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Neuroferritinopathy: From ferritin structure modification to pathogenetic mechanism

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ABSTRACT

Neuroferritinopathy is a rare, late-onset, dominantly inherited movement disorder caused by mutations in L-ferritin gene. It is characterized by iron and ferritin aggregate accumulation in brain, normal or low serum ferritin levels and high variable clinical feature. To date, nine causative mutations have been identified and eight of them are frameshift mutations determined by nucleotide(s) insertion in the exon 4 of L-ferritin gene altering the structural conformation of the C-terminus of the L-ferritin subunit. Acting in a dominant negative manner, mutations are responsible for an impairment of the iron storage efficiency of ferritin molecule. Here, we review the main characteristics of neuroferritinopathy and present a computational analysis of some representative recently defined mutations with the purpose to gain new information about the pathogenetic mechanism of the disorder. This is particularly important as neuroferritinopathy can be considered an interesting model to study the relationship between iron, oxidative stress and neurodegeneration.

Contents

Abbreviations: NF, Neuroferritinopathy; *FTL1*, Ferritin light chain gene; FtL, Ferritin light chain protein; FtH, Ferritin heavy chain protein; Tg, transgenic; WT, wild type; ROS, reactive oxygen species; MRI, magnetic resonance imaging.

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Neuroferritinopathy

The Neuroferritinopathy (NF) (OMIM, 606159, also labeled as hereditary ferritinopathies or NBIA3) (Curtis et al., 2001; Ohta and Takiyama, 2012) is a rare monogenic autosomal-dominant disease caused by mutations in the gene encoding the ferritin L-chain (*FTL1*)

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one of the two subunits of the main iron storage protein. The disease is classified as belonging to a growing collection of movement disorders named Neurodegeneration with Brain Iron Accumulation (NBIA). The NBIA are a group of degenerative extrapyramidal monogenic genetic diseases determining, in affected patients, radiological evidence of focal accumulation of iron in the brain, usually in the basal ganglia. They are characterized by early- or late onset with main symptoms that are problems encountered in the movement, spasticity and cognitive deficits (Levi and Finazzi, 2014). Among the causative genes, it can be distinguished between those encoding proteins directly involved in iron metabolism (*FTL1* and *CP*) and those encoding proteins responsible for other functions, such as: i) fatty acid metabolism and other mitochondrial functions (*PANK2*, *PLA2G6*, *C19orf12*, *COASY*, and *FA2H* genes); ii) lysosomal and autophagosome activity (*WDR45* and *ATP13A2* genes); and iii) a nuclear protein of still unknown function (*C2orf37* gene) (for an extensive review see Levi and Finazzi, 2014). A small subgroup of the identified NBIA cases is represented by NF, which is the only form inherited in an autosomal dominant manner.

From an epidemiological point of view, it is important to note that this disorder is extremely rare, thus so far, there is no available data on the prevalence of the disease in the population. However, due to overlapping of symptoms and MRI signs with the other forms of NBIA, it is conceivable that other incorrectly diagnosed cases may exist.

Genetics

NF was initially identified by Curtis among the members of a large family from the Cumbrian region of North England (Curtis et al., 2001). Using a genome wide linkage analysis, the authors identified the insertion of an adenine in position c.460 of exon 4 of the *FTL1* gene as the causative mutation of a previously unacknowledged neurodegenerative disorder that they named neuroferritinopathy (Curtis et al., 2001). Initially, the disease appeared to be confined to the population of North England, where more than 40 cases with the same mutation were identified, suggesting that they originated from a common founder (Chinnery et al., 2007). Subsequently, other cases were described in different parts of the world. Up to now, other 8 types of mutations have been identified in different ethnic groups (Vidal et al., 2003); (Mancuso et al., 2005);(Maciel et al., 2005); (Ohta et al., 2008); (Kubota et al., 2009); (Devos et al., 2009; Moutton et al., 2014; Nishida et al., 2014; Storti et al., 2013); they are reported in Table 1, adopting the HGVS nomenclature (den Dunnen and Antonarakis, 2000 and www.hgvs.org/mutnomen). The *FTL1* gene is located on chromosome 19q13.33 and it is composed by 4 exons and 3 introns. All the NF causative mutations, except one, are located on the exon 4 of the gene in a short DNA fragment of 58 nucleotides in length. They are single or multiple (from 2 to 16) nucleotides resulting in an altered sequence and length of the C-terminal portion of the encoded protein (Fig. 1). Interestingly, the mutation c.469_484dup, involving the duplication of 16 nucleotides, has been identified in two patients belonging to different and geographically distant ethnic groups, i.e. Japan (Ohta et al., 2008) and Italy (Storti et al., 2013). Together, all these observations insinuate that exon 4 of the *FTL1* might be recognized as a mutation hotspot. It must be noted that another region of about 70 nts in length characterized by high mutation frequency was identified in *FTL1* (Ferrari et al., 2006); (Luscieti et al., 2013). The region is located at 5′ UTR of the L-ferritin mRNA, corresponding to the iron responsive element sequence (IRE). It folds in a stem loop structure, and is involved in the iron-mediated post-trascriptional regulation of ferritin expression (Hentze et al., 2010). Anomalies in IRE sequence cause a disease named hereditary hyperferritinemia cataract syndrome (HHCS, OMIM# 600886). It is a rare autosomal dominant disease characterized by increased serum ferritin levels and early onset of bilateral cataract (Girelli et al., 1995). Affected individuals show high serum ferritin levels, with normal serum iron and transferrin saturation, and without signs of systemic or brain iron overload (Cazzola, 2002). The lack of post-transcriptional control of ferritin expression produces L-ferritin (FtL) accumulation in lens, where it induces cataract formation by altering the delicate equilibrium between other water-soluble proteins, such as crystallins (Levi et al., 1998).

