Abstracts

Articles appearing in the February 2018 issue

AP4 deficiency: A novel form of neurodegeneration with brain iron accumulation?

Objective To describe the clinicoradiologic phenotype of 3 patients harboring a homozygous novel *AP4M1* pathogenic mutation.

Methods The 3 patients from an inbred family who exhibited early-onset developmental delay, tetraparesis, juvenile motor function deterioration, and intellectual deficiency were investigated by magnetic brain imaging using T1-weighted, T2-weighted, T2*-weighted, fluid-attenuated inversion recovery, and susceptibility-weighted imaging (SWI) sequences. Whole exome sequencing was performed on the 3 patients.

Results In the 3 patients, brain imaging identified the same pattern of bilateral SWI hypointensity of the globus pallidus, concordant with iron accumulation. A novel homozygous nonsense mutation was identified in *AP4M1*, segregating with the disease and leading to truncation of half of the adapt domain of the protein.

Conclusions Our results suggest that *AP4M1* represents a new candidate gene that should be considered in the neurodegeneration with brain iron accumulation (NBIA) spectrum of disorders and highlight the intersections between hereditary spastic paraplegia and NBIA clinical presentations.

[NPub.org/NG/9014a](https://pubmed.ncbi.nlm.nih.gov/30144)

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/9014b](https://pubmed.ncbi.nlm.nih.gov/3014b)

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