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Phenotypic variation in a Caucasian kindred with Chorea-Acanthocytosis

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Introduction and Background:

Chorea-Acanthocytosis (ChAc) is an autosomal recessive (AR) disorder caused by a *VPS13A* (*CHAC)* mutation on chromosome 9q21, encoding the chorein protein[1] for which a protein sorting role has been suggested .[1,2]

Presentation is usually in the third to fifth decade with a progressive movement disorder (chorea, dystonia, bradykinesia, ataxia, rigidity), seizures and red cell acanthocytes. [1-5] Intra-familial phenotypic variation is described, along with myopathy, neuropathy and cardiomyopathy.[6-10]

Characteristic of ChAc are involuntary movements affecting face, tongue and oropharynx. Involuntary vocalizations (phonic tics) are present in two-thirds of cases .[11] Swallowing and speech difficulties may occur due to orofacial dystonia and pseudobulbar palsy, and ChAc may mimic anterior horn cell disease.[12]

ChAc can be diagnosed with some certainty on clinical grounds, with supporting evidence from reduced chorein expression on Western Blot.[10] This report highlights the spectrum of presenting features, severity and variety of movement disorder, neuromuscular and radiological features in a new, genetically confirmed ChAc kindred.

Methods:

Three brothers with features suggestive of ChAc presented to neurology services. Blood samples were obtained from the 3 siblings, their parents, and their clinically unaffected brother. Genomic DNA was extracted (QIAamp Blood Kit (Qiagen) and samples were

assigned a unique ‘PATH’ number. Haplotype analysis was performed by PCR-genotyping of fluorescently labelled microsatellite markers from the *VPS13A* gene region. Genotypes of SNPs in the locus were determined by sequencing using specifically designed primers. Mutation screening of exons 68 to 73 of *VPS13A* was performed by sequencing using previously reported primers.[13]

Results

Case 1

A 25-year-old, Irish male developed unprovoked generalised seizures treated sequentially with valproate and levetiracetam, remaining seizure free for several years. He had phonic and orofacial motor tics. When reviewed at a specialist service 9 years later, he reported dysarthria and dysphagia, partly ameliorated by neck extension. Self-biting of tongue and lips necessitated mouth guard usage.

Orofacial tics included pursed lip movements with an audible "click". Choreiform movements were evident in the left lower limb, with a ‘rubber man’ irregular gait, truncal instability and impulsivity. He had distal atrophy of limb musculature but normal power and preserved reflexes. Creatine kinase (CK) level was elevated at 600-1800 U/L (40-180) with elevated transaminases and lactate dehydrogenase (LDH) (Table 1, clinical features). Acanthocytes were detected on blood film.

Case 2

A younger brother first attended neurology services aged 22 with stammering and dysfluency. Birth history and early milestones were normal. He attended 3rd level education. No movement disorder or abnormal signs were evident.

At age 29 he re-presented with a choreiform disorder, prominent orofacial dyskinesia, involuntary vocalisations, and dystonia. Continuous tongue and lip biting had caused soft tissue mutilation. Tongue protrusion dystonia caused severe dysphagia. Rigidity was present, with two to three beats of clonus. Gait examination showed dystonic upper and lower limb posturing and a bouncing or 'rubber man' type appearance.[14] (Video).

CK was elevated at 2,728 U/L (40-180), AST 88 U/L (6-42), ALT 71 U/L (4-45), LDH 681 U/L (220-450). Acanthocytes were detected on blood film. Nerve conduction studies and electromyography (EMG) showed features of a mild sensory axonal polyneuropathy but no evidence of myopathy or denervation. Right quadriceps biopsy showed a single degenerated fibre undergoing necrosis with some small fibres and fibre grouping, reported as suggestive of a denervation/reinnervation pattern.

Now, 17 years after presentation, he requires feeding via percutaneous gastrostomy, botulinum toxin injection for orofacial dystonia, uses an electronic communication device and is wheelchair bound.

Case 3

At age 29 another younger brother, who had attained 3rd level education, presented with *de novo* status epilepticus without a history of movement disorders. Subtle involuntary facial grimacing, temporalis thinning and symmetrical distal lower limb muscle wasting without fasciculations or weakness was noted.

Deep tendon reflexes were reduced at the ankle. Sensory examination was normal.

Over time, mild wasting of vastus medialis and lateralis along with mild hip flexion weakness (MRC 4-5/5) became appreciable. Tongue biting and teeth grinding was reported age 34. Mild orofacial dystonia and chorea developed. 7 years following initial presentation, seizures remain well controlled, he is physically active and independently mobile.

Non-ictal CK was elevated (1500 – 4200 U/L) transaminases AST 572 U/L (6-42), ALT 687 U/L (4-45). Acanthocytes were detected on blood film. Electroencephalogram was encephalopathic with notched rhythmical 3-4Hz delta and generalised irregular 5-6Hz theta activity. Neuropsychological testing showed attentional deficits, but preserved memory and language.

