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Negative results

hnRNPA2B1 and hnRNPA1 mutations are rare in patients with "multisystem proteinopathy" and frontotemporal lobar degeneration phenotypes

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ABSTRACT

hnRNPA2B1 and *hnRNPA1* mutations have been recently identified by exome sequencing in three families presenting with multisystem proteinopathy (MSP), a rare complex phenotype associating frontotemporal lobar degeneration (FTLD), Paget disease of bone (PDB), inclusion body myopathy (IBM), and amyotrophic lateral sclerosis (ALS). No study has evaluated the exact frequency of these genes in cohorts of MSP or FTD patients so far. We sequenced both genes in 17 patients with MSP phenotypes, and in 60 patients with FTLD and FTLD-ALS to test whether mutations could be implicated in the pathogenesis of these disorders. No disease-causing mutation was identified. We conclude that *hnRNPA2B1* and *hnRNPA1* mutations are rare in MSP and FTLD spectrum of diseases, although further investigations in larger populations are needed.

1. Introduction

A rare, or underdiagnosed, multisystem syndrome that variably combines frontotemporal lobar degeneration (FTLD), Paget disease of bone (PDB), inclusion body myopathy (IBM), and amyotrophic lateral sclerosis (ALS) was first described in families carrying *VCP* mutations (Johnson et al., 2010; Watts et al., 2004). In recent years, the acronym IBMPFD (IBM with PDB and frontal dementia) has

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been commonly used for this complex phenotype. Genetic heterogeneity was demonstrated later in families presenting a more or less complete phenotype that carried mutations in *hnRNPA1*, *hnRNPA2B1* (Benatar et al., 2013; Kim et al., 2013) and *SQSTM1* genes (Fecto et al., 2011; Le Ber et al., in press; Rubino et al., 2012). The term of "multisystem proteinopathy" (MSP) and a nomenclature (MSP1, MSP2, MSP3) have been proposed that designate *VCP*-, *hnRNPA2/B1*-, and *hnNRNPA1*-associated diseases (Benatar et al., 2013). We have studied a relatively large cohort of 28 French patients presenting sporadic or familial MSP phenotypes. *VCP* (n = 10) and *SQSTM1* (n = 1) mutations explained a minority of cases. To better evaluate the genetic contributions of the *hnRNPA1* and *hnRNPA2B1* genes to the pathogenesis of the MPS and FTLD, we have sequenced both genes in probands of MSP families, as well as in an independent series of patients with familial FTLD or familial FTLD associated with ALS (FTLD-ALS).

2. Methods

DNA samples of French FTLD patients have been collected through the French research network on FTLD/FTLD-ALS. Mutations in known FTLD and ALS genes (*C9ORF72*, *PGRN*, *MAPT*, *VCP*, *SQSTM1*, *TARDBP*, *CHMP2B*, *FUS/TLS*, *SOD1*, *PFN1*, *UBQLN2*, *ANG*) have been excluded in all the patients. We studied 17 unrelated French patients presenting with the sporadic (n = 7) or familial (n = 10) phenotype of multiple system proteinopathy. The patients presented with FTLD or FTLD-ALS that aggregated with PDB (n = 16) or IBM (n = 1) in the proband or in his or her family. We fully sequenced the 12 exons of *hnRNPA2/B1* and the 10 exons of *hnRNPA1* as described (Kim et al., 2013). Additionally, we analyzed *hnRNPA2/B1* and *hnRNPA1* in 60 probands with familial FTLD (n = 34) or FTLD-ALS (n = 26). This study was approved by the Ethics Committee of Assistance Publique-Hôpitaux de Paris, Paris; all the patients signed a written informed consent.

3. Results

No disease-causing mutation has been identified. We identified 4 intronic single nucleotide polymorphisms in *hnRNPA2/B1* (rs200943057, rs186110422) and *hnRNPA1* (rs7967622, rs74625894).

4. Discussion

hnRNPA2B1 and hnRNPA1 are 2 ribonucleoproteins that contains prionlike domains and are binding partners of TDP-43. Mutations in *hnNPA2B1* and *hnRNPA1* have recently been identified in 3 families with a complex phenotype of MSP (*hnNPA2B1*) and in 1 ALS family (*hnRNPA1*) and were shown to increase the propensity of these proteins to self-aggregate (Kim et al., 2013). This study is the first to evaluate the genetic contribution of *hnRNPA1* and *hnRNPA2B1* in patients with MSP. Although our MSP cohort is limited (n = 17), it represents the largest studied so far for such rare phenotypic association. More widely, we evaluated the contribution of *hnRNPA1* and *hnRNPA2B1* in familial forms of FTLD and FTLD-ALS without PDB or IBM. No disease-causing mutation has been identified, indicating that *hnRNPA1* and *hnRNPA2B1* mutations are rare in MSP, as well as in FTLD spectrum of disease. We conclude that *hnRNPA2B1* and *hnRNPA1* should not be screened systematically in FTLD patients even in the subset of families with PDB or IBM. However, further investigations are needed in larger series of patients with FTLD-spectrum of disorders, as well as in independent cohorts of patients with ALS or with PDB, to further clarify the role of *hnRNPA1* and *hnRNPA2B1* genes. In our French MSP families *VCP* (50%, 10 of 20) and *SQSTM1* (5%, 1 of 20) are the most frequent genetic causes; however, disease-causing mutations have not been identified thus far in a significant portion of MSP families (n = 9/20, 45%). Benatar et al. (2013) previously reported 8 MSP families: 6 carrying *VCP* mutations, 1 carrying an *hnRNPA2B1* mutation, and no disease-causing mutation identified in the remaining family. Together, these studies demonstrate that *VCP* is the major cause of MSP and that at least 1 gene remains to be identified in this complex phenotype.

Disclosure statement

The authors have no actual or potential conflicts of interest.

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