

**UCC Library and UCC researchers have made this item openly available.  
Please [let us know](#) how this has helped you. Thanks!**

<b>Title</b>	Chorea–acanthocytosis and the Huntington disease allele in an Irish family
<b>Author(s)</b>	Murphy, Olwen C.; O'Toole, Orna; Hand, Collette K.; Ryan, Aisling M.
<b>Publication date</b>	2018-10-26
<b>Original citation</b>	Murphy, O.C., O'Toole, O., Hand, C.K. and Ryan, A.M., 2018. Chorea–Acanthocytosis and the Huntington Disease Allele in an Irish Family. Tremor and Other Hyperkinetic Movements, 8.(4pp). DOI:10.7916/D8R22J6M
<b>Type of publication</b>	Article (peer-reviewed)
<b>Link to publisher's version</b>	<a href="https://tremorjournal.org/index.php/tremor/article/view/604">https://tremorjournal.org/index.php/tremor/article/view/604</a> <a href="http://dx.doi.org/10.7916/D8R22J6M">http://dx.doi.org/10.7916/D8R22J6M</a> Access to the full text of the published version may require a subscription.
<b>Rights</b>	© 2018 Murphy et al <a href="https://creativecommons.org/licenses/by-nc-nd/4.0/">https://creativecommons.org/licenses/by-nc-nd/4.0/</a>
<b>Item downloaded from</b>	<a href="http://hdl.handle.net/10468/8448">http://hdl.handle.net/10468/8448</a>

Downloaded on 2021-09-18T05:02:14Z

## New Observations Letters

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

Olwen C. Murphy<sup>1,2\*</sup>, Orna O'Toole<sup>2</sup>, Collette K. Hand<sup>3</sup> & Aisling M. Ryan<sup>1</sup>

<sup>1</sup>Department of Neurology, National Neuroscience Centre, Cork University Hospital, Cork, IE, <sup>2</sup>Department of Neurology, Mercy University Hospital, Cork, IE, <sup>3</sup>Department of Pathology, University College Cork, Cork, IE

**Keywords:** Chorea–acanthocytosis, neuroacanthocytosis, Huntington disease, chorea, epilepsy

**Citation:** Murphy OC, O'Toole O, Hand CK, Ryan AM. Chorea–acanthocytosis and the Huntington disease allele in an Irish family. *Tremor Other Hyperkinet Mov.* 2018; 8. doi: 10.7916/D8R22J6M

\*To whom correspondence should be addressed. E-mail: omurphy2@jhmi.edu

**Editor:** Elan D. Louis, Yale University, USA

**Received:** August 27, 2018 **Accepted:** October 3, 2018 **Published:** October 26, 2018

**Copyright:** © 2018 Murphy et al. This is an open-access article distributed under the terms of the Creative Commons Attribution–Noncommercial–No Derivatives License, which permits the user to copy, distribute, and transmit the work provided that the original authors and source are credited; that no commercial use is made of the work; and that the work is not altered or transformed.

**Funding:** None.

**Financial Disclosures:** Olwen Murphy has received educational funding from Roche.

**Conflicts of Interest:** The authors report no conflicts of interest.

**Ethics Statement:** This study was performed in accordance with the ethical standards detailed in the Declaration of Helsinki and all patients provided written informed consent.

## 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).<sup>1</sup> 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,<sup>2</sup> 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
<i>VPS13A</i> 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 1

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.<sup>3</sup>

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.<sup>4,5</sup> Furthermore, while routine laboratory techniques actually demonstrate limited sensitivity in detecting acanthocytosis, the use of isotonicity diluted blood and unfixed wet blood preparation improves sensitivity and specificity.<sup>6</sup> In addition, muscle creatine kinase is another useful blood marker that is almost ubiquitously elevated in affected individuals.<sup>7</sup>

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.<sup>7</sup> 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.<sup>7</sup>

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).<sup>8</sup> 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  $\geq 36$  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.<sup>9</sup> 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),<sup>10</sup> 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).<sup>9</sup> 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;<sup>11</sup> therefore, HD alleles in the reduced penetrance range that become symptomatic typically cause late-onset disease, sometimes with no family history of the disorder.<sup>12</sup> However, accurately determining age of onset is challenging in HD,<sup>13</sup> 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.<sup>14</sup> 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,<sup>15–17</sup> potential therapeutic targets may be identified in future.

