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Case Report

KCNMA1 mutation in children with paroxysmal dyskinesia and epilepsy: Case report and literature review

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Abstract. Patients with *KCNMA1* gene mutation present with paroxysmal dyskinesia and/or epilepsy. We describe a male with heterozygous mutation c.3158A>G, (p.N1053S) in *KCNMA1* gene, displaying paroxysmal dyskinesia and moderate mental retardation. We also review 20 reported cases with *KCNMA1* mutation. We summarize that there is clinical heterogeneity in these patients. The onset age of episodic events ranges from 20 days to 15 years old. 6/21 (29%) patients merely had epilepsy, 10/21(48%) patients had paroxysmal dyskinesia only, and 5/21 (24%) had both epilepsy and paroxysmal dyskinesia. Seizure types were various, including absence, generalized tonic–clonic seizures, and myoclonic seizures. Paroxysmal dyskinesia was nonkinesigenic, but can be induced by alcohol, fatigue or stress. Most patients had variable degrees of mental retardation. The clinical outlook for this condition is in general not good. Epilepsy or non-epileptic events were resistant in most patients. Most patients presented with mild to severe intellectual disability and developmental delay.

Keywords: Paroxysmal dyskinesia, Epilepsy, *KCNMA1*

1. Introduction

KCNMA1 gene encodes α-subunit of the large conductance calcium-sensitive potassium channel ($K_{ca1.1}$) [1]. $K_{ca1.1}$ has a wide distribution in central nervous system, especially in excitatory neurons of cortex and hippocampus. It plays important roles in regulating neuronal excitability [1–3]. In 2005, *KCNMA1* gene was first reported as a pathogenic gene in a large family with autosomal dominant paroxysmal nonkinesigenic dyskinesia and generalized epilepsy [4]. Since then, several *KCNMA1* gene mutations in twenty patients have been described [5, 6]. Here, to delineate the clinical characteristics of the disease caused by *KCNMA1* gene mutation further, one patient with a *de novo KCNMA1* gene mutation is described. Besides, the reports associated with diseases caused by *KCNMA1* gene mutations are summarized.

2. Case report

The 3.5-year-old boy is the first child of nonconsanguineous Chinese parents. Pregnancy was uneventful. He has a normal birth and an early development. Head circumference was 33 cm at birth. At 16 months old, he developed episodes of sudden weakness of lower limbs, occasionally accompanied

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by rolling his eyes, lasting one to ten seconds. It occurred 10–20 times per day, with higher frequency with fatigue or excitement. Symptoms were not trigged by starvation. Before coming to our hospital, he was treated with valproate (VPA) at 16 months old with no response. When oxcarbazepine (OXC) was added to his therapy, the frequency of episodic events increased. Consequently, OXC was stopped. At 3 years of age, lamotrigine (LTG) was added, but there was still no response. Then clonazepam (CLZ) was administrated, and the frequency of paroxysmal dyskinesia was reduced to 3–5 times per day, and the longest interval could be up to three weeks.

Development is moderately delayed. He could control his head at 3 months, sit independently at 6 months, walk alone at 2 years old and say single words at 3 years old. Head circumference was 48 cm at his age of 2 years and 11 months. There was no family history of epilepsy or dyskinesia with him.

Electroencephalogram (EEG) at age of 2 years and 11 months showed generalized spike wave complexes. Episodic events presented during the EEG test; there were no epileptic discharges simultaneously. MRI at age of 16 months revealed no anomalies. Lumbar puncture was performed so as to exclude GLUT1-deficiency syndrome. Routine CSF test was unremarkable. Glucose level of CSF (2.66 mmol/L, ref 2.5∼4.5 mmol/L) and serum (6.28 mmol/L, ref 3.9∼6.9 mmol/L) were normal.

