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Seizures as presenting and prominent symptom in Chorea-Acanthocytosis with c.2343del *VPS13A* gene mutation

Running title: Seizures in Chorea-Acanthocytosis

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ABSTRACT

Objective: The aim of the study was to characterize the clinical features of nine patients in three families with Chorea-acanthocytosis (ChAc) sharing the same rare c.2343del mutation in the *VPS13A* gene.

Methods: Genetic test results, clinical description, MRI and EEG as well as laboratory results are summarized.

Results: ChAc is a rare genetic disorder characterized by hyperkinetic movements, seizures, cognitive decline, neuropsychiatric symptoms, and acanthocytes on peripheral blood smear. This unique cohort of nine patients is characterized by seizures as a first and prominent symptom. In our patients other features of ChAc appeared later, including tics, other movement disorders, dysarthria and mild to moderate cognitive decline.

Significance: Chorea-Acanthocytosis patients carrying the described rare mutation can present with focal, treatment resistant seizures.

Keywords: Epilepsy, choreoacanthocytosis, *VPS13A*, chorein, genetics.

1. Introduction

Chorea-acanthocytosis (ChAc, MIM 200150) is one of the core neuroacanthocytosis syndromes, which also include McLeod syndrome, Huntington's disease-like 2 (HDL2), and a subtype of pantothenate-kinase-associated neurodegeneration (PKAN) [1].

ChAc follows autosomal recessive inheritance [2] and the causative gene is *VPS13A* (vacuolar protein sorting 13A): a large gene on chromosome 9q21 comprising 73 exons [3,4]. Reported variants of the gene comprise missense, nonsense, frameshift, splice site, duplication, and deletion mutations [4]. *VPS13A* is expressed primarily in the brain and red blood cells and encodes chorein, a 360-kDa protein. Chorein is involved in the trafficking of membrane proteins between cellular compartments and is absent or markedly reduced in tissues of ChAc patients [5].

The mean age of onset of ChAc is about 35 years, but symptoms may begin before age 20 or after age 40. The best-characterized symptom complex is a hyperkinetic movement disorder, exhibiting choreiform as well as dystonic components, tics, and involuntary movements of facial, oral, lingual, pharyngeal and laryngeal muscles [3]. Other features of the syndrome are ocular motility abnormalities, neuropathy and myopathy, cognitive and neuro-psychiatric symptoms. An increased number of acanthocytes in peripheral blood is characteristic but not pathognomonic, and may appear only late in the course [6], as well in other disorders. Epilepsy is also part of the ChAc syndrome, occurring in over 40% of the patients. Seizures have been described as a late manifestation in well-established cases, but only rarely as the presenting symptom [7,8]. The seizure type most commonly mentioned is generalized tonic clonic (GTCS), but simple and complex partial seizures (CPS) of temporal lobe origin have infrequently been described [9,10].

The several *VPS13A* mutations described so far have not been reported to correlate with a specific clinical phenotype [11]. We here report nine patients diagnosed with ChAc due to the same *VPS13A* c.2342del mutation. Interestingly, all but one patient presented with seizures as a first symptom.

2. Methods

Patients

Nine affected members of three families were interviewed and examined, and their medical records were scrutinized. EEG was assessed and described in 8/9 and MRI had been performed in all nine. Neuropsychological testing was done for 2 patients. Peripheral blood smears were tested for acanthocytes in 5/9 and DNA analysis was carried out on all nine affected individuals as well as in several healthy members of their families. All the participants gave informed consent, fulfilling local Institutional Review Board (IRB) requirements.

DNA Amplification and Sequence Analysis

Genomic DNA (gDNA) was extracted from peripheral leukocytes by standard methods as described elsewhere. cDNA was prepared by reverse transcription of mRNA using BD PowerScript! Reverse Transcriptase (BD Biosciences Clontech, Palo Alto, CA) with random hexamers.

