Table S1. *ATP1A3* mutations found in *ATP1A3*-related disorders other than AHC

Amino acid change	NKA α_3 domain	Residue conservation	CDS change	Primary diagnosis (other than AHC)	References
V129M	M2	M, D, C	c.385G>A	COS	Smedemark-Margulies et al., 2016
S137del*	M2	M, D	c.410_412del-CCT*	RDP (without parkinsonism)	Wilcox et al., 2015
Q140H	M2	M, D, C	c.420G>T	D-DEMØ	Prange et al., 2020
I274T	M3	M, D, C	c.821T>C	RDP	de Carvalho Aguiar et al., 2004; Kamphuis et al., 2006
E277K**	M3	M, D, C	c.829G>A	RDP	de Carvalho Aguiar et al., 2004
L292R	M3	M, D, C	c.875T>G	PMG	Vetro et al., 2021
G316S	M4	M, D, C	c.946G>A	ARA	Sweadner et al., 2016
G316V	M4	M, D, C	c.947G>T	PMG	Vetro et al., 2021
I318M	M4	M, D, C	c.954C>G	Parkinsonism with ID	Kwong et al., 2021
E324G	M4	M, D, C	c.971A>G	D-DEMØ	Prange et al., 2020
G325D	M4	M, D, C	c.974G>A	D-DEMØ	Prange et al., 2020
L327del	M4	M, D, C	c.979_981delCTG	RDP	Kamm et al., 2008
G358V	P	M, D, C	c.1073G>T	EIEE	Paciorkowski et al., 2015
T360R	P	M, D, C	c.1079C>G	D-DEMØ	Prange et al., 2020
S361P	P	M, D, C	c.1081T>C	PMG	Vetro et al., 2021

Amino acid change	NKA α_3 domain	Residue conservation	CDS change	Primary diagnosis (other than AHC)	References
I363N	P	M, D, C	c.1088T>A	EIEE	Paciorkowski et al., 2015
T370N**	P	M, D, C	c.1109C>A	RDP	Rosewich et al., 2014b
W382R	N	M, D, C	c.1144T>C	RDP	Rosewich et al., 2014b
D583Y	N	M, D, C	c.1747G>T	RDP (infantile)	Nicita et al., 2016
D591V	N	M, D, C	c.1772A>T	adCORD	Zhou et al., 2020
C596Y	P	M, D, C	c.1787G>A	PMG	Miyatake et al., 2021
D609Y	P	M, D, C	c.1825G>T	Hypotonia with dyspneic episodes	Marzin et al., 2018
D609Y	P	M, D, C	c.1825G>T	PMG	Vetro et al., 2021
T613M	P	M, D, C	c.1838C>T	RDP	de Carvalho Aguiar et al., 2004
A681T	P	M, D, C	c.2041G>A	ASD	Torres et al., 2018
S684F	P	M, D, C	c.2051C>T	RDP	Svetel et al., 2010
G706R**	P	M, D, C	c.2116G>A	EE with strabismus and autistic features	Hully et al., 2017
N744K	P	M, D, C	c. 2232C>A	AHC/RDP intermediate	Sival et al., 2018
R756C	M5	M, D, C	c.2266C>T	RECA	Dard et al., 2015; Jaffer et al., 2017; Nakamura et al., 2018; Nicita et al., 2016; Sabouraud et

Amino acid change	NKA α_3 domain	Residue conservation	CDS change	Primary diagnosis (other than AHC)	References
					al., 2019; Sival et al., 2018
R756C	M5	M, D, C	c.2266C>T	ASD	Takata et al., 2018
R756C	M5	M, D, C	c.2266C>T	CRA	Schirinzi et al., 2018b
R756H**	M5	M, D, C	c.2267G>A	RDP (infantile)	Brashear et al., 2012b
R756H**	M5	M, D, C	c.2267G>A	RECA	Sabouraud et al., 2019; Yano et al., 2017
R756L	M5	M, D, C	c.2267G>T	RECA	Yano et al., 2017
I758S	M5	M, D, C	c.2273T>G	RDP	de Carvalho Aguiar et al., 2004
K764del	M5	M, D, C	c.2290_2292delAAG	PMG	Vetro et al., 2021
P775R	M5	M, D, C	c.2324C>G/	PMG	Vetro et al., 2021
F780L	M5	M, D, C	c.2338T>C	RDP	de Carvalho Aguiar et al., 2004
D801N**	M6	M, D, C	c.2401G>A	PMG	Vetro et al., 2021
D801Y**	M6	M, D, C	c.2401G>T	RDP	de Carvalho Aguiar et al., 2004
A813V	M6	M, D, C	c.2438T>C	COS	Chaumette et al., 2020
E818K	L6–7	M, D, C	c.2452G>A	CAPOS	Demos et al., 2014; Duat Rodriguez et al., 2017; Stavropoulos et al., 2016;

