

ONLINE MUTATION REPORT

Neuroferritinopathy in a French family with late onset dominant dystonia

P F Chinnery, A R J Curtis, C Fey, A Coulthard, D Crompton, A Curtis, A Lombès, J Burn

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We recently described a dominantly inherited movement disorder in a large family from Cumbria in the north west of England resulting from an adenine insertion at position 460-461 in the ferritin light polypeptide gene (*FTL*).¹ The disease presented between the ages of 38 and 58 years with chorea in some subjects, focal dystonia in other subjects, and an akinetic rigid parkinsonian syndrome in others. Brain imaging showed basal ganglia cavitation that was confirmed at necropsy. Neuronal loss was accompanied by the formation of neuroaxonal spheroids, with intraneural and extraneural iron deposition. Serum ferritin levels were low in the presence of normal serum iron, transferrin and haemoglobin levels. The results of these investigations provided a direct link between a primary disorder of iron storage metabolism and a late onset neurodegenerative movement disorder.¹

Cumbria has a stable, largely white population of Anglo-Saxon and Norman origins. All of the affected subjects described in the original report lived within a 30 mile radius and were traced, using parish records, back to a probable common founder born around 1790.¹ A further 10 familial cases with the same mutation were found by screening over 100 patients from northern England with undiagnosed extrapyramidal disease and a small number of other cases referred to us from other parts of the country. The nature of the mutation and our report here of a common haplotype around the gene suggested to us that neuroferritinopathy would be a rare disorder in the UK, likely to have been inherited from a single founder.

However, a careful review of published reports identified a number of potentially similar families outside the United Kingdom, including one family from the north of France.

SUBJECTS AND METHODS

Clinical features

The French family consisted of seven subjects with dystonia as the primary clinical feature who developed symptoms between 24 and 58 years of age.² Additional features included dysarthria, chorea, parkinsonism, blepharospasm, and cerebellar signs. Detailed cognitive testing showed a frontal syndrome in two subjects and dementia in one. Mitochondrial respiratory chain defects were reported in four subjects from whom samples were available and magnetic resonance imaging (MRI) in three living subjects showed cystic changes within the basal ganglia that were similar to the abnormalities seen in the most affected patients in the original Cumbrian family (fig 1).

Molecular genetic analysis

Mutation analysis for the *FTL* exon 4 mutation (460-461InsA) was carried out by PCR amplification of total genomic DNA followed by *Eco*NI restriction digestion as described previously.¹ Haplotype analysis was carried out using microsatellite markers flanking the *FTL* gene. Patients were

Key points

- We recently described a novel autosomal dominant basal ganglia disorder caused by an adenine insertion at position 460-461 of the gene for ferritin light polypeptide (*FTL*) in a large family from Cumbria in the north west of England.
- Here we report the same mutation in a French family that shares only one intragenic microsatellite marker with 10 British families.
- It is possible that the British and French families have a common but distant ancestor or that the same mutation has arisen independently on two occasions.

genotyped using an ABI Prism 310 automated sequencer and haplotypes were reconstructed manually. Marker details and primer sequences were as follows: D19S596, D19S879, HRC.PCR3, D19S604, D19S867, and D19S866 were identified from the Marshfield chromosome 19 genetic linkage map (<http://research.marshfieldclinic.org/genetics/>) and span 3.47 cM. The physical order and position of these markers was determined from the draft genome sequence obtained from UCSC Genome Browser (<http://genome.ucsc.edu/index.html>; Dec 22, 2001 Freeze). Additional repeat tracts were identified in a BAC that contains the *FTL* gene (AC026803) and polymorphism determined using a panel of normal DNA samples. These included the previously described marker 31598C for which primers sequences were obtained from the Genome Database (<http://www.gdb.org>). Primer sequences for the novel markers along with PCR product lengths in parentheses are given below.

