

Title: Alexander Disease *GeneReview* Table 3

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Updated: November 2020

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

Table 3. GFAP Mutation Screening in Individuals with Alexander Disease %

Exon	Nucleotide Change (Amino Acid Change)	Infantile	Juvenile	Adult	Asymptomatic	Total Affected Individuals	References [†]
1	187A>C Lys63Gln			1		1	[1A] (Li et al 2005, van der Knaap et al 2005)
1	197G>A Arg66Gln			3		3	[1A] Hida et al 2012 [1A] Pedroso et al 2014 [1A] Prust et al 2011 ^{aa}
1	205G>A Glu69Lys		1			1	[1J] Davison et al 2011
1	~ Arg70Trp			1		1	[1A] Yoshida et al 2011b
1	208C>T Arg70Trp			4		4	[1A] Salvi et al 2005 [1A] Sreedharan et al 2007 [1A] Caroli et al 2007 [1A] (Farina et al 2008, Pareyson et al 2008)
1	209G>A Arg70Gln			4		4	[1A] Caroli et al 2007 [1A] Sechi et al 2008 [1A] (Farina et al 2008, Pareyson et al 2008) [1A] Graff-Radford et al 2014
1	214G>A Glu72Lys	1				1	[1I] Prust et al 2011 ^{bb}
1	218T>G Met73Arg		1			1	[1J] Gorospe et al 2002
1	218T>C Met73Thr	2				2	[1I] Li et al 2005 [1I] Vasquez et al 2008
1	218T>A Met73Lys	1				1	[1I] Caroli et al 2007
1	~ Met74Thr			3		3	[1A] Yonezu et al 2012 [1A] Yoshida et al 2011b [1A] Yoshida et al 2011a
1	221T>C Met74Thr			1		1	[1A] Ohnari et al 2007

Exon	Nucleotide Change (Amino Acid Change)	Infantile	Juvenile	Adult	Asymptomatic	Total Affected Individuals	References [†]
1	226C>T Leu76Phe	2				2	[1I] Rodriguez et al 2001 [1I] Li et al 2005
1	226C>G Leu76Val	1				1	[1I] Li et al 2005
1	229A>T Asn77Tyr	1				1	[1I] Rodriguez et al 2001
1	230A>G Asn77Ser	2				2	[1I] Li et al 2005 [1I] Caroli et al 2007
1	232G>A Asp78Asn			2	1	3	[2A 1As] Wada et al 2013 ^l
1	234C>A Asp78Glu		1	4	1	6	[1J 4A 1As] Stumpf et al 2003 ^a
1	~ Arg79Cys	4				4	[4I] Yoshida et al 2011a
1	235C>G Arg79Gly	1				1	[1I] Gorospe et al 2002
1	235C>T Arg79Cys	14	2			16	[2I] Brenner et al 2001 [1I] Gorospe et al 2002 [2I] Shiroma et al 2003 ^b [1J] Probst et al 2003 [1I] Ma et al 2005 [2I 1J] Li et al 2005 [3I] Caroli et al 2007 [1I] Mignot et al 2009 [1I] Poloni et al 2009 [1I] Biancheri et al 2013
1	~ Arg79His		2	1		3	[1J] Yoshida et al 2013 [1J] Yoshida et al 2011a [1A] Yoshida et al 2011b
1	236G>A Arg79His	10	2			12	[1I 1J] Brenner et al 2001 [4I] Rodriguez et al 2001 [2I] Gorospe et al 2002 [2I] (Meins et al 2002, Brockmann et al 2003a) ^b [1J] Asahina et al 2006 [1I] Ashrafi et al 2013
1	[236G>A; 667G>C] [Arg79His; Glu223Gln]	1				1	[1I] Dotti et al 2009 ^w
1	~ Arg79Leu		1			1	[1J] Yoshida et al 2011a

