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Plasma progranulin levels in frontotemporal dementia (FTD) patients

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PURPOSE / OBJECTIVES

Frontotemporal Dementia (FTD) is as common as Alzheimer's disease in patients <65y and concerns about 5-15% of the total dementia patients worldwide [1]. It involves a number of clinic-pathologico-anatomical characteristics and major subtypes involve bvFTD (behavioral variant FTD), PNFA (Primary non-fluent Aphasia) and SV-FTD (semantic variant). The FTD spectrum also includes PSP (Progressive Supranuclear Palsy) and CBD (Cortico-basal Degeneration).

Progranulin gene (*PGRN)* is one of many FTD-associated genes (others include *MAPT, C9orf72*,*TARDBP* etc.). It encodes for a 593-amino acid secreted protein that can lead to neurodegeneration in case of reduced concentrations. It can be easily detected in CSF or plasma and our goal is to examine whether it could assist in a referral for *PGRN* genetic analysis.

MATERIALS & METHODS

In 36 well-ascertained FTD patients, we collected EDTA peripheral blood after obtaining their informed consent.

After centrifugation, plasma was separated and stored in cryovials at -40 ℃ till analysis and DNA was isolated from leucocyte buffy-coat with High pure PCR template preparation kit (Roche).

We performed **both DNA genetic analysis** in 21 FTD genes with NGS (Next Generation Sequencing) methodology (among them the *PGRN* gene as well) [2] **and plasma progranulin measurements** with an ELISA Progranulin kit (Adipogen Life Science) in a ELx800 BioTek reader [3].

RESULTS

In the genetic analysis, three patients were detected with deleterious *PGRN* frameshift mutations, one patient with a rare missense variant of unknown clinical significance and 32 were negative for any alteration in the *PGRN* gene (some of them were positive for pathogenic mutations in other genes such as *MAPT, C9orf72*,*TARDBP*).

FTD is a highly heterogeneous disease.

A small percentage of FTD patients bear pathogenic *PGRN* (progranulin) mutations.

Nowadays, a novel gene-therapy approach exists for these patients.

When no sophisticated NGS equipment exists, a simple ELISA method measuring plasma progranulin levels could identify these few patients.

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RESULTS (continued)

Plasma progranulin measurement of these 32 *PGRN* mutation-negative patients showed a normal distribution with an average 232.78 ng/ml (SD= 48.57). The reference values were calculated according to mean±2SD, therefore the min-max range was 136-329 ng/ml.

The 3 *PGRN* pathogenic mutation-positive patients showed a range between 59-92 ng/ml (non-parametric estimation for 25-75th interquartile range).

The rare *PGRN* VUS variant of unknown significance (rs969767392, c.928A>C, p.T310P) had an intermediate concentration of 134 ng/ml. According to various bioinformatics software tools (Mutation taster, CADD), this missense alteration is considered a benign polymorphism.

SUMMARY/CONCLUSION

Based on the used ELISA method and statistical analysis, FTD patients with plasma progranulin levels > 136 ng/ml can be safely considered that they do not bear *PGRN* mutations with 95% confidence.

Patients with plasma progranulin levels < 92 ng/ml should proceed to *PGRN* genetic analysis due to the high likelihood of detecting a deleterious *PGRN* mutation**.** These few patients could benefit from novel, emerging Precision Medicine therapeutic approaches such as intracisternal *PGRN* gene therapy (or intrathecal anti-sortilin antibodies) that work by trying to restore the necessary normal progranulin levels in the brain cells.

Patients with levels between 92 and 136 ng/ml belong to the grey zone and *PGRN* genetic analysis could be considered. In this case, *PGRN* DNA variants might be detected. Evaluation of *PGRN* gene expression through plasma progranulin protein levels, could shed light in assessment of the pathogenicity of these *PGRN* gene alterations.