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Brief communication

Portuguese family with the co-occurrence of frontotemporal lobar degeneration and neuronal ceroid lipofuscinosis phenotypes due to progranulin gene mutation

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ABSTRACT

We and others have reported heterozygous progranulin mutations as an important cause of frontotemporal lobar degeneration (FTLD). It has been identified a complete progranulin deficiency because of a homozygous mutation in a sibling pair with neuronal ceroid lipofuscinosis (NCL). Here, we describe the first case of NCL caused by a homozygous progranulin mutation segregating in a family with neuropathological confirmed FTLD. In this FTLD-NCL family, we detail the clinical phenotype, neuropsychological evaluation and imaging data of our proband harboring a homozygous mutation, c.900_901dupGT, with serum progranulin level (<6 ng/mL). Symptoms included rapidly progressive visual deficit, slightly dysarthria, and cerebellar ataxia. The electroretinogram confirmed a severe attenuation of rod and cone responses compatible with retinal dystrophy diagnosis and magnetic resonance imaging showed severe global cerebellar atrophy. In contrast, heterozygous relatives presented behavioral variant of frontotemporal dementia (FTD) and some also developed extrapyramidal features compatible with corticobasal syndrome. Our findings suggest the importance of assessing serum progranulin levels in suspected recessive adult-onset NCL cases. Overall, a more holistic neurologic intervention is needed to guarantee a proper genetic counseling in cases like the present family where two distinct phenotypes are generated according to the individuals' mutation state.

1. Introduction

Heterozygous mutations in the progranulin (*GRN*) gene are a common cause of frontotemporal lobar degeneration (FTLD) with transactive response DNA binding protein 43 kDa (TDP-43) inclusions (Baker et al., 2006; Cruts et al., 2006). Thus far, 70 *GRN* mutations in 233 families are currently known worldwide, which account for up to 20% of the familial FTLD-TDP cases (http://www.molgen.vibua.be/FTDMutations/; Cruts et al., 2012). The clinical presentation of mutation carriers is extremely heterogeneous in terms of symptoms, disease duration and age of onset, even in family members carrying the same mutation (Chen-Plotkin et al., 2011). Besides the classical FTLD presentations, there is also in some cases an involvement of the extrapyramidal and motor systems (Boeve, 2007). Most of the mutations reported are loss-of-function mutations, leading to GRN haploinsufficiency and resulting in a severe reduction of GRN levels in several biological fluids such as cerebrospinal fluid (CSF), plasma, and serum, even in unaffected mutation carriers (Almeida et al., 2014).

Surprisingly, a homozygous loss-of-function mutation resulting in a complete loss of protein was reported in 2 siblings with recessive adult-onset neuronal ceroid lipofuscinosis (NCL). In that study, using massively parallel sequencing, a homozygous four base pairs deletion, c.813_816del (p.Thr272Serfs*10) was identified in the siblings (Smith et al., 2012). Besides the usual association of epilepsy, ataxia and subtle cognitive dysfunction, they also developed visual failure which is unusual in adult-onset forms of NCL, as well as palinopsia related to hiperexcitability of the occipital cortex (Canafoglia et al., 2014). Noteworthy, this particular mutation has been previously identified in patients with FTLD phenotype with ubiquitinated TDP-43 inclusions (Benussi et al., 2008; Le Ber et al., 2008; Yu et al., 2010).

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Here, we describe an FTLD-NCL family, in which an NCL case is caused by a homozygous progranulin mutation segregating in a family with neuropathologic confirmed FTLD. Clinical phenotypes, neuropsychological and imaging evaluations are detailed since it represents a unique opportunity to investigate the genotype-phenotype correlations regarding GRN dosage effect.

2. Material and methods

All the available family members provided a written consent for their participation in the study. The studied individuals underwent a thorough biochemical, neurologic and imaging evaluations at the Neurometabolic unit and/or Memory clinic of the Centro Hospitalar e Universitário de Coimbra. Detailed family history, neurologic examination, neuropsychological assessment, and brain imaging were performed. The diagnosis of FTLD was based on the Lund and Manchester clinical criteria revised by the Work Group on Frontotemporal Dementia and Pick's Disease (McKhann et al., 2001) and more recently according to the International Behavioural Variant Frontotemporal Dementia Criteria Consortium for bvFTD (Rascovsky et al., 2011). The clinical diagnosis of adult-onset NCL was based on the age of onset and clinical features presented by the index patient which included visual loss, progressive intellectual, and motor deterioration. The laboratory determinations such as mutation analysis, GRN level assessment, and CSF analysis were performed as previously described by our group (Almeida et al., 2014; Baldeiras et al., 2012).