All 73 exons and flanking regions of *VPS13A* (GenBank NC_000009.11) were amplified from gDNA, while the two primary transcripts (transcript variant A: GenBank NM_033305.2; transcript variant B: GenBank NM_015186.3) of *VPS13A* were amplified from the cDNA of those patients for whom RNA was available. Annealing temperatures and times were determined according to the primer sequences and amplicon lengths. Amplified products were purified using a QIAquick PCR purification kit (Qiagen) or a BigDye Xterminator purification kit (Applied Bio- systems, Foster City, CA). Then, they were labeled in both directions using a BigDye Terminator v3.1 Cycle Sequencing kit (Applied Biosystems) or AmpliTaq Gold 360 Master Mix (Life Technologies) and were directly sequenced on an ABI PRISM 3100 Avant Genetic Analyzer (Applied Biosystems).

3. Results

Following is a detailed description of several patients from each family. Clinical features of all affected members are summarized in Table 1 and the timecourse of the appearance of clinical symptoms is visualized in Fig. S1. The families are not known to be related but all three are of Jewish-Tunisian origin from the island of Djerba, now living in Israel.

A. Clinical Features:

Family I. The family lives in Israel originating from Tunisia (Island of Djerba). The grandparents of the four tested and described family members were siblings. An additional three members of the family could not be tested or examined but per history also suffer from ChAc (Fig. 1).

Patient 1: At the time of study, this 35-year old female was the only one affected of four siblings. At the beginning of her academic engineering studies (age 18) she started having seizures, simple partial (SPS), CPS, and secondarily generalized (2-GTCS). She described auras consisting of a déjà-vu sensation, dizziness, and apprehension. These were followed by impairment of consciousness, staring, oral and manual automatisms. Her head and gaze sometimes deviated, possibly to the left, and she muttered incomprehensible words. Seizures occurred during both wakefulness and sleep. Generalized seizures occurred frequently, mainly during sleep. Several anti-epileptic drugs (AEDs) failed to control her seizures

(Carbamazepine, CBZ; Valproic acid, VPA) and only a combination of oxcarbazepine (OXC) and clobazam (CLB) improved her seizure control with occasional CPS and rare 2-GTCS (twice a year). Topiramate (TPM) precipitated an acute psychosis requiring psychiatric hospitalization. At age 26 she and her family noted mild cognitive decline. On examination, the patient's behavior was impulsive, with mild disinhibition. Motor restlessness, with infrequent motor tics involving the neck, arms and eyes (repetitive blinking) and occasional phonic tics were noted on exam. Tongue movements were slow, and saccades hypometric. Neuropsychological testing at age 27 revealed an impairment of selective attention, with difficulty restraining automatic responses and suppressing competing stimuli; impaired retrieval during memory tasks, with errors of omission, confabulations and perseverations as well as a tendency to impulsive responses; impaired executive functions also characterized by difficulty focusing on the task. Interictal EEG showed left temporal slowing with intermittent focal delta activity and her MRI scan revealed bilateral mild caudate atrophy. A peripheral blood smear was abnormal due to an increased number of acanthocytes.

Patient 2: This second-degree male cousin of patient #1 is married with four children, has two sisters with ChAc (patients #3, #4) and four healthy siblings. At age 32 he started having seizures, both CPS and 2-GTCS. There were no auras. The CPS manifested as unresponsiveness, muttering or murmuring, and slow head and gaze deviation to the left, followed by deep sleep. Both CPS and 2-GTCS were mostly nocturnal and tended to occur in clusters with very poor response to phenytoin (PHT), CBZ, phenobarbital (PB), lamotrigine (LTG) and CLB. On the combination of VPA and TPM there was temporary improvement, however he developed a confusional state with psychotic symptoms and elevated ammonia levels, which subsided after TPM discontinuation. The seizures eventually stopped completely with levetiracetam (LEV). On clinical examination at age 45 a mild cognitive decline was present, mainly affecting executive functions. Intermittent involuntary movements, mainly affecting the mouth and lower face, with multiple motor tics and occasional sniffing were present. Dysarthria was mild initially but gradually became more severe, associated with drooling. Tongue movements were slow, and saccades hypometric. His gait initially had very mild choreiform features, but gradually worsened and he became unstable, with gross choreic movements.

