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Phenotype and Psychometric Characterization of Phelan-Mcdermid Syndrome Patients

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Abstract : Background: The Phelan-McDermid syndrome (PMS) is a genetic disorder caused by the deletion of the terminal region of chromosome 22 or mutation of the SHANK3 gene. Shank3 disruption in mice leads to dysfunction of synaptic transmission, which can be restored by epigenetic regulation with both Lysine Specific Demethylase 1 (LSD1) inhibitors. PMS subjects result in a variable degree of intellectual disability, delay or absence of speech, autistic spectrum disorders symptoms, low muscle tone, motor delays and epilepsy. Vafidemstat is an LSD1 inhibitor in Phase II clinical development with a well-established and favorable safety profile, and data supporting the restoration of memory and cognition defects as well as reduction of agitation and aggression in several animal models and clinical studies. Therefore, vafidemstat has the potential to become a first-in-class precision medicine approach to treat PMS patients. Aims: The goal of this research is to perform an observational trial to psychometrically characterize individuals carrying deletions in SHANK3 and build a foundation for subsequent precision psychiatry clinical trials with vafidemstat. Methodology: This study is characterizing the clinical profile of 20 to 40 subjects, > 16-year-old, with genotypically confirmed PMS diagnosis. Subjects will complete a battery of neuropsychological scales, including the Repetitive Behavior Questionnaire (RBQ), Vineland Adaptive Behavior Scales, Escala de Observación para el Diagnostico del Autismo (Autism Diagnostic Observational Scale) (ADOS)-2, the Battelle Developmental Inventory and the Behavior Problems Inventory (BPI). Results: By March 2021, 19 patients have been enrolled. Unsupervised hierarchical clustering of the results obtained so far identifies 3 groups of patients, characterized by different profiles of cognitive and behavioral scores. The first cluster is characterized by low Battelle age, high ADOS and low Vineland, RBQ and BPI scores. Low Vineland, RBQ and BPI scores are also detected in the second cluster, which in contrast has high Battelle age and low ADOS scores. The third cluster is somewhat in the middle for the Battelle, Vineland and ADOS scores while displaying the highest levels of aggression (high BPI) and repeated behaviors (high RBQ). In line with the observation that female patients are generally affected by milder forms of autistic symptoms, no male patients are present in the second cluster. Dividing the results by gender highlights that male patients in the third cluster are characterized by a higher frequency of aggression, whereas female patients from the same cluster display a tendency toward higher repetitive behavior. Finally, statistically significant differences in deletion sizes are detected comparing the three clusters (also after correcting for gender), and deletion size appears to be positively correlated with ADOS and negatively correlated with Vineland A and C scores. No correlation is detected between deletion size and the BPI and RBQ scores. Conclusions: Precision medicine may open a new way to understand and treat Central Nervous System disorders. Epigenetic dysregulation has been proposed to be an important mechanism in the pathogenesis of schizophrenia and autism. Vafidemstat holds exciting therapeutic potential in PMS, and this study will provide data regarding the optimal endpoints for a future clinical study to explore vafidemstat ability to treat shank3-associated psychiatric disorders.

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