Amino acid change	NKA α_3 domain	Residue conservation	CDS change	Primary diagnosis (other than AHC)	References
					Stenshorne et al., 2019
E818K	L6–7	M, D, C	c.2452G>A	CRA	Schirinzi et al., 2018b
Q851R	M7	M, D, C	c.2552A>G	PMG	Smith et al., 2021
G854_F856del	M7		c.2560_2568del	PMG	Miyatake et al., 2021
F857del	M7	M, D, C	c.2570_2572del	PMG	Miyatake et al., 2021; Vetro et al., 2021
G867D	L7–8	M, D, C	c.2600G>A	AHC/RDP intermediate	Rosewich et al., 2014a
D887Y	L7–8	M, D	c.2659G>T	PMG (familial)	Vetro et al., 2021
L888P	L7–8	M, D	c.2663T>C	PMG with AHC	Panagiotakaki et al., 2015; Gurrieri et al., 2016; Vetro et al., 2021
G893W	L7–8	M, D, C	c.2677G>T	PMG	Vetro et al., 2021
Q895P	L7–8	M	c.2684A>C	PMG	Miyatake et al., 2021
R901M	L7–8	M, D, C	c.2702G>T	PMG	Smith et al., 2021
D923N**	M8	M, D, C	c.2767G>A	RDP	Zanotti-Fregonara et al., 2008
D923N**	M8	M, D, C	c.2767G>A	RDP (infantile)	Anselm et al., 2009; Brashear et al., 2012b
L924P	M8	M, D, C	c.2771T>C	PMG	Smith et al., 2021

Amino acid change	NKA α_3 domain	Residue conservation	CDS change	Primary diagnosis (other than AHC)	References
L924P	M8	M, D, C	c.2771T>C	EIEE	Arystarkhova et al., 2019
E951K**	M9	M, D, C	c.2851G>A	AHC/RDP intermediate	Termsarasab et al., 2015
P972del	L9–10	M, D	c.2915_2917delCTC	PMG	Vetro et al., 2021
abolition splice donor site			c.2921+1G>A	PMG	Smith et al., 2021
D992del	M10	M, D, C	c.2976_2978del	PMG	Miyatake et al., 2021
D992dup	M10	M, D, C	c.2976_2978dupCGA	PMG	Vetro et al., 2021
Y4_I994delinsFAHLHL	M10	M, C	c.2972_2982delins	PMG	Miyatake et al., 2021
I994_R995insHEI	M10	M, C	c.2975_2983dup	PMG	Miyatake et al., 2021
Y1013dup	C-term	M, D, C	c.3038_3040dup	RDP	Blanco-Arias et al., 2009

CDS, coding sequence; M, conserved in mouse *Atp1a3*; D, conserved in *D. melanogaster ATPα*; C, conserved in *C. elegans eat-6*; EE, epileptic encephalopathy; ID, intellectual disability. Nucleotide and residue numbering are based on *ATP1A3* variant 1/isoform 1 (NM_152296). *Reported as p.S148del and erroneously as c.443_445del-GAG with NKA α_3 isoform 2 numbering in Wilcox et al. (2015). **Mutation also identified in AHC (Boelman et al., 2014; Heinzen et al., 2012; Hoei-Hansen et al., 2014; Panagiotakaki et al., 2015; Rosewich et al., 2014b; Viollet et al., 2015; Yang et al., 2014).

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Table S2. *ATP1A3* mutations found in AHC patients

