

Clinical heterogeneity and novel pathogenic variants of Chinese patients with neuroacanthocytosis

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Research

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Abstract

Background: Neuroacanthocytosis (NA) syndromes are a group of exceedingly rare diseases, including McLeod syndrome (MLS) and chorea-acanthocytosis (ChAc). The characteristic phenotypes comprise a variety of movement disorders, including chorea, dystonia, and parkinsonism. We aimed to investigate the clinical heterogeneity and novel pathogenic variants of Chinese patients with neuroacanthocytosis.

Results: Three novel *XK* variants (c.942G>A, c.970A>T, c.422_423del) were identified in three index MLS patients and three novel *VPS13A* variants (c.3817C>T, c.9219C>A, c.3467T>A) in two index ChAc patients. In addition, we summarized the genotypes and phenotypes of reported MLA patients and ChAc patients in the Chinese population.

Conclusion: Our study expands the genetic spectrum of *XK* and *VPS13A* and helps the clinical diagnosis of neuroacanthocytosis.

Introduction

Neuroacanthocytosis (NA) is a group of syndromes, including McLeod syndrome (MLS), chorea-acanthocytosis (ChAc), Huntington's disease-like 2 (HDL2), and pantothenate kinase-associated neurodegeneration (PKAN). The acanthocytosis is a frequent finding in MLS and ChAc, but only occurs in approximately 10% of HDL2 and PKAN patients [1, 2]. The "core" neuropathologic finding in NA syndromes is the degeneration affecting the basal ganglia, thus their clinical presentations can be remarkably similar [3]. The characteristic phenotypes comprise psychiatric and cognitive symptoms, and a variety of movement disorders including chorea, dystonia, and parkinsonism. The age of onset, inheritance pattern and ethnic background provide diagnostic clues in each condition, but clinical diagnosis remains challenging. Genetic diagnosis provides a definitive diagnosis and is important for genetic counseling.

In the two core NA syndromes, MLS is inherited in an X-linked way with pathogenic variants of *XK* gene, while ChAc is an autosomal recessive disorder caused by pathogenic variants in *VPS13A*. It is estimated that there are likely a few hundred of MLS patients and around one thousand ChAc patients in the world [3]. Although more than 50 NA patients have so far been reported in China [4-13], most of which were not confirmed by specific molecular tests [4]. The distribution of pathogenic variants within *XK* and *VPS13A* has not been conclusively determined in China.

Targeted next-generation sequencing (NGS) has been successfully utilized to diagnose neurological diseases which may be difficult to differentiate from clinical symptoms. In this study, we collected 14 unrelated Chinese patients who exhibited involuntary movements and had been ruled out the Huntington's disease (HD) by the *HTT* gene testing. We performed targeted NGS in these patients and 5 index patients were diagnosed with MLS or ChAc by Sanger sequencing verification. Three novel *XK* variants and three novel *VPS13A* variants were identified.

Methods

Subjects

Fourteen unrelated patients who presented suspected chorea with negative *HTT* genetic testing and their familial members were recruited between June 2015 and March 2019. The neurological examinations and clinical evaluations were performed by at least two senior neurologists. Routine blood tests and radiological examinations were performed. The study was approved by the Ethics Committee of Second Affiliated Hospital, Zhejiang University School of Medicine. Written informed consent was obtained from each participant.

Acanthocyte examination

Blood was collected into the tube containing ethylene-diamine-tetracetic acid (EDTA) and examined by scanning electron microscopy (SEM). Red cells were fixed in a 1% solution of glutaraldehyde and stored at 4°C until the time of examination. The red cells were absorbed onto tissue paper and gold-coated with an Emscope Sputter Coater. They were then examined in a Nova nano 450 electron microscope operating at 5 kV. The acanthocyte rate was counted as the method described previously[14].

