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***TMEM106B* and frontotemporal lobar degeneration: Can overexpression tell us how reductions are beneficial?**

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The inheritance of risk for frontotemporal lobar degeneration (FTLD) the disease state underlying frontotemporal dementia (FTD; for a comprehensive review, see Sieben *et al.* 2012) seems to be getting increasingly complicated with each new publication of a genetic study. In addition to the causal mutations in five major genes such as progranulin (*GRN*) and microtubule-associated protein Tau (*MAPT*), several quantitative trait loci and other low-penetrance, modifying genes have been identified in the last six years. While this latter category of risk-modifying polymorphisms (*vis-à-vis* “causal” genes) are not considered strictly causative, one might think that such a growing list would begin to fall within a signaling pathway or other mechanistic relationship that would serve to outline the pathogenesis of FTLD. Discovering such a common pathogenic process would be a coup for our understanding of this group of disorders that is increasingly appreciated as making a rather large demographic contribution to the total cases of age-related dementia. However, only vague and obtuse connections have been unveiled to date.

If phenotypes are any hint, the complexity in this class of dementing conditions probably reflects a somewhat artificial grouping of several different disorders. Among the sporadic and familial cases alike, one finds categories in which intracellular inclusions alternatively consist of Tau, p62, or transactive response (TAR) DNA-binding protein 43 kDa (TDP-43); in other cases the inclusions are devoid of these proteins, and accumulations of ubiquitin are apparent, either complexed to these inclusions or not. Even among the TDP-43-positive cases, four main types of pathology have been codified, having distributions of neuronal inclusions that vary across individual cells and across brain regions (Cairns *et al.* 2007). In its phenotypic and genotypic diversity, FTLD—along with the genotypically and phenotypically overlapping amyotrophic lateral sclerosis—may even be as broad a category of “protein-storage diseases” as that of the lysosomal-storage diseases, which also preferentially impact the CNS.

The risk of developing the TDP-43-positive forms of FTLD (FTLD-TDP) can be modified by a polymorphism in a gene known as *TMEM106B* (odds ratio ~1.6). There is no single nucleotide polymorphism (SNP) more closely linked to the phenotype than one designated rs3173615, a coding-region SNP that dictates whether the amino acid at position 185 in the *TMEM106B* open reading frame will be a threonine (disease-associated) or serine (disease-protective). Curiously, the gene is particularly important in FTLD-TDP cases arising from a mutation in *GRN* (Van Deerlin *et al.* 2010). Also intriguing is the fact that the most common

allele of *TMEM106B* is the one that is associated with higher rates of FTL-D-TDP, perhaps because the gene has escaped selective pressures by having its strongest effects restricted to the very small subpopulation carrying a *GRN* mutation. Nicholson *et al.* (2013) have added to the data confirming the collaboration of *TMEM106B* SNP rs3173615 with *GRN* mutation in favoring development of FTL-D-TDP. But they have also carried the story forward mechanistically.

Chief among the questions currently perplexing the FTL-D field is how loss-of-function or gain-of-function modes of action relate to the mutations and polymorphisms impacting this condition. It seems quite clear that the genetic alterations in *GRN* that result in FTL-D convey loss-of-function effects; some are even gross deletions of the gene. The jury is still out on the effect of FTL-D-associated mutations in *TARDBP*, the gene encoding TDP-43. Indeed, it is not clear what consequences, if any, TDP-43 inclusions have for neuronal function and survival. It is possible that the aggregates actively interfere with cellular processes in a way that compromises health; it is also possible that they represent inert accumulation of protein that is passively nonfunctional. Overexpression and knockout studies in mice have not been particularly helpful in resolving this question, as both manipulations produce maladaptive phenotypes with some relationship to FTL-D.

Because FTL-D is associated with loss-of-function mutations in *GRN*, one might predict that the protein this gene encodes (PGRN) would be diminished by the risk-associated allele of *TMEM106B*. Indeed, higher levels of PGRN are detected in the plasma of individuals carrying the protective S185 allele (or SNPs in linkage disequilibrium with that allele) (Cruchaga *et al.* 2011; Finch *et al.* 2011). However, Nicholson *et al.* report that overexpression of either the T or the S variant of *TMEM106B* leads to elevated steady-state levels of PGRN protein. This replicates a finding first reported by Chen-Plotkin *et al.* (2012) and confirmed just a few months ago by Brady *et al.* (2013). What neither of those previous papers documented was any direct effect of the T185S distinction on activity or metabolism of *TMEM106B* itself.

