Noonan Syndrome spectrum panels should include mutations in LZTR1 gene

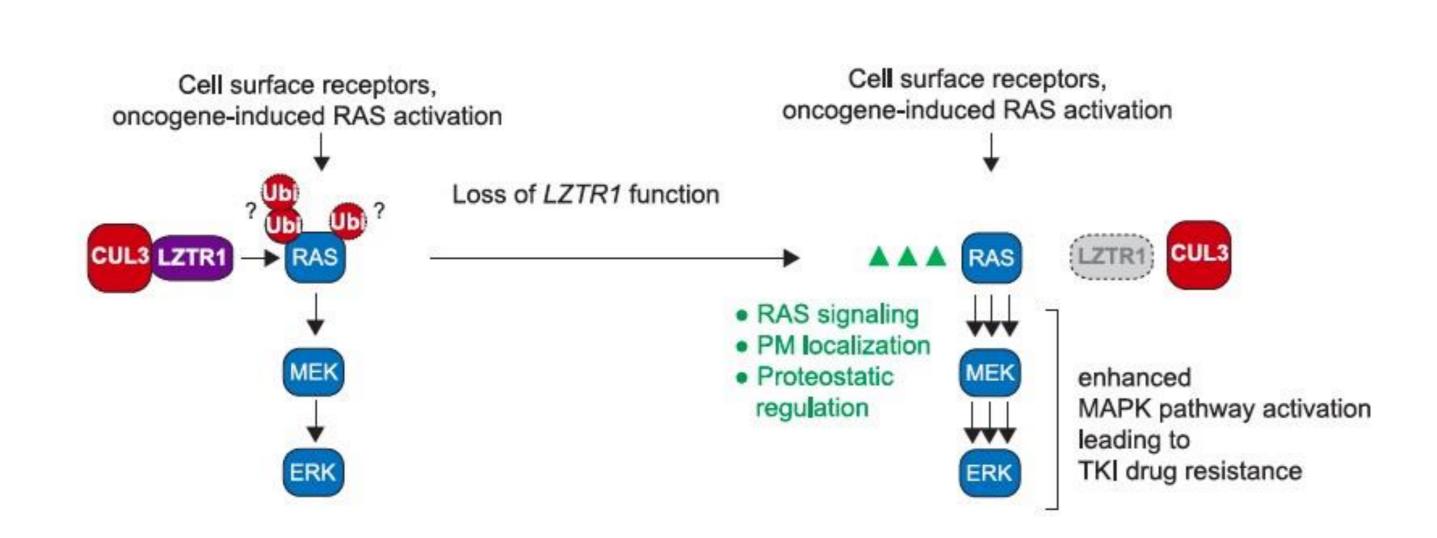
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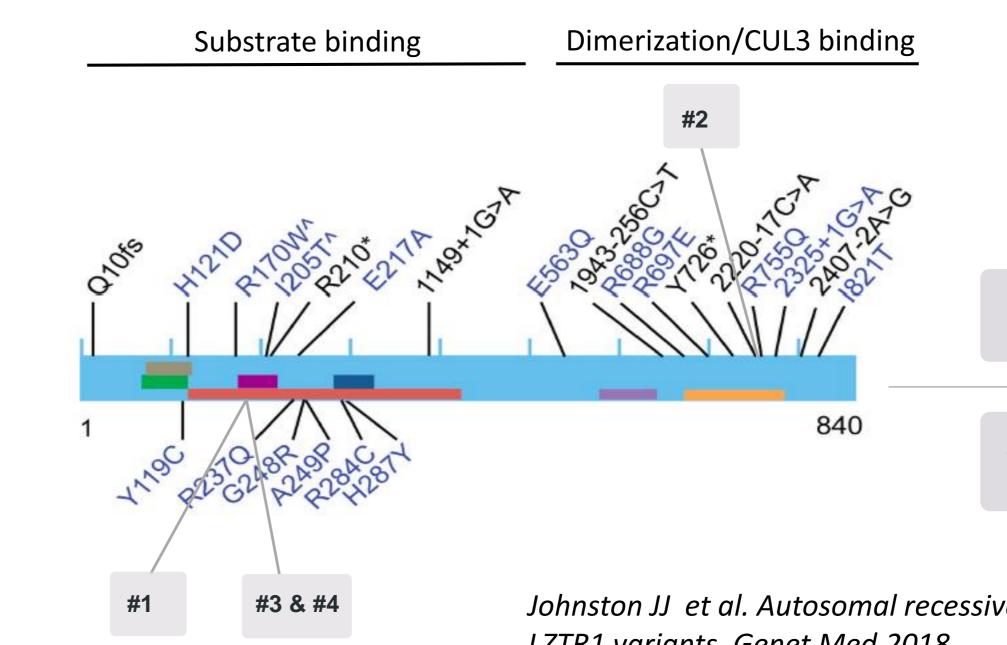
iemes M^{1,2}, Martín-Rivada Á¹, Ortiz-Cabrera NV¹, Martos-Moreno GÁ^{1,2,3,4,5}, Pozo-Román J^{1,2,3,4,5}, Argente J^{1,2,3,4,5}

