In-Frame Insertion Mutation in the SPG11 Gene Causes Autosomal Recessive Spastic Paraplegia with Thin Corpus Callosum “In A” Turkish Family with Late Age of Onset of the Phenotype

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Abstract

Autosomal recessive hereditary spastic paraplegia with thin corpus callosum (ARHSP-TCC) is one of the most prevalent forms of complex ARHSP. Mutations in the SPG11 gene are the most common cause for ARHSP-TCC and accounts for up to 70% of all cases. The mutational spectrum of SPG11 gene is broad as all types of DNA alterations are detected in the gene and most mutations lead to a premature truncation of the protein, suggesting “loss of function” as the likely pathogenic mechanism. In the current study, we report a consanguineous Turkish family with ARHSP inheritance manifesting white matter abnormalities including TCC with relatively late age of onset. Sequencing of SPG11 gene revealed a homozygous insertion of 15 nucleotides at position 6886 in exon 38 (c.6886_6900Dup15) leading to an in-frame insertion of five amino acids at codon 2296 (p.K2296_L2300Dup5), which resides within a predicted, highly conserved, intradial ring-cleavage dioxygenase domain (2104 -2381 residues). In silico structural prediction of intradial domain of the mutated Spatacsin protein revealed that the duplication of five amino acids leads to an extra turn in α-helix and a slightly longer loop region. Our structural analysis suggests that it is unlikely that insertion mutation (c.6886_6900Dup15) causes dysfunctional protein rather the minor conformation changes may elicit a “gain of function”, which may be detrimental to endogenous function of Spatacsin thus cause HSP.

Keywords: Spastic paraplegia; SPG11; Thin corpus callosum; In-frame insertion

Introduction

Hereditary spastic paraplegias (HSP) are a heterogeneous group of neurodegenerative disorders, in which the prominent clinical features are progressive spasticity and weakness of the lower limbs [1-4]. On the basis of clinical phenotypes, HSP can be classified into two forms: the pure and the complex HSP. In pure HSP, spasticity occurs in relative isolation. However, when spasticity is associated with additional neurological and/or non-neurological symptoms then it is termed as complex HSP [2,4] Up till now, over 48 HSP loci were mapped and 24 causative genes have been identified. All types of inheritance are reported for HSP, including autosomal dominant, recessive and X-linked.

Autosomal recessive hereditary spastic paraplegia with thin corpus callosum (ARHSP-TCC) is one of the most prevalent forms of complex ARHSP. Besides TCC, the disease is characterised by progressive spastic paraparesis, mild mental retardation with learning difficulties and severe peripheral neuropathy [5-8]. Among ARHSP loci, the TCC phenotype is manifested at least in six sub-types namely, SPG11, SPG15, SPG18, SPG21, SPG32 and SPG46, of which four causative genes have been identified to date, Spatacsin (SPG11), Spastizin (SPG15), ERLIN2 (SPG18) and ACP33 (SPG21) [9-13]. However, the most frequently mutated gene in ARHSP is SPG11 [5,7,8] and accounts for 41-77% of all ARHSP-TCC cases, depending upon the ethnic origin of the selected cohort of patients.

SPG11 gene spans 40 exons and encodes 2443 amino acids Spatacsin protein. The molecular function of Spatacsin is unknown. Spatacsin show broad expression in central nervous system with high expression in cerebellum, cerebral cortex, hippocampus and pineal gland. In silico sequence analysis revealed that Spatacsin consists of a Leucine zipper, a short-coiled coil domain, a Myb domain, a glycosyl hydroxylase F1 signature, intradial ring-cleavage dioxygenase domain and four transmembrane domains [14]. The presence of such domain/motif suggests that Spatacsin is likely involved in vesicular transport. A recent study reported that Spatacsin partially colocalizes with microtubules and vesicles [15].

Screening for mutations in the SPG11 gene by various groups has identified over 120 different mutations in most exons of the gene. The SPG11 mutations are summarized in the Human Gene Mutation Database Professional release 7.1 (http://www.biobase.de/hgmd/pro/start.php). All types of DNA alterations are detected in the SPG11 gene, including missense, nonsense, splice site mutations and insertions/ deletions. With exception of few missense mutations all mutations cause a premature truncation of the protein suggesting “loss of function” as the likely pathogenic mechanism.

Case Report

Patient I13 is the index patient who was first examined at the age of 30 years and followed up for more than 14 years. He manifests a short stature and mild macrocephalus. Initially, gait disturbance in the

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In conclusion, we identified a novel SPG11 gene mutation in a consanguineous Turkish family causing a form of ARHSP with relatively late age of onset and white matter abnormalities including TCC. In silico structural prediction of intradiol domain of the mutated Spatacsin protein revealed no major conformational changes in the mutated protein due to addition of five amino acids (Figure 3A). However, when structural prediction of the core region (Table S1) was performed using PHYRE2 prediction server [19], it revealed that the presence of additional five amino acids in the mutant Spatacsin (red) leads to an extra turn in α-helix and a slightly longer loop region (Figure 3B).

Figure 1: Brain magnetic resonance imaging of individual II3. (A) Axial FLAIR (B) T2-weighted coronary and T1-weighted sagittal images (C) show supratentorial brain atrophy with enlargement of the lateral ventricles and outer liquor spaces as well as pronounced thinning of the corpus callosum.
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Acknowledgment

We thank the HSP family for their participation in this study and M. Steckel and B. Brandt for excellent technical assistance.

References