Riboflavin Transporter Deficiency

Updated Feb 2023

Table 1. Report Pathogenic Variants in SLC52A2 (previously GPR172A) Reference Sequence: NM_ 024531.4

DNA nucleotide changed	Amino Acid	dbSNP	Frequency (n=198)	ExAC Frequency	Type	Exon	Publication	Other Source
c.-110–1G> A	5′ Ex2 Splice site	rs1554853682	1	0	Splice site	In1–2	Cirali 2017	
c.92 G>C	p.W31S	rs797045199	1	0	Missense	2	Foley 2013	
c.103 C>T			2	1	Missense	2		Cure RTD Registry
c.135 G>T			1	0	Missense	3		Cure RTD Registry
c.155 C>T	p.S52F	rs397514657	5	3	Missense	3	Ciccolella 2012	
c.185 T>G			8	2	Missense	3		Cure RTD Registry
c.231G>A	p.E77K		1	0	Missense	3	Manole 2017	
c.245 G>C			2	6	Missense	3		Cure RTD Registry
c.287 C>T			1	1	Missense	3		Cure RTD Registry
c.297 G>C	p.W99C	rs782591841	1	9	Missense	3	Cirali 2017	
c.322C>T	p.Q108X				Nonsense	3	Carreau 2021	
c.353C>A	p.A118D	rs117500243			Missense	3	Allison 2017, Carreau 2021	
c.368 T>C	p.L123P	rs397514538	2	1	Missense	3	Haack 2012	
c.377 G>A			1	0	Missense	3		Cure RTD Registry
c.383 C>T	p.S128L	rs374071862	3	7	Missense	3	Manole 2017, SSIEM - Abstract 2016	
c.401 C>T	p.P134L	rs1447838904	4	3	Missense	3	Guissart 2015	
c.421C>A	p.P141T	rs377740960	2	1	Missense	3	Udhayabanu 2016	
c.477c>G			2	0	Missense	3		Cure RTD Registry
c.505 C>T	p.R169C	rs782345472	9	5	Missense	3	Woodcock 2017, Allison 2017	
c.700 C>T	p.Q234X	rs797045200	1	0	Nonsense	3	Foley 2013	
c.751C>T			1	0		3		Cure RTD Registry
c.808 C>T	p.Q270X	rs375088539	2	5	Nonsense	3	Shashi 2017, Petrovski 2015	
c.824G>T	p.R275L	rs144912258			Missense	3	Carreau 2021	
c.851 C>A	p.A284D	rs398123067	2	0	Missense	3	Foley 2013	
c.861C>A			1	0		3		Cure RTD Registry
c.863 C>T	p.A288V	rs764545993	2	25	Missense	3	Carreau 2021, Manole 2017	
c.865 C>T			1	1	Missense	3	Manole 2017	
c.911C>T			2	0	Missense	3	SMID 2018 - Abstract	
c.914 A>G	p.Y305C	rs398123068	1	2	Missense	3	Foley 2013, Allison 2017, Carreau 2021, Al-Twaijri 2002	
c.916 G>A	p.G306R	rs398124641	63	14	Missense	3	Johnson 2012, Foley 2013, Srour 2014, Menenze 2015, Sanchez 2017	
c.917 G>A	p.G306E	rs781923855	2	1	Missense	3	Nimmo 2017	
c.935 T>C	p.L312P	rs754320812	8	7	Missense	3	Foley 2013, Allison 2017, Manole 2017,	
c.968 T>C	p.L323P	rs781842708	2	8	Missense	3	Gorcenco 2018	
c.973 T>G	p.C325G		8	0	Missense	3	Badanejad 2018	
c.1016 T>C	p.L339P	rs148234606	39	18	Missense	4	Haack 2012, Foley 2013, Menenze 2015, Shashi 2017, Manole 2017,	
c.1052G>A			1	0		4		Cure RTD Registry