A gene panel consisting of 380 genes (Additional files 1) related with epilepsy and/orparoxysmal dyskinesia was performed on the proband. In total, 34 variants (Additional file 2) were discovered, of which 32 variants were reported polymorphisms. Pathogenicity of one heterozygous variant in *ACY1* gene was ruled out, as it is inherited as autosomal recessive pattern. Consequently, the mutation (c.3158A>G, p.N1053S) in *KCNMA1* gene deserved most attention. PCR-Sanger sequencing was used to confirm the mutation and parental origin, which revealed *de novo* occurrence (Fig. 1). It was a known pathogenic mutation, which had been reported previously in a patient with paroxysmal dyskinesia and developmental delay [6]. The clinical information of patients with *KCNMA1* mutation is summarized in Table 1.

3. Discussion

KCNMA1 gene, which is located at 10q22.3, encodes the alpha-subunit of the $K_{Ca1.1}$, consisting of seven transmembrane domains (S0–S6) at the N terminus, and an extensive C-terminal cytosolic domain which confers Ca^{2+} sensitivity to the channel. There are two putative high affinity Ca^{2+} binding sites, RCK domain and Ca^{2+} bowl, respectively [7, 8]. $K_{ca1.1}$ has a wide distribution in central nervous system, and prominent expression is observed in excitatory neurons of cortex and hippocampus. It plays vital roles in driving action potential repolarization, mediating fast phase of AHP (after hyperpolarization potential), and regulating neurotransmitter release and dendritic excitability [1–3].

Since 2005, *KCNMA1* gene has been associated with early onset epilepsy, paroxysmal dyskinesia and developmental delay [4]. To date, three publications with 21 patients (13 males and 8 females), have been found with *KCNMA1* gene mutations, including two pedigrees (16 and 2 affected members, respectively) and three sporadic patients [4–6]. The age of onset ranged from 20 days after birth to 15 years old. Among the 18 patients with detailed clinical description, 33% (6/18) of patients had the onset of episodes within one year after birth, 55% (10/18) patients had symptoms between 2∼7 years old, and 17% (2/18) after age of 7 years.

The pathology associated with *KCNMA1* mutations can manifest in patients as paroxysmal dyskinesia or epilepsy only, or both [4–6]. 10/21 (48%) had paroxysmal dyskinesia only, 6/21 (29%) had epilepsy only, 5/21 (24%) had both epilepsy and paroxysmal dyskinesia, including one patient who had paroxysmal dyskinesia within 6 months after birth and seizures attacks at age of 3 years, while the other four patients had epilepsy and paroxysmal dyskinesia simultaneously. Among 11 patients with epilepsy, 4 had absence seizure, 2 had absence seizures accompanied by GTCS (generalized

