

CLIPPINGS

 Mutations disrupting neurogenetic genes confer risk for cerebral palsy (*Nature Genetics*. 2020;52:1046-56).

Cerebral Palsy (CP) is a neurodevelopmental disorder with multifactorial etiology including environmental and genetic factors. Previous studies have predicted deleterious CNVs in 10-31% cases of CP, however, insufficient availability of controls, limits the statistical inferences. In this study, whole exome sequencing (WES) was performed on 250 CP families from US, Australia and China. Within the 250 family cohort, 157 (62.8%) were classified as idiopathic, 84 cases (33.6%) had a known environmental insult and the remaining 9 trios (3.6%) were not able to be assigned to either category (unclassified). Control trios consisting of 1,789 unaffected siblings of autism cases and their unaffected parents were analyzed in parallel. WES was performed for 250 parent offspring trio which showed enrichment of damaging de-novo mutations. Eight genes had multiple damaging de novo mutations; of these, 2 met genome-wide significance (*TUB1A* and *CTNNT1*). Also, two novel monogenic etiologies were identified (*FBXO31* and *RHOB*). Candidate CP risk genes overlapped with neurodevelopmental disorder genes. It was estimated that 14% of cases could be attributed to an excess of damaging de novo or recessive variants.

The authors inferred that genomic variants should be considered alongside environmental insults when assessing the etiology of an individual's CP. Also, over time, mechanistic insights derived from the identification of core pathways via genomic studies of CP may help guide therapeutic development efforts.

 Autism Spectrum Disorder may be linked to impaired production of myelin (*Nature Neuroscience*. 2020;23:375-85)

Research has revealed some mechanistic underpinnings of syndromic forms of autism spectrum disorder. A study at John Hopkins University performed transcriptomic analyses of seven independent mouse models covering three syndromic forms of ASD i.e. five models of Pitt Hopkins syndrome (PTHS) (a syndromic form of ASD caused by autosomal dominant mutations in the transcription factor 4 (TCF4) gene and characterized by intellectual disability, failure to acquire language, deficits in motor learning, hyperventilation, gastrointestinal abnormalities), 1 model of PTEN mutation and 1 model of Mecp2 mutation. Then, they assessed dysregulated genes (DEGs) and their pathways in human post mortem brain from individuals with ASD and neurotypical controls. The PTHS mouse models showed cell-autonomous reductions in oligodendrocytes (OL) numbers and myelination, functionally confirming OL transcriptional signatures. Significant enrichment of overlapping DEGs and common myelination associated pathways were found in human idiopathic ASD post mortem brain also. Importantly, DEGs from syndromic ASD mouse models, and reduced deconvoluted OL numbers, differentiated human idiopathic ASD cases from controls. These results implicate disruptions in OL biology as a cellular mechanism in

ASD pathology and opens a future prospect to tap therapeutic opportunity throughout the life span.

 Reduced tactile neural repetition suppression is an early marker of later ASD traits in infants (*J Neurodevelopmental Disord*. 2021;13:1)

This longitudinal study from 2013-2019 was done to investigate behavioural and neural markers of tactile sensory processing in ninety one 10-month-old infants at elevated likelihood of ASD or ADHD (i.e. by virtue of having a first-degree relative with a clinical diagnosis of ASD or ADHD) compared to infants at typical likelihood of the disorders. A tactile repetition suppression paradigm administering repeated pairs of vibrotactile stimuli (S1-S2) was used and coupled with the recording of EEG. Behavioural markers were quantified by coding looking and moving behaviours before and after receiving the pair of tactile stimuli by a computerized frame-by-frame coding system. The longitudinal associations between early neural and behavioural markers of tactile processing and later ASD traits [by Autism Diagnostic Observation Schedule (ADOS-2)] or ADHD traits [by Early Childhood Behaviour Questionnaire (ECBQ)] were assessed at 24 months. It was observed that all infants, independent of their likelihood status, exhibited a decrease in screen-directed looking and an increase in body movement from the pre to the post-stimulus phase. Infants with an elevated ASD likelihood manifested reduced neural repetition suppression to tactile stimulation ($P=0.02$). The hierarchical linear regression with Tactile Suppression Index (TSI) as predictor and ADOS as outcome was statistically significant ($P < 0.001$), indicating that infants with lower neural repetition suppression of tactile stimulation at 10 months exhibited higher levels of ASD traits at 24 months. In contrast, there was no significant main effect of ADHD likelihood status.

The authors underlined the need for future research to assess the existence of continuity between the marker identified in the current study and the heterogeneous spectrum of sensory features documented later in development, including sensory hyper/hyposensitivity manifestations.

 Viloxazine as a new drug for treatment of Attention Deficit Hyperactivity Disorder in school-aged children (*Clin. Therap*. 2020 Aug;42(8):1452-1466)

A phase III, multisite, randomized, double-blind, placebo-controlled, 6-week trial was conducted in United States to assess the efficacy and safety of a newer drug viloxazine (SPN-812) in treatment of ADHD in school aged children. It is a multimodal serotonergic and noradrenergic modulating agent (SNMA) having activity at serotonin receptors and norepinephrine transporters, although the mechanism of action remains to be fully elucidated. Side effect profile is usually mild, comprising of somnolence, decreased appetite, headache, fatigue, nausea, and irritability and is usually reversible after discontinuation. A total of 477 children (6-11 year old) with ADHD were randomized into 3 arms (159 in placebo, 157 in 100mg/d and 161 in 200mg/d) between October 2017 and September 2018. The efficacy endpoints were the change from

baseline in total score of ADHD-RS-5, Clinical Global Impression-Improvement (CGI-I), Conner's 3 scale and Weiss Functional Impairment Rating Scale (WFIRS-P). The majority of subjects were male (63%) with similar demographic and baseline characteristics between groups. Statistically significant improvements in ADHD-RS-5 Total score were observed in both the 100- and 200-mg/day SPN-812 treatment groups compared to placebo at week 1 of treatment, which was maintained through end of the study ($P<0.0004$ and $P<0.0001$).

Significant improvements were also observed in the CGI-I scale, Conner's 3-Composite T-score, and WFIRS-P average score. Treatment-related adverse events (AEs) were reported in $\geq 5\%$ of subjects and the discontinuation rate due to AEs was $<5\%$. The authors deduced that SPN-812 is an effective and well tolerated pharmacotherapy that could be future treatment option for children with ADHD, though more evidence is required.

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