Progranulin gene variability decreases the risk to develop Bipolar Disorder and Schizophrenia and plasma levels are decreased in patients with Bipolar Disorder

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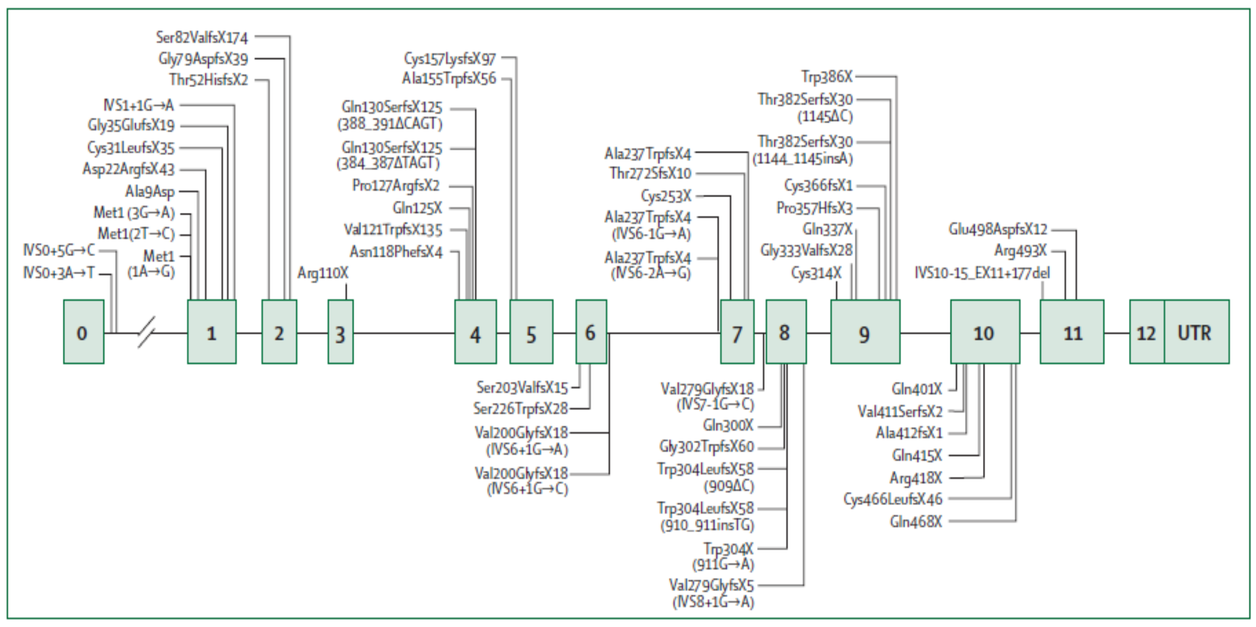
Background

Mutations in the progranulin gene (GRN) are the most frequent cause of autosomic dominant frontotemporal lobar degeneration (FTLD). Age at disease onset, as well as clinical phenotypes associated with such mutations, are extremely heterogenous. Basing on the assumption that frontotemporal lobar degeneration (FTLD), schizophrenia and bipolar disorder (BD) might share common aetiological mechanisms, we analyzed genetic variation in the FTLD risk gene progranulin (GRN) in a German sample of patients with schizophrenia and BD as compared with age-, gender- and ethnicity-matched controls. Furthermore, we measured plasma progranulin levels in German BD patients as well as in Italian BD patients and matched controls[1,2].

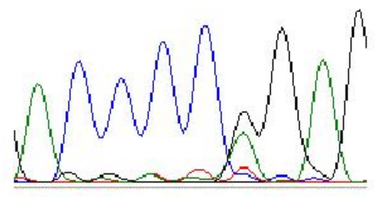
Methods

We analyzed genetic variation in the FTLD risk gene progranulin (GRN) in a German population of 508 patients with schizophrenia and BD as compared with 567 age-, gender- and ethnicity-matched controls. Furthermore, we measured plasma progranulin levels in 26 German BD patients as well as in 61 Italian BD patients and 29 matched controls.



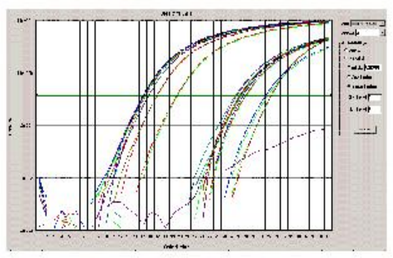
Methods

- Direct sequencing of *PGRN* gene (exons+intron junctions)

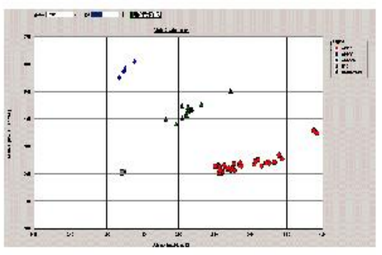


- TaqMan technology (ABI PRISM 7000)

Expression analysis



Allelic discrimination



- Statistics: Haploview software for association, Sigmastat 3.1 for expression analysis

Results

A significantly decreased allelic frequency of the minor versus the wild-type allele was observed for rs2879096 (23.2 versus 34.2%, P<0.001, OR:0.63, 95%CI:0.49-0.80), rs4792938 (30.7 versus 39.7%, P=0.005, OR: 0.70, 95%CI: 0.55-0.89) and rs5848 (30.3 versus 36.8, P=0.007, OR: 0.71, 95%CI: 0.56-0.91). Progranulin plasma levels were significantly decreased in BD patients, either Germans or Italians, as compared with controls (89.69:3.97 ng/ml and 116.14 5.80 ng/ml, respectively, versus 180,81:18.39 ng/ml P<0.01) and were not correlated with age.

Conclusions

Taken as a whole, *GRN* variability decreases the risk to develop BD and schizophrenia, and progranulin plasma levels are significantly lower in patients than in controls. Nevertheless, a larger replication analysis is needed to confirm these preliminary results.

References

1. Pietroboni, A.M., et al., 2011. Phenotypic heterogeneity of the GRN Asp22fs mutation in a large Italian kindred. J. Alzheimers Dis. 24(2), 253-259.
2. Galimberti, D., al., 2010. GRN variability contributes to sporadic Frontotemporal Lobar Degeneration. J Alzheimers Dis. 19(1), 171-177.

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