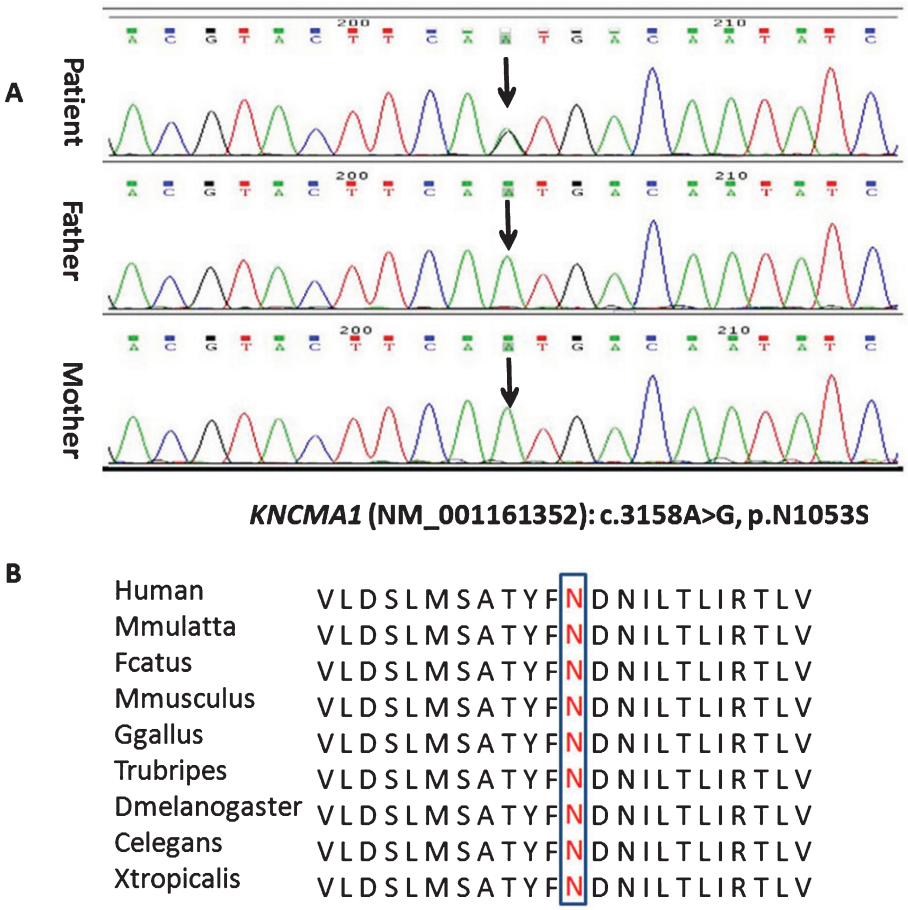

Fig. 1. Sequence chromatogram showing one base pair substitution in *KCNMA1* gene (A) and conservation of the altered amino acid shown in the ClustalW alignments (B).

tonic clonic seizures) occasionally, 2 had myoclonic seizures or myoclonic seizures evolving to tonicand GTCS, and 3 had epilepsy with no description about seizure types. Paroxysmal dyskinesia was nonkinesigenic, but in some patients it can be induced by alcohol, fatigue or stress. Patients presented different degrees of mental retardation. EEG abnormity was observed in patients with or without epilepsy, including generalized spike wave complexes, Lennox–Gastaut pattern, and mild background slowing.

There are not so many related reports on the treatments of patients with *KCNMA1* mutations. In Zhang's report, one patient with paroxysmal dyskinesia only was controlled by CLZ [6]. In Tabarki's report, the seizure-free state was achieved in two patients with epilepsy only, by VPA and VPA combined with levetiracetam (LEV), respectively [5]. Three patients with both paroxysmal dyskinesia and epilepsy were partially responsive to antiepileptic drugs (Table 1) [4]. For our patient, OXC aggravated his paroxysmal events, while VPA and LTG had poor curative effective. He was partially responsive to CLZ, and the frequency of episodic events was reduced after CLZ was added. *In vitro* functional analysis revealed that gain of function of the BK channel leads to greater macroscopic potassium conductance, which results in more rapid repolarization of action potentials. Enhancing this repolarization leads to faster removal of inactivation of sodium channels, hence the neurons fire more frequently [5]. Consequently, considering previous reports and our study, sodium-channel blockers might be effective. Moreover, activation of inhibitory $GABA_B$ receptors by CLZ is effective as well.

Table 1
Clinical features of patients with *KCNMA1* gene mutation

Patients	Du et al. [4]	Zhang et al. [6]		Tabarki et al. [5]		Our study
Sex	10 M, 6 F	M	M	F	F	M
Age of onset	6 mo- 15 y	20 d	7 mo	8 mo	8 mo	16 mo
E and PD	4 with E alone, 5 with E+PD, 7 with PD alone	PD	PD	E	E	PD
Seizure type	4 with Ab, 2 with Ab and GTCS	No	No	Myoclonic seizures evolving to tonicand GTCS	Myoclonic seizures evolving to tonicand GTCS	No
PD	Involuntary dystonic or choreiform movements of the mouth, tongue and extremities	1) Sudden onset of asymmetric limbdystonic posture, sometimes with nystagmus and strabismus, lasted several minutes to half an hour, and occurring once a week initially to 2–7 times per day after 1 year.2) Sudden decrease in voluntary movement of limbs, with hypotonia and occasional esotropia and yawning, lasting as long as 1 hour, and occurringonce to twice a day.	Paroxysmal dystonic postures, lasting several seconds to minutes, and occurring 3–5 times per day to once a week.	No	No	Sudden weakness of lower limbs, occasionally accompanied by rolling his eyes, and occurring 10–20 times per day

