Identification of Genotype-Phenotype Associations in Phelan-McDermid Syndrome Using Patient-Sourced Data

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Phelan-McDermid Syndrome (PMS) is a syndromic form of autism caused by terminal deletions of the long arm of chromosome 22 affecting at least the SHANK3 gene. It variably associates autism, global developmental delay, delayed speech, neonatal hypotonia, and mildly dysmorphic features. Isolated haploinsufficiency of SHANK3 has been shown to be responsible of a subset of PMS features. The PMS International Registry (PMSIR) compiles clinical data in the form of patient-reported outcomes, as well as patient-sourced genetic test results. Data from the PMSIR have been harmonized and integrated into the BD2K i2b2/tranSMART clinical & genomics data warehouse. We conducted genotype-phenotype analyses using regression models associating the deletion size as a predictor of the different clinical outcomes. 156 patients were included, with deletion sizes ranging from 10.34 kb to 9.057 Mb, with 6 patients presenting small isolated SHANK3 mutations. Increased deletion size is significantly associated with delay in gross motor acquisitions, vesicoureteral reflux, socio-emotional and behavioral development delays, verbal speech, mild dysmorphic features (large fleshy hands, dysplastic toenails/fingernails and sacral dimple), and a spectrum of conditions related to poor muscle tone, suggesting the implication of genes upstream of SHANK3. In this study using data from the PMSIR, we demonstrate the use of entirely patient-sourced registry data consisting of PRO items filled by the parents, and curated genetic test reports to conduct genotype-phenotype analyses. Known results are replicated and novel findings show the ability of registry data to uncover new associations between comorbidities and deleted chromosomal regions in PMS.