The involuntary movements did not respond well to haloperidol nor risperidone, moderate improvement was achieved with tetrabenazine and olanzapine. Depressive symptoms responded to citalopram. Interictal EEG showed intermittent left temporal theta activity and

generalized asynchronous theta activity, without epileptiform abnormalities. Brain MRI revealed bilateral mild caudate atrophy. A peripheral blood smear was abnormal due to increased number of acanthocytes.

Patient 3: The sister of patient #2 was examined at age 43. Her disease presented at the age of 41 with CPS preceded by a brief loss of vision and GTCS. Clinical details are presented in Table 1.

Patient 4: This is the younger sister of patients #2 and #3, evaluated in our center at the age of 42. She presented at age 29 with GTCS without auras or CPS. Her EEG showed mild left temporal slowing. Clinical details are shown in Table 1.

Family II: In this consanguineous family five out of six siblings were diagnosed with ChAc. One additional affected family member died before the study (Fig. 2). The family originates from the island of Djerba in Tunisia.

Patient 5: 41 years old today, the eldest daughter of the family, this patient started to experience seizures at age 16 (CPS and later 2-GTCS) partially controlled by VPA. Previous development was normal with an average school performance. At age 18 involuntary movements appeared, at first restricted to the right upper extremity, including choreo-athetotic movements and sudden hand jerks, which progressed and spread to other parts of the body. Later orofacial automatisms including tongue biting, and severe gait instability with frequent falls developed. Additionally, progressive cognitive decline was noted and the patient became aphasic. At age 32 she became wheelchair bound, living in a nursing home. The patient is still experiencing infrequent generalized seizures. She needs help feeding and with all activities of daily life (ADL). Her EEG showed generalized slowing without localized features and brain MRI revealed generalized atrophy. Her CK-levels are elevated two fold beyond normal upper limits (700 IU), and on blood smears acanthocytes are visible.

Patient 6: The today 39-year-old eldest brother of patient #5 is unmarried and lives with his mother. GTCS started at age 28. He is not compliant with his AED treatment and experienced several episodes of status epilepticus (SE). Currently the seizures are controlled by VPA. In addition slow cognitive deterioration was noted in the last years with difficulty concentrating. Since age 34 the patient experiences tics with quick episodic eye blinking and grunting. Repeated interictal EEG recordings showed no abnormalities. MRI showed mild atrophy of the caudate nucleus bilaterally. EMG muscle analysis did not show any pathology. Mild sensory polyneuropathy of a demyelinating type was seen with slow conduction velocities in

both legs. Baseline CK levels are about twice the normal range increasing up to tenfold after seizures. Blood smear showed an increased number of acanthocytes.

Patient 7: The younger brother of patient #5 and #6 is today 36-year old, unmarried, unemployed and receiving disability due to a left shoulder trauma during the military service and after a motorcycle accident at age 21 with multiple fractures in the lower extremities. The patient experienced a single unprovoked GTCS at age 32 and was then treated for one year with VPA, but stopped treatment on his own. At age 35 he experienced a second GTCS and is now medicated with VPA without any recurrences. For two years he suffers from progressively worsening involuntary oro-facial movements like lip smacking and vocal tics such as burping sounds. Additionally, he developed sudden choreoathetotic hand and arm movements, which he incorporates into semi-purposeful movements. There are no cognitive or psychiatric changes. EEG and MRI of the brain are normal. His baseline CK-levels range between 2000 and 3000 IU/ml. EMG and NCS revealed bilateral mild carpal tunnel syndrome.

