Title: POLR3-Related Leukodystrophy *GeneReview* Tables 3-5
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Updated: May 2017

Note: The following information is provided by the authors listed above and has not been reviewed by *GeneReviews* staff.

Table 3. Selected *POLR3A* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Exon	Reference(s)	Reference Sequences
c.169G>A	p.Asp57Asn	2	1	NM_007055.3 NP_008986.2
c.272C>T	p.Pro91Leu	3	1	
c.364_366delAAG	p.Lys122del	4	1	
c.418C>T	p.Arg140Ter	4	2	
c.441dupT	p.Asp148Ter	4	1	
c.496G>A	p.Val166Ile	5	1	
c.550_553delinsAAT	p.Lys184fsTer218	5	1	
c.930G>C	p.Trp310Cys	7	3	
c.1114G>A	p.Asp372Asn	8	1,2	
c.1160C>G	p.Ala387Gly	8	1	
c.1186G>T	p.Val396Leu	9	1	
c.1302insA	p.Tyr434Ter	10	1	
c.1433C>G	p.Ala478Gly	11	1	
c.1658C>T	p.Thr553Ile	13	1	
c.1674C>G	p.Phe558Leu	13	1,2	
c.1741insA	p.Val581SerfsTer28	13	1	
c.1795C>A	p.Gln599Lys	14	1	
c.1797G>C	p.Gln599His	14	1	
c.1804A>C	p.Ser602Arg	14	1	
c.1907C>A	p.Ser636Tyr	14	2	
c.1930G>A	p.Glu644Lys	15	1	
c.1935G>C	p.Leu645Phe	15	1	
c.2005C>G	p.Arg669Gly	15	1	
c.2011T>C	p.Trp671Arg	15	1	
c.2015G>A	p.Gly672Glu	15	1,2	
c.2039T>C	p.Met680Thr	15	1	
c.2045G>A	p.Arg682Gln	15	1	
c.2098A>T	p.Ile700Phe	16	1	
c.2171G>A	p.Cys724Tyr	16	2	
c.2324A>T	p.Asn775Ile	17	1,2	

DNA Nucleotide Change	Predicted Protein Change	Exon	Reference(s)	Reference Sequences
c.2350G>A	p.Gly784Ser	17	1	
c.2381A>C	p.Gln794Pro	18	4	
c.2411T>C	p.Ile804Thr	18	3	
c.2542T>C	p.Phe848Leu	19	1	
c.2547C>G	p.Phe849Leu	19	1	
c.2549A>G	p.His850Arg	19	4	
c.2554A>G	p.Met852Val	19	1,2,5	
c.2618G>A	p.Arg873Gln	20	1	
c.2660A>T	p.Asp887Val	20	1	
c.2690T>A	p.Ile897Asn	20	6	
c.2710G>A	p.Gly904Arg	20	4	
c.2810A>T	p.Glu937Val	21	1	
c.2821A>C	p.Ser941Arg	21	1	
c.2830G>T	p.Glu944Ter	21	1,2	
c.3013C>T	p.Arg1005Cys	23	1,2,6	
c.3014G>A	p.Arg1005His	23	1,7	
c.3205C>T	p.Arg1069Trp	24	4	
c.3407G>A	p.Arg1136Gln	26	1	
c.3718G>A	p.Gly1240Ser	28	1	
c.3742insACC	p.1248insThr	28	1,2	
c.3745A>C	p.Asn1249His	28	5	
c.3781G>A	p.Glu1261Lys	29	1	
c.3991G>A	p.Ala1331Thr	30	1,7	
c.4006C>T	p.Gln1336Ter	30	2	
c.-35C>G		5' UTR	4	
c.1048+1G>A		Intron 7	4	
c.1289+3A>C		intron 9	4	
c.1771-6C>G		intron 13	4,8	
c.1909+18G>A	p.Tyr637CysfsTer650	intron15	2	
c.1909+22G>A		intron15	4	
c.2617-1G>A	p.Arg873AlafsTer878	Intron 19	1,2	
c.2988+1G>T		intron 21	1	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Table 4. Selected *POLR3B* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Exon	Reference(s)	Reference Sequences
c.79T>C	p.Trp27Arg	2	1	NM_018082.5 NP_060552.4
c.308G>A	p.Arg103His	6	1	
c.312G>T	p.Leu104Phe	6	1	
c.802A>G	p.Ser268Gly	10	1	
c.832_833dup	p.Thr279SerfsTer7	10	1	
c.1018C>T	p.Arg340Ter	12	1	
c.1112_1113delTT	p.Leu371fs	13	1	
c.1244T>C	p.Met415Thr	13	4	
c.1253C>T	p.Ala418Val	13	1	
c.1324C>T	p.Arg442Cys	14	1	
c.1325G>T	p.Arg442Leu	14	1	
c.1346T>C	p.Leu449Pro	14	1	
c.1648C>T	p.Arg550Ter	14	6	
c.1477G>T	p.Val493Phe	15	1	
c.1508C>A	p.Thr503Lys	15	1,9	
c.1533delT	p.Ile511MetfsTer3	15	1,9	
c.1568T>A	p.Val523Glu	15	1,9-11	
c.1579T>C	p.Cys527Arg	15	9,11	
c.1788C>A	p.Tyr596Ter	17	1	
c.1900G>A	p.Asp634Asn	18	1	
c.1939G >A	p.Glu647Lys	18	12	
c.1999G>A	p.Val667Met	19	1	
c.2180T>C	p.Leu727Ser	20	1	
c.2190delT	p.Phe730fs	20	1	
c.2302C>T	p.Arg768Cys	21	4	
c.2303G>A	p.Arg768His	21	6	
c.2683G>A	p.Asp895Asn	23	1	
c.2686A>T	p.Lys896Ter	23	1,9	
c.2707delC	p.Gln903fsTer	23	1	
c.2774C>T	p.Pro925Leu	24	4	
c.2778C>G	p.Asp926Glu	24	6	
c.2899A>C	p.Ser967Arg	25	1	
c.2918G>T	p.Cys973Phe	25	1	
c.2920G>T	p.Glu974Ter	25	1	
c.2944A>G	p.Asn982Asp	25	1,13	

