p-280

Friday

Animal models of TMEM106B confirm functional effect of the p.T185S variant and show that increased TMEM106B protein levels lead to severe lysosomal dysfunction in vivo.

Jolien Perneel, Bavo Heeman, Nele Peeters, Reindert Jehoul, Mieu Brooks, Ralph Perkerson, Cat Lutz, Aamir Zuberi, Xiaolai Zhou, Rosa Rademakers

State of the art: In the last decade, multiple studies have established *TMEM106B* as an important modifier of disease risk in several neurodegenerative disorders, including FTLD. As a lysosomal transmembrane protein, TMEM106B regulates lysosomal function and proper TMEM106B levels are crucial for lysosomal health. Yet, it remains unclear how TMEM106B modulates disease risk.
Methodology: There is only one coding variant in *TMEM106B* that differentiates the risk from the protective haplotype (p.T185S). To study its possible consequence on TMEM106B function, we generated a CRISPR knock-in mouse model of the orthologous variant in mice (p.T186S). In addition, to study the effect of increased TMEM106B levels, we generated transgenic mice overexpressing human TMEM106B.
Results: In the CRISPR knock-in model, we found that Tmem106b protein levels are reduced in mice carrying the protective ('SS') genotype as compared to wild-type ('TT'), validating a functional effect of this variant and supporting the hypothesis that increased TMEM106B levels confer disease risk. We next characterized our TMEM106B overexpressing mice and show that they stably express the transgenic cassette resulting in increased TMEM106B levels, unlike a previous model that failed to induce overexpression. We show that embryonic fibroblasts derived from this model are filled with vacuole-like enlarged lysosomes which are not acidic, indicating severe lysosomal dysfunction. Detailed characterization of this model at multiple time points is currently ongoing.
Conclusion: Our data confirm that increased levels of TMEM106B may underly the disease-modifying effect and that overexpression of TMEM106B induces severe lysosomal dysfunction which may contribute to neurodegeneration *in vivo*.

Conflicts of interest

N.A.