Patient 8: The youngest sibling is 28-years old, unmarried biochemistry student living with his mother. Interestingly, as part of a work-up for an incidental finding of hyper-CK-emia at age 6, a muscle biopsy was performed which was inconclusive and he was diagnosed with idiopathic hyper-CK-emia. From age 20 he started to suffer from tics including facial right sided sudden twitching and verbal tics with grunting. At age 24 behavioral changes were noted: megalomaniac ideation including finding the cure for all diseases and at the same period his religious belief became strong with extreme dependence on prayers and religious rituals. He experienced his first seizure (GTCS) at age 25. The patient is not compliant regarding his anti-epileptic medication due to his belief that “the medication causes his disease”. In the last two years he suffered a total of four SE episodes, but when adherent to VPA treatment he is seizure-free. EEG displayed bitemporal slowing. Repeated brain MRI scans showed no anatomic or signal abnormalities. His baseline CK-levels are elevated up to 3000 IU but post seizure they regularly increase to 35000 IU. Blood smear showed an increased amount of acanthocytes.

One additional family member (the second eldest daughter) passed away suddenly at age 32 during a seizure and before the study commenced. The cause of death was determined as sudden unexpected death in epilepsy (SUDEP). No genetic testing is available. According to the family, she experienced seizures from age 16. Seizures were of sudden onset without warning and with generalized convulsions and frequent head trauma. She was treated with AEDs but specifics are unknown.

Family III: The family originates from Tunisia (Djerba island) living in Israel today. The parents are first-degree cousins (Fig. 3).

Patient 9: The only affected child of this family is a 58-year old woman with normal development until age 22 when she experienced a first seizure. Despite treatment with CBZ \ CPS recurred every 2-3 months in a catamenial fashion. Years after the beginning of her seizure disorder, dyskinesia and vocalizations began and progressed until she became wheelchair bound at 50 years of age. A suicide attempt was reported around age 40, attributed to her severe dyskinesia. On examination she has ongoing involuntary movements of her face, ataxia of her limbs, and is unable to stand unsupported. No tendon reflexes could be elicited. Her EEG was reported as normal.

B. Genetic Results:

All affected individuals in the three families with a clinical diagnosis of ChAc were found to be homozygous for c.2343del deletion mutation in the chorein gene. Additionally, in Family I all parents of affected individuals were tested and all are heterozygous for the same mutation (Fig. 1). In Family II, the mother of the affected individuals and a non-symptomatic sister were tested and are heterozygous for the c.2343del mutation. The non-symptomatic father and one symptomatic sister passed away before testing (Fig. 2). In Family III only the symptomatic individual was tested (Fig. 3). All results are summarized in the table.

4. Discussion

This is a description of nine members of three unrelated Israeli families of Jewish-Tunisian origin diagnosed clinically and genetically as ChAc carrying the same deletion mutation c.2343del in the chorein gene *VPS13A*. *VPS13A* c.2342del causing ChAc has only been reported once before in a single patient lacking a detailed description of the phenotype [11]. Affected members of the families reported here share the clinical syndrome of epileptic seizures, tics, chorea, cognitive impairment, and psychiatric manifestations. The onset of clinical symptoms varied from 16 to 41 years (mean: 26.4 ±8.1y).

Seizures are quite common as part of the clinical picture of ChAc: About 42% of ChAc patients have at least one seizure at some point of their clinical course [12]. However, the seizure disorder is usually not the prominent feature of ChAc, and is overshadowed by the

hyperkinetic movement disorder and other symptoms as most patients with ChAc previously described were suffering already from involuntary movements and behavioral symptoms when the first seizure appeared [13]. In Hardie's series of 19 neuroacanthocytosis patients (some of whom had neuroacanthocytosis syndromes other than ChAc), only five (26%) presented with seizures at an early stage of their disease [14] while Al-Asmi et al. found only 5 earlier reported ChAc patients whose presenting symptom was epilepsy [7,15,16]. Interestingly, in their own series of 6 ChAc patients exclusively of French-Canadian origin, seizure onset preceded other disease manifestations by up to 15 years [9].