Exon	Nucleotide Change (Amino Acid Change)	Infantile	Juvenile	Adult	Asymptomatic	Total Affected Individuals	References †
1	236G>T Arg79Leu	1				1	[1I] Shiroma et al 2003
1	236G>C Arg79Pro		1			1	[1J] Caroli et al 2007
1	239T>C Phe80Ser	1				1	[1I] da Silva Pereira et al 2013
1	247T>C Tyr83His	1				1	[1I] Wu et al 2008
1	256A>G Lys86Glu	2				2	[1I] Prust et al 2011 ^{cc} [1I] Barreau et al 2011 ^{cc}
1	256_259delinsGAGT Lys86_Val87delinsGluPhe		1			1	[1J] van der Knaap et al 2006
1	~ Val87Gly			2	1	3	[1A] Yoshida et al 2011b [1A 1As] Yoshida et al 2011a
1	260T>G Val87Gly			3		3	[3A] Okamoto et al 2002 ^c
1	259G>C Val87Leu			1		1	[1A] Suzuki et al 2012 ^{dd}
1	259G>A Val87Ile		1	1		2	[1A] Graff-Radford et al 2014 [1J] Restrepo et al 2011
1	~ Arg88Cys	1	1			2	[1I 1J] Yoshida et al 2011a
1	262C>T Arg88Cys	4	10			14	[2I] Rodriguez et al 2001 [2J] Gorospe et al 2002 ^d [1J] Nobuhara et al 2004 ^e [1J] Li et al 2005 [1I] Kyllerman et al 2005 [3J] van der Knaap et al 2006 ^x [1I] Caroli et al 2007 [1J] Kmiec et al 2007 [2J] Wu et al 2008
1	262C>A Arg88Ser	1				1	[1I] Rodriguez et al 2001
1	269T>C Leu90Pro	1				1	[1I] Suzuki et al 2004
1	278A>C Gln93Pro		1			1	[1J] Kyllerman et al 2005
1	290T>C Leu97Pro	2				2	[1I] Meins et al 2002 [1I] Li et al 2005

Exon	Nucleotide Change (Amino Acid Change)	Infantile	Juvenile	Adult	Asymptomatic	Total Affected Individuals	References †
1	~ Leu101Pro			1		1	[1A] Yoshida et al 2011a
1	302T>C Leu101Pro			1		1	[1A] Kaneko et al 2009
1	365_373dup Arg124_Leu125insGlnLeuArg			1		1	[1A] Schmidt et al 2013
1	375_380dupGCGGCT Arg126_Leu127dup		1			1	[1J] van der Knaap et al 2006
1	382G>A Asp128Asn			1		1	[1A] (Farina et al 2008, Pareyson et al 2008)
3	613G>A Glu205Lys			2		2	[2A] (Farina et al 2008, Pareyson et al 2008)
4	619G>A Glu207Lys		1			1	[1J] (Li et al 2005, van der Knaap et al 2005, Franzoni et al 2006)
4	619G>C Glu207Gln		1			1	[1J] (Li et al 2005, van der Knaap et al 2005)
4	628G>A Glu210Lys		2	1		3	[1A] Li et al 2005 [1J] Kyllerman et al 2005 [1J] van der Knaap et al 2006
4	667G>C Glu223Gln			2		2	[2A] Brockmann et al 2003b ^f
4	692T>A Leu231His			2		2	[2A] Delnooz et al 2008 ^g
4	704T>C Leu235Pro		3			3	[3J] (Li et al 2005, van der Knaap et al 2005) ^b
4	707A>C Lys236Thr	1				1	[1I] Prust et al 2011 ^{ee}
4	~ Arg239Gly		1			1	[1J] Osorio et al 2012
4	715C>G Arg239Gly			1		1	[1A] Graff-Radford et al 2014
4	~ Arg239Cys	1	2			3	[1I 2J] Yoshida et al 2011a