Initial EMG showed mild myopathic motor units in proximal upper limbs (right deltoid, biceps brachii). Interestingly, repeat study six years later did not replicate these findings. MRI of proximal lower limb musculature after presentation was normal, without significant atrophy. A repeat study (coronal T1, coronal STIR and axial T2 sequences) of proximal and distal lower limbs 6 years later remained normal.

Both parents are asymptomatic with normal CK and liver function tests, despite detection of acanthocytes in the 79-year old father.

Genetics results

Haplotype analysis of the *VPS13A* gene region in the family detected a shared haplotype in both parents with each of the 3 affected sons homozygous across this 9.6 cM / 5.2 Mb locus (Figure 1). There is no known consanguinity. An unaffected brother does not carry a copy of the shared haplotype. Each parent has 2 distinguishable haplotypes across the interval.

Mutation screening of exons at the C- terminus of the *VPS13A* gene identified a sequence variant c. 9431_9432delAG (p. 3134Rfsx5). Both parents are heterozygous for this mutation, all three affected sons are homozygous for the 2 base pair deletion and the unaffected son is homozygous wildtype. (Figure 1)

Discussion

This report illustrates the variation in presenting features and temporal evolution of ChAc within a family, adding the phenotypic description clinically and with radiological characterisation of its neuromuscular aspects.

Notable in this kindred is the hyper-CK-aemia, muscle thinning and variability in severity of neuromuscular involvement. Case 1 demonstrated generalised muscle atrophy and elevated CK. Case 2, with a more severe presentation overall, had an axonal polyneuropathy and a muscle biopsy showing mild denervation. Case 3 also had generalised muscle thinning which evolved to measurable weakness over time but without corresponding neurophysiological or MRI evidence of neuropathy or myopathy.

Neuromuscular features may be under appreciated in this hyperkinetic movement disorder, although amyotrophy featured in its early descriptions. [8,9,15]. Pathophysiological correlates of muscle CK and transaminase elevation in ChAc is unclear.[13,16,17] Axonal neuropathy is described in ChAc but may be limited to vibration sensation loss.[13] Electrophysiologic tests may demonstrate a sensory axonopathy with normal conduction velocities, butreduced sensory action potentials, similar to case 2 here.[13] EMG and muscle biopsy in ChAc have been reported to have nonspecific myopathic changes.[5,7] Myopathy may be progressive,characterized by distal muscle wasting and weakness, or can remain subclinical. CT imaging of leg muscles in one report showed a selective pattern of symmetric fatty change.[18] Reports of MRI imaging in ChAc describe symmetric increased signal in both gastrocnemius on T1-sequences, but not in our imaged patient.[19]

The differential diagnosis of a movement disorder with neuromuscular features includes mitochondrial disorders, GM2 gangliosidosis (Tay Sachs disease), or oculomotor apraxia type 2 as well other disorders associated with acanthocytes.[20-22] ChAc belongs to the neuroacanthocytosis group of progressive movement disorders that includes, pantothenate-kinase associated neurodegeneration (PKAN), Huntington's disease-like type 2, abetalipoproteinemia, hypobetalipoproteinemia and McLeod syndrome.[22] McLeod syndrome has myopathic features and sensorimotor axonopathy, but in contrast to ChAC frequently has cardiomyopathy and inheritance is X linked. [18] Abetalipoproteinemia and hypobetalipoproteinemia share neuropathy, dysarthria, and areflexia, with ChAc but differ in their hallmark findings of retinopathy, steatorrhea, vitamin E deficiency and absence of movement disorder.

Using a combination of haplotype analysis and mutation screening approach the causative mutation was identified in this family confirming autosomal recessive inheritance. Genotype data revealed a haplotype shared by both parents and supported the involvement of the *VPS13A* gene. Due to the large gene size (73 exons), mutation screening began with exons at the 3' end. The 2-bp deletion detected in exon 72 was previously reported as one of two distinct mutations in a compound heterozygote ChAc patient ("proband 29").[1] Our study is the first report of this mutation in a homozygous state. Both parents are heterozygous for the 2 base pair deletion, and remain asymptomatic except for acanthocytes detected in the father. This is similar to a previous report of this single feature of ChAc in a heterozygous carrier in an AR choreoacanthocytosis pedigree .[23]

The striking variability of presenting features in this kindred ranges from early dysarthria with a movement disorder, to status epilepticus and distal muscle atrophy. Interestingly the most severely affected sibling (case 2), has a normal EEG and no seizures. Chorea, gait abnormalities and phonic tics are prominent features in case 1 and case 2, but not case 3. Absence of clear markers of disease severity or progression is noted in this family and is a challenge in ChAc patient management.

Although dystonia, chorea, dysarthria and dysphagia are common presenting features of ChAc, this kindred illustrates the variability in phenotype, presentation and progression. A movement disorder combined with neuromuscular features should prompt consideration of the diagnosis of chorea-acanthocytosis.

