p-114

Thursday

TMEM106B haplotype alters disease penetrance in FTLD-GRN mutation carriers

Masood Manoochehri, Jolien Perneel, Edward Huey, Rosa Rademakers, Jill Goldman, On behalf of the ALLFTD Consortium

State of the art: Variants in *TMEM106B* have been proposed as modifiers of FTLD disease risk, especially for *GRN* mutation carriers. The 'protective' haplotype is reported to confer lower odds of developing symptomatic disease. However, *TMEM106B* genotyping is not routinely implemented in diagnostic testing and genetic counseling.

Methodology: A 56-year-old female presented to our clinic with progressive cognitive and behavioral impairment. Age of onset was 54, including forgetfulness, difficulty with computers, lack of initiative, increased appetite, and mood swings. The clinical impression was bvFTD, which neuropsychological testing and neuroimaging supported. Family history was unremarkable, including parents (age 82 and 78), paternal aunt (age 78) and brother (age 48), all asymptomatic. Despite lack of family history, we performed a full dementia-ALS genetic testing panel.

Results: Genetic testing revealed a pathogenic variant, c.349+1G>C (Splice donor site) in *GRN*. Follow-up of the family showed the mutation was inherited from the patient's father and the brother also carries the mutation. We next evaluated *TMEM106B* genotype which revealed that the asymptomatic father and brother carry two copies of the protective *TMEM106B* allele (c.554C>G, p.Thr185Ser) while the patient is heterozygous. The family was counseled that the father and brother have a theoretical 50% reduced risk for symptoms compared to those with no protective alleles.

Conclusion: *TMEM106B* genotyping is important for a deeper understanding of risk- and disease-modifying effects in FTLD, especially *GRN,* and could lead towards new therapeutic avenues. Appropriate genetic counseling about penetrance for such families can allow them to better plan for their future.

Conflicts of interest

None