Exon	Nucleotide Change (Amino Acid Change)	Infantile	Juvenile	Adult	Asymptomatic	Total Affected Individuals	References [†]
4	715C>T Arg239Cys	18	5			23	[4] Brenner et al 2001 [4] Rodriguez et al 2001 [1] Shiroma et al 2001 [1] Gorospe et al 2002 [1J] Shiihara et al 2002 [1] (Meins et al 2002, Brockmann et al 2003a) [1] Shiroma et al 2003 [4] 2J] (Li et al 2005, van der Knaap et al 2005) [1] Wakabayashi et al 2005 ^h [2] Li et al 2006 [1J] Barreau et al 2011 ^{ff}
4	~ Arg239His	1				1	[1] Yoshida et al 2011a
4	716G>A Arg239His	10				10	[1] Brenner et al 2001 [1] Rodriguez et al 2001 [5] Li et al 2005 [1] Caroli et al 2007 [1] Sakakibara et al 2007 [1] Ashrafi et al 2013
4	716G>C Arg239Pro	2	1			3	[1] (Meins et al 2002, Brockmann et al 2003a) [1J] (Li et al 2005, van der Knaap et al 2005) [1] Caroli et al 2007
4	716G>T Arg239Leu	2				2	[1] Lee et al 2006 [1] Shiihara et al 2011 ^{gg}
4	724T>G Tyr242Asp	1				1	[1] Gorospe et al 2002
4	~ Ala244Val		1	1		2	[1J 1A] Yoshida et al 2011a
4	731C>T Ala244Val	1	1			2	[1] Aoki et al 2001 [1J] (Li et al 2005, van der Knaap et al 2005)
4	739T>C Ser247Pro		1	2	2	5	[1J 2A 2As] Messing et al 2012 ⁿ
4	758C>G Ala253Gly	1				1	[1] (Li et al 2005, van der Knaap et al 2005)
4	770A>G Tyr257Cys			1		1	[1A] Howard et al 2008

Exon	Nucleotide Change (Amino Acid Change)	Infantile	Juvenile	Adult	Asymptomatic	Total Affected Individuals	References [†]
4	~ Arg258Cys			3		3	[1A] Spritzer et al 2013 [1A] Yoshida et al 2011b [1A] Yoshida et al 2011a
4	772C>T Arg258Cys		1			1	[1J] Van Poppel et al 2009
4	773G>C Arg258Pro	1				1	[1I] Brenner et al 2001
5	~ Leu264Pro			1		1	[1A] Yoshida et al 2011a
5	791T>C Leu264Pro			1		1	[1A] Graff-Radford et al 2014 ^{jj}
5	791_792delinsCT Leu264Pro			1		1	[1A] Ayaki et al 2010
5	799G>C Ala267Pro		1			1	[1J] Hinttala et al 2007 ^e
5	~ Ala268Asp		1			1	[1J] Yoshida et al 2013
5	~ Arg276Leu			3	1	4	[3A] Yoshida et al 2011a [1As] Yoshida et al 2011a
5	827G>T Arg276Leu		1	2		3	[2A] Namekawa et al 2002 ^g [1J] Namekawa et al 2012
5	835A>G Lys279Glu		1			1	[1J] Li et al 2005
5	868C>G Gln290Glu	1				1	[1I] Barreau et al 2011
6	934G>T Glu312Ter			1		1	[1A] Nam et al 2014
6	[988C>G; 994G>A] [Arg330Gly; Glu332Lys]			4		4	[4A] Balbi et al 2008 ⁱ
6	992T>C Leu331Pro	1			2	3	[1I 2As] Shiihara et al 2004 ^j
6	994G>A Glu332Lys			1		1	[1A] (Farina et al 2008, Pareyson et al 2008)
6	Tyr349_Gln350insHisLeu	1				1	[1I] Li et al 2005
6	1051G>C Asp351His			1		1	[1A] Tschampa et al 2011 ^q
6	1055T>C Leu352Pro	2				2	[1I] (Bassuk et al 2003, Li et al 2005) [1I] Niinikoski et al 2009

Exon	Nucleotide Change (Amino Acid Change)	Infantile	Juvenile	Adult	Asymptomatic	Total Affected Individuals	References †
6	~ Leu357Pro			1		1	[1A] Yoshida et al 2011b
6	1073C>T Ala358Val	1				1	[1I] Dinopoulos et al 2006
6	1074C>G Leu359Val		1			1	[1J] Li et al 2005
6	1075C>G Leu359Val	1				1	[1I] Ramesh et al 2013
6	1076T>C Leu359Pro			2		2	[1A] (Caroli et al 2007, Romano et al 2007) [1A] (Farina et al 2008, Pareyson et al 2008)
6	~ Asp360Val		1			1	[1J] Yoshida et al 2011a
6	~ Glu362Gly		1			1	[1J] Yoshida et al 2013
6	1086>C Glu362Asp		1			1	[1J] Sawaishi et al 2002
6	~ Ala364Thr			2		2	[2A] Yoshida et al 2011a
6	1090G>C Ala364Pro	1				1	[1I] Li et al 2005
6	1091C>T Ala364Val	1				1	[1I] Hartmann et al 2007
6	1096T>C Tyr366His	1				1	[1I] Li et al 2005
6	1097A>G Tyr366Cys	1				1	[1I] Hartmann et al 2007
6	1112A>G Glu371Gly	1				1	[1I] Kawai et al 2006
6	1111G>C Glu371Gln	1				1	[1I] Prust et al 2011 ^{hh}
6	1112A>T Glu371Val	1				1	[1I] Prust et al 2011 ⁱⁱ
6	~ Glu373Asp		1			1	[1J] Yoshida et al 2011a
6	1117G>A Glu373Lys	5				5	[1I] Gorospe et al 2002 [2I] Li et al 2005 [1I] Matej et al 2008 [1I] Larsen et al 2012