REP9/F: 5'-atgctgggattaagccatgagc-3' and /R: 5'-gctgtggctgggtattacagc-3' (223-253 bp); REP8a/F: 5'-gaccaaaatgaatcagcctgg-3' and /R: 5'-tttctgccacttgaccaagg-3' (114-128 bp); REP8b/F: 5'-ccttgtaagtggcagaaa-3' and /R: 5'-ttgtacctgtctcctcacacc-3' (154-178 bp).

RESULTS

The *FTL* mutation described in the original Cumbrian family was identified in affected subjects from the French family by *Eco*NI digestion of the exon 4 PCR product. Microsatellite analysis showed the likely presence of a common haplotype in the affected members of the UK families and a different haplotype shared by the affected members of the French family (table 1). The two haplotypes only share an allele at one marker, D19S879, which lies approximately 100 kb telomeric of the *FTL* mutation.

DISCUSSION

Here we describe the first non-British family with a mutation in the *FTL* gene causing neuroferritinopathy. The clinical phenotype of the French family is similar to the original

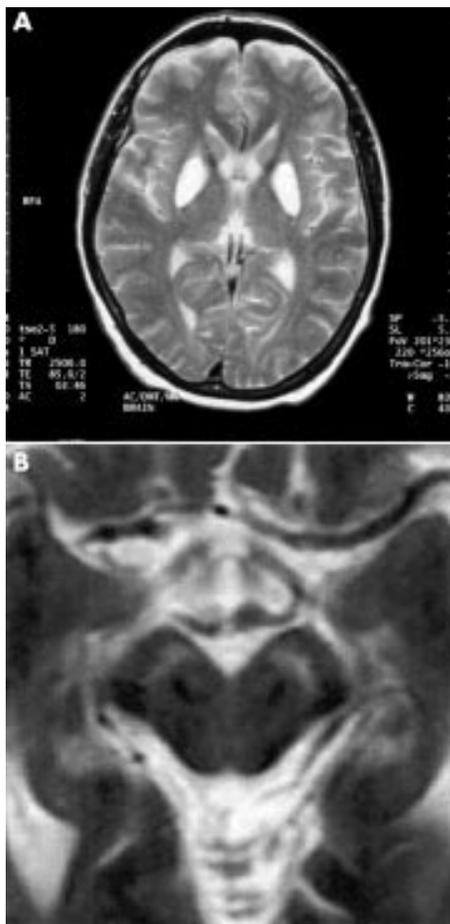


Figure 1 (A) Axial T2 weighted image at the level of the corpus striatum in a 49 year old patient with neuroferritinopathy from the Cumbrian family. There is symmetrical cystic degeneration of the globus pallidus and putamen, with low signal intensity in the internal capsule, similar to the appearances reported by Caparros-Lefebvre *et al.*² (B) Axial T2 weighted image through the midbrain in a 69 year old patient with neuroferritinopathy from the Cumbrian family. There is symmetrical increased signal intensity involving the substantia nigra and the central aspect of the red nuclei bilaterally. These appearances are similar to the figures illustrating case 5 in the French family described by Caparros-Lefebvre *et al.*²

Cumbrian family. Both display a range of different movement disorders including dystonia, chorea, and a Parkinsonian syndrome. Both blepharospasm and a spastic dysarthrophonia

were prominent in some subjects. Two members of the French family developed symptoms in their 20s, and one young woman from Cumbria had symptoms dating back to a similar age, but all other cases became apparent in the late 30s or older. Cognitive features were not prominent in the original Cumbrian family, but two of the four subjects in the French family had evidence of frontal lobe dysfunction, and one of five subjects had dementia. A similar neuropsychological deficit has recently been described in another British patient related to the original Cumbrian pedigree.³ This is not surprising, given the widespread pathology seen in our family.¹ The accumulation of iron, and the subsequent neurodegeneration were seen throughout the brain, including frontal cortex and subcortical structures.