### References

1. Walker RH. Untangling the thorns: advances in the neuroacanthocytosis syndromes. *J Mov Disord* 2015;8:41–54. doi: 10.14802/jmd.15009
2. Merwick A, Mok T, McNamara B, Parfrey NA, Moore H, Sweeney BJ, et al. Phenotypic variation in a Caucasian kindred with chorea-acanthocytosis. *Mov Disord Clinical Pract* 2015;2:86–89. doi: 10.1002/mdc3.12117
3. Föller M, Hermann A, Gu S, Alesutan L, Qadri SM, Borst O, et al. Chorein-sensitive polymerization of cortical actin and suicidal cell death in chorea-acanthocytosis. *FASEB J* 2012;26:1526–1534. doi: 10.1096/fj.11-198317
4. Adjobo-Hermans MJ, Cluitmans JC, Bosman GJ. Neuroacanthocytosis: observations, theories and perspectives on the origin and significance of acanthocytes. *Tremor Other Hyperkinet Mov* 2015;5. doi: 10.7916/D8VH5N2M
5. Bayreuther C, Borg M, Ferrero-Vacher C, Chaussonot A, Lebrun C. [Chorea-acanthocytosis without acanthocytes]. *Rev Neurol (Paris)* 2010;166:100–3.
6. Storch A, Kornhass M, Schwarz J. Testing for acanthocytosis. A prospective reader-blinded study in movement disorder patients. *J Neurol* 2005;252:84–90. doi: 10.1007/s00415-005-0616-3
7. Velayos Baeza A, Dobson-Stone C, Rampoldi L, Bader B, Walker RH, Danek A, et al. Chorea–acanthocytosis. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. *GeneReviews*®. Seattle, WA: University of Washington, Seattle; 1993–2016. (updated 2014 January 30). Available from <http://www.ncbi.nlm.nih.gov/books/NBK1387/>
8. Liu J, Heinsen H, Grinberg LT, Alho E, Amaro E, Pasqualucci CA, et al. Subcortical neurodegeneration in chorea: similarities and differences between chorea-acanthocytosis and Huntington's disease. *Parkinsonism Relat Disord* 2018;49:54–59. doi: 10.1016/j.parkreldis.2018.01.009
9. Kay C, Collins JA, Miedzzybrodzka Z, Madore SJ, Gordon ES, Gerry N, et al. Huntington disease reduced penetrance alleles occur at high frequency in the general population. *Neurology* 2016;87:282–288. doi: 10.1212/WNL.0000000000002858
10. Quarrell OW, Rigby AS, Barron L, Crow Y, Dalton A, Dennis N, et al. Reduced penetrance alleles for Huntington's disease: a multi-centre direct observational study. *J Med Genet* 2007;44:e68. doi: 10.1136/jmg.2006.045120
11. Langbehn DR, Hayden MR, Paulsen JS; and the PREDICT-HD Investigators of the Huntington Study Group. CAG-repeat length and the age of onset in Huntington disease (HD): a review and validation study of statistical approaches. *Am J Med Genet B Neuropsychiatr Genet* 2010;153B:397–408. doi: 10.1002/ajmg.b.30992
12. Koutsis G, Karadima G, Kladi A, Panas M. Late-onset Huntington's disease: diagnostic and prognostic considerations. *Parkinsonism Relat Disord* 2014;20:726–730. doi: 10.1016/j.parkreldis.2014.03.017
13. Orth M, Schwenke C. Age-at-onset in Huntington disease. *PLoS Curr* 2011;3:RRN1258. doi: 10.1371/currents.RRN1258

14. Ranen NG, Stine OC, Abbott MH, Sherr M, Codori A-M, Franz ML, et al. Anticipation and instability of IT-15 (CAG)<sub>n</sub> repeats in parent-offspring pairs with Huntington disease. *Am J Hum Genet* 1995;57:593–602.
15. De Franceschi L, Scardoni G, Tomelleri C, Danek A, Walker RH, Jung HH, et al. Computational identification of phospho-tyrosine sub-networks related to acanthocyte generation in neuroacanthocytosis. *PLoS One* 2012;7:e31015. doi: 10.1371/journal.pone.0031015
16. Siegl C, Hamminger P, Jank H, Ahting U, Bader B, Danek A, et al. Alterations of red cell membrane properties in neuroacanthocytosis. *PLoS One* 2013;8:e76715. doi: 10.1371/journal.pone.0076715
17. De Franceschi L, Tomelleri C, Matte A, Brunati AM, Bovee-Geurts PH, Bertoldi M, et al. Erythrocyte membrane changes of chorea-acanthocytosis are the result of altered Lyn kinase activity. *Blood* 2011;118:5652–63. doi: 10.1182/blood-2011-05-355339