Exon	Nucleotide Change (Amino Acid Change)	Infantile	Juvenile	Adult	Asymptomatic	Total Affected Individuals	References [†]
6	1117G>C Glu373Gln	1				1	[1I] Li et al 2005
6	1118A>C Glu373Ala			2		2	[2A] Graff-Radford et al 2014 ^z
6	1121A>G Glu374Gly	1				1	[1I] Li et al 2005
6	~ Arg376Trp	1		1		2	[1J] Zafeiriou et al 2013 [1A] Yoshida et al 2011a
6	1126C>T Arg376Trp		1	1		2	[1J 1A] Hirayama et al 2008 ^f
7	1148C>T Thr383Ile			1		1	[1A] Schmidt et al 2011
7	1154C>T Ser385Phe	1				1	[1I] Torisu et al 2013
7	1154C>G Ser385Cys			2		2	[2A] Graff-Radford et al 2014 ^k
7	1157A>T Asn386Ile	1				1	[1I] Caceres-Marzal et al 2006
8	~ Ser393Ile			1		1	[1A] Yoshida et al 2011a
8	1178G>T Ser393Ile		1	2		3	[1J 1A] Salmaggi et al 2007 ^f [1A] (Farina et al 2008, Pareyson et al 2008)
8	~ Ser398Phe			2		2	[1A] Yoshida et al 2011a [1A] Sueda et al 2009
8	1193C>A Ser398Tyr			1		1	[1A] (Farina et al 2008, Pareyson et al 2008)
8	~ Met415Ile		1	1		2	[1J] Rezende et al 2012 ^y
8	~ Arg416Trp	1				1	[1I] Nishri et al 2014
8	1246C>T Arg416Trp	2	4	5		11	[2I] Brenner et al 2001 [2J] Gorospe et al 2002 [1A] Kinoshita et al 2003 [2A] Thyagarajan et al 2004 ^f [1A] Li et al 2005 [1J] van der Knaap et al 2006 [1J] Caroli et al 2007 [1A] (Farina et al 2008, Pareyson et al 2008)

Exon	Nucleotide Change (Amino Acid Change)	Infantile	Juvenile	Adult	Asymptomatic	Total Affected Individuals	References †
8	1250A>C Asp417Ala		1	2	1	4	[1J 2A 1As] Messing et al 2012
8	1249delG Asp417MetfsTer15	3				3	[1I] Murakami et al 2008 ^u [1I] Flint et al 2012 [1I] Yoshida et al 2011a
9	1277A>T Gln426Leu			1	1	2	[1A] Messing et al 2012 ^{p,v}
9	1292_1299delinsATC Val431_Met432delinsAspArgGlnAspProProGlyGlyLeuCysProValSer (Val431AspfsTer14)	1				1	[1I] Flint et al 2012 ^m
7A ^s	1289G>A Arg430His			2		2	[2A] Melchionda et al 2013 ^{r,t}
Splice site	619-3C>G Glu207_Lys260del (exon 4 skip)			1		1	[1A] Flint et al 2012
Splice site	IVS4-24_c812delins (56bp del, 20bp ins) Phe261_Thr302del (exon 5 skip)			1		1	[1A] Graff-Radford et al 2014
TOTAL Mutation-confirmed Cases		124	63	96	10	293	
	No mutations identified	2	2	2		6	[1I] Brenner et al 2001 [1I] Rodriguez et al 2001 [1J] Gorospe et al 2002 [1J 1A] Li et al 2005 [1A] Huttner et al 2007
TOTAL Mutation-screened Cases		126	65	98	10	299	

[%] A separate list of *GFAP* mutations has been maintained by Dr. Albee Messing and is viewable at www.waisman.wisc.edu/alexander-disease/mutation-table.pdf

†[] indicates the number of patients and the form of Alexander disease described in the reference: I=infantile, J=juvenile, A=adult, As=asymptomatic.