Author roles:

Dr Merwick, Dr Mok, Dr McNamara, Dr Moore, Dr Sweeney and Dr Ryan acquired the clinical data and drafted the manuscript. Dr Hand acquired the clinical data, performed the laboratory analysis, drafted the manuscript and was involved in critical revision of the manuscript. Prof Parfrey reviewed and critiqued the manuscript.

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Legend to the video

Video 1: Patient 2 (aged 32 years). Gait examination shows an irregular gait with truncal instability and dystonic limb posturing observed with a ‘rubber man’ type appearance.

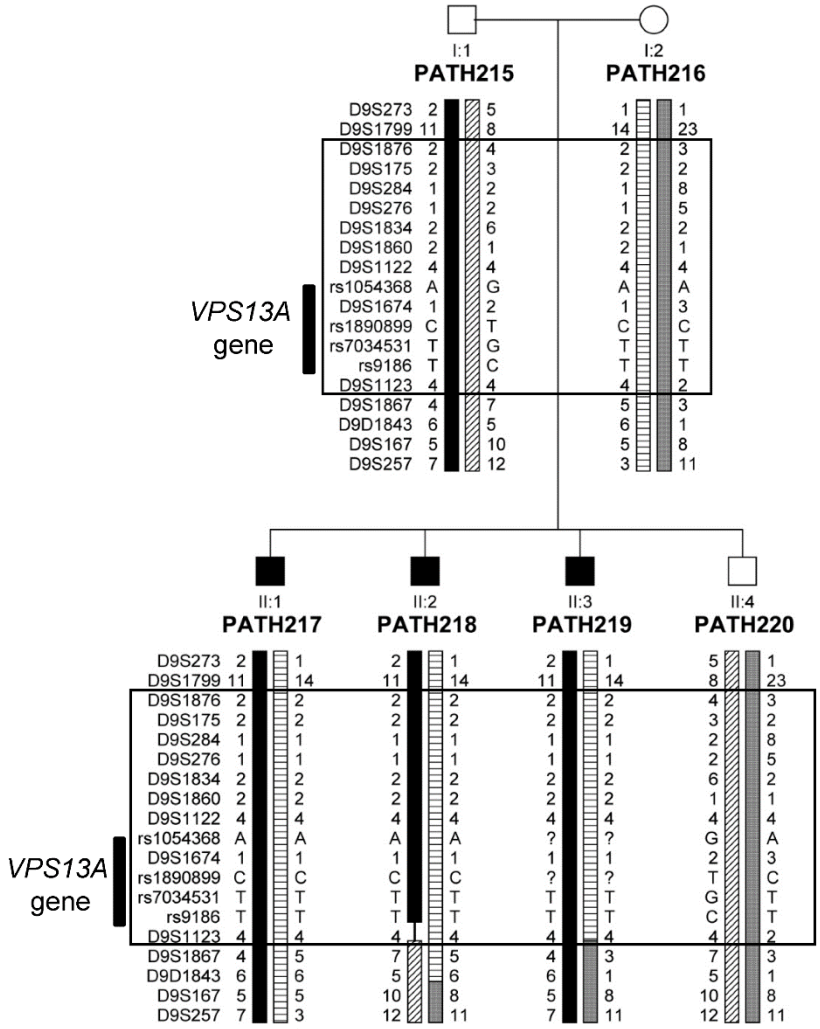

Figure 1: Pedigree of chorea-acanthocytosis family with haplotype data.

Affected individuals are denoted by filled symbols. All participants have a unique sample (PATH) number. Genotypes for the investigated microsatellite markers and SNPs in the region are indicated. Haplotypes were generated based on parental genotypes. The location of the *VPS13A* gene is indicated and lies within the disease haplotype which is bound by the box.

Case No.	Age at presentation	Initial main presenting feature	Movement Disorder	Neuromuscular features	Seizures	EEG	Blood results	Imaging
1	25 years	Generalised seizure	Tics – motor and vocal at presentation. Subsequent choreiform lower limb movements	Atrophy of distal lower limb musculature	Generalised	Interictal EEG : Abnormal with encephalopathic features and, diffuse underlying slow wave activity	CK 670-1800 U/L (range 40-180 U/L) Acanthocytes detected	CT brain: normal
2	22 years	Stammering Vocal Tics	Ataxia and chorea. Orofacial dystonia including tongue Tics (motor & verbal).	Axonal neuropathy (sensori-motor) Muscle biopsy shows features of denervation/ re-innnervation	nil	EEG: Normal	CK 300-3800 U/L (range 40-180 U/L) Acanthocytes detected	MRI brain: Normal
3	29 years	Multiple generalised seizures	Subtle Involuntary orofacial grimacing movements at presentation	Distal and proximal lower limb muscle atrophy. Myopathic features on EMG.	Generalised	Interictal EEG: Abnormal showing encephalopathic pattern, with notched rhythmical 3-4Hz delta and generalised irregular 5-6Hz theta activity	CK 1500 – 4200 U/L (range 40-180 U/L) Acanthocytes detected	MRI brain : Normal MRI lower limb musculature: normal

Table 1: Clinical, neurophysiology and radiology findings in series of 3 male siblings with chorea-acanthocytosis.