Triggers	Alcohol, fatigue and stress	No	No	No	No	Fatigue or agitation
Development	NA	Severe delay	Mild delay	Severe delay	Severe delay	Moderate delay
EEG	Generalized spike wave complexes (the proband)	Normal	Normal	Lennox–Gastaut pattern	Mild background-slowing	Generalized spike wave complexes
MRI	NA	Normal	Normal	Cerebellar atrophy	Cerebellar atrophy	Normal
Treatment	Seizure frequency was reduced from daily to monthly with VPA and LTG in the proband; seizures and PD partially responsive to CLZ in other two patients	No response to OXC, VPA, LEV	Controlled by CLZ	Controlled by VPA	Controlled by VPA, LEV	Aggravated by OXC; VPA, LTG were not effective; frequency of episodic events was decreased after CLZ was added.
Mutation (NM_1161352)	c.1301A>G (heterozygous)	c.2650G>A (heterozygous)	c.3158A>G (heterozygous)	c.2026dupT (homozygous)	c.2026dupT (homozygous)	c. 3158A>G (heterozygous)
AA changed	D434G	E884K	N1053S	Y676Lfs*7	Y676Lfs*7	N1053S

M, male; F, female; mo, months; y, year; E, epilepsy; PD, paroxysmal dyskinesia; Ab, absence; GTCS, generalized tonic clonic seizures; NA, not available; OXC, oxcarbazepine; VPA, valproate; LEV, levetiracetam; CLZ, clonazepam; LTG, lamotrigine.

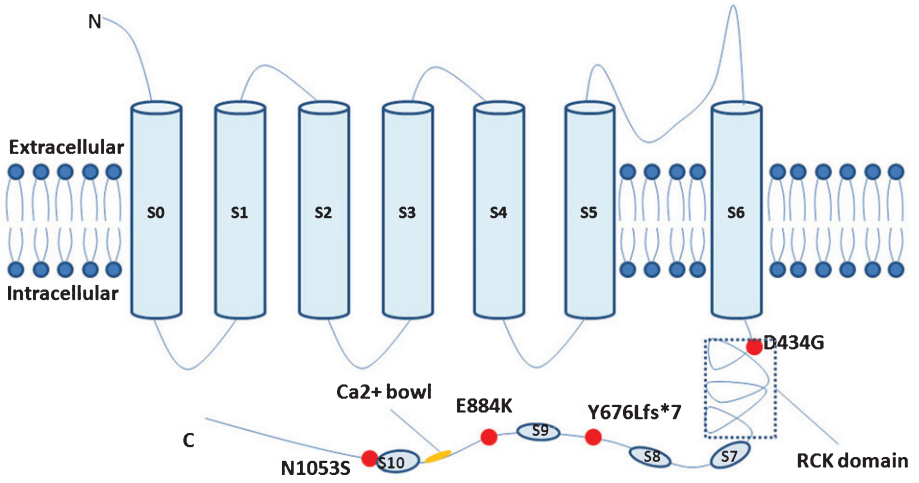

Fig. 2. Simplified schematic of the large-conductance Ca^{2+}-activated K+ channel and *KCNMA1*mutations ever identified.

The missense mutation (c.3158A>G, p.N1053S) identified in this study was previously mentioned by Zhang et al. [6]. Both patients merely presented with paroxysmal dyskinesia and developmental delay, while without epilepsy. But phenotype of patient in this study was a bit more severe (Table 1), which indicated the clinical heterogeneity of disorders caused by *KCNMA1* mutations.

