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Expanding Glucocerebrosidase Involvement in Neurodegeneration: D419H Mutation Causing Dementia with Lewy Bodies

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Abstract

Mutations in the glucocerebrosidase gene (GBA) are a common genetic risk factor for Dementia with Lewy Bodies (DLB). Hereby, we describe an Italian family with three DLB relatives harboring the D419H *GBA* variant. The pedigree analysis indicates a dominant inheritance pattern, suggesting that heterozygous *GBA* mutations may differently affect the risk of Parkinson-dementia syndromes. This should be taken into account for genetic counseling in relatives of patients with GBA associated Parkinson's Disease/DLB.

Keywords: Glucocerebrosidase; Dementia with lewy bodies; Parkinson's disease

Introduction

Interest in glucocerebrosidase (GBA) gene variants has markedly increased since the coexistence with Parkinsonian symptoms in Gaucher disease (GD) has been suggested, and heterozygous *GBA* mutations are considered the most common genetic risk factor for Parkinson's Disease (PD) to date [1]. So far, more than 350 different *GBA* mutations have been identified, and several have been linked to PD [2]. Generally, these PD subjects show an earlier onset of parkinsonian motor symptoms and a higher risk of cognitive impairment than those without *GBA* mutations.

GBA mutations have been encountered with higher frequency in subjects with Dementia with Lewy Bodies (DLB) and, as in PD, they also seem to affect age of onset, symptom severity and rate of progression [3,4]. DLB penetrance in *GBA* mutation carriers is unknown, but specific *GBA* mutations have been associated with a greater risk of a Parkinson-dementia syndrome [5].

Materials and Methods

We conducted a genetic study to identify potential pathogenic gene defects in PDD (Parkinson's disease Dementia) and DLB patients referred to the Movement Disorders Center of Pisa. The procedures were approved under the Research Local Ethics Committee Protocols and a written informed consent was obtained from all participants. Blood samples (3 mL) were collected in K- EDTA tubes, and genomic DNA was isolated from peripheral blood leukocytes by means of the QIAamp® Blood Mini Kit (Quiagen, Milan, Italy) according to the manufacturer's protocol.

Specifically, long-range polymerase chain reaction (PCR) was used to selectively amplify the functional GBA gene using primers GBA_F (5'CGACTTTACAAACCTCCCTG3') and GBA_R (5' CCAGATCCTATCTGTGCTGG 3'), as previously described by Siebert and co-workers [6]. Coding sequences and flanking regions (exons 1 to 11) were amplified by PCR using long-range PCR products as templates. The GBA coding region was divided into 10 different amplicons, with exons 10 and 11 analyzed together. Amplicons were purified using 2 µl of ExoSAP (GE Healthcare). Direct DNA sequencing was performed with a BigDye® Terminator Cycle Sequencing kit v. 1.1 (Applied Biosystems, Foster City, CA, USA) following the manufacturer's instructions, and sequences were analyzed with DNA Sequencing Analysis software (Applied Biosystems) in an ABI PRISM® 310 Genetic Analyzer. The nomenclature of the exons and nucleotide position in the cDNA sequence is based on the sequence accession number NM_000157. The nomenclature of amino acid residues using this accession number includes the 39 amino acid residue poly-peptide signal.

Results

We identified an atypical heterozygous *GBA* mutation in a 2-generation family in which 3 members presented with DLB, without signs of GD (Figure 1). They are all of Italian descent and they all live in Tuscany. The G to C change at position 1255 of the cDNA (exon 9 of *GBA*) resulted in a substitution of aspartic acid to histidine at residue 419 of the protein (p.Asp419His; CM054757) (Figure 2). The variant is predicted to be pathogenic by both PolyPhen and the Mutation Taster and other computer prediction programs and occurs at a highly evolutionary conserved amino acid residue and nucleotide position to underlie its functional relevance (Figure 3).

Furthermore, none of the other PDD/DLB patients (a total of 52 patients were prospectively enrolled in our cohort) was found to have this GBA mutation. The D419H variant has been reported in three GD Colombian patients, but it has never been reported in association with parkinsonism and cognitive decline so far [7].

The proband (III:4) is a 67-year-old Italian male, born from non-consanguineous parents, who had DLB diagnosed when he was 62. Onset of first symptoms was two years earlier, initially presenting with "delirium." Within one year, he developed the full clinical phenotype of DLB (dementia, parkinsonism, visual hallucinations, fluctuating cognition and REM sleep behavior disorder, which was also documented with overnight polysomnography) [8]. The diagnosis of DLB was supported by abnormal DatSCAN and hypometabolism in the bilateral occipital lobes seen at fluorodeoxyglucose PET imaging

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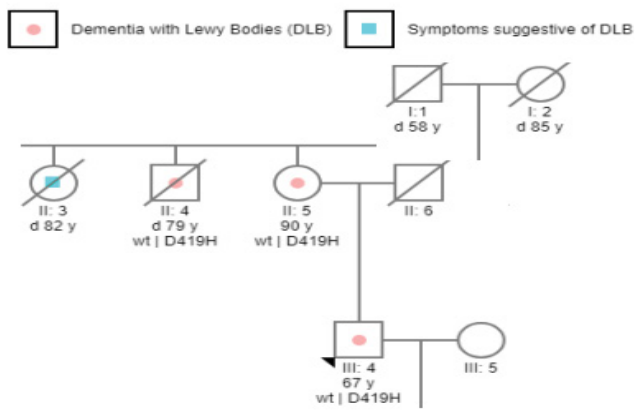

Figure 1: Pedigree showing the GBA D419H variant segregating with dementia with lewy bodies. Alleles are shown as D419H or wt (wild type).

