVATIONS
Sex	F	M	F	F	M	
Age	4,6	6	1		5	
Height (SDS)	-5,5	-10,2			-7,1	
Bone Age						4/4 Delayed bone age
Hands and Feet						3/4 Bullet Shaped Middle phalanges
Pelvic Bones						3/3 Hypoplastic Ilia – 2/3 Coxa Vara
Vertebral Column						2/4 Cervical Spine instability



Barrazza *et al*, 2017

No Data Positive patient Negative for the symptoms/Others signs reported

Patients 1 and 2 = Barrazza *et al*, 2017
Patients 3 and 4 = Glazov *et al*, 2011
Patient 5 = Elalaoui ,2016

CONCLUSION We describe two new families with *POP1* mutations encountered in patients clinically suspected for CHH and achondroplasia, enhancing that the phenotypical spectrum is larger than AD type 2. Larger cohorts of patients are needed to improve the clinical characterization, especially the risk of having associated symptoms such as immune deficiency.

POP1 Patients features

*Severe short stature of prenatal onset

*Very short adult height (less than 1 meter – our patients 120 cm and 160 cm)

*Hypodontia

*Midface hypoplasia

*Mild intellectual disability

*Radiological specific findings – But only 5 patients described until now

POP1 : More associated features?

*Immune deficiency?

* Positive response to growth hormone?

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* The authors have nothing to disclose.
* The authors thank the OSCAR Rare Medical Disease Center , Necker, Paris for its advice for family 1 (medical staff).