DNA Nucleotide Change	Predicted Protein Change	Exon	Reference(s)	Reference Sequences
c.3005T>C	p.Ile1002Thr	26	1	
c.3008A>G	p.Tyr1003Cys	26	1,10	
c.3035T>C	p.Leu1012Pro	26	1	
c.3071C>T	p.Ala1024Val	26	1,13	
c.3349C>G	p.Leu1117Val	28	1	
c.3352C>T	p.Gln1118Ter	28	1	
c.303+1G>A		intron 5	1	
c.967-15A>G		intron 11	1	
c.1101+1G>C		intron 12	1	
c.1263+2T>C		intron 13	1	
c.1464+1G>A		intron 14	1	
c.1857-12A>G		intron 17	1	
c.1857-2A>C	p.Asn620_Lys652del	intron 17	6	
c.2083+1G>A		intron 19	1	
c.2084-6A>G	p.G695VfsTer5	Intron 19	1,4,12	
c.2570+1G>A	p.Gly818AlafsTer13	intron 22	1	
c.2817+30T>A		intron 24	1	
Del exons 21-22			10	
Del exons 26-27			10	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Table 5. Selected *POLR1C* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Exon	Reference	Reference Sequences
c.77C>T	p.Thr26Ile	2	14	NM_203290.3 NP_976035
c.95A>T	p.Asn32Ile	2		
c.193A>G	p.Met65Val	3		
c.221A>G	p.Asn74Ser	3		
c.281T>C	p.Val94Ala	4		
c.326G>A	p.Arg109His	4		
c.395G>A	p.Gly132Asp	5		
c.436T>C	p.Cys146Arg	5		
c.461_462delAA	p.Lys154ArgfsTer4	5		
c.572G>A	p.Arg191Gln	6		
c.785T>C	p.Ile262Thr	7		
c.883_885delAAG	p.Lys295del	8		
c.970G4>A	p.Glu324Lys	9		

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

References

1 Wolf NI, Vanderver A, van Spaendonk RM, Schiffmann R, Brais B, Bugiani M, Sistermans E, Catsman-Berrevoets C, Kros JM, Pinto PS, Pohl D, Tirupathi S, Stromme P, de Grauw T, Fribourg S, Demos M, Pizzino A, Naidu S, Guerrero K, van der Knaap MS, Bernard G, 4H Research Group. Clinical spectrum of 4H leukodystrophy caused by POLR3A and POLR3B mutations. Neurology. 2014; 83:1898-905

2 Bernard G, Chouery E, Putorti ML, Tetreault M, Takanohashi A, Carosso G, Clement I, Boespflug-Tanguy O, Rodriguez D, Delague V, Abou GJ, Jalkh N, Dorboz I, Fribourg S, Teichmann M, Megarbane A, Schiffmann R, Vanderver A, Brais B. Mutations of POLR3A encoding a catalytic subunit of RNA polymerase Pol III cause a recessive hypomyelinating leukodystrophy. Am J Hum Genet. 2011; 89:415-23.