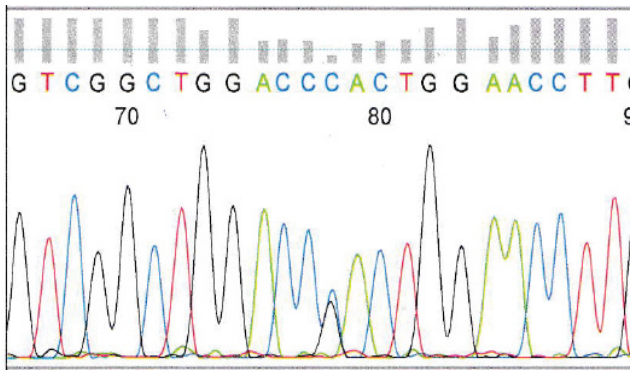

Figure 2: Electropherogram. GBA gene sequencing revealed the G to C mutation at position 1255 of the cDNA (arrow).

Figure 3: Conservation of Asparagine-419 residue in GBA gene shown in PolyPhen-2.

[9]. He was treated with a combination of carbidopa-levodopa medication, showing an initial positive response. Dementia progressed with the development of delusions associated with agitation and rapid neurological deterioration within five years. The patient also suffered of prostatic hyperplasia for which he developed chronic urinary retention and recurrent episodes of urinary tract infection, requiring urinary indwelling catheterization. Mutations in known PD genes were excluded in the proband through custom targeted sequencing [10]. Two family members, the mother (II:5) and a maternal uncle (II:4), were available for genetic screening. Molecular analysis revealed the same *GBA* mutation.

Both members (II:5 and II:4) had been diagnosed with PD, had REM sleep behavior disorder and showed a positive response to levodopa. However, cognitive disturbances and visual hallucinations occurred early. Symptom onset in the proband's mother (II:5) was at 78-yrs, with progressive parkinsonism (without tremor), cognitive difficulties and auditory and visual hallucinations. During the first eight years, she exhibited a good improvement in parkinsonian motor symptoms with levodopa treatment, and she manifested a slowly progressive cognitive decline continuing to function at home without great difficulties for some years. Twelve years after the onset of parkinsonism-dementia syndrome, her condition worsened with progressive functional decline, loss of mobility and of language abilities.

The proband's maternal uncle (individual II:4) had dementia symptoms that began when he was 72 years old. He also developed early motor symptoms with a bilateral symmetric parkinsonism and prominent axial rigidity and bradykinesia, without resting tremor. He experienced a beneficial response to levodopa, but later he manifested severe behavioral disturbances with poor clinical response to multiple psychotropic medications. He died at the age of 79 from acute bronchopneumonia.

Another maternal uncle and the proband's son (individuals II:10 and IV:1) did not exhibit any of DLB symptoms or typical features of GD. After genetic counseling, they were hesitant about predictive testing for themselves, and at the time of interview none had undergone genetic testing. Additionally, family history was notable for a maternal aunt of proband (II:3) with dementia, slowness of movement and gait difficulties. However, she was deceased and this information was not supported by patient's clinical records.

Other second-degree relatives on the same side of the family were reportedly asymptomatic; in particular there was no family history of parkinsonism, cognitive dysfunction or visual hallucinations. The proband's grandmother (I:2) died of "old age" at 85 years of age, while the maternal grandfather (I:1) died in a motor vehicle crash at 58 years of age. All subjects, both affected and unaffected individuals, were also referred to the hematologist, but none had clinical signs typical of the systemic involvement of GD.

Discussion

To our knowledge, this is the first report of the D419H *GBA* mutation in synucleinopathies. We found a pathogenic DLB-causing *GBA* variant in three members of an Italian family, further supporting the strong genetic component of DLB and solidifying the link *GBA*–Lewy body disease as already investigated [4]. Our results agree with previous analyses reporting a classical phenotype in *GBA* mutation carriers, with parkinsonian manifestations similar to those noted in sporadic PD and a favourable response to levodopa [11]. However, in contrast with previous studies, this variant is apparently not associated with an earliest age at onset, gender and disease severity or progression [12].

D419H mutation may represent a severe *GBA* mutation associated with the development of parkinsonism and cognitive decline. This pedigree demonstrates an autosomal-dominant inheritance of a *GBA* mutation, which was never described in DLB, raising the consideration that specific *GBA* variants may be a plausible pathogenic mutations of Lewy body diseases. Thus, our report confirms the complex and

heterogeneous genotype-phenotype correlation in *GBA* mutation carriers. Generally, there is a prevalence of severe *GBA* mutations among patients with PD and carriers of severe mutations have a substantially increased disease risk [13].

Conclusion

Although further studies are needed to support any conclusion on this association, it is still a significant finding because it suggests the opportunity to suspect the heterozygous D419H *GBA* mutation in families presenting with symptoms and signs similar to classical DLB. Analysis of *GBA* gene in families with PD or DLB could identify severe mutations possibly related to the Parkinson-dementia syndrome. Better interpretation of these variants can have practical implications in genetic counseling of patients and their family members and in the understanding the pathological processes in PD and the mechanism that links *GBA* mutations and PD, but it will also important to offer more effective treatments, once available (on-going therapeutic approaches targeting *GBA* will have direct applicability in *GBA*-parkinsonism-dementia) [14].

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Funding Sources and Conflicts of Interest

No specific funding was received for this work. The authors declare that there are no conflicts of interest relevant to this work.

Ethical Compliance Statement

We have read the pages on Ethics in publishing and Ethical guidelines for journal publication and affirm that this work is consistent with those guidelines. We also guarantee that patients have given their consent to anonymously report their clinical reports in accordance with current ethical standards.

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