Abstracts

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 × 10 − 16; OR for PDD 29.57, 95% CI = 14.07–62.13, p = 3.86 × 10 − 19; OR for DLB 102.7, 95% CI = 31.38–336.1, p = 1.91 × 10 − 14). However, an unexpectedly high risk for dementia was conferred by p.E326K (OR for PDD 4.80, 95% CI = 14.07–30.24, p = 5.71 × 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 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), neuro-imaging, 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: 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 DNAL1 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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