Genetic analysis

Genomic DNA was extracted from peripheral EDTA-treated blood by Blood Genomic Extraction Kit (Qiagen, Hilden, Germany). A customized panel was designed to cover 54 genes for chorea and dystonia, including *VPS13A*, *XK*, *PRNP*, 10 genes of neurodegeneration with brain iron accumulation (NBIA), 4 genes of primary familial brain calcification (PFBC), and other 37 genes of hereditary dystonia (**Supplemental Table 1**). A detailed protocol of NGS was reported in our previous study [15]. Sanger sequencing was performed on an ABI 3500xl Dx Genetic Analyzer (Applied Biosystems, Foster City, USA) as our previous report to verify the filtered potential variants [16]. Co-segregation analysis was carried out in families with genetic variants. SIFT and PolyPhen-2 were used to predict the pathogenicity of the identified variants.

Results

Identification of novel *XK* and *VPS13A* variants

After targeted NGS and Sanger sequencing, three novel hemizygous variants within *XK* gene were found in three index patients (**Fig. 1A-C**). Among these three variants, two are nonsense (c.942G>A and c.970A>T) and one is frameshift (c.422_423del). They are all absent in 1000G, gnomAD and our NGS database containing 500 Chinese matched controls. According to American College of Medical Genetics and Genomics (ACMG) standards [17], c.942G>A is classified as pathogenic and the other two variants c.970A>T and c.422_423del are classified as likely pathogenic (**Table 1**).

In addition, three novel variants within *VPS13A* gene were detected in another two index patients, one of whom harbored a homozygous variant (c.3817C>T) and the other harbored compound heterozygous variants (c.3467T>A and c.9219C>A) (**Fig. 1D-E**). Among these variants, two are nonsense (c.3817C>T and c.9219C>A) and one is missense (c.3467T>A). The three variants are at extremely low frequency in gnomAD (≤ 2) and absent in 1000G and our NGS database. The missense variant c.3467T>A was predicted to be deleterious by SIFT and PolyPhen-2. According to ACMG standards, c.9219C>A is classified as pathogenic, while c.3817C>T and c.3467T>A are classified as likely pathogenic (**Table 1**).

Clinical features of five genetically diagnosed patients

The detailed clinical features of five NA patients are summarized in **Table 2**. Three MLS index patients were all males with no family history of NA (**Fig. 1A-C**). Two ChAc index patients were females, one of which was from consanguineous marriage (**Fig.1D**) and the other had a positive family history (**Fig.1E**). All five patients had mild to moderate elevated creatine kinase (CK). Four patients had generalized chorea-like symptoms, and the brain magnetic resonance imaging (MRI) of them revealed atrophy of either caudate or putamina (**Fig. 2A-D**). One MLS case (Case 2) showed gait disturbance, mild involuntary movements and markedly elevated CK, which made it confused with myopathy at first. Reflexes of five NA patients were all reduced. Two of them received electromyogram (EMG) and showed axonal neuropathy. Apart from one case undetected, the acanthocyte rate of peripheral blood in four patients was between 18-32%, which was easily recognized in electron microscopy (**Fig. 2E-F**). Only Case 2 received the Kell blood group phenotype in blood centre. The Kell antigen was absent in his erythrocytes, as well as the K, Kpa and Kpb antigens. The k antigen was weakly positive.

Case 1 (II-2 in Family 1, **Fig. 1A**) was a 47-year-old male with involuntary tongue and limb movements for over 20 years. At age 43, he noted progressive gait disturbance and tendency to fall. He went to the hospital and was diagnosed with "chorea". Then he was treated with risperidone and discontinued after several months. At age 47, he had a general tonic-clonic seizure and was treated with valproate. Neurological examinations showed dysarthria and 4/5 weakness of left proximal lower limb.

Case 2 (II-4 in in Family 2, **Fig. 1B**) was a 41-year-old male with gait disturbance for 4 years. At age 37, he noted progressive gait disturbance and tendency to fall. His serum CK was markedly elevated, which could be over 4000U. Therefore, he was previously diagnosed with "metabolic myopathy". Neurological examinations showed mild postural instability and slight wadding gait. When he was sitting, mild involuntary movements of his toes and trunk were noted, just like akathisia. The muscle force, muscle tone, finger-to-nose test and heel-to-knee test were normal, which suggested that his gait instability was due to mild involuntary movements in trunk and lower limbs.

Case 3 (II-1 in Family 3, **Fig. 1C**) was a 57-year-old male with involuntary limb movements for 4 years. At age 53, he noted episodic involuntary movements of lower limbs. The frequency and region developed progressively. At age 56, the involuntary movements affected the upper limbs and neck, and gait disturbance was significant with frequent falls. Neurological examinations showed general choreiform movements and gait unsteadiness.