Including this study, four mutations of *KCNMA1* were identified to be associated with epilepsy and/or paroxysmal dyskinesia. The majority of patients were heterozygous and the mutations were inherited as autosomal dominant. But patients with homozygous mutation in *KCNMA1* gene were also reported, while the mutation was inherited from their heterozygous parents. Those parents were second cousins and had normal phenotype (Table 1) [5, 6]. All the mutations were located in the C-terminal of $K_{ca1.1}$ (Fig. 2). D434G was located in the RCK domain, and the functional analysis revealed that the D434G speeds up channel activation and enhances Ca^{2+} sensitivity, suggesting a *gain-of-function* of $K_{ca1.1}$ channel [4]. The functional impact of other mutations on BK channel activity remains unknown. The mutated N1053S identified in this study was located nearby S10, which might change the spatial conformation of the channel [6]. On the other hand, previous reports also indicated loss-of-function of *KCNMA1* gene was pathogenic. Besides, Tabarki et al. described two siblings with homozygous truncated mutation in *KCNMA1* gene, which presented with epilepsy and severe psychomotor retardation [5]. *Kcnma1* homozygous knockout mice displayed severe motor dysfunction and cerebellar ataxia [9]. Taking all the above studies together, we could conclude that both *gain-of-function* and *loss-of-function* of $K_{ca1.1}$ were responsible for epilepsy and movement disorders.

Our report summarized the mutation spectrum of *KCNMA1*and phenotypic profile of *KCNMA1* gene related disorders. More mutations reports and function researches in the future might help to figure out the structure-function relationships of $K_{ca1.1}$ and the mechanisms of its pathogenesis in neurological disorders.

Acknowledgments

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Additional file 1. 380 genes in the panel related with epilepsy accompanied with/without paroxysmal dyskinesia