3 Shimojima K, Shimada S, Tamasaki A, Akaboshi S, Komoike Y, Saito A, Furukawa T, Yamamoto T. Novel compound heterozygous mutations of POLR3A revealed by whole-exome sequencing in a patient with hypomyelination. Brain Dev. 2014; 36:315-21.

4 La Piana R, Cayami FK, Tran LT, Guerrero K, van Spaendonk R, Ounap K, Pajusalu S, Haack T, Wassmer E, Timmann D, Mierzewska H, Poll-The BT, Patel C, Cox H, Atik T, Onay H, Ozkinay F, Vanderver A, van der Knaap MS, Wolf NI, Bernard G. Diffuse hypomyelination is not obligate for POLR3-related disorders. Neurology. 2016; 86:1622-6.

5 Terao Y, Saitsu H, Segawa M, Kondo Y, Sakamoto K, Matsumoto N, Tsuji S, Nomura Y. Diffuse central hypomyelination presenting as 4H syndrome caused by compound heterozygous mutations in POLR3A encoding the catalytic subunit of polymerase III. J Neurol Sci. 2012; 320:102-5.

6 Saitsu H, Osaka H, Sasaki M, Takanashi JI, Hamada K, Yamashita A, Shibayama H, Shiina M, Kondo Y, Nishiyama K, Tsurusaki Y, Miyake N, Doi H, Ogata K, Inoue K, Matsumoto N. Mutations in POLR3A and POLR3B encoding RNA polymerase III subunits cause an autosomal-recessive hypomyelinating leukoencephalopathy. Am J Hum Genet. 2011; 89:644-51.

7 Potic A, Brais B, Choquet K, Schiffmann R, Bernard G. 4H syndrome with late-onset growth hormone deficiency caused by POLR3A mutations. Arch Neurol. 2012; 69:920-3.

8 Azmanov DN, Siira SJ, Chamova T, Kaprelyan A, Guergueltcheva V, Shearwood AJ, Liu G, Morar B, Rackham O, Bynevelt M, Grudkova M, Kamenov Z, Svechtarov V, Tournev I, Kalaydjieva L, Filipovska A. Transcriptome-wide effects of a POLR3A gene mutation in patients with an unusual phenotype of striatal involvement. Hum Mol Genet. 2016; 25:4302-14.

9 Tetreault M, Choquet K, Orcesi S, Tonduti D, Balottin U, Teichmann M, Fribourg S, Schiffmann R, Brais B, Vanderver A, Bernard G. Recessive mutations in POLR3B, encoding the second largest subunit of Pol III, cause a rare hypomyelinating leukodystrophy. Am J Hum Genet. 2011; 89:652-5.

10 Gutierrez M, Thiffault I, Guerrero K, Martos-Moreno G, Tran L, Benko W, van der Knaap M, van Spaendonk R, Wolf N, Bernard G. Large exonic deletions in POLR3B gene cause POLR3-related leukodystrophy. Orphanet J Rare Dis. 2015; 10:69.

11 Synofzik M, Bernard G, Lindig T, Gburek-Augustat J. Teaching neuroImages: hypomyelinating leukodystrophy with hypodontia due to POLR3B: Look into a leukodystrophy's mouth. Neurology. 2013; 81:e145.

12 Jurkiewicz E, Dunin-Wasowicz D, Gieruszczak-Bialek D, Malczyk K, Guerrero K, Gutierrez M, Tran L, Bernard G. Recessive mutations in POLR3B encoding RNA polymerase III subunit causing diffuse hypomyelination in patients with 4H leukodystrophy with polymicrogyria and cataracts. Clin Neuroradiol. 2015 Oct 19.

13 Cayami FK, La Piana R, van Spaendonk RM, Nickel M, Bley A, Guerrero K, Tran LT, van der Knaap MS, Bernard G, Wolf NI. POLR3A and POLR3B mutations in unclassified hypomyelination. Neuropediatrics. 2015; 46:221-8.

14 Thiffault I, Wolf NI, Forget D, Guerrero K, Tran LT, Choquet K, Lavallee-Adam M, Poitras C, Brais B, Yoon G, Sztriha L, Webster RI, Timmann D, van de Warrenburg BP, Seeger J, Zimmermann A, Mate A, Goizet C, Fung E, van der Knaap MS, Fribourg S, Vanderver A, Simons C, Taft RJ, Yates III JR, Coulombe B, Bernard G. Recessive mutations in POLR1C cause a leukodystrophy by impairing biogenesis of RNA polymerase III. Nat Commun. 2015; 6:7623-31.