c.1087 C>G			1	1	Missense	4		Cure RTD Registry
c.1088 C>T	p.P363L	rs797045202	1	0	Missense	4	Manole 2017, Carreau 2021, Yilmaz 2021	
c.1243 G>A			1	0	Missense	5		Cure RTD Registry
c.1244 G>C			4	3	Missense	5		Cure RTD Registry
c. 1245C>T	p. G415=		2	0	Synonymous	5	Kranthi 2020	
c.1250 T>C			1	5	Missense	5		Cure RTD Registry
c.1255 G>A	p.G419S	rs397514658	1	0	Missense	5	Ciccolella 2012	
c.1258 G>A	p.A420T	rs368924997	7	4	Missense	5	Foley 2013, Schwartz 2015	
c.1259 C>T			4	0	Missense	5		Cure RTD Registry
c.1267 A>G			2	9	Missense	5		Cure RTD Registry
c.1268T>C			2	0		5		Cure RTD Registry
c.1289 A>G			2	1	Missense	5		Cure RTD Registry
c.1327 T>C	p.C443R		4	0	Missense	5	Manole 2017	
c.1328 G>A	p.C443Y		1	0	Missense	5	Shi 2019	
DEL_1030_1031			2	0		4		Cure RTD Registry
DEL_750_751			1	0		3		Cure RTD Registry
DEL_292_293			1	0		3		Cure RTD Registry
DEL_1140			2	0		5		Cure RTD Registry
c.405_407delCTT	p.F135del		2	0	Frameshift	3	Pillai 2020	
c.1022_1023insC	p.L342fs	rs1374925248	1		Frameshift	4	Shi 2019	
c.1161_1189del21			1					Cure RTD Registry
c.131-1G>C			1					Cure RTD Registry
Phe197del			1					Cure RTD Registry
p.Pro48Leu			2					Cure RTD Registry
Phe197del			1	0	Deletion			Cure RTD Registry

ExAC = Exome Aggregation Consortium (http://exac.broadinstitute.org/)

Riboflavin Transporter Deficiency

Table 2. Report Pathogenic Variants in SLC52A3 (previously C20orf54)
Reference Sequence: NM_ 033409.3

DNA nucleotide changed	Publication	Other Source
c.44G>T	Horoz 2015	
c.49T>C	Bosch et al 2011	
c.62A>G	Dezfouli et al 2012, Udhayabanu 2017	
c.71G4A (stop)	Hossain 2017	
c.82C>A	Johnson et al 2010	
c.106G>A	Green et al 2010,Rosser 2015, Manole 2017	
c.173T>A	Ciccolella et al 2012	
c.193C>T	Davis 2015	
c.211G>A	Green et al 2010	
c.211G>T	Green et al 2010	
c.224T>C	Johnson et al 2010	
c.354 G>A	Manole 2017	
c.361C>G	Poggio 2013	
c.374C>A	Chaya 2017, Manole 2017	
c.376A>G	Poggio 2013	
c.383C>T	Cosgrove 2015	
c.394C>T	Green et al 2010	
c.403A>G		Manole et al, unpublished
c.446G>A		Cure RTD Registery
c.436G>A	Hockaday 1981	
c.639C>G	Green et al 2010, Chaya 2017	
c.634 C>T	Manole 2017	
c.659C>A	Dezfouli et al 2012	
c.670T>C	Green et al 2010	
c.765C>T		Cure RTD Registery
c.796C>T	Ciccolella et al 2012	
c.935C>T	Dezfouli et al 2012, Khadilkar 2017	
c.955C>T	Ciccolella et al 2012	
c.989G>T	Koy et al 2012	
c.1048T>A	Green et al 2010	
c.1074 G>A	Manole 2017	
c.1121G>A		Cure RTD Registery
c.1156T>C	Thulasi 2017	
c.1198-2A>C	Bosch et al 2011	
c.1198-20_c.1237dup (insertion)		Cure RTD Registery

c.1237T>C	Green et al 2010, Bashford 2016, Rosser 2015, Manole 2017	
c.1238T>C	Ciccolella et al 2012, Davis 2015	
c.1296C>A	Ciccolella et al 2012	
c.1325_1326delTG	Green et al 2010	
c.1371C>G	Green et al 2010	
c.634C>T	Manole 2017	
c.671T>G	Manole 2017	
c.1128-1129_insT	Manole 2017	
c.1232_1233ins	Camargos 2018	
c.1223G>A	Nimmo 2017	
c.1255G>A		Manole et al, unpublished
c.1238T>C	Davis 2015	
c.1292G>A	Cosgrove 2015	
c.1294G>A		Manole et al, unpublished
c.1381T>G	Bashford 2016	
c.1316G>A	Woodcock 2017	
c.1313T>C		Cure RTD Registery
c.1124G>A	Dezfouli 2012	WT

References

Anand G, Hasan N, Jayapal S et al (2012) Early use of high-dose riboflavin in a case of Brown-Vialetto-Van Laere syndrome. Dev Med Child Neurol 54:187–9

Andreea Manole, Zane Jaunmuktane, Iain Hargreaves, et al 2017 Clinical, pathological and functional characterization of riboflavin-responsive neuropathy. Brain 2017 Nov 1;140(11):2820-2837

Allison, T, Roncero, I, et al. (2017) Brown-Vialetto-Van Laere Syndrome as a Mimic of Neuroimmune Disorders: 3 Cases From the Clinic and Review of the Literature. Journal of Child Neurology i-5:

