Title: Characterization of the genetic and phenotypic spectrum of a novel neurodevelopmental syndrome, *TCF7L2*-related neurodevelopmental disorder (TRND)

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Background: TCF7L2 is a transcription factor and critical effector of the Wnt/beta-catenin pathway, with pleiotropic roles across human biology and disease. Intronic SNPs in TCF7L2 have been linked to increased risk for type 2 diabetes, colon cancer, schizophrenia, and autism spectrum disorder (ASD). In 2021, 11 pediatric patients with mono-allelic predicted loss-of-function (pLOF) variants in TCF7L2 were described as having potentially syndromic features, including developmental delays and variable myopia, autism, and ADHD, among other features. Defining the genetic and phenotypic spectrum and natural history of this patient population is urgently required.

Methods: We leveraged multiple recruitment strategies (GeneMatcher, DECIPHER, literature review, and public/private repositories) to identify an international cohort of 76 patients with neurodevelopmental features and pLOF TCF7L2 variants, herein referred to as TCF7L2-related neurodevelopmental disorder (TRND), from 2022-2024 and phenotypically characterized them using a clinician-facing survey. We also conducted a retrospective screen of ~60,000 adult PennMedicine BioBank (PMBB) patients, identifying a

distinct group of 11 patients with pLOF TCF7L2 variants and unconfirmed neurodevelopmental phenotype.

Findings: 76 patients had truncating (n = 10), out-of-frame indel (n = 18), missense (n = 33), splice site (n = 10), in-frame indel (n = 1), and CNV (n = 4) variants in TCF7L2. Speech delay (95.31%), craniofacial dysmorphisms (73.33%), ophthalmologic conditions (65.52%), ASD (62.07%), and orthopedic abnormalities (52.63%) were most commonly observed. Ear morphology abnormalities (22.03%), hypertelorism (20.69%), down-slanted palpebral fissures (18.97%), and frontal bossing (15.52%) were the most frequent craniofacial features, co-occurring in a subset of patients. Phenotypic differences did not grossly cluster by variant type or genomic locus. Among PMBB patients, compared to an age/sexmatched PMBB control group, there was a nominal increased risk for type 2 diabetes with renal manifestations (unadjusted-P=0.03), warranting additional screens, neurodevelopmental follow-up to correlate with our cohort of pediatric patients, and further functional investigation.

Implications: This study represents the most comprehensive characterization of patients to date with TRND, a novel syndromic neurodevelopmental disorder, providing insights regarding its phenotypic and genotypic spectrum and a foundation for longitudinal study. We launched a natural history study with Simons Searchlight that is now open for enrollment for TRND patients.