ABCC8	CEP152	EIF2B1	HP	MTHFR	PPT1	SLC9A6
ACADSB	CHI3L1	EIF2B2	HRAS	NDN	PRICKLE1	SLC9A9
ACTB	CHRNA2	EIF2B3	HSD17B10	NDUFA1	PRICKLE2	SNIP1
ACY1	CHRNA3	EIF2B4	HSD17B4	NDUFA11	PROC	SNRPN
ADK	CHRNA4	EIF2B5	HTR2A	NDUFAF1	PRODH	SOBP
ADSL	CHRNA5	ELP4	HTT	NDUFAF2	PRRT2	SPAST
AFG3L2	CHRNA7	EMX2	ICCA	NDUFAF3	PTPN22	SPTAN1
AKT1	CHRNB2	EPB41L1	IDH2	NDUFAF4	PUS1	SPTLC2
ALDH7A1	CLCN2	EPM2A	IDS	NDUFB3	QDPR	SRPX2
ALG1	CLN3	ERBB4	IER3IP1	NDUFS1	RAB39B	STRADA
ALG11	CLN5	ERLIN2	IFNG	NDUFS2	RANBP2	STS
ALG3	CLN6	EVC	IL6	NDUFS4	RELN	STXBP1
AMACR	CLN8	FADD	INS	NDUFS6	ROGDI	SUOX
AMT	CNTNAP2	FAM123B	KCNA1	NDUFV1	RPIA	SYN1
APOL2	COG7	FASTKD2	KCNJ10	NDUFV2	RTN4R	SYN2
APOL4	COH1	FCGR2B	KCNJ11	NEU1	RYR1	SYNGAP1
APP	COMT	FKTN	KCNMA1	NF1	SCARB2	SYP
ARG1	COX6B1	FLNA	KCNQ1	NHLRC1	SCN1A	TBC1D24
ARHGAP31	CPA6	FOLR1	KCNQ2	NHS	SCN1B	TBP
ARHGEF9	CPS1	FOXG1	KCNQ3	NOTCH3	SCN2A	TCF4
ARSA	CSTB	FOXRED1	KCTD7	NR3C1	SCN8A	TMEM165
ARSE	CTSA	GABRA1	KDM5C	NRXN1	SCN9A	TPP1
ARX	CTSD	GABRB3	KIF11	NTNG1	SCZD1	TREM2
ASAH1	CYB5R3	GABRD	KIF1A	NUBPL	SCZD11	TREX1
ATIC	D2HGDH	GABRG2	KRAS	OFD1	SCZD12	TSC1
ATN1	DAO	GAMT	L2HGDH	OPHN1	SCZD2	TSC2
ATP1A2	DAOA	GBA	LBR	PAFAH1B1	SCZD3	TSEN2
ATP2A2	DBH	GCK	LGI1	PAH	SCZD5	TSEN34
ATP6AP2	DCX	GCSH	LIAS	PAK3	SCZD6	TSEN54
ATRX	DHFR	GLB1	LMX1B	PANK2	SCZD7	TUBGCP6
ATXN10	DISC1	GLDC	MAGI1	PCDH19	SCZD8	TYROBP
BANK1	DISC2	GLRA1	MAGI2	PDHA1	SERPINI1	UBE3A
BOLA3	DMPK	GOSR2	MAN1B1	PGK1	SETBP1	XK
BRP44L	DNAJC5	GPHN	MANBA	PHF6	SGCE	ZDHHC15
C10orf2	DNASE1	GPR48	MAPK10	PHGDH	SHH	ZEB2
C12orf62	DOCK6	GPR98	MCCC2	PIGL	SIAT9	ZFYVE26
C20orf7	DPYD	GRIN1	MCPH1	PIGV	SIX3	ZNF41
C2orf64	DRD2	GRIN2A	MECP2	PLA2G6	SLC17A5	STK11
C4A	DRD3	GSS	MEF2C	PLCB1	SLC19A3	HCN2
CACNA1H	DTNBP1	GYS1	MFSD8	PLP1	SLC20A2	SCN3A
CACNB4	DXS423E	HAX1	MLC1	PNKP	SLC25A15	GABRA6
CACNG2	EBP	HFE	MOCS1	PNPO	SLC25A22	CAPS
CASR	ECM1	HLA-DQA1	MOCS2	POLG	SLC26A4	SYNE1
CCM1	EFHC1	HLA-DQB1	MOCS3	POMGNT1	SLC2A1	VLDLR
CDKL5	EHMT1	HNF1B	MR1	PPOX	SLC46A1	VPS13
ABCB7	ATP2B3	AXK	FMR1	NOP56	POLG1	TBP
AFG3L2	ATPX	BEAN	FXN	NPHP1	PPP2R2B	TDP1
AHI1	ATTP	C10orf2	ITPR1	PANR2	PRKCG	TGM6
APTX	ATXN1	CA8	JPH3	PDYN	RPGRIP1L	TMEM216
ARL13B	ATXN10	CABC1	KCNA1	PEX1	SACS	TTBK2
ARX	ATXN2	CACNA1A	KCNC3	PEX2	SETX	TTBK2
ATCAY	ATXN3	CACNB4	KCNJ10	PEX26	SIL1	TTPA
ATM	ATXN7	CC2D2A	MPZ	PLEKHG4	SLC1A3	ADH3
ATN1	ATXN8OS	FGF14	MRE11A	PMP22	SPTBN2	ATP13A2
AAOPD	ADH1C					