In our series of nine patients with *VPS13A* c.2342del, seizures were not only the first presenting symptom (8/9) but epilepsy remained the predominant clinical manifestation for years. When other neurological symptoms eventually appeared, they were misinterpreted as "complications of epilepsy" and of its treatment, e.g. patient #1's personality change and cognitive deterioration were attributed solely to the sequelae of a TPM-induced psychotic episode. Patient #2's behavioral changes and cognitive deficits were regarded as the results of chronic temporal lobe epilepsy. Epilepsy as presenting feature of ChAc can delay the correct diagnosis for years. In Al-Asmi's families there was a delay in diagnosis of up to 11 years [9]. In the cases of Patient #2 and Patient #4 reported here, the diagnosis of ChAc was made only 13 years after epilepsy onset while e.g. Patient #5 was diagnosed with “only” a 4-year delay due to early involuntary motor symptoms.

Seizure types in ChAc are mostly GTCS if described at all. There have been some reports of CPS as well [17,18]. Tiftikcioglu et al. performed a video-EEG investigation on a ChAc patient with drug-resistant epilepsy, and found CPS originating in the left temporal lobe, [19] and in a report of an Italian family seizure type and semiology were not mentioned, but EEG in two out of three siblings was reported to show bitemporal, epileptiform abnormalities [20]. Seizures were localized to the temporal lobe origin according to semiology and ictal video-EEG recordings in the six previously mentioned patients from two French-Canadian kindreds with ChAc[9] and Scheid et al. reported three patients with ChAc presenting with mesial temporal lobe sclerosis[8]. In our reported patients, the affected members of the second family mainly showed GTCS according to history and EEG. Two out of the four described experienced multiple SE episodes. Regarding the first family described, three out of four affected members showed a localization-related epilepsy. Patient #1 has auras and CPS with mesial temporal lobe semiology and intermittent left temporal delta activity on EEG, and her GTCS

are mostly nocturnal. Patient #2 also has CPS with temporal lobe semiology, and his EEG also shows left temporal focal slowing. Patient #3 has GTCS with a visual aura suggesting an occipital origin while Patient #4 has GTCS without any localizing features, but her EEG shows mild left temporal focal slowing. The explanation for focal seizures arising unilaterally in a neurodegenerative disorder is lacking.

Seizures in patients with ChAc are usually difficult to manage and to control [7,21]. The effectiveness of AEDs to control seizures in the patients here reported is variable. While Patient #3,6,7, and 8 show good control of seizures when compliant, Patient 1 continues to experience occasional seizures and is currently taking OXC and CLB, after having tried five different AEDs. Patient #2 had recurrent 2-GTCS, some of them prolonged, on seven different AEDs, but has gained complete seizure freedom with LEV. Patients #1, #2, #4, #5, and #9 are not seizure free having tried 1-3 AEDs, but suboptimal compliance with treatment is a confounder. Patient #5 is still experiencing infrequent seizures having tried four different AEDs. Interestingly, psychotic symptoms developed in two ChAc patients involving TPM: Patient #1 had a psychotic episode on TPM, and Patient #2 suffered from encephalopathy with psychotic features on a combination of TPM and VPA with hyperammonemia.

In Family II five out of six siblings are affected and this is congruent with a previous report of a Japanese family suffering from ChAc and initially thought to be of an autosomal dominant pattern [22] but corrected later and a pseudo-dominant autosomal recessive pattern was suggested [2]. In the French-Canadian ChAc population a founder mutation was previously reported (EX70_EX73del) [23]. The entire here described ChAc patients with *VPS13A* c.2342del belong to families originating from the island of Djerba, Tunisia. Interestingly, we found two case reports of ChAc patients from Tunisia but unfortunately none of those were tested genetically [24,25]. The identification of the c.2343del mutation in three apparently unrelated ChAc families with origin from the island of Djerba suggests a founder mutation in Jewish Tunisians; this community is known to be ancient and relatively isolated with other founder mutations [26,27]. Routine testing for c.2343del in suspected ChAc cases may therefore be worthwhile in this population.