Amino acid change	NKA α_3 domain	Residue conservation	CDS change	No. of AHC cases[†]	% of AHC cases
S137F	M2	M, D	c.410C>T	3	0.61
S137Y	M2	M, D	c.410C>A	6	1.22
Q140L	M2	M, D, C	c.419A>T	2	0.41
A264_A289delinsVLG*	A	M, D, C	c.791_866delinsTTCTGGG	1	0.20
I274N	M3	M, D, C	c.821T>A	7	1.42
V322D	M4	M, D, C	965T>A	1	0.20
E324D**	M4	M, D, C	c.972G>C	1	0.20
E324Q	M4	M, D, C	c.970G>C	1	0.20
L326R	M4	M, D, C	c.977T>G	2	0.41
abolition splice donor site			c.993+1_993+2del	1	0.20
C333F	M4	M, D, C	c.998G>T	4	0.81
T335P	M4	M, D, C	c.1003A>C	1	0.20
G358C	P	M, D, C	c.1072G>T	1	0.20
G358S	P	M, D, C	c.1072G>A	1	0.20
T370N	P	M, D, C	c.1109C>A	1	0.20
L371P	P	M, D, C	c.1112T>C	1	0.20
C596R	P	M, D, C	c.1786T>C	2	0.41
G706R	P	M, D, C	c.2116G>A	1	0.20
L715P	P	M, D, C	c.2144T>C	1	0.20
G755A	M5	M, D, C	c. 2264G>C	1	0.20
G755C	M5	M, D, C	c.2263G>T	4	0.81
G755S	M5	M, D, C	c.2263G>A	12	2.43
G755V	M5	M, D, C	c.2264G>T	1	0.20
R756H	M5	M, D, C	c.2267G>A	3	0.61
L757P	M5	M, D, C	c.2270T>C	1	0.20
N761H	M5	M, D, C	c.2281A>C	1	0.20
Y768C	M5	M, D, C	c.2303A>G	1	0.20
Y768H	M5	M, D, C	c.2302T>C	1	0.20
T769P	M5	M, D, C	c.2305A>C	1	0.20
L770R	M5	M, D, C	c.2309T>G	1	0.20
T771I	M5	M, D, C	c.2312C>T	1	0.20
T771N	M5	M, D, C	c.2312C>A	2	0.41
S772R	M5	M, D, C	c.2314A>C	2	0.41
S772R	M5	M, D, C	c.2316C>A	2	0.41
S772R	M5	M, D, C	c.2316C>G	2	0.41
N773I	M5	M, D, C	c.2318A>T	1	0.20
N773S	M5	M, D, C	c.2318A>G	3	0.61
N773T	M5	M, D, C	c.2318A>C	1	0.20
D801E	M6	M, D, C	c.2403T>A	4	0.81
D801N	**M6**	**M, D, C**	**c.2401G>A**	**194**	**39.35**
D801V	M6	M, D, C	c.2402A>T	1	0.20
D801Y	M6	M, D, C	c.2401G>T	1	0.20
L802P	M6	M, D, C	c.2405T>C	1	0.20
T804I	M6	M, D, C	c.2411C>T	5	1.01

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Amino acid change	NKA α_3 domain	Residue conservation	CDS change	No. of AHC cases[†]	% of AHC cases
D805E	M6	M, D, C	c.2415C>G	2	0.41
D805H	M6	M, D, C	c.2413G>C	1	0.20
D805N	M6	M, D, C	c.2413G>A	1	0.20
M806K	M6	M, D, C	c.2417T>A	1	0.20
M806R	M6	M, D, C	c.2417T>G	2	0.41
P808L	M6	M, D, C	c.2423C>T	2	0.41
I810F	M6	M, D, C	c.2428A>T	2	0.41
I810N	M6	M, D, C	c.2429T>A	2	0.41
I810S	M6	M, D, C	c.2429T>G	1	0.20
S811P	M6	M, D, C	c.2431T>C	9	1.83
E815K	**L6–7**	**M, D, C**	**c.2443G>A**	**107**	**21.70**
L839P	M7	M, D, C	c.2516T>C	3	0.61
abolition splice donor site			c.2542+1:G>A	4	0.81
abolition splice donor site			c.2542+2T>C	2	0.41
R901T	L7–8	M, D, C	c.2702G>C	1	0.20
V919del	M8	M, D, C	c.2755_2757delGTC	3	0.61
V919del	M8	M, D, C	c.2751_2753delTGT	2	0.41
D923N	M8	M, D, C	c.2767G>A	3	0.61
D923Y	M8	M, D, C	c.2767G>T	2	0.41
C927F	M8	M, D	c.2780G>T	3	0.61
C927W	M8	M, D	c.2781C>G	1	0.20
C927Y	M8	M, D	c.2780G>A	3	0.61
G947R	**M9**	**M, D, C**	**c.2839G>A** **c.2839G>C**	**44**	**8.92**
E951K	M9	M, D, C	c.2851G>A	2	0.41
A955D	M9	M, D, C	c.2864C>A	2	0.41
D992Y	M10	M, D, C	c.2974G>T	3	0.61
				n=493	100%

CDS, coding sequence; M, transmembrane domain; P, phosphorylation domain; L, extracellular loop; M, conserved in mouse *Atp1a3*; D, conserved in *D. melanogaster ATPα*; C, conserved in *C. elegans eat-6*. Nucleotide and residue numbering are based on *ATP1A3* variant 1/isoform 1 (NM_152296). The three most common mutations (D801N, E815K and G974R) are shown in bold text. *p.A264_A289delinsVLG is an in-frame indel. **G324D was erroneously listed as Q324D by Viollet et al. (2015). ***Reported as c.2542-1:G>A in Heinzen et al. (2012). [†]Cases collated from cohorts of Heinzen et al. (2012), Rosewich et al. (2012), Ishii et al. (2013), Hoei-Hansen et al. (2014), Rosewich et al. (2014b), Sasaki et al. (2014), Yang et al. (2014), Panagiotakaki et al. (2015), Viollet et al. (2015).

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