Thus, the most novel finding by this latest study is that the *TMEM106B* protective polymorphism (S185) results in a relatively destabilized protein product. This lends some credence to the idea that the risk allele (T185) manifests as a toxic gain-of-function: a longer-lived protein leads to higher steady-state levels, which should enhance whatever function *TMEM106B* has. From another perspective, it may be more intuitive to think of the S186 allele as conveying loss of a toxic function, as this allele is less prevalent in the population and confers its greatest protection in the context of a mutation in *GRN*. But the data itself offers us a head-scratcher: the common effect consistently reported for both the T185 and the S185 variants is elevation cellular levels of PGRN, a finding now reported for the third time. Nevertheless, elevated cellular levels are not tantamount to elevated function.

It should be borne in mind that proteins can have surprising and even misleading actions when they are overexpressed. Overexpression of human TDP-43 in mouse cells, for instance, leads to a corresponding down-regulation of the endogenous mouse genes. Commonly, overexpression leads to spillover effects whereby mass-action kinetics drive proteins to interact with cellular components in novel ways. Similarly, it is possible that

overexpression of the less stable S185 variant of TMEM106B amounts to a greater overall abundance than would be seen under normal expression, resulting in effects more similar to those seen under normal levels of expression of the T185 variant—in other words, the effects common to both variants under conditions of overexpression may be those that predispose to disease. But how can this be if FTLTDP results from reductions of PGRN? It is possible that PGRN abundance in cell extracts reflects an interruption in secretion and therefore a loss in some function of PGRN or its proteolytic products. PGRN can be chopped into more than a dozen different products by extracellular proteases, and these products can have very different—even opposite—effects from those exerted by intact PGRN. Chen-Plotkin *et al.* (2012) reported a “trend” toward reduced extracellular levels of PGRN after TMEM106B protein overexpression. However, Nicholson *et al.* (*in hoc*) and Brady *et al.* (2013) found that levels of both the cell-associated and the secreted PGRN were elevated by overexpression of TMEM106B. Still, it is possible that PGRN secreted after TMEM106B overexpression is inappropriately processed.

It should also be noted that the effects of TMEM106B overexpression on the steady-state levels of PGRN are rather small. It is possible therefore that the mechanistic mediation of the *TMEM106B* genotype has less to do with elevation of PGRN than with some other alteration in function of TMEM106B protein. In this regard, it is intriguing that Nicholson *et al.* found circumstantial evidence that the S185 variant is aberrantly glycosylated. Just two amino acids away from the SNP-dependent position, at position 183, is an asparagine previously reported to host complex glycosylation. Mutation of this N-linked site obliterated the differences in steady-state levels of the T185 and S185 variants of TMEM106B. S185 still receives complex glycosylation, and that glycosylation appears to confer approximately the same shift in size as that seen in the T185 variant. Likewise, there is no major difference in the proportions of total TMEM106B that are glycosylated as a result of the T185→S conversion. It may be instructive to compare the stability of the N183 mutant to that of T185 and S185 to determine whether the glycosylation event at this site effects a relative stabilization of T185 or destabilization of S185.

At this stage, there is still much to be learned about the interactions of the *TMEM106B* polymorphism with FTLTDP phenotypes. Whereas loss of *GRN* expression can be expected to deplete PGRN protein along with all its GRN products, elevation of PGRN by TMEM106B may not rescue the same proportional profile of these proteins/peptides. It could be fruitful, therefore, to analyze more carefully the GRN profiles of patients carrying different forms of *GRN* mutation, as well as those who vary across the *TMEM106B* locus. But Nicholson *et al.* seem to have given us a more compelling effect on which to focus. Compared to the changes in PGRN levels effected by TMEM106B overexpression (~15%), the differential abundance of TMEM106B protein itself is much more impressive; the T185 version was present at levels as much as 250% those of S185. Nicholson *et al.* also confirm the prominent colocalization of TMEM106B with PGRN in lysosomes, and they further show that the protein is degraded in this compartment. Could TMEM106B serve as one of the rather elusive receptors for PGRN/GRNs? Sorting out the consequences of the *TMEM106B* coding-region SNP for metabolism and function of PGRN/GRN, as well as TDP-43, may prove very helpful to our understanding of FTLTDP and of this enigmatic

class of disorders in general. But homologous recombination or other strategies for “knock-in” of *TMEM106B* alleles may be necessary to overcome the potential artifacts of overexpression.

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