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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

AUTOSOMAL Dominant

AUTOSOMAL

RECESSIVE

dea

alimentacion

Kelch_4; galactose oxidase, central domain

Kelch_3; galactose oxidase, central domain

Kelch-1 motif

KELCH repeat

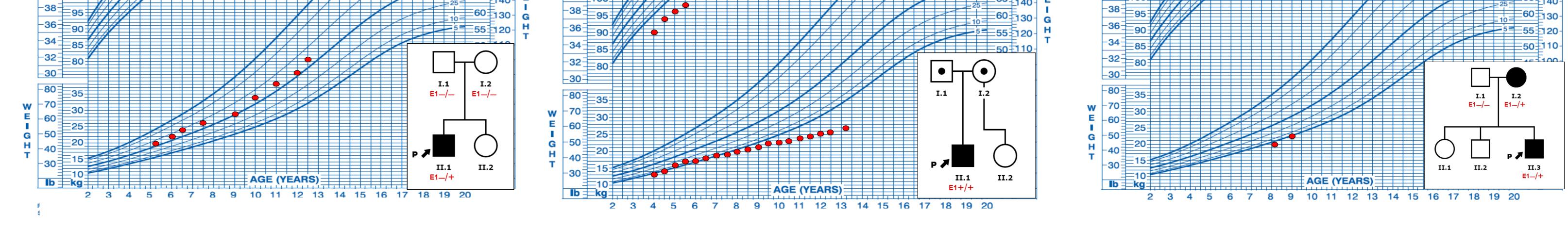
BTB domain

SPOP-C domain

Epithiospecifier domain

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

PATIENTS Case 2 Case 1 Cases 3 and 4 14 15 16 17 18 19 20 12 13 14 15 16 17 18 19 20 12 13 14 15 16 17 18 19 20 AGE (YEARS) AGE (YEARS) AGE (YEARS) 190 190-180 70-180 180 -70 in \pm cm $\pm 3 \pm 4 \pm 5 \pm 6 \pm 7 \pm 8 \pm 9 \pm 10 \pm 11 =$ 165 -64-165 3=4=5=6=7=8=9=10=11 in ± cm 64 -64 160] Case 4 160 -62-160 160 62 62 62 62 155 (155 cm, Tanner I 155 155 155 60--60 60 -60 60--1.9 SD) 150 150 150 150--58--58 145 56-56 105 230 -56-105 230 140 105 230 54 100‡220 1002220 135 135 100 220 135 ⊢52 130[±] Tanner II 52 **1**95]210 -52 95 210 95 210 130 -130 50 -50 -<u>90</u>200 90 200 50 -<u>90</u>200 =125 125 125 **5**85 -85=190+ 48 48 48 190 120 120 120 85 Tanner II ⁻⁴⁶±115[⊥] ±180 £180 46 46-±180 115 80± 115 -80 ⊢44 <u>=</u>110[±] £170 -44 E110 -110 -75 -75 160 -42 105 160 E160 **∞70** 150 42 42⁻ 105 105 150-40 E65 140 40-40 <u></u> =65 - 140 [⊥] E65 140 100 100 100



	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)	<i>PTPN11, SOS1</i> (direct sequencing): no mutations	<i>PTPN11, SOS1, RAF-1, N-RAS, SHOC2, BRAF, KRAS, HRAS</i> (direct sequencing): no mutations	A2ML1, BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, SOS1, SPRED1 (RASopathy panel): no mutations	N/A
<i>LZTR1</i> Genotype Exon	c.742G>A; p.(Gly248Arg) exon 8 (Kelch 4 functional domain)	c.2074T>C; p.(Phe692Leu) exon 18	c.730T>C; p.(Ser244Pro) exon 8 (Kelch 4 functional domain)	c.730T>C; p.(Ser244Pro) exon 8 (Kelch 4 functional domain)
Zigosity Inheritance	Heterozygous <i>de novo</i>	Homozygous maternal/paternal	Heterozygous maternal	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.



Growth and syndromes (to include Turner syndrome)