Case 4 (II-2 in Family 4, **Fig. 1D**) was a 35-year-old female with involuntary limb movements for over 10 years. Her parents had a consanguineous marriage. At early of 20s, she presented mild involuntary movements which did not affect daily life. The symptoms worsen gradually and she developed dysarthria, drooling, orofacial dyskinesias with tongue and lip biting in the following years. At age 35, she had two generalized tonic-clonic seizures and was treated with levetiracetam. Neurological examinations showed general choreiform movements with dysarthria and orofacial dyskinesias.

Case 5 (II-2 in Family 5, **Fig. 1E**) was a 61-year-old female with involuntary limb movements for over 10 years. At age of about 50, she began to present with progressive general involuntary movements and then gradually developed dysarthria, orofacial dyskinesias and shoulder shrugging. Her neurological examinations showed general choreiform movements with dysarthria and orofacial dyskinesias. She had a 50-year-old brother who presented with similar symptoms at age of 40s. The brother could not walk and stayed in bed in a rehabilitation hospital for many years. He did not undergo the genetic testing.

The prognosis of most cases was poor. Case 3 died from falling in the paddyfield one year after diagnosis. Case 1, Case 4 and Case 5 progressed to bed after 2-3 years after diagnosis, and Case 5 finally died from pneumonia. Case 2 had mildest symptoms and was able to take care of himself 4 years after diagnosis.

Discussion

Neuroacanthocytosis syndromes are all exceedingly rare with an estimate prevalence of less than 1 to 5 per 1,000,000 for each disorder worldwide [3]. Currently, 43 pathogenic variants of *XK* gene have been included in the Human Gene Mutation Database (HGMD, v2019.4), including 13 missense/ nonsense variants, 6 splicing variants, 12 small deletion/ insertion/ indels and 12 gross deletions. In the Chinese population, six pathogenic variants of *XK* gene have been reported (**Table 3**), two of which were included in HGMD. Combined with three novel variants in the current study, there are 9 pathogenic *XK* variants including five nonsense variants, two small deletions and two gross deletions. ChAc are relatively more common than MLS. There are 126 pathogenic variants of *VPS13A* in HGMD, including 41 missense/ nonsense variants, 25 splicing variants, 48 small deletion/ insertion/ indels and 12 gross deletion/ insertion/ complex rearrangements. Combined with three novel variants in our study, there are 10 pathogenic *VPS13A* variants in the Chinese population (**Table 1** and **Table 3**), including 7 missense/ nonsense variants, one splicing variant and two small insertion/ deletions. These 19 pathogenic variants were all from single families and we did not find any hotspot variant in the Chinese population.

MLS and ChAc share a number of similar features [18] and there is a striking phenotypic overlap in these two disorders, including age at onset, chorea, dysarthria, orofacial dyskinesia, seizures, psychiatric symptoms and brain MRI, but some clues may help to differentiate them. First, in genetics, MLS is inherited in an X-link way and ChAc in an autosomal recessive manner. Therefore, the family history and the gender can give important clues to help diagnosis. Besides, the large deletion in *XK* gene often involves multiple adjacent genes such as *DMD*, *CYBB*, *RPGR* and *OTC*, and leads to concomitant

disorders such as dystrophinopathy, chronic granulomatous disease, retinitis pigmentosa and ornithine transcarbamylase deficiency [19]. Although our patients did not have large deletions, two Chinese patients with chronic granulomatous had been reported that their *XK* genes were involved in multigenic deletions [7]. It is important to screen MLS phenotype in males with chronic granulomatous disease for complication monitoring and management. In clinical manifestations, the orolingual dystonia is more frequently presented in ChAc. In our study and previous reports in the Chinese population, all ChAc patients had orolingual dystonia, but less than half MLS had the condition. In addition, the severity often disproportionate to other involuntary movements in ChAc. For example, self-mutilating tongue and lip biting, which present in 40% of Caucasians [20] and 85% (6/7) of reported Chinese ChAc patients, are very rare in MLS patients [18].

