Abstracts

Articles appearing in the February 2018 issue

Duplications at 19q13.33 in patients with neurodevelopmental disorders

Objective After the recent publication of the first patients with disease-associated missense variants in the *GRIN2D* gene, we evaluate the effect of copy number variants (CNVs) overlapping this gene toward the presentation of neurodevelopmental disorders (NDDs).

Methods We explored ClinVar (number of CNVs = 50,794) and DECIPHER (number of CNVs = 28,085) clinical databases of genomic variations for patients with copy number changes overlapping the *GRIN2D* gene at the 19q13.33 locus and evaluated their respective phenotype alongside their frequency, gene content, and expression, with publicly available reference databases.

Results We identified 11 patients with microduplications at the 19q13.33 locus. The majority of CNVs arose de novo, and comparable CNVs are not present in control databases. All patients were reported to have NDDs and dysmorphic features as the most common clinical phenotype ($n = 8/11$), followed by seizures ($n = 6/11$) and intellectual disability ($n = 5/11$). All duplications shared a consensus region of 405 kb overlapping 13 genes. After screening for duplication tolerance in control populations, positive gene brain expression, and gene dosage sensitivity analysis, we highlight 4 genes for future evaluation: *CARD8*, *C19orf68*, *KDELR1*, and *GRIN2D*, which are promising candidates for disease causality. Furthermore, investigation of the literature especially supports *GRIN2D* as the best candidate gene.

Conclusions Our study presents dup19q13.33 as a novel duplication syndrome locus associated with NDDs. *CARD8*, *C19orf68*, *KDELR1*, and *GRIN2D* are promising candidates for functional follow-up.

[NPub.org/NG/9017a](https://doi.org/10.1214/17-NE.017)

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 [^{18}F]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 (MA) 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. MA 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, MA carriers had a lower $A\beta$ load ($p = 0.03$). Global cognition was higher in MA carriers, which was found to be mediated by $A\beta$.

Conclusion Together, these findings point to an association between *CYP2C19* polymorphism and $A\beta$ pathology, suggesting a protective effect of the MA 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.

[NPub.org/NG/9017b](https://doi.org/10.1214/17-NE.017b)

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