Key Points:

- ChAc is a rare genetic disorder characterized by hyperkinetic movements, seizures, cognitive decline, neuropsychiatric symptoms, and acanthocytes.

- The rare c.2343del mutation in the VPS13A gene causing ChAc is found in Israeli families from Tunisian origin.
- A divers phenotype is present but most affected individuals presented with seizures as a first and dominant symptom.
- Seizures can be of temporal lobe origin and can be treatment resistant.

Figure Legend:

Fig. 1: Pedigrees of family I with *VPS13A* c.2342del. Diagonal lines indicate deceased individuals. Also individuals with tics or seizure unrelated to ChAc are listed.

Fig. 2: Pedigrees of family II with *VPS13A* c.2342del. Diagonal lines indicate deceased individuals.

Fig. 3: Pedigrees of family III with *VPS13A* c.2342del. Diagonal lines indicate deceased individuals.

Fig.S1: Time course of symptoms appearing in individual patients according to age. Roman numbers indicates families.

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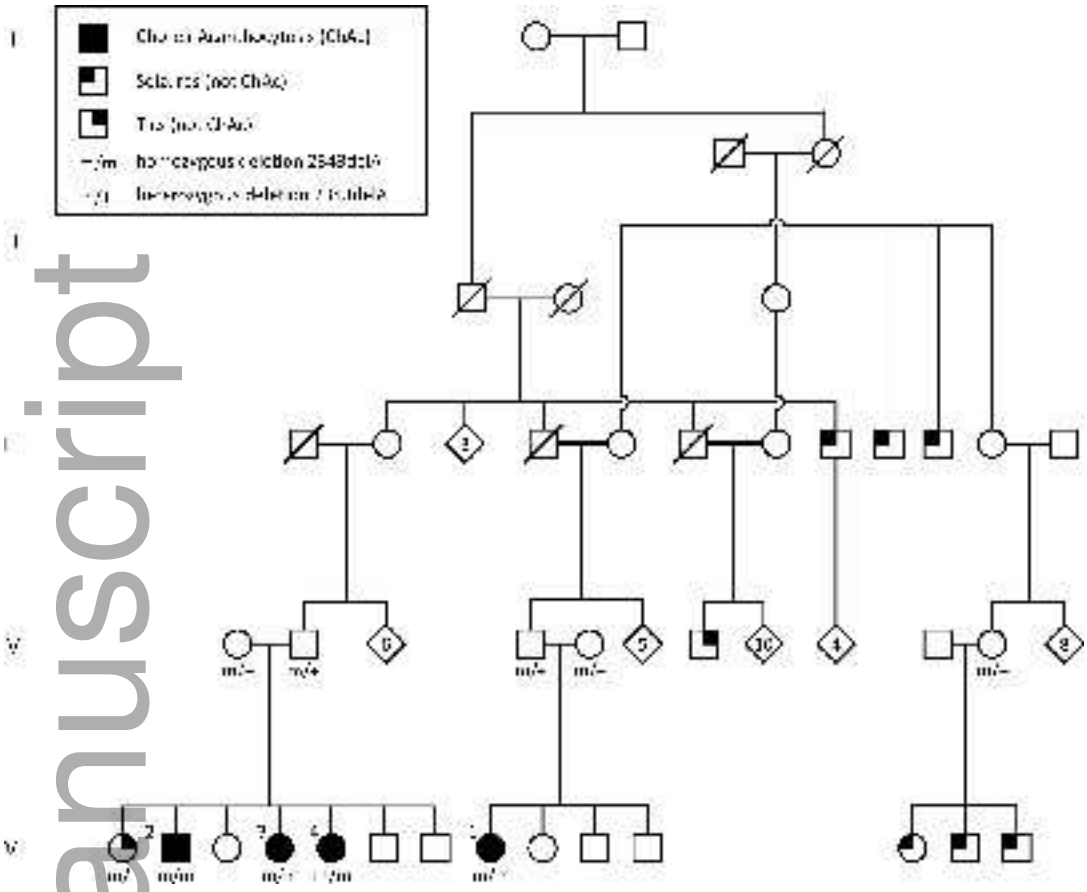
We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure statement:

None of the authors has any conflict of interest to disclose.