In the other hand, MLS patients seemed to have higher CK levels than ChAc in the Chinese population. About 78% of MLS patients (7/9) had CK above 1000 U/L, whereas only one of six ChAc patient reached this level. Moreover, MLS patients can have muscle complaints with mild involuntary movements, which often lead to a confusion with myopathy [5, 6]. However, the EMG usually show axonal neuropathy, so sometimes these patients can be misdiagnosed with Kennedy's disease, which is also an X-link neurological disease manifests with proximal weakness, hyperCKemia, and axonal neuropathy-mimic EMG [21]. Therefore, it is important to pay attention to mild involuntary movement and differentiate MLS in males with both hyperCKemia and a neuropathic EMG. The acanthocyte rate in peripheral blood can usually fall 5-50% in ChAc and 8-30% in MLS [3], which is consistent with our results. However, the presence of acanthocytes may vary over time and can be absent in some cases [22-25], thus cannot be used to distinguish different NA syndromes.

Conclusion

In conclusion, we reported five Chinese NA families and identified three novel *XK* variants (c.942G > A, c.970A > T, c.422_423del) in 3 index MLS patients and three novel *VPS13A* variants (c.3817C > T, c.9219C > A, c.3467T > A) in two index ChAc patients. In addition, we summarized the genotypes and phenotypes of reported MLA patients and ChAc patients in the Chinese population. Our study expands the genetic spectrum of *XK* and *VPS13A* and helps the clinical diagnosis of neuroacanthocytosis.

Declarations

Ethics approval and consent to participate

The study protocol was in accordance with the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Second Affiliated Hospital, Zhejiang University School of Medicine. Written informed consents were obtained from all the participants.

Consent for publication

Written informed consents for publication were obtained from all the participants.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Hao Yu and Liang Zhang: data acquisition, analysis and interpretation, and manuscript preparation; Xiao-Yan Li: data acquisition, analysis and interpretation; Zhi-Ying Wu: study design and conception, data acquisition, analysis and interpretation, critical revision of the manuscript.

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Tables

Table 1

The identified variants of five patients with neuroacanthocytosis syndromes

Gene	Case no.	Refseq NM	Nucleotide change	Amino acid change	ExonVariant type	1000G (All)	gnomAD (All)	SIFT	Polyphen2	ACMG classification (pathogenic criterion)
XK	1	NM_021083.3c.422_423del		p.V141Dfs*57	2 Hemi	0	0	NA	NA	Likely Pathogenic (I) (PVS1 + PM2)
XK	2	NM_021083.3c.942G > A		p.W314*	3 Hemi	0	0	NA	NA	Pathogenic (Ia) (PVS1 + PS1 + PM2)
XK	3	NM_021083.3c.970A > T		p.R324*	3 Hemi	0	2	NA	NA	Likely Pathogenic (I) (PVS1 + PM2)
VPS1344		NM_033305.2c.3817C > T		p.R1273*	34 Hom	0	1	NA	NA	Likely Pathogenic (I) (PVS1 + PM2)
VPS1345		NM_033305.2c.3467T > A		p.I1156N	32 Het	0	0	D	Prob D	Likely Pathogenic (V) (PM2 + PM3 + PP3 + PP4)
VPS1345		NM_033305.2c.9219C > A		p.Y3073*	69 Het	0	0	NA	NA	Pathogenic (Ia) (PVS1 + PS1 + PM2 + PP4)

Hemi: hemizygous; Hom: homozygous; Het: heterozygous; 1000G: 1000 Genomes Project; gnomAD: Genome Aggregation Database; PolyPhen 2/SIFT: Software prediction programs used for sequence variant effect explanation; D: damaging; Prob D, probably damaging; NA: not available; ACMG: American College of Medical Genetics and Genomics. Each pathogenic criterion is weighted as very strong (PVS1), strong (PS1-4), moderate (PM1-6), or supporting (PP1-5).

