Noonan Syndrome spectrum panels should include mutations in *LZTR1* gene

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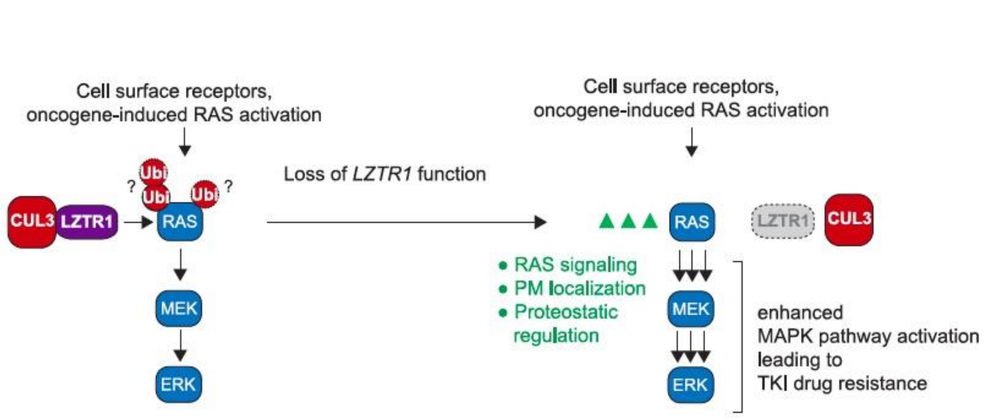
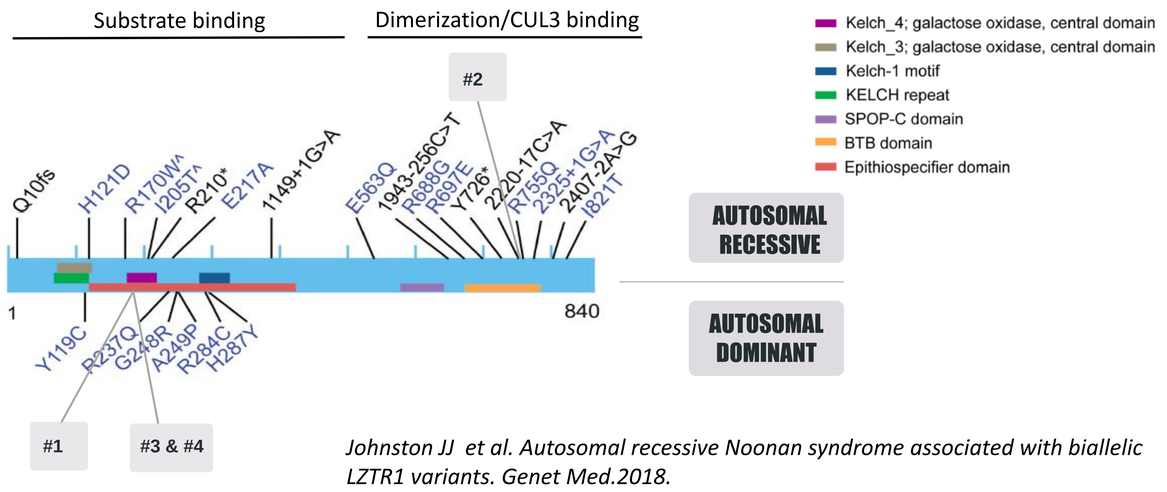
INTRODUCTION

A few patients with Noonan Syndrome (NS) have been reported to harbour pathogenic variants in *LZTR1* gene. RAS/MAPK pathway regulation by LZTR1-mediated ubiquitination provides an explanation for the role of *LZTR1* in human disease. Pathogenic variants in this gene could hence lead to NS phenotype. Four patients with mutations in this gene due to a different genetic transmission pattern and compatible NS phenotype are herein characterized.

