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REPLY

Reply to: Adult-onset leukoencephalopathy caused by *CSF1R* mutations: Is all that glitters gold?

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We appreciate Salsano and Benzoni for their interest in our work and their letter emphasizing rigorous interpretation for the pathogenicity of variants at the colony-stimulating factor 1 receptor (*CSF1R*) gene in patients with adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP).[1] We agree that our patient carrying the *CSF1R* p.Thr79Met variant had an unusual late disease onset, and the presence of multiple cardiovascular comorbidities may raise the concern of vascular dementia.[2] However, this patient could be designated as "possible ALSP" according to the diagnostic criteria of ALSP[3] for fulfilling three core features (cognitive impairment, sporadic occurrence, and bilateral cerebral white matter lesions on MRI), one supporting feature (frontal lobe dysfunction shown by cognitive tests), and lacking any of the three exclusionary findings (onset age ≦10 years, stroke-like episodes more than twice, and prominent peripheral neuropathy). Based on the clinical features including heterogeneous disease durations (1–29 years) and variable onset ages (18–78 years) of 122 genetically confirmed ALSP patients described in a previous study,[4] individuals carrying a *CSF1R* mutation may have a protracted course and mild phenotype. Furthermore, the p.Thr79Met variant is classified as "likely pathogenic variant" by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) guideline as described in our paper.[2]

As in their Figure, Salsano and Benzoni[1] argued that variants located at the extracellular immunoglobulin-like domains (IgLD) of *CSF1R*, such as p.Thr79Met, would lose the ability to form CSF1R protein dimers but still have half amount of the wild-type CSF1R dimer molecules to maintain normal phenotype. They presumed individuals carrying a heterozygous *CSF1R* variant at IgLD would not develop ALSP. Actually, we are not sure whether the p.Thr79Met mutation will affect the CSF1R dimerization or not. In addition, multiple lines of evidence have supported that haploinsufficiency of *CSF1R* genetic function is sufficient to cause disease. The *CSF1R* p.Ser688Glufs*13 and p.Pro104Leufs*8 frameshift mutations, which lead to nonsense-mediated mRNA decay and reduced CSF1R protein levels, are identified in two ALSP patients with symptoms onset at age 41 and 22 years, respectively.[5,6] *Csf1r*-haploinsufficient ($Csf1r^{+/-}$) mice have cognitive decline, sensorimotor deficits, and psychiatric behavior, as well as dysmyelination and neurodegenerative changes in the white matter at the electromicroscopic images.[7] It still needs further investigations to understand whether the diverse mechanisms of different *CSF1R* variants, including dominant-negative effect and haploinsufficiency, could partly explain the incomplete penetrance and variable disease severity among patients with ALSP.[8]

Conflict of Interest

There is no conflict of interest.

References

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