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Tremor and Other Hyperkinetic Movements

New Observations Letters

# Chorea–Acanthocytosis and the Huntington Disease Allele in an Irish Family

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## Introduction

The presence of peripheral blood film acanthocytes can help narrow the differential diagnosis of a familial choreiform disorder. Acanthocytosis is associated with chorea–acanthocytosis (ChAc), McLeod syndrome, pantothenate kinase-associated neurodegeneration (PKAN), and Huntington's disease-like 2 (HDL-2).[1] Huntington disease (HD) can present at a similar age with a similar phenotype, but without acanthocytosis. We report the cases of three adult siblings with genetically confirmed ChAc, and discuss the unusual finding of a co-existing abnormal HD allele (CAG repeat expansion in the range of reduced penetrance) in two of these siblings.

## Case series

Three siblings developed progressive neurological syndromes beginning in their third or fourth decade (Table 1). Psychiatric symptoms were an early feature in all siblings, including anxiety and obsessive–compulsive features. Over the years, all siblings developed dysarthria and orofacial features, including self-injurious biting, feeding dystonia, and orofacial chorea. Siblings 1 and 3 developed epilepsy (complex partial seizures in sibling 1 and generalized seizures in sibling 3). Limb chorea, and frontal and temporal cognitive deficits occurred further into the disease process, and were present in the elder siblings (1 and 2) by the time of assessment. Sibling 1 died suddenly during follow-up and autopsy suggested cardiorespiratory collapse as the cause of death.

## Family history

There are seven siblings in this Irish family, three of whom are unaffected. The final sibling reportedly has some neurological symptoms but has not been fully investigated. There is no other family history of neurological disorder, and no known consanguinity.

## Investigations

Laboratory and imaging studies screening for biochemical, infective, or autoimmune causes were unremarkable in each case. Sibling 1 (the eldest) presented first and genetic testing for HD demonstrated that he carried a single normal allele and a HD allele with 37 CAG repeats, in the reduced penetrance range (also subsequently identified in sibling 2). Investigation for ChAc was prompted a short time later after siblings 2 and 3 were also evaluated, because of recognition of the prominent orofacial features, symptom onset in the 20s or 30s, and presence of acanthocytes in peripheral blood. Genetic analysis of the *VPS13A* (ChAc) gene (NM_033305.2) demonstrated that the three affected siblings are compound heterozygotes, with one copy of the Arg3143fs*5 (c.9427_9428delAG in exon 72) mutation that was previously reported in a homozygous state in another (unrelated) Irish family from the same region,[2] and one copy of the novel Pro322Alafs*19 (c.962dupT in exon 12) mutation. Both mutations cause a frameshift resulting in a truncated protein. Genetic analysis of the unaffected mother and one unaffected brother showed they each carry a single mutation (Pro322Alafs*19). We assume that the Arg3143fs*5 mutation was inherited from the siblings' father, who had no history of neurological or psychiatric symptoms and died in his 40s of non-neurological disease. Sibling 3 underwent HD testing at a later date and was found to have 2 normal alleles.

Table 1. **Clinical Characteristics of Affected Siblings**

| | Sibling 1 | Sibling 2 | Sibling 3 |
|---|---|---|---|
| Age at assessment | 44 | 42 | 36 |
| Gender | Male | Female | Female |
| Age at symptom onset | 36 | 38 | 28 |
| First symptoms | Psychiatric | Psychiatric | Epilepsy |
| Psychiatric symptoms | ✓ | ✓ | ✓ |
| Dysphagia | ✓ | ✓ | ✗ |
| Dysarthria | ✓ | ✓ | ✓ |
| Self-injurious biting | ✗ | ✓ | ✓ |
| Vocal tics | ✗ | ✓ | ✓ |
| Orofacial chorea/dystonia | ✓ | ✓ | ✗ |
| Truncal and limb chorea | ✓ | ✓ | ✗ |
| "Rubber man" gait | ✓ | ✗ | ✗ |
| Cognitive deficits | ✓ | ✓ | ✗ |
| Signs of peripheral neuropathy | ✓ | ✓ | ✗ |
| Epilepsy | ✓ | ✗ | ✓ |
| Peripheral blood acanthocytes | ✓ | ✓ | N/A |
| Creatine phosphokinase (U/L) (normal 40–180) | 193 | 375 | 433 |
| *VPS13A* gene mutation | Compound heterozygote | Compound heterozygote | Compound heterozygote |
| Huntington disease allele | Abnormal allele: 37 CAG | Abnormal allele: 37 CAG | Normal allele |

Abbreviations: ✓, Present; ✗, Absent; N/A, Not available.

