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Of Mice and Men: What a mouse model of microglial *C9ORF72* deficiency does (and does not) tell us about human neurodegenerative diseases

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Abstract

Expansions in *C9ORF72*, which cause frontotemporal dementia and amyotrophic lateral sclerosis, result in formation of aberrant peptide and RNA species, and decreased expression of the normal gene. In this issue of *Neuron*, Lall *et al*. report the consequences of microglial *C9ORF72* deficiency in mouse models of aging and Alzheimer's Disease.

In their initial report of the association between hexanucleotide repeat expansions (HRE) in *C9ORF72* and frontotemporal dementia (FTD)/amyotrophic lateral sclerosis (ALS), DeJesus-Hernandez and colleagues questioned whether toxic gain of function or *C9ORF72* haploinsufficiency led to subsequent neurodegeneration (DeJesus-Hernandez et al., 2011). Ten years later, the question is still open. While evidence for toxic effects from both the dipeptide repeats and RNA species generated by the HRE has certainly accumulated – to the extent that therapeutic strategies using antisense oligonucleotides to target the expanded *C9ORF72* allele have proceeded into human clinical trials (NCT00103181) – an increasingly important role for the normal function of *C9ORF72* has also emerged.

In this issue of *Neuron*, Lall *et al*. present molecular, histopathological, and behavioral data from animals with heterozygous or homozygous loss of *C9ORF72* in microglia, on a wild-type or 5XFAD (mouse model of Alzheimer's Disease (AD)) background (Lall et al., 2021). They find that *C9ORF72* deficiency in microglia leads to an altered microglial signature and increased synaptic pruning, resulting in neurobehavioral deficits. Moreover, on the AD mouse model background, while microglial *C9ORF72* deficiency leads to greater clearance of amyloid plaques, the synaptic loss effect "wins," with animals exhibiting impaired learning and memory behaviors. Based on these findings, the authors argue that microglial impairment from decreased *C9ORF72* expression directly contributes to neurodegeneration in HRE carriers.

Certainly, this study sheds light on the microglial function of *C9ORF72*, which is known to be highly expressed in myeloid lineage tissues, with decreased expression in humans

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carrying the HRE (Rizzu et al., 2016). But what does this study really tell us about human neurodegenerative diseases? As with many things, the devil is in the details.

First, in the current study, the vast majority of the effects seen with *C9ORF72* deficiency at the molecular, cellular, and organismic levels are seen only in the null animals, with the heterozygous state closely resembling the wild-type state. However, in humans, heterozygous loss of *C9ORF72* is sufficient to cause neurodegenerative disease. Moreover, the authors draw comparisons to another gene in which haploinsufficiency is causal for FTD, *GRN*, for which minimal effects are seen with heterozygous loss in mice. However, an important point about the differing insights from human genetics for *GRN* vs. *C9ORF72* needs to be made. Specifically, humans with haploinsufficiency in *GRN* develop FTD, but humans with homozygous loss of *GRN* develop an altogether different, childhood-onset lysosomal storage disease phenotype (Smith et al., 2012). In contrast, the rare humans with two HREs in *C9ORF72* are largely indistinguishable from the vast majority with one HRE who develop FTD and ALS (Fratta et al., 2013). Put another way, loss of *GRN* demonstrates a dosage effect for both mice and humans, with more severe phenotypes with homozygous loss in both cases. In contrast, loss of *C9ORF72* demonstrates a dosage effect for mice that is not seen in humans. Thus, it is entirely possible that the work shown here, while informative with respect to the normal function of *C9ORF72*, is less informative about pathogenic mechanisms in FTD and ALS.

Second, the decision to intersect *C9ORF72* expansion with an AD model is interesting for several reasons. At face value, this is a strange decision, since few *C9ORF72* HRE carriers manifest with AD neuropathologically. In 523 neuropathological AD disease cases characterized genetically at the University of Pennsylvania, for example, only one case carried a *C9ORF72* expansion (Mao et al., 2021). Viewed another way, however, especially in light of the recent decisions by the FDA to approve and/or fast-track multiple AD therapeutics largely on the basis of their ability to decrease the burden of amyloid plaque, the current study offers a sobering truth: both mice (Lall et al., 2021) and humans (Knopman et al., 2021) can show a disconnect between cognitive performance and amyloid plaque burden.

In the end, the most analogous situation to our current state of knowledge with respect to *C9ORF72* expansion may come from another repeat expansion disease whose genetic basis was established nearly 30 years ago. Huntington's Disease (HD), characterized, like *C9ORF72*-associated FTD/ALS, by a combination of motor and cognitive features due to degeneration of specific neuronal populations over time, results from a trinucleotide repeat expansion in *HTT*. As with the *C9ORF72* HRE, there are rare individuals homozygous for *HTT* expansion. As with *C9ORF72* HRE, the phenotype for these rare *HTT* homozygotes is largely the same as for heterozygotes, although disease might be more severe. Over the decades since discovery of its genetic cause, the dominant theme from HD studies is that toxic gain of function from the polyglutamine species generated by the repeat expansion is the main contributor to neurodegeneration (Jimenez-Sanchez et al., 2017). However, an alternate thread in the literature notes that *HTT* may have an essential neuronal function. Taken together, most strategies to treat HD have targeted the expanded allele while simultaneously trying to avoid decreasing expression of the normal allele.

Given the increasing evidence for *C9ORF72* role in neuronal health from this paper and others – notably, reports that loss of *C9ORF72* function augments toxicity from gain-of-function mechanisms in motor neuron (Shi et al., 2018) and animal (Zhu et al., 2020) models – such a strategy is also wise for therapeutic development in *C9ORF72*-associated FTD and ALS.

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