Mojgan Babanejad, Omid Ali Adeli, Nooshin Nikzat et al 2018. SLC52A2 mutations cause SCABD2 phenotype: A second report International Journal of Pediatric Otorhinolaryngology, 104 (2018) 195–199

Bandettini Di Poggio M, Monti Bragadin M, Reni L et al (2014) Brown-Vialetto-Van Laere syndrome: clinical and neuroradiological findings of a genetically proven patient. Amyotroph Lateral Scler Frontotemporal Degener 15:141–4

Bosch AM, Abeling NGG, Ijlst L et al (2011) Brown-Vialetto-Van Laere and Fazio Londe syndrome is associated with a riboflavin transporter defect mimicking mild MADD: a new inborn error of metabolism with potential treatment. J Inherit Metab Dis 34:159–64

Ciccolella M, Catteruccia M, Benedetti S et al (2012) Brown-Vialetto-van Laere and Fazio-Londe overlap syndromes: a clinical, biochemical and genetic study. Neuromuscul Disord 22:1075–82

CiccolellaM, Corti S, CatterucciaMet al (2013) Riboflavin transporter 3

involvement in infantile Brown-Vialetto-Van Laere disease: two novel mutations. J Med Genet 50:104–7

Cosgrove J, Datta S, Busby M (2015) Adult onset Brown-Vialetto-Van Laere syndrome with opsoclonus and a novel heterozygous mutation: a case report. Clin Neurol Neurosurg 128:1–3

Davis A, Josifova D, Lloyd-Owen S et al (2015) Brown-Vialetto-Van Laere syndrome: a 28-year follow-up. J Neurol Neurosurg Psychiatry. doi:10.1136/jnnp-2014-310088

DezfouliMA, Yadegari S, Nafissi S, Elahi E (2012) Four novel C20orf54 mutations identified in Brown-Vialetto-Van Laere syndrome patients. J Hum Genet 57:613–7

Foley AR, Menezes MP, Pandraud A et al (2014) Treatable childhood neuronopathy caused bymutations in riboflavin transporter RFVT2. Brain 137:44–56

Green P, Wiseman M, Crow YJ et al (2010) Brown-Vialetto-Van Laere syndrome, a ponto-bulbar palsy with deafness, is caused by mutations in c20orf54. Am J Hum Genet 86:485–9

Haack TB,Makowski C, Yao Yet al (2012) Impaired riboflavin transport due to missense mutations in SLC52A2 causes Brown-Vialetto-Van Laere syndrome. J Inherit Metab Dis 35:943–8

Horoz OO, Mungan NO, Yildizdas D et al (2015) Brown-Vialetto-Van Laere syndrome: two siblings with a new mutation and dramatic therapeutic effect of high-dose riboflavin. J Pediatr Endocrinol Metab. doi:10.1515/jpem-2015-0198

Johnson JO, Gibbs JR, VanMaldergem L et al (2010) Exome sequencing in Brown-Vialetto-van Laere syndrome. Am J Hum Genet 87:567–9, author reply 569–70
Johnson JO, Gibbs JR, Megarbane A et al (2012) Exome sequencing reveals riboflavin transporter mutations as a cause of motor neuron disease. Brain 135:2875–82

Koy A, Pillekamp F, Hoehn T et al (2012) Brown-Vialetto-Van Laere syndrome: a riboflavin-unresponsive patient with a novel mutation in the C20orf54 gene. Pediatr Neurol 46:407–9

Malafronte P, Clark HB, Castaneda-Sanchez I et al (2013) Brown-Vialetto-Van Laere syndrome: clinical and neuropathologic findings with immunohistochemistry for C20orf54 in three affected patients. Pediatr Dev Pathol 16:364–71

Menezes MP, Farrar MA, Webster R et al (2016) Pathophysiology of motor dysfunction in a childhood motor neuron disease caused by mutations in the riboflavin transporter. Clin Neurophysiol 127(1): 911–8

Graeme A. M. Nimmo, Resham Ejaz, Dawn Cordeiro et al. 2017 Riboflavin transporter deficiency mimicking mitochondrial myopathy caused by complex II deficiency Am J Med Genet. 2017;1–5.

Spagnoli C, Pitt MC, Rahman S, De Sousa C (2014) Brown-Vialetto-van Laere syndrome: a riboflavin responsive neuronopathy of infancy with singular features. Eur J Paediatr Neurol 18:231–4

Srour M, Putorti ML, Schwartzentruber J et al (2014) Mutations in riboflavin transporter present with severe sensory loss and deafness in childhood. Muscle Nerve 50:775–9

Woodcock IR, Menezes MP et al (2017) Genetic, Radiologic and Clinical Variability in Brown-Vialetto-Van Laere Syndrome. *Seminars in Pediatric Neurology* DOI: http://dx.doi.org/10.1016/j.spen.2017.03.001