There are two possible explanations for the identification of the same adenine insertion at position 460-461 of the *FTL* gene in both French and UK families. Exactly the same mutation at position 460-461 may have occurred on two separate occasions. This would raise the possibility that this is a “mutational hotspot”. Evidence for separate mutation events is provided by the presence of a different haplotype flanking *FTL* in the two sets of affected subjects. Alternatively, the two families may share a common ancestor in whom this *FTL* mutation arose. Evidence for this is provided by the presence of the shared allele of D19S879, which lies approximately 100 kb telomeric to the gene. However, allele frequency data reported in the Genome Database indicate that the allele in question may be relatively common within the general population (frequency 0.25-0.30). Furthermore, all four of the additional polymorphic markers, including REP8a and 8b, which lie approximately 60 kb centromeric of *FTL*, showed different alleles in the two haplotypes.

The mean lifespan in western Europe only exceeded 45 years in 1901.⁴ Since the majority of patients with neuroferritinopathy develop symptoms after this age, the disorder will have had a very low penetrance until relatively recently. Genealogical evidence suggests that at least part of the Cumbrian family may have originated from a Norman founder called Coutharde, who came to Britain at the time of the Norman Conquest following 1066. Such a time scale would result in a severe reduction of the shared region around the *FTL* gene by a combination of mutation and recombination events. Distinguishing between the two possibilities would require the development of additional microsatellite markers and single nucleotide polymorphisms even closer to the site of the mutation.

Whichever explanation is correct, this report clearly shows that neuroferritinopathy is not a “British disease” and there may be many more cases world wide. Perhaps the most intriguing features of the French family are the clear cut

Table 1 Haplotypes of markers around the *FTL* mutation in affected subjects in the Cumbrian (UK) and French families

Marker	Linkage (cM)*	Physical (Mb)†	Haplotypes	
			UK	French
D19S596	74.07	65.98	5	3
31598C	–	66.03	5	6
REP9	–	66.04	3	6
REP8b	–	66.16	5	4
REP8a	–	66.16	4	2
<i>FTL</i> exon 4 mutation	–	66.22	insA	insA
D19S879	75.41	66.31	3	3
HRC.PCR3	75.41	66.45	9	8
D19S604	75.41	66.69	2	4
D19S867	77.54	67.35	6	5
D19S866	77.54	67.59	9	2

*Marshfield genetic linkage map of chromosome 19: <http://research.marshfieldclinic.org/genetics/>

†UCSC Genome Browser (December 2001 freeze): <http://genome.ucsc.edu/index.html>

abnormalities of mitochondrial respiratory chain function that were measured in skeletal muscle from four patients.² These involved complex I and III in all three subjects who were studied in detail, and a mild defect of complex IV seen in one subject. This raises the possibility that mitochondrial dysfunction may play an important part in the pathophysiology of neuroferritinopathy. Neuronal iron accumulation is important in Friedreich's ataxia, where excess iron within mitochondria is associated with abnormalities of the iron-sulphur cluster enzymes including complexes I and III.³ Further studies are under way to determine whether intra-mitochondrial iron storage might be important in neuroferritinopathy.

We have shown that a primary disorder of iron storage is directly responsible for a dominantly inherited progressive neurodegenerative disorder in two European families.^{1,2} Our understanding of the pathophysiology raises important questions about treatment aimed at modulating neuronal iron stores. It is therefore important to identify further cases because the investigation of the families may have broader implications for our understanding of neurodegenerative movement disorders and their treatment.

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Authors' affiliations

P F Chinnery, Department of Neurology, The University of Newcastle upon Tyne, UK

P F Chinnery, A R J Curtis, C Fey, D Crompton, A Curtis, J Burn, Institute of Human Genetics, The University of Newcastle upon Tyne, UK

A Coulthard, Department of Radiology, Newcastle upon Tyne Hospitals NHS Trust, UK

A Lombès, INSERM UR523, Institut de Myologie, Hôpital de La Salpêtrière, Paris, France

Correspondence to: Dr P F Chinnery, Department of Neurology, The Medical School, Framlington Place, Newcastle upon Tyne NE2 4HH, UK; P.F.Chinnery@ncl.ac.uk

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