Table 2 Clinical features of five index patients with neuroacanthocytosis syndromes

Variable	Case 1	Case 2	Case 3	Case 4	Case 5
Diagnosis	MLS	MLS	MLS	ChAc	ChAc
Gender/Age	Male/47	Male/41	Male/57	Female/35	Female/61
Age of onset	26	37	53	Early of 20s	50
Family history	-	-	-	-	+
Primary symptoms	Involuntary tongue and limb movements	Gait disturbance	Involuntary limb movements	Involuntary tongue and limb movements	Involuntary tongue and limb movements
Chorea	Generalized	Mild	Generalized	Generalized	Generalized
Dysarthria	+	-	+	+	+
Orofacial dyskinesias	+	-	+	+	+
Tongue and lip biting	-	-	-	+	-
Seizure	Generalized	-	-	Generalized	-
Psychiatric symptoms	Depression	Anxiety	Depression	Depression	Anxiety
EMG	Axonal neuropathy	Axonal neuropathy	NA	NA	NA
CK (U/L)	753	2244-4469	345	332	252
ALT/AST (U/L)	24/31	90/85	119/29	14/18	28/28
Acanthocyte ratio	18%	22%	NA	32%	30%
Kell antigen	NA	Absent	NA	NA	NA
MRI	atrophy of the heads of the caudate nuclei	NA	atrophy of putamina and caudate	atrophy of putamina and caudate	atrophy of putamina and caudate

EMG: electromyography; CK: creatine kinase; ALT: alanine transaminase; AST: aspartate transaminase; MRI: magnetic resonance imaging; MLS: McLeod syndrome; -: negative; +: positive; NA: not available; ChAc: chore-acanthocytosis.

Table 3 Reported Chinese patients with neuroacanthocytosis

Index no.	Gene	Nucleotide change (Amino acid change)	Exon	Variant type	HGMD	AAO	Main clinical symptoms	CK (U/L)	Language
1	<i>XK</i>	c.856_860del (p.L286Yfs*16)	3	Hemi	DM	40+Y	Wasting of limb muscles, chorea of feet	2148	English [5]
2	<i>XK</i>	c.154C>T (p.Q52*)	1	Hemi	DM	62Y	Myalgia, muscle fatigue, chorea of toes	602-3328	English [6]
3	<i>XK</i>	Multigenic deletion: entire gene + <i>CYBB</i> + ex.1-44 <i>DMD</i>	1-3	Hemi	NA	4Y1M	Chronic granulomatous disease	7149	Chinese [7]
4	<i>XK</i>	Multigenic deletion: entire gene + <i>CYBB</i> + ex.1-2 <i>DMD</i>	1-3	Hemi	NA	1Y9M	Chronic granulomatous disease	2837	Chinese [7]
5	<i>XK</i>	c.89C>A (p.S30*)	1	Hemi	NA	10M	Fever, seizure	14889	English [8]
6	<i>XK</i>	c.1004G>A (p.W335*)	3	Hemi	NA	40+Y	Chorea of limbs, orolingual dystonia	928-1280	Chinese [9]
7	<i>VPS13A</i>	c.7280_7284del (p.Y2427Sfs*6) c.8278C>T (p.Q2760*)	52 60	Het Het	DM DM	30Y	Chorea of limbs, orolingual dystonia, tongue and lip biting, seizure	1122	English [10]
8	<i>VPS13A</i>	c.8282C>G (p.S2761*) c.9276-1G>A	60 70	Het Het	DM DM?	45Y	Orolingual dystonia, tongue and lip biting	137	English [10]
9	<i>VPS13A</i>	c.486T>G (p.Y162*)	6	Hom	NA	28Y	Chorea of limbs, orolingual dystonia, tongue and lip biting, seizure	404	Chinese [11]
10	<i>VPS13A</i>	c.8823C>G (p.Y2941*)	65	Hom	DM	26Y	Chorea of limbs, orolingual dystonia, tongue and lip biting, seizure	NA	English [12]
11	<i>VPS13A</i>	c.80dup (p.S28Lfs*17)	1	Het	NA	26Y	Chorea of limbs, orolingual dystonia, tongue and lip biting	453	English [13]

XK: NM_021083.3; *VPS13A*: NM_033305.2; Het: heterozygote; Hemi: hemizygous; Hom: homozygous; Het: heterozygous; HGMD: Human Gene Mutation Database (v2019.4); DM: disease causing; NA: not available; AAO: age at onset; Y: years old; M: months; CK: creatine kinase.

