A systematic review of progranulin concentrations in biofluids in over 7,000 people - assessing the pathogenicity of *GRN* mutations and other influencing factors

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Background

- Heterozygous mutations in the *GRN* gene are a major cause of genetic frontotemporal dementia (FTD), causing an estimated 5-10% of all FTD cases (*1*).
- *GRN* encodes for progranulin (PGRN) and mutations lead to haploinsufficiency.
- Mutations are associated with significantly lower concentrations of PGRN in biofluids in mutation carriers compared to controls (*2,3*).

Methods

- We contacted all authors who have published data on PGRN concentrations in serum, plasma or CSF (in any medical condition) up to December 2019.
- We asked if they were able to share anonymised data including PGRN concentrations and clinical data such as specific mutation if present, clinical diagnosis, age at onset of dementia, sex, and *GRN* rs5848 polymorphism.
- Data from 7,071 people was collated and analysed, including PGRN measured with a range of assays and in different fluid types (Table 1).

	A&G	Adipogen	BioVendor	Mediagnost	R&D	Others
Total (*GRN* mutation carriers)	**149** (7)	**5058** (564)	**56** (38)	**55** (0)	**1481** (6)	**272** (1)
Plasma (*GRN* mutation carriers)	**0** (0)	**3301** (438)	**0** (0)	**0** (0)	**671** (0)	**147** (1)
Serum (*GRN* mutation carriers)	**149** (7)	**758** (125)	**53** (35)	**49** (0)	**649** (6)	**0** (0)
CSF (*GRN* mutation carriers)	**0** (0)	**1346** (19)	**32** (23)	**55** (0)	**0** (0)	**125** (0)

***Table 1**: Number of PGRN measurements across different assay and fluid types*

Results

- Using levels measured with the Adipogen assay in plasma, we found considerable variability in PGRN concentrations across 109 different *GRN* mutations spanning the GRN gene (figure 1).

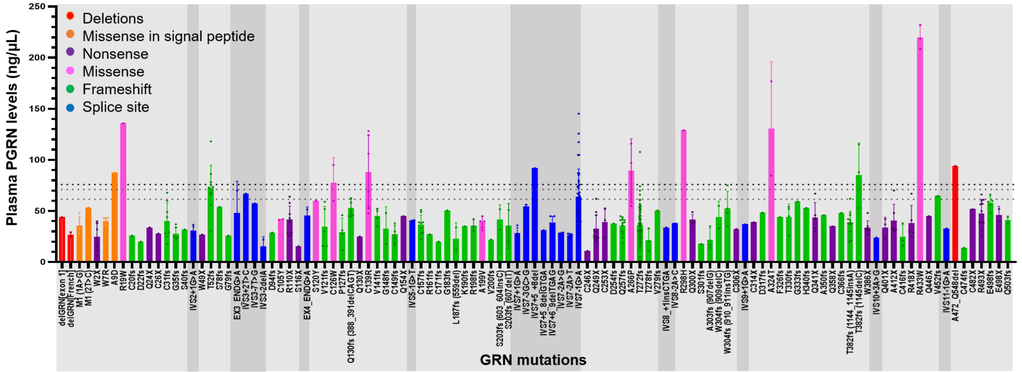


***Figure 1**. Plasma PGRN concentrations measured with the Adipogen assay spanning the GRN gene. Dotted lines indicate suggested cut-offs of 61.55ng/μL, 71.00ng/μL and 75.95ng/μL, as defined in (1), (2) and this dataset, respectively. Exonic mutations are in light grey and intronic mutations are in dark grey.*

- Missense variants outside the signal peptide have significantly higher levels compared to other groups (figure 2).
- This suggests that these mutations are less likely to be pathogenic.
- Based on this, we defined a cut-off of 75.95ng/μL with a Youden's index of 0.92.

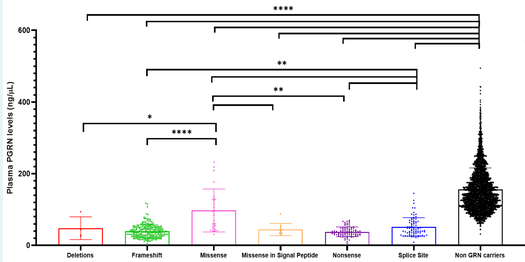


***Figure 2**. Differential plasma PGRN concentrations across six different mutation groups and compared to non GRN mutation carriers. *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001, two-tailed Mann-Whitney test.*

- The *GRN* rs5848 polymorphism affects plasma PGRN levels, with the TT genotype linked to significantly lower levels than CC.

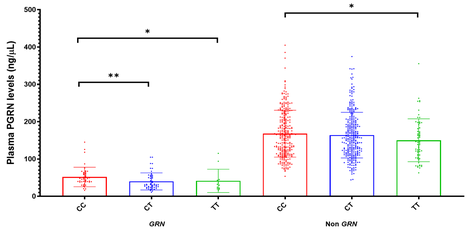
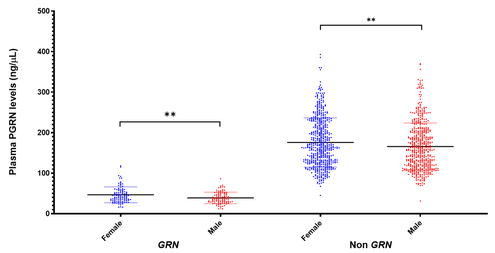


***Figure 3**. GRN polymorphism rs5848 influences plasma PGRN concentrations in this data set.*

***Figure 4.** Sex differences in plasma PGRN concentrations in this data set.*



- We also found that females have significantly higher PGRN levels than males.

Conclusions

- These findings highlight the variable pathogenicity of different *GRN* mutations and the importance of considering other factors when looking at biofluid concentrations of PGRN.
- This is important for upcoming clinical trials of progranulin-associated FTD where PGRN levels are being used as outcome measures.

References

1) Greaves CV, Rohrer JD. An update on genetic frontotemporal dementia. J Neurol. 2019 Aug;266(8):2075-2086.
2) Ghidoni R, Stoppani E, Rossi G, Piccoli E, Albertini V et al. Optimal plasma progranulin cut off value for predicting null progranulin mutations in neurodegenerative diseases: a multicenter Italian study. Neurodegener Dis. 2012;9(3):121-7.
3) Sellami L, Rucheton B, Ben Younes I, Camuzat A, Saracino D et al. Plasma progranulin levels for frontotemporal dementia in clinical practice: a 10-year French experience. Neurobiol Aging. 2020 Jul;91:167.e1-167.e9.