



Abstracts

Papers appearing in the December 2020 issue

The SPID-GBA Study: Sex Distribution, Penetrance, Incidence, and Dementia in GBA-PD

Objective To provide a variant-specific estimate of incidence, penetrance, sex distribution, and association with dementia of the 4 most common Parkinson disease (PD)-associated *GBA* variants, we analyzed a large cohort of 4,923 Italian unrelated patients with primary degenerative parkinsonism (including 3,832 PD) enrolled in a single tertiary care center and 7,757 ethnically matched controls.

Methods The p.E326K, p.T369M, p.N370S, and p.L444P variants were screened using an allele-specific multiplexed PCR approach. All statistical procedures were performed using R or Plink v1.07.

Results Among the 4 analyzed variants, the p.L444P confirmed to be the most strongly associated with disease risk for PD, PD dementia (PDD), and dementia with Lewy bodies (DLB) (odds ratio [OR] for PD 15.63, 95% confidence interval [CI] = 8.04–30.37, $p = 4.97 \times 10^{-16}$; OR for PDD 29.57, 95% CI = 14.07–62.13, $p = 3.86 \times 10^{-19}$; OR for DLB 102.7, 95% CI = 31.38–336.1, $p = 1.91 \times 10^{-14}$). However, an unexpectedly high risk for dementia was conferred by p.E326K (OR for PDD 4.80, 95% CI = 2.87–8.02, $p = 2.12 \times 10^{-9}$; OR for DLB 12.24, 95% CI = 4.95–30.24, $p = 5.71 \times 10^{-8}$), which, on the basis of the impact on glucocerebrosidase activity, would be expected to be mild. The 1.5–2:1 male sex bias described in sporadic PD was lost in p.T369M carriers. We also showed that PD penetrance for p.L444P could reach the 15% at age 75 years.

Conclusions We report a large monocentric study on *GBA*-PD assessing mutation-specific data on the sex distribution, penetrance, incidence, and association with dementia of the 4 most frequent deleterious variants in *GBA*.

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Heterozygous Variants in *DCC*: Beyond Congenital Mirror Movements

Objective To perform a comprehensive characterization of a cohort of patients with congenital mirror movements (CMMs) in Sweden.

Methods Clinical examination with the Woods and Teuber scale for mirror movements (MMs), neuroimaging, navigated transcranial magnetic stimulation (nTMS), and massive parallel sequencing (MPS) were applied.

Results The cohort is ethnically diverse and includes a total of 7 patients distributed in 2 families and 2 sporadic cases. The degree of MMs was variable in this cohort. MPS revealed 2 novel heterozygous frameshift variants in *DCC* netrin 1 receptor (*DCC*). Two siblings harboring the pathogenic variant in c.1466_1476del display a complex syndrome featuring MMs and in 1 case receptive-expressive language disorder, chorea, epilepsy, and agenesis of the corpus callosum. The second *DCC* variant, c.1729delG, was associated with a typical benign CMM phenotype. No variants in *DCC*, *NTN1*, *RAD51*, or *DNAL4* were found for the 2 sporadic CMM cases. However, one of these sporadic cases had concomitant high-risk myelodysplastic syndrome and a homozygous variant in ERCC excision repair-like 2 (*ERCC6L2*). Reorganized corticospinal projection patterns to upper extremities were demonstrated with nTMS.

Conclusions The presence of chorea expands the clinical spectrum of syndromes associated with variants in *DCC*. Biallelic pathogenic variants in *ERCC6L2* cause bone marrow failure, but a potential association with CMM remains to be studied in larger cohorts.

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