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▶ **To cite this version:**

Vincent Huin, Mathieu Barbier, Alexandra Durr, Isabelle Le Ber. Reply: Two heterozygous Progranulin mutations in progressive supranuclear palsy. Brain - A Journal of Neurology , 2021, 10.1093/brain/awaa456 . hal-03113276

HAL Id: hal-03113276

https://hal.sorbonne-universite.fr/hal-03113276

Submitted on 18 Jan 2021

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Reply: Two heterozygous Progranulin mutations in progressive supranuclear palsy

Madam, Sir,

Thank you for the opportunity to respond to Yang *et al.*, 2020, reporting a patient diagnosed with progressive supranuclear palsy (PSP) who carried two novel heterozygous missense variants in *GRN* gene. The authors report one case, a 65-year-old man who presented with an akinetic-rigid syndrome, postural instability and supranuclear gaze palsy. Clinical signs fulfilled the Movement Disorder Society's clinical diagnostic criteria for probable PSP (Hoglinger *et al.*, 2017). Sequencing of nine genes which pathogenic variants cause dementia (*GRN*, *MAPT*, *C9orf72*, *VCP*, *TARDP*, *CHMP2B*, *APP*, *PSEN1* and *PSEN*2) revealed two heterozygous missense variants, c.745C>G, p.(Gln249Glu) and c.802A>C, p.(Thr268Pro), in the *GRN* gene. The authors suggested that biallelic *GRN* mutations might cause a PSP-like phenotype, allowing further expansion of the phenotypic spectrum of homozygous *GRN* mutations reported by our team (Huin *et al.*, 2020).

Atypical presentations with parkinsonism are known to be less frequent in heterozygous *GRN* mutations carriers than behavioral variant of FTD or primary progressive aphasias. They mainly manifest as a corticobasal syndrome, or a clinical picture resembling dementia with Lewy bodies (Le Ber *et al.*, 2008; Orme *et al.*, 2020; Carneiro *et al.*, 2020). Conversely to *MAPT* mutations or *C9orf72* repeat expansions, pathogenic *GRN* mutations were reported to be a very rare cause of possible PSP (Ogaki *et al.*, 2013). Only a few studies have reported patients with PSP-like phenotypes associated with heterozygous *GRN* null mutations (Rusina *et al.*, 2011; Tremolizzo *et al.*, 2011; Picillo *et al.*, 2020). We previously reported a patient who carried homozygous *GRN* mutations and initially presented, at age 61, with atypical parkinsonism characterized by akinetic-rigid syndrome, unresponsive to L-DOPA treatment, tremor and postural instability, but not fitting criteria for PSP. He rapidly developed frontal cognitive, behavioral and language impairments, within the two first years of the disease, that were consistent with a behavioral variant of FTD (Huin *et al.*, 2020).

The case reported by Yang *et al.*, raises therefore some concerns. It would have been useful to have access to eye movement recordings, a more in-depth cognitive evaluation (in particular, frontal executive functions), and in particular, to details of the clinical progression. Lastly,

information on genetic screening of other genes involved in parkinsonism (particularly *SCNA*, *LRRK2* and *PRKN*) would also have been of interest. The absence of a positive family history, without parental censure, does not provide supportive evidence in favor of variant pathogenicity. Additionally, testing of parents or other first-degree relatives is requested to determine the phase, and for establishing if the two variants are carried by two different alleles, *i.e.* in *trans*, according to the international guidelines for the interpretation of sequence variants (Richards et al., 2015). The study of Yang *et al.*, does not provide clear evidence that the *GRN* variants are in *trans* as no familial segregation analyses were conducted. Without phasing, we cannot exclude that the two variants actually constitute a single pathogenic haplotype, rather than compound heterozygous variants.

Most pathogenic *GRN* mutations are null mutations producing a premature stop codon, leading to the degradation of mutant mRNA and, thereby, to a loss-of-function through haploinsufficiency (Baker *et al.*, 2006; Cruts *et al.*, 2006). PGRN protein, coded by *GRN*, is secreted in bodily fluids, and can be measured in plasma. As a consequence of haploinsufficiency, plasma progranulin level is decreased in *GRN* mutations carriers. Plasma progranulin dosage is thus a simple, reliable and cost-effective marker suitable as a screening tool and to support the causative role of *GRN* mutations with unknown pathogenicity (Guven *et al.*, 2019; Sellami *et al.*, 2020). We and others reported that homozygous *GRN* mutations were associated with an almost complete loss of function of progranulin, accompanied with very low or undetectable plasma progranulin levels (Smith *et al.*, 2012; Canafoglia *et al.*, 2014; Almeida *et al.*, 2016; Faber *et al.*, 2017; Kamate *et al.*, 2019 ; Huin *et al.*, 2020). Although *in vitro* experiments in the study of Yang *et al.* suggested that the p.(Gln249Glu) and p.(Thr268Pro) variants reduce the stability of progranulin protein, these results would be strongly reinforced *in vivo* by plasma level measurement that, if decreased or undetectable, would provide convincing arguments for variants pathogenicity. This would be of importance, as the majority of *GRN* missense mutations are not, or not proven to be pathogenic, and only rare missense mutations have been associated with reduced gene expression (Shankaran *et al.*, 2008; van der Zee *et al.*, 2007; Saracino *et al.*, 2020) or splice defect (Luzzi *et al.*, 2017), leading to haploinsufficiency as well.

Depending to the interpretation of the level of evidence provided by the *in vitro* experiments, these two missense variants may be classified as "VUS" (Variants of Unknown Significance) according to the American College of Medical Genetics and Genomics guidelines for the interpretation of sequence variants (Richards *et al.*, 2015).

In summary, the study of Yang *et al.*, reports a PSP-like phenotype in a patients carrying two missense variants in *GRN* gene, putatively compound heterozygous. Finally, we suggest that further analyses (including segregation analyses and plasma proganulin dosage) are warranted to draw definite conclusion about the association of these two missense variants with a PSP-like phenotype.

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Competing interests

The authors report no competing interests.

Funding

This work received funding from the VERUM foundation and 'Investissements d'avenir' ANR-11-INBS-0011 – NeurATRIS: Translational Research Infrastructure for Biotherapies in Neurosciences. This work was funded by the Programme Hospitalier de Recherche Clinique (PHRC) FTLD-exome (to I.L.B., promotion by Assistance Publique – Hôpitaux de Paris) and PHRC Predict-progranulin (to I.L.B., promotion by Assistance Publique – Hôpitaux de Paris).

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