Family	I				II				III
Patient no.	1	2	3	4	5	6	7	8	9
Gender/Age at onset	f/18	m/32	f/41	f/29	f/16	m/28	m/32	m/20	f/22
Presenting symptom	Seizures	Seizures	Seizures	Seizures	Seizures	Seizures	Seizures	Tics and behavior	Seizures
Seizure type	SPS, CPS, 2-GTCS	CPS, 2-GTCS	SPS, 2-GTCS	CPS, GTCS	CPS, GTCS	GTCS	GTCS	GTCS	CPS, 2-GTCS
SE	-	-	-	-	-	+	-	+	-
EEG	Lt temporal slowing	Lt temporal & generalized slowing	Generalized slowing	Lt temporal slowing	Generalized slowing	“normal”	“normal”	bitemporal slowing	“normal”
Response to AEDs	incomplete	difficult to control seizures	good	incomplete	incomplete	good	good	good / low compliance	incomplete
Hyperkinetic Movements	+	+++	+	+	+++	+	++	++	+++
Dysarthria	+	++	++	+	+++	-	-	-	+
Cognitive symptoms	+	++	+	-	+++	-	-	+	+
Psychiatric	++	+++	+/-	-	+	-	-	++	+

symptoms									
Neuropathy	ND	ND	+	-	-	+	+/-	-	+
MRI	mild caudate atrophy	mild caudate atrophy	"normal"	"normal"	mild cerebral atrophy	mild caudate atrophy	“normal”	“normal”	ND
CK baseline/max	ND	ND	ND	ND	700	700/3000	3000	3000/35000	ND
Acanthocytes	+	+	ND	ND	+	+	ND	+	+
Genetics	c.2343del								



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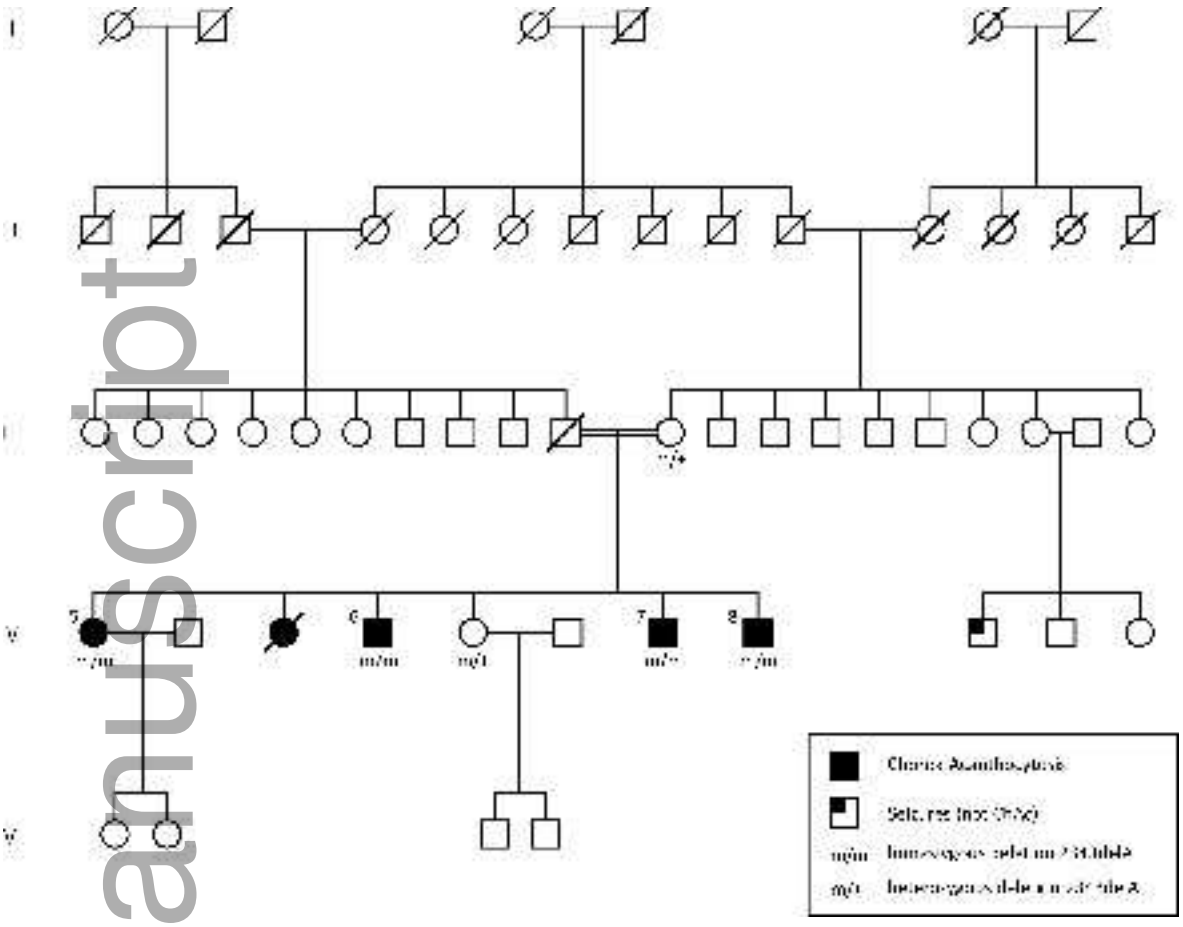