Figures

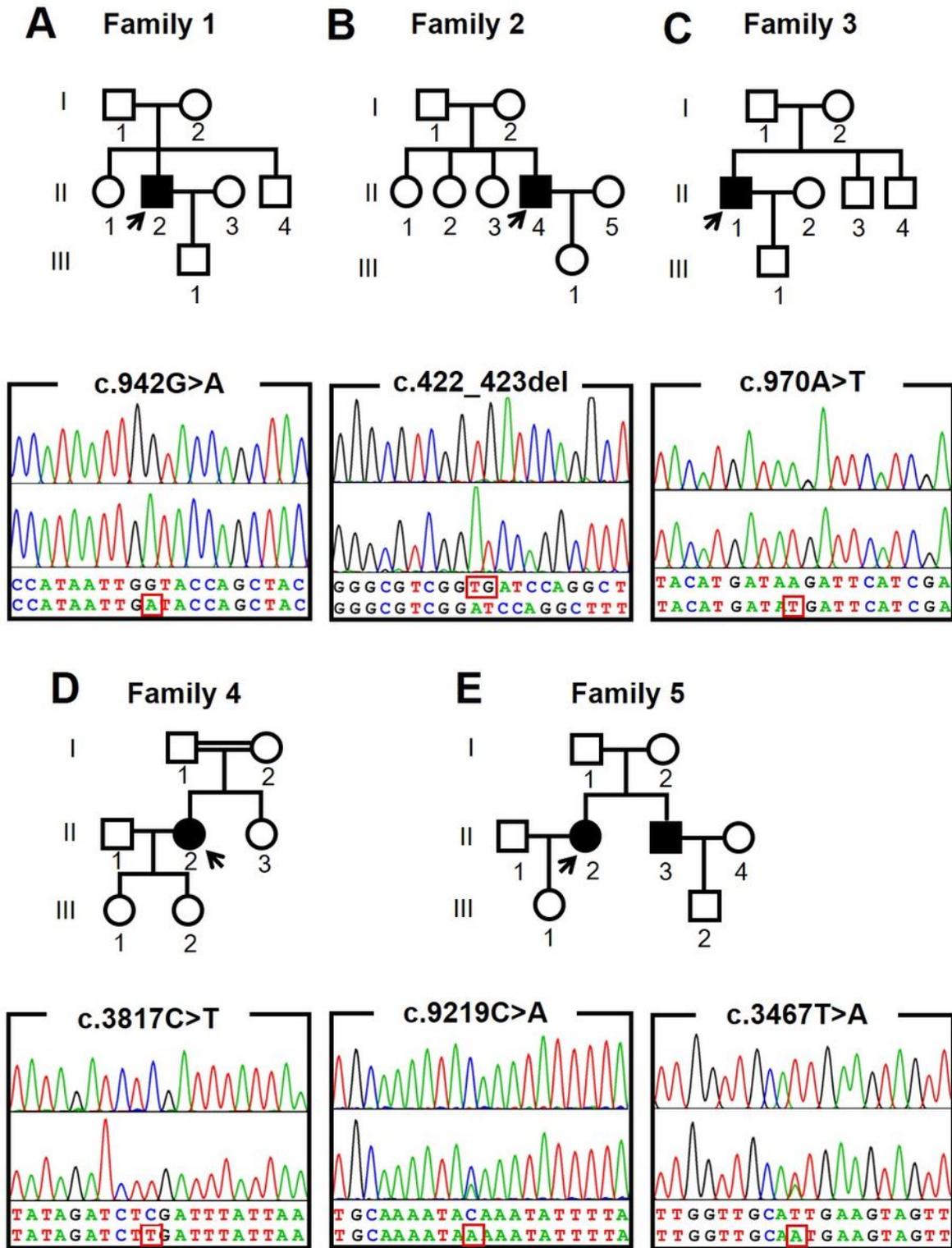


Figure 1

Pedigree chart of index families and chromatogram of novel variants detected in each family. Squares indicate males; circles indicate females; the black symbols indicate affected individuals; arrows indicate the probands. The upper panel in chromatogram depicts the reference sequence. The lower panel represents heterozygous mutated sequence.

