C9orf72 mutations and the puzzle of cerebro-cerebellar network degeneration

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Sir,

The recent work of Guo and colleagues (2016) underlines the important and specific involvement of the cerebellum in canonical dementia syndromes of Alzheimer’s disease and frontotemporal dementia. This new evidence poses the puzzle of how molecular pathology, regional cerebellar atrophy and phenotype are linked together in these diseases. Here we draw attention to an important missing piece of this puzzle that was not represented in the study of Guo and colleagues: the case of \textit{C9orf72} mutations.

Pathogenic expansions in the \textit{C9orf72} gene involve the cerebellum histologically and macroanatomically, as part of a signature profile of distributed cortico-thalamo-cerebellar network degeneration: a molecular nexopathy (Mahoney et al., 2012; Whitwell et al., 2012; Warren et al., 2013). This profile appears early in the course of the disease and appears to be relatively specific for mutations in \textit{C9orf72} versus other genes causing frontotemporal dementia (Rohrer et al., 2015; Bocchetta et al., 2016). Moreover, \textit{C9orf72} mutations are associated with a high frequency of neuropsychiatric symptoms (Mahoney et al., 2012; Snowden et al., 2012): such symptoms may collectively reflect abnormal body schema coding, which has been shown to be selectively impaired in patients with \textit{C9orf72} mutations relative to other forms of frontotemporal dementia (Downey et al., 2014), in line with the key role played by the cerebellum in self-nonself differentiation in the healthy brain (Blakemore et al., 2000).

Taken together, this evidence suggests that \textit{C9orf72} mutations are an informative model system for understanding how molecular lesions translate to complex dementia phenotypes and in particular, illustrate the crucial involvement of the cerebellum in this linkage. Such genetic test cases should be directly compared with sporadic disease phenotypes in future work addressing this issue.
References