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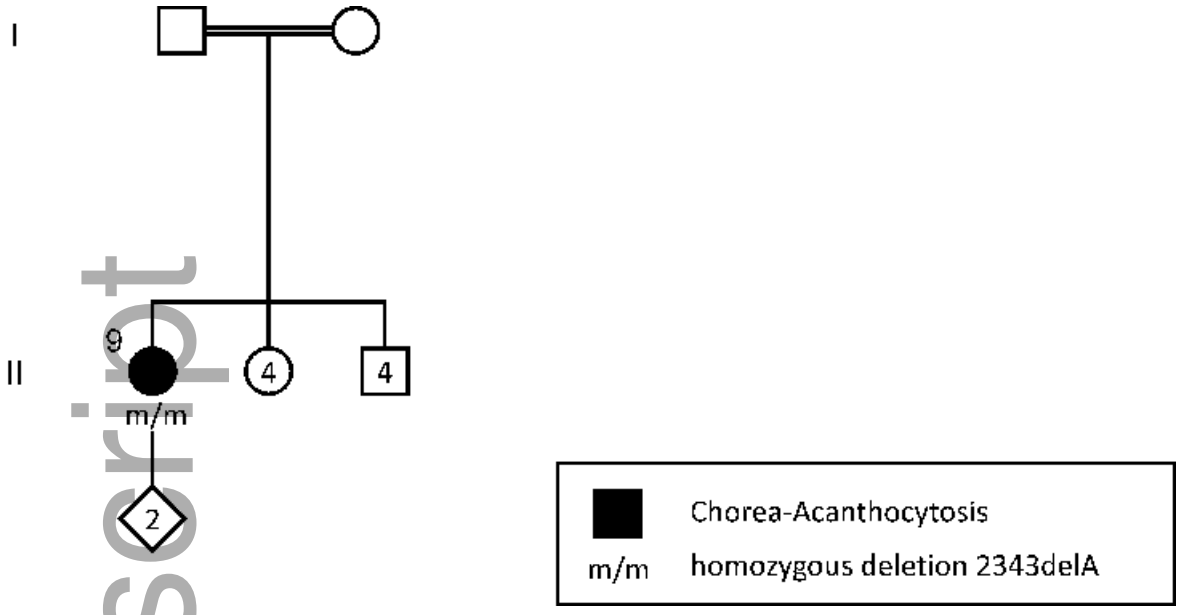

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