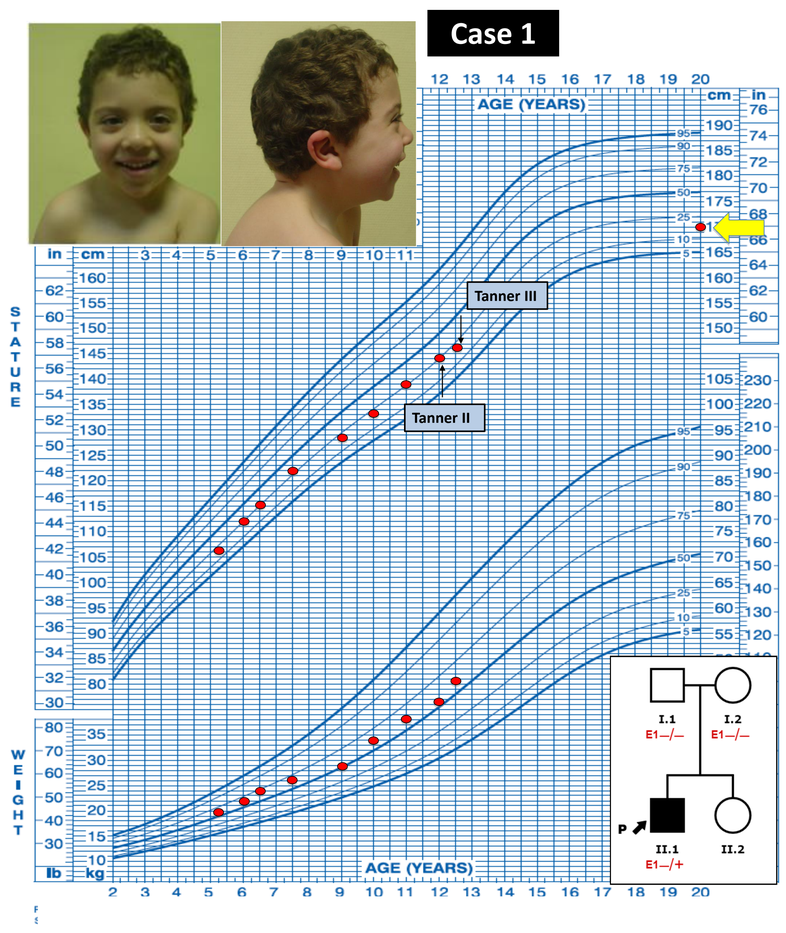


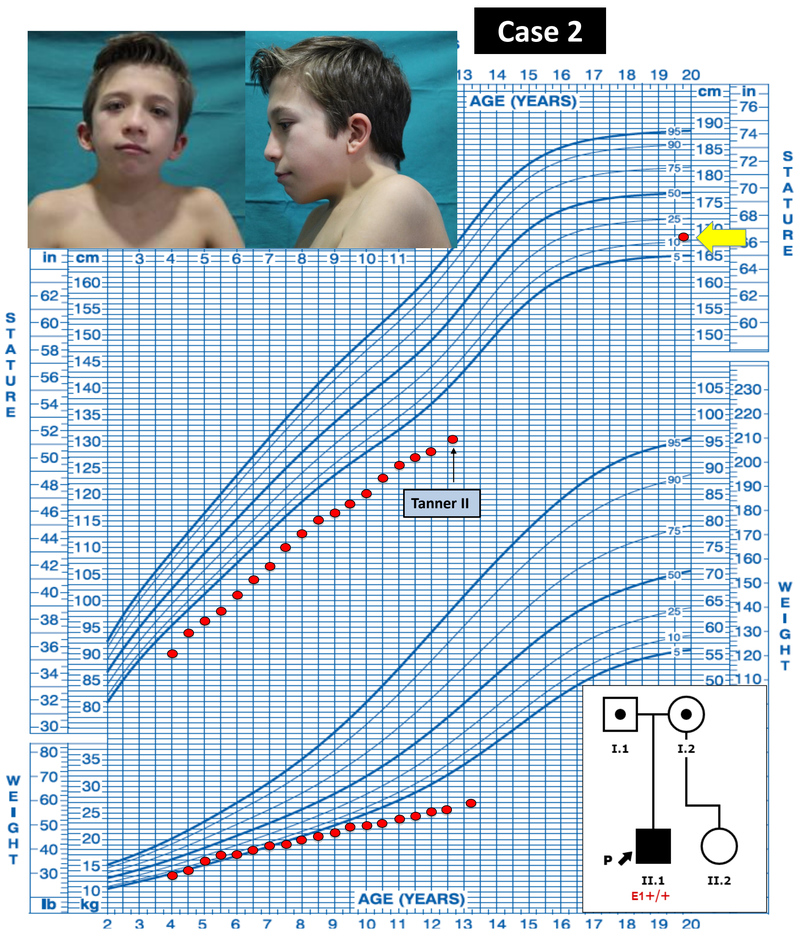
Bigenzahn et al. LZTR1 is a regulator of RAS ubiquitination and signaling. Science 2018:362,1171-1177