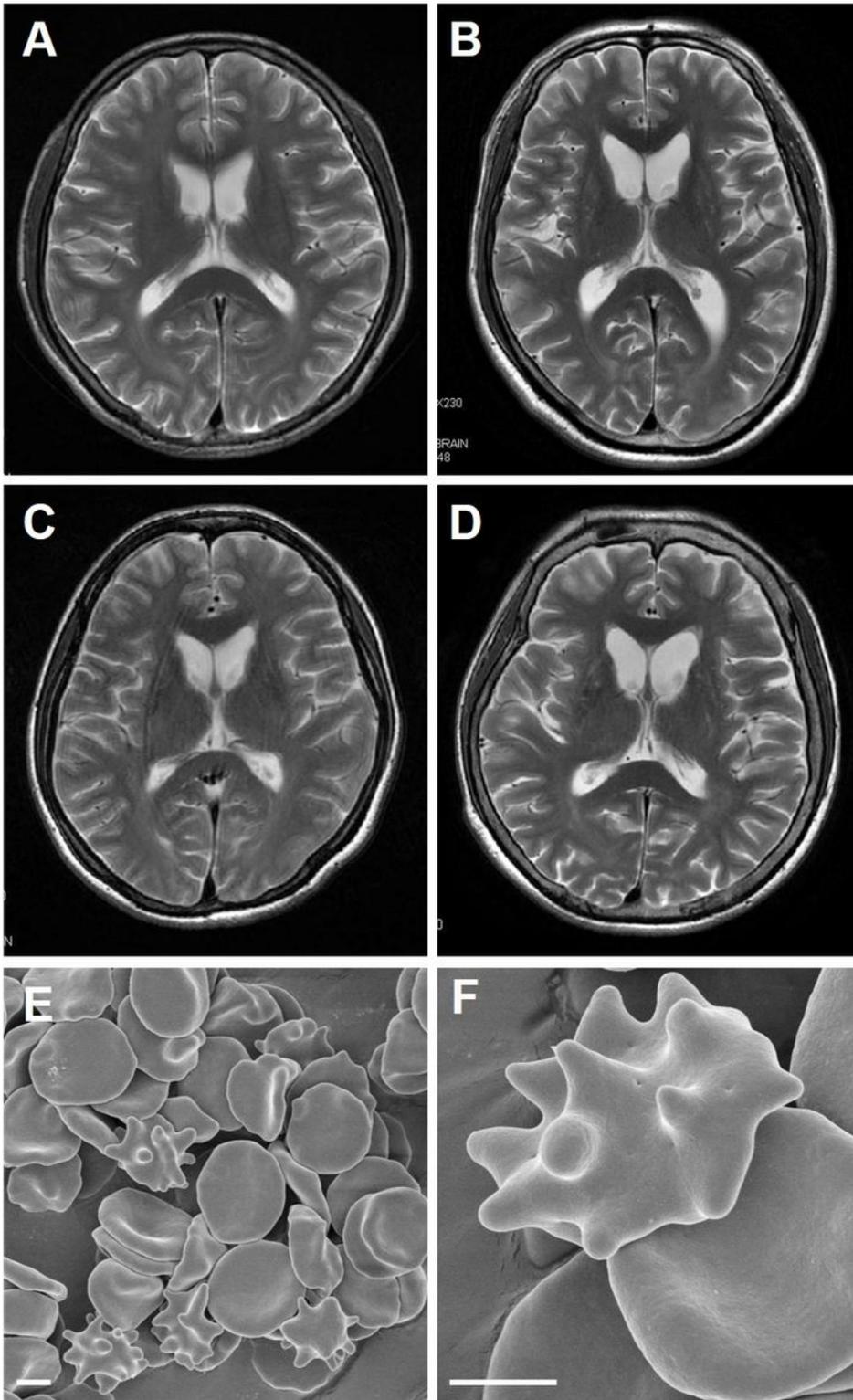


Figure 2

Clinical features of five genetically diagnosed patients. (A-D) Brain MRI of Case 1 (A), Case 3 (B), Case 4 (C) and Case 5 (D). Note the atrophy of caudate and the enlarged anterior horns of lateral ventricles. (E-F) Pictures of acanthocytes in peripheral blood of Case 5 by scanning electron microscopy. Scale bar: 2 μ m.

Supplementary Files

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- [TableS1.docx](#)