References enclosed in () described the same patient(s).

~ indicates the nucleotide change has not been reported.

^a All six individuals belong to a three-generation family [Stumpf et al 2003].

^b References describe cases of monozygotic twin pairs.

^c All three individuals belong to the same pedigree [Okamoto et al 2002].

^d One patient is the same patient described in Guthrie et al 2003.

^e A concomitant mitochondrial mutation was identified.

^f Mother and child pair.

^g Patients described are siblings.

^h Infantile-onset patient atypical for being a long-term survivor [Wakabayashi et al 2005].

^l All four individuals belong to the same family [Balbi et al 2008].

^jAll three patients belong to the same family. The proband showed megalencephaly at 4m with no other abnormalities. MRI at 16m revealed abnormalities in the frontal white matter and basal ganglia. An elder sister (7y) and the mother (34y) showed the same nucleotide change but were asymptomatic and showed only mild abnormalities in the frontal and caudate regions by MRI [Shiihara et al 2004].

^kFather, child pair

^lMembers of a family in which the affected adults are sisters, and the unaffected individual is the son of one of the sisters

^mChimera

ⁿMembers of a 2-generation pedigree with affected members being the father and his 4 children. The father is being counted as asymptomatic, though this is unclear, as he had multiple chronic health problems, including alcoholism, sleep apnea, and scoliosis which began in young adulthood. His mutation was confirmed with sequencing of DNA isolated from paraffin blocks from a testicular biopsy.

^oMembers of a multi-generation pedigree

^pMother, daughter pair

^qPatient also has a heterozygous variant in intron 3 (c.619-35_-21del) and heterozygous polymorphism in exon 2 (rs59291670)

^rHalf-siblings, sharing the same healthy mother (who is suspected of having germinal mosaicism)

^sMutation in alternative exon 7A of transcript NM_001131019.2

^tOne of the patients also has a hemizygous variant in *HDAC6* (c.2566C>T; p.P856S); the mother was heterozygous for this variant.

^uMutation reported as “1247-1249GGG>GG (Asp417Met14STOP)”

^vIndividual who is asymptomatic had scoliosis at age 9 years but no neurologic symptoms. She developed bipolar affective disorder and abused alcohol, and she died with elevated blood alcohol level.

^wThe *GFAP* variant c.667G>C (p.Glu223Gln) is felt to be a rare variant rather than disease causing but its exact pathogenicity is unclear.

^x2 of the patients are a mother-son pair

^yMother, daughter pair. Daughter, but not mother, has a *GFAP* variant p.Asp157Gln; the pathogenicity of this variant is unclear.

^zMother-daughter pair, both affected by Alexander disease, though only daughter's mutation reported.

^{aa}Nucleotide change reported as c.211G>A; nucleotide sequence written in table is with respect to the start of the coding sequence

^{bb}Nucleotide change reported as c.228G>A; nucleotide sequence written in table is with respect to the start of the coding sequence

^{cc}Nucleotide change reported as c.270A>G; nucleotide sequence written in table is with respect to the start of the coding sequence

^{dd}Nucleotide change reported as c.273G>C; nucleotide sequence written in table is with respect to the start of the coding sequence

^{ee}Nucleotide change reported as c.721A>C; nucleotide sequence written in table is with respect to the start of the coding sequence

^{ff}Nucleotide change reported as c.729C>T; nucleotide sequence written in table is with respect to the start of the coding sequence

^{gg}Nucleotide change reported as c.730G>T; nucleotide sequence written in table is with respect to the start of the coding sequence

^{hh}Nucleotide change reported as c.1125G>C; nucleotide sequence written in table is with respect to the start of the coding sequence

ⁱⁱNucleotide change reported as c.1126A>T; nucleotide sequence written in table is with respect to the start of the coding sequence

^{jj}Nucleotide change reported as c.701T>C; nucleotide sequence written in table is with respect to the start of the coding sequence

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