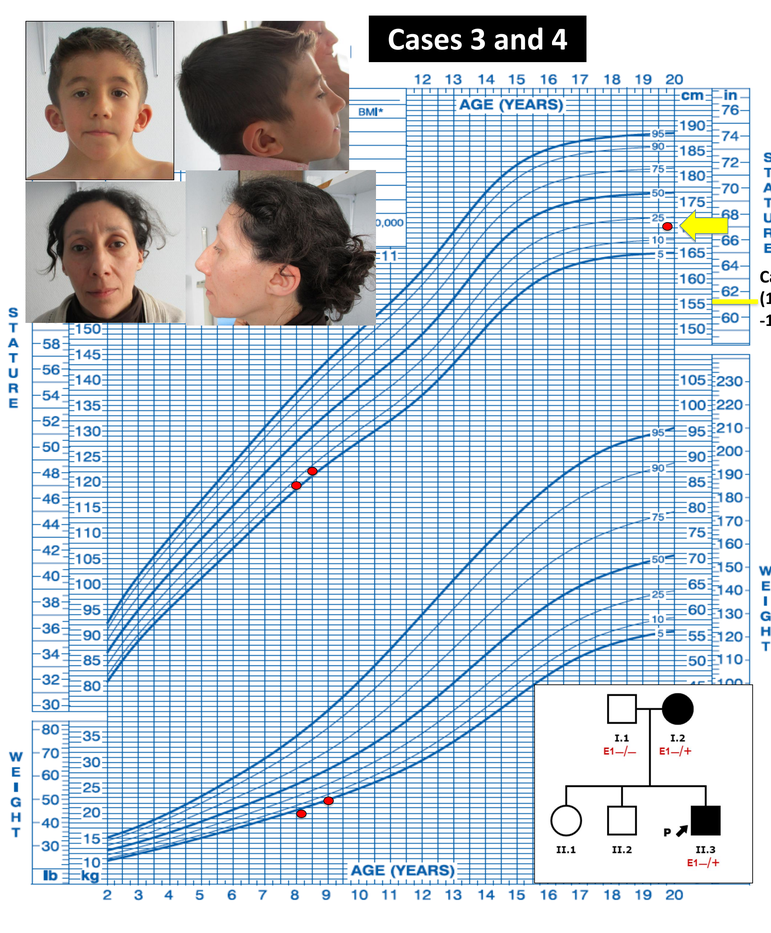


Johnston JJ et al. Autosomal recessive Noonan syndrome associated with biallelic LZTR1 variants. Genet Med.2018.

PATIENTS







	Case 1	Case 2	Case 3	Case 4 (mother of Case 3)
Congenital heart defect	Mild pulmonary supravalvular stenosis	Mild pulmonary supravalvular stenosis	No	No
Neurodevelopment	Normal	Normal	Normal, speech delay	Normal
Chest skeletal deformities	*Pectum excavatum*	No	Wide thorax, *pectum carinatus*	*Pectum excavatum*
Cryptorchidism	Yes, bilateral	Yes, unilateral	No	N/A
Clotting issues	No	Von Willebrand disease	No	No
Genes previously studied (technique)	*PTPN11*, *SOS1* (direct sequencing): no mutations	*PTPN11, SOS1, RAF-1, N-RAS, SHOC2, BRAF, KRAS, HRAS* (direct sequencing): no mutations	*A2ML1, BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, SOS1, SPRED1* (RASopathy panel): no mutations	N/A
***LZTR1* Genotype** **Exon** **Zigosity** **Inheritance**	c.742G>A; p.(Gly248Arg) exon 8 (Kelch 4 functional domain) Heterozygous *de novo*	c.2074T>C; p.(Phe692Leu) exon 18 Homozygous maternal/paternal	c.730T>C; p.(Ser244Pro) exon 8 (Kelch 4 functional domain) Heterozygous maternal	c.730T>C; p.(Ser244Pro) exon 8 (Kelch 4 functional domain) Heterozygous ?
Predicted effect on protein, using bioinformatic algorithms	deleterious effect	deleterious effect	deleterious effect	deleterious effect
Previously described to cause NS	Yes	No	No	No

CONCLUSIONS

Albeit functional studies are still required to confirm causality of each mutation in *LZTR1* leading to NS, this gene ought to be incorporated into RASopathy genetic panels. Whole exome sequencing may add the opportunity to re-analyze the study in patients with no molecular confirmation as new genes related to the clinical diagnosis are discovered. Patients with pathogenic mutations in *LZTR1* seem to exhibit characteristic NS facial features but variable expression in heart, stature and neurodevelopment, where dominant inheritance may associate a milder phenotype.

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Growth and syndromes (to include Turner syndrome)

Maria Gemes

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