Additional file 2. Variants identified by NGS panel

Gene	Transcript	Base change	AA change	Heterohomo	dbSNP	MAF	SIFT	PolyPhen-2
ACY1	NM_001198898.1	c.584-9C>T		Hetero			Uncertain Significance	
APOL2	NM_145637.2	c.733A>G	p.V245V	Homo	rs132760	0	Benign	
ATP1A2	NM_000702.3	c.1704C>T	p.F568F	Hetero	rs17846714	0.0278	Benign	
CASR	NM_000388.3	c.2244G>C	p.P758P	Homo	rs2036400	0.0272	Benign	
CNTNAP2	NM_014141.5	c.3716-6C>G		Hetero	rs77025884		Likely Benign	
CPS1	NM_001122633.2	c.13_14insTCT	p.I5_K6insF	Hetero	rs3835047	0.477	Benign	
CPS1	NM_001122633.2	c.204C>T	p.G68G	Hetero	rs529836556	0.0002	Uncertain Significance	
CPS1	NM_001122633.2	c.1048A>G	p.T344A	Hetero	rs1047883		Benign	Damaging
DNAJC5	NM_025219.2	c.144C>T	p.P48P	Hetero	rs113987077	0.0278	Benign	
DTNBP1	NM_001271667.1	c.268+7281C>A	Homo	rs6926401	0.0281	Benign		
HTT	NM_002111.7	c.7182A>C	p.L2394L	Homo	rs2857790	0.0152	Benign	
KCNA1	NM_000217.2	c.1296C>G	p.S432S	Hetero	rs76066681	0.025	Benign	
KCNQ1	NM_000218.2	c.54C>T	p.I145I	Hetero	rs1800170	0.009	Likely Benign	
KRAS	NM_004985.4	c.451-5617G>A	p.R161R	Homo	rs4362222	0.0024	Benign	
LGI1	NM_001308275.1	c.657T>C	p.F171F	Homo	rs1111820	0.0226	Benign	
MCPH1	NM_024596.3	c.1175A>G	p.D344G	Homo	rs2515569	0.0056	Benign	Tolerated
NDUFAF3	NM_199070.1	c.166+8G>A		Hetero	rs554862207	0.0002	Uncertain Significance	
NHS	NM_001291868.1	c.566-12_566-11insT	Homo	rs5901624		Benign		
NR3C1	NM_001018074.1	c.1764C>T	p.H491H	Hetero	rs6194	0.0198	Benign	
PDHA1	NM_001173456.1	c.958A>C	p.M251L	Homo	rs2229137	0.0495	Benign	Tolerated
PRICKLE2	NM_198859.3	c.816T>C	p.D272D	Homo	rs27673	0.0162	Benign	
PRRT2	NM_145239.2	c.751T>C	p.L251L	Homo	rs11150573	0.0082	Benign	
RANBP2	NM_006267.4	c.8253G>A	p.E2751E	Homo	rs826580	0.0128	Benign	
RELN	NM_173054.2	c.3060C>T	p.D1020D	Hetero	rs115886170	0.0022	Uncertain Significance	
RELN	NM_173054.2	c.1888A>C	p.S630R	Hetero	rs115734214	0.0172	Likely Benign	Damaging
SLC46A1	NM_080669.5	c.4417delA		Homo	rs5819844	0	Benign	
SPTAN1	NM_001195532.1	c.1330G>A	p.V444I	Hetero	rs77358650	0.0176	Likely Benign	Tolerated
SPTAN1	NM_001195532.1	c.5085A>G	p.L1690L	Homo	rs1415568	0.0152	Benign	
TCF4	NM_001243226.2	c.28G>C	p.P10P	Homo	rs611326	0.0032	Benign	
TUBGCP6	NM_020461.3	c.4861G>C	p.L1621L	Homo	rs4838864	0.0012	Benign	
TYROBP	NM_198125.2	c.130G>T	p.V44L	Hetero	rs77782321	0.0232	Benign	Activating
ZFYVE26	NM_015346.3	c.6405G>A	p.L2135L	Hetero	rs76327447	0.017	Benign	
ZFYVE26	NM_015346.3	c.453C>T	p.S151S	Hetero	rs75391113	0.016	Benign	
KCNMA1	NM_1161352	c.3158A>G	p.N1053S	Hetero			Pathogenic	Damaging