3. Results

Our index case (Fig. 1, III1) is a Caucasian 34-year-old woman with the diagnosis of adult-onset NCL (*CLN11,* MIM 138945). She was the first child of healthy Portuguese parents working in France. Until 24 years of age, she had normal psychomotor development, no learning disabilities, completed 12 years of education and was employed as a factory worker. At 25-year old, she presented a rapidly progressive visual deficit leading to incapacitating amaurosis within 3 years and later on developed progressive disequilibrium and dysarthria. She was firstly referred to the Neurometabolic unit of Centro Hospitalar e Universitário de Coimbra, at the age of 30 years. Examination revealed a bilateral visual acuity of 1 of 10, cerebellar ataxia with assynergia, slight dysarthria, and an ataxic gait. The electroretinogram confirmed a severe attenuation of rod and cone responses compatible with the diagnosis of retinal dystrophy of both cellular elements (Fig. 2) and magnetic resonance imaging showed severe global cerebellar atrophy (Fig. 3). Although the patient also displayed jerks elicited by sudden-sounds and an isolated episode of faint, myoclonus or seizures were never observed and the repeated electroencephalograms were normal. At this time, the suspected clinical diagnosis included NCL, mitochondrial disorder, and SCA 7. Electron microscopy analysis of a skin biopsy revealed sparse nonspecific lipofuscin inclusion, and the molecular studies were negative for *CLN1, CLN2, CLN4, CLN13*, excluding the most frequent forms of Adult NCL. Biochemical, pathologic, and molecular studies on blood and muscle biopsy ruled out mitochondrial disease. The expansion in the *ATXN7* gene was also excluded, discarding the hypothesis of SCA 7. She remained with no proven clinical diagnosis until the age of 35 years (2014), when her mother (Fig. 1, II5) started with subtle complaints of cognitive impairment at 60 years of age, and thereby was investigated at the Memory Clinic of the same hospital. Family referred executive dysfunction with impact on instrumental activities and some unusual symptoms, namely spatial disorientation and attention deficit on driving, always deviating to the right side. The neurologic examination revealed slight paratonia and frontal release signs more pronounced on the left side, left visual inattention but no alien limb. Considering mental assessment, the scores obtained in the Minimental State Examination (Guerreiro et al., 1994) and on the Montreal Cognitive Assessment (Freitas et al., 2010) were both abnormal and compatible with mild dementia (respectively, 21 of 30 and 11 of 30). Comprehensive neuropsychological assessment revealed marked frontal dysfunction with impairment in tests of motor control (Luria), verbal initiative (Verbal Semantic Fluency) and

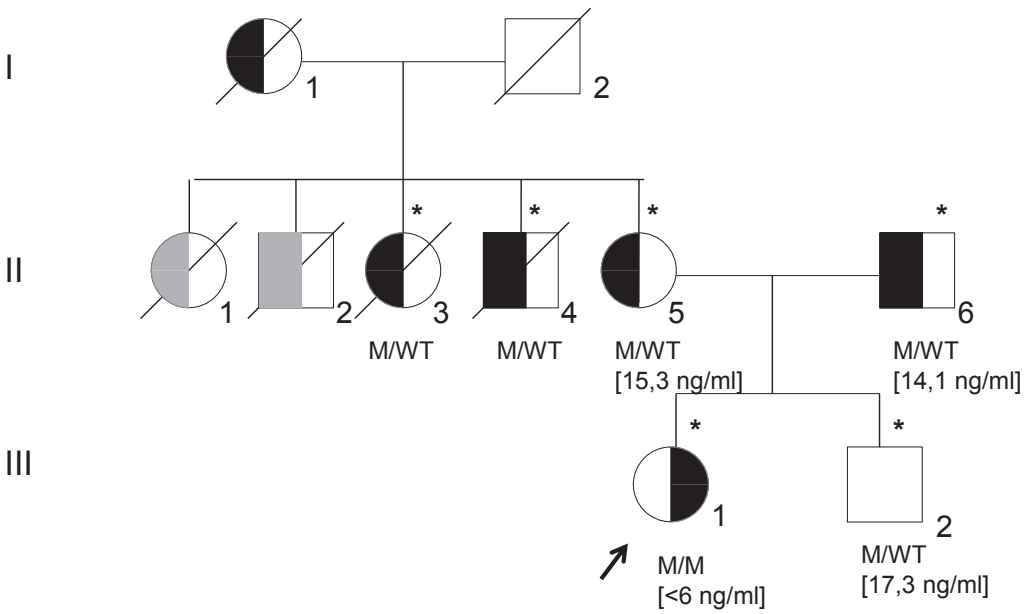

Fig. 1. Family pedigree (arrow indicates proband) indicating the mutation status for GRN mutation, c.900_901dupGT. M/WT = heterozygous for the mutation; M/M = homozygous for the mutation. Serum progranulin values are shown inside square brackets (ng/mL). Black symbols represent patients affected with behavioral variant of frontotemporal dementia or dementia (left-side filled) or Neuronal Ceroid Lipofuscinosis (right-side filled). The grey symbol indicates signs of dementia plus Parkinsonism (left-side filled). White symbols represent unaffected individuals. The Roman numeral to the left of the pedigree denotes the generation. Individuals with obtainable DNA are shown with an asterisk to the right of the symbol. Bars indicate deceased family members. Abbreviation: GRN, progranulin.