Table 1
List of reported cases and related mutations of neuroferritinopathy.

Families from:	DNA[a] mutations	Protein variant[b]	Symptomatology	Serum ferritin[c]	References
Cumbrian region (UK)	c.460dupA	p.Arg154LysfsX27	Extrapyramidal dysfunction choreathetosis, dystonia, spasticity, rigidity	4–16 (N.R.)	Curtis et al. (2001)
Northwest of UK	c.460dupA	p.Arg154LysfsX27	Extrapyramidal dysfunction including palatal tremor and cognitive decline	60 (25–350)	Wills et al. (2002)
France	c.460dupA	p.Arg154LysfsX27	Dystonia, dysarthria, chorea, parkinsonism, blepharospasm, cerebellar signs	N.R.	Chinnery (2003)
North of UK	c.460dupA	p.Arg154LysfsX27	Extrapyramidal dysfunction	3–23 (25–400)	Crompton (2005)
South of UK	c.460dupA	p.Arg154LysfsX27	Generalized dystonia, psychiatric symptoms	30 (18–300)	Mir (2005)
France	c.497_498dup	p.Phe167SerfsX26	Tremor, cerebellar ataxia, parkinsonism and pyramidal signs, behavioral disturbances, cognitive dysfunction	Normal	Vidal (2003)
Gypsy ancestry	c.285G > A	p.Ala96Thr	Parkinsonism, ataxia, and corticospinal signs	16 (20–300)	Maciel (2005)
French Canadian and Dutch ancestry	c.442dupC	p.His148ProfsX33	Dystonia, dysarthria, chorea, blepharospasm, cerebellar signs and mitochondrial respiratory chain defects	14 (10–291)	Mancuso (2005)
Japan	c.469_484dup	p.Leu162ArgfsX24	Tremor, hypotonia, hyperextensibility, aphonia and cognitive impairment	5 (33–330)	Ohta et al. (2008)
France	c.458dupA	p.His153GlnfsX28	Dystonia, dysarthria, dysphagia	N.R.	Devos et al. (2009)
Japan	c.439_442dup	p.His148ArgfsX34	Chorea, tremor, dyskinesia, dysarthria, dysphagia	46 (40–200)	Kubota et al. (2009)
Italy	c.469_484dup	p.Leu162ArgfsX24	Axial ataxia, severe dysarthria, dystonia, bilateral hand tremor, parkinsonism	3 (17–400)	Storti et al. (2013)
Japan	c.468_483dup	p.Leu162TrpfsX24	Chronic headache, orolingual dystonia, disarthria, cerebellar ataxia, pyramidal tract signs, psychiatric symptoms	20 (5–204)	Nishida et al. (2014)
France	c.468dupT	p.Gly157TrpfsX24	Dystonia, dysarthria, dysphagia,dysmetria	49 (80–250)	Moutton et al. (2014)

DNA mutations (a) and protein variants (b) are named according to the HGVS nomenclature guidelines (den Dunnen 2000). Nucleotides and aminoacid numbers correspond to CCDS database entry 33070.1.
c: Serum ferritin values were reported in μg/L, in brackets the reference ranges for normal individuals,
N.R. = not reported, Normal = value in normal range.