### Post-mortem neuropathological findings in sibling I

Findings in the brain were interpreted as consistent with ChAc. There was prominent loss of neurons and gliosis in the caudate and to a lesser extent the putamen and pallidum, with some early similar changes within the substantia nigra. Furthermore, there was evidence of chronic cerebrovascular disease with vascular lipohyalinosis, and there were acute established changes of preterminal hypoxia-ischemia. The spinal cord and sural nerve were normal. In the deltoid and quadriceps muscles there were myopathic features with some fiber size variability, increased number of fibers containing internal nuclei, type I fiber predominance with grouping, and small type II fibers.

## Discussion

ChAc is a rare autosomal recessive disorder caused by mutations of the *VPS13A* gene on chromosome 9, which encodes the chorein protein. The function of this protein is not well understood, but it is thought to be involved in architecture of the cytoskeleton and cell survival.[3] Cytoskeletal abnormalities may explain the unusual erythrocyte morphology seen in this condition, but the degree of acanthocytosis is variable and does not seem to correlate with clinical severity.[4,5] Furthermore, while routine laboratory techniques actually demonstrate limited sensitivity in detecting acanthocytosis, the use of isotonically diluted blood and unfixed wet blood preparation improves sensitivity and specificity.[6] In addition, muscle creatine kinase is another useful blood marker that is almost ubiquitously elevated in affected individuals.[7]

Symptoms of ChAc typically begin in the third decade (or less frequently in the fourth decade) with dysphagia, dysarthria, chorea, and unsteady or "rubber man'" gait.[7] Involuntary movements of the orofacial region, with feeding dystonia and self-mutilation from teeth grinding and lip biting are characteristic of the disorder. Involuntary vocalizations are frequent. Psychiatric symptoms, cognitive impairment, epilepsy, and neuropathy are recognized non-motor symptoms.[7]

The phenotype of our patients is strongly suggestive of ChAc, with orofacial dystonia, self-injurious behavior, and epilepsy early in the

disease. Their clinical features are certainly within the range of severity and age of onset as that described in typical ChAc cases. However, the co-existing *VPS13A* and *HTT* gene abnormalities were an interesting finding in siblings 1 and 2. We propose that our patients have clear clinical manifestations of ChAc and the finding of an abnormal HD allele in the reduced penetrance range could simply be an incidental finding. Indeed, post-mortem neuropathological findings in the eldest sibling were consistent with the clinical diagnosis of ChAc, demonstrating marked gliosis and extensive neuronal loss in the striatum (less gliosis would be expected in HD, and neuronal loss should only be extensive in advanced HD).[8] Further support for the hypothesis that the abnormal HD allele is an incidental finding includes evidence that the incidence of the HD allele in the general population is almost certainly higher than previously suspected. A recent large study reported 18 of 7,315 individuals from Western populations had ⩾36 CAG repeats (15 of these were in the reduced penetrance range of 36–39 CAG repeats), suggesting an incidence of HD gene abnormalities of approximately one in 400 in the general population.[9] While penetrance rates of up to 65% have been reported with 36–39 CAG repeats in a cohort attending for diagnostic/predictive testing for HD (i.e., in those with a known family history),[10] the penetrance rate with 36–39 CAG repeats among the general population is closer to 0.2% (although under-ascertainment of clinical cases or capturing individuals at a pre-symptomatic age is possible in a cross-sectional population study such as this).[9] On the other hand, an alternative hypothesis that should be considered is that, should the remaining affected sibling with the CAG repeat expansion live long enough, she could experience a "double-hit" from both genetic abnormalities, resulting in compound neurodegenerative changes in affected regions. CAG repeat length demonstrates an inverse correlation with age of onset;[11] therefore, HD alleles in the reduced penetrance range that become symptomatic typically cause late-onset disease, sometimes with no family history of the disorder.[12] However, accurately determining age of onset is challenging in HD,[13] and we expect that the co-existence of another choreiform disorder seen in our patients could make this almost impossible to define. This being said, we will certainly monitor the surviving siblings closely for evolution of phenotype over time, and it will be particularly useful to compare the clinical course of the sibling with the abnormal HD allele to the sibling without this abnormality.

A final important issue raised in this family is the implications of detection of the HD allele in the reduced penetrance range for subsequent generations. Regardless of whether an individual carrying this abnormal allele becomes symptomatic in their lifetime, there is a possibility of anticipation with expansion of CAG repeats between parent and offspring, a phenomenon that occurs far more commonly with paternal transmission of the gene.[14] The deceased male sibling 1 has one son who has received genetic counseling and will be followed by clinical genetics over the long term.

## Conclusion

We report an Irish kindred with classic presenting features of ChAc, who are compound heterozygotes for this rare neurodegenerative disorder, but also carry a reduced penetrance range expansion of the *HTT* gene. This case series emphasizes the importance of a detailed family history and clinical examination in the assessment of chorea, and the diagnostic utility of identifying acanthocytes on a peripheral blood film. With recent studies elucidating potential pathophysiologic pathways in ChAc,[15–17] potential therapeutic targets may be identified in future.

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