



Abstracts

Articles appearing in the February 2018 issue

CYP2C19 variant mitigates Alzheimer disease pathophysiology in vivo and postmortem

Objective To verify whether *CYP* polymorphisms are associated with β -amyloid ($A\beta$) pathology across the spectrum of clinical Alzheimer disease using in vivo and postmortem data from 2 independent cohorts.

Methods A candidate-gene approach tested the association between 5 genes (28 single nucleotide polymorphisms) and $A\beta$ load measured in vivo by the global [¹⁸F]florbetapir PET standardized uptake value ratio (SUVR) in 338 Alzheimer's Disease Neuroimaging Initiative participants. Significant results were then tested using plasma $A\beta$ and CSF $A\beta$ and $A\beta$ /phosphorylated tau ($A\beta$ /p-tau) ratio in the same cohort. The significant association was also generalized to postmortem $A\beta$ load measurement in the Rush Religious Orders Study/Memory and Aging Project cohorts. In addition, global cognition was used as a phenotype in the analysis in both cohorts.

Results Analysis of $A\beta$ PET identified a variant in the *CYP2C19* gene (rs4388808; $p = 0.0006$), in which carriers of the minor allele had a lower global SUVR. A voxel-wise analysis revealed that the variant is associated with a lower $A\beta$ load in the frontal, inferior temporal, and posterior cingulate cortices. Minor allele carriers also had higher CSF $A\beta$ ($p = 0.003$) and $A\beta$ /p-tau ratio ($p = 0.02$) but had no association with $A\beta$ plasma levels. In postmortem brains, minor allele carriers had a lower $A\beta$ load ($p = 0.03$). Global cognition was higher in minor allele carriers, which was found to be mediated by $A\beta$.

Conclusions Together, these findings point to an association between *CYP2C19* polymorphism and $A\beta$ pathology, suggesting a protective effect of the minor allele of rs4388808. Despite the several possibilities in which *CYP2C19* affects brain $A\beta$, the biological mechanism by which this genetic variation may act as a protective factor merits further investigation.

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Familial monophasic acute transverse myelitis due to the pathogenic variant in VPS37A

Objective To identify genetic differences among siblings with a family history of idiopathic transverse myelitis (ITM).

Methods We compared whole-exome sequencing (WES) on germline samples from 2 affected sisters with ITM with 3 of their healthy siblings.

Results The 2 sisters with ITM both had acute onset of sensory loss in the legs, weakness, and bowel/bladder dysfunction. The first developed ITM at age 15 years with a clinical nadir of complete paralysis, which slowly recovered over a few years. MRI demonstrated a persistent T2 lesion in the lower thoracic cord. The second developed ITM at age 50 years with a nadir of sensory loss from T6 down and paraparesis in the legs, associated with an MRI lesion at T6. She also made a partial recovery with treatment. Both sisters are homozygous for a missense variant in *VPS37A* (c.700C>A, p.Leu234Ile) identified by WES. We performed targeted sequencing of *VPS37A* in an additional 86 samples from patients with ITM and 175 with other diseases to investigate the p.Leu234Ile variant. We identified another patient with ITM homozygous for the same rare variant. No patients with multiple sclerosis, neuromyelitis optica, or other neurologic conditions, or any healthy controls in public databases were homozygous for this variant.

Conclusions A rare missense variant in *VPS37A* may predispose to development of ITM. Further studies are necessary to determine the frequency of this variant in the patient population and the mechanism through which it contributes to the risk of disease.

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