ESCO Science Spotlight, Sept 2025-Jan 2026

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In the last 3 months there were several publications in the field of STXBP1 related both to basic science and clinical research which will be described in this summary and in addition to it posters and presentations related to STXBP1 presented in the recent AES (American epilepsy society) meeting in Atlanta in December 2025 will be briefly summarized.

An interesting animal study was pubished **Gangting Xu et al in "Human Molecular Genetics" 2025** presenting new evidence for the role of the serotoninergic system in STXBP1 pathogenesis in addition to the known major involvement of the gabaergic and glutamaergic systems.

In C.elegans model (worm) of STXBP1 analog knock out they show deficits in serotonergic neurons, manifested in gradual change in dendrites becoming slender with progressive neurite thinning during adulthood that can be interpreted as dendritic atrophy. In addition experiments in both general and conditional (cell type related) haploinsuffient STXBP1 mice models were described. The researchers show reduced tryptophan hydroxylase (enzyme responsible for serotonin production) and serotonin in serotoninergic neurons in the dorsal raphe nucleus (DRN), the primary origin of serotonergic neurons in the brain, and reduced quantity of serotonin (5-HT) and its primary metabolite 5-hydroxyindoleacetic acid (5-HIAA) in brain stem tissues compared to wild animals accompanied by upregulation (increased expression) of several types of serotonin receptors in the animal brains. The phenotype of mices with STXBP1 deficiency only in the serotoninergic system was charecterized. The mice were similar in size and weight to wild type animal but showed epileptiform activity recorded from their cortex, no evidence of spasticity (seen in generally deficient mice) , they did not show cognitive deficits but were hyperactive and showed significant aggressive behaviour and other features of psychiatric phenotype which could be ameliorated by Fluoxetine (SSRI) treatment.

The positive response of the behavioral charecteristics to SSRI (fluoxetine) is worth consideration also in the clinical field.

Several posters related to basic science research were presented in the last AES meeting and are worth acknowledging :

Impaired interneuron migration from human STXBP1 loss of function medial ganglionic eminence-like organoids. K Stoke et al from University of Michigan.

Using CRISPR-Cas9 STXPB1 heterozygous and isogenic control human pluripotent stem cell (hPSC) lines were created in addition to hPSCs from a patient harboring a pathogenic variant for STXBP1 as well as from his unaffected sibling (control). These lines were differentiating into medial ganglionic eminence-like cortical organoids (early neural progenitor cells) and these cells migration was followed in the extracellular matrix of the organoids. In both knock out models and patient originated model there was a negative mild change in movement of this progenitor cells through the ECM which can indicate slower migration of affected early neuronal progenitors to the cortex that may impact proper network formation leading to hyperexcitability. This is a preliminary first study which requires further investigation .

Second poster title was: **Non-synaptic function and localization of STXBP1 in a mouse model of STXBP1 related epileptic encephalopathy By Tao Yang et al from the university of Michigan and just recently published in Annals neurology Jan .2026**

The localization of STXBP1 protein in the mice cerebral cortex with immunohistochemistry techniques was investigated showing that the protein is developmentally regulated in vivo and can be detected in both neuronal soma (cell body) and processes (dendrites and axons). Stxbp1 protein (Munc-18) was present in both synaptic and cytosolic fractions, interacting with neuronal cytoskeleton and membrane periodic structures. They also demonstrated interaction between STXBP1 and αII Spectrin and Arpc2 and being required for their localization on the neuronal membrane suggesting its role in regulating the trafficking of membrane cytoskeleton proteins in the brain. Their conclusion is: STXBP1 is both a synaptic and non-synaptic protein interacting with membrane periodic skeleton that plays critical roles in neural development.

Additional research presentation was : **AAV Gene Therapy in Juvenile Mice of STXBP1 Haploinsufficiency by N. Rodriguez et al from UCB, Braine l'Alleud, Belgium**

The group evaluated the efficacy and safety of a Gene therapy administered intracerebrally to the striatum of STXBP1 KO mice (basal ganglia) at juvenile age and measured its impact on multiple disease symptoms. The gene construct used included human long splice variant of STXBP1 attached to a neuronal promoter. The animals were injected at post natal day 24-28 in two different dosages and were followed by behavioral tests and EEG recording . Following gene therapy in both low and high dosages rapid and sustained reduction of spike wave discharges (SWD) was detected but no other disease symptoms change in disease symptoms were demonstrated. In addition unexpected generalized convulsive seizures and mortality in the high-dose GT was detected while the low doze was tolerated and was safe up to 6 months. . they conclude that intervention with an intracerebral GT (direct cerebral injection) at a post-symptomatic stage does not confer efficient impact on disease symptoms in STXBP1 HET KO mice with high doze being detrimental in this model.

This is a single study with a specific construct injected directly to brain parenchyma . the results of this study implicate looking for different constructs , and other dosages and roots of administration.

Clinically related papers coming from US STXBP1 research group in phyladelphia is mainly looking at developing appropriate tools for patients' assessments in future clinical intervention studies

The first paper is relates to R**eliability and stability of Cerebral Palsy Classification Scales for Individuals with STXBP1 Related Disorders and SYNGAP1 Related Disorders Samuel R. Pierce et al in a pre print format in MedRvix**

Evaluation scales for specific neurodevelopmental disorders are difficult to produce and require immense efforts .Because of significant resemblance between neurodevelopmental genetic disorders and Cerebral palsy which is more common and already have many appropriate assessment scales in use investigators in genetic neurodevelopmental disorders tend to use this already established scales in the specific genetic population they are investigating and it becomes crucially important to find out if the chosen scales are appropriate to use in a specific population especially when planning to be utilized in intervention studies .

Two raters assessed 83 individuals with STXBP1-RD (mean age = 9.8 years) by using the Gross Motor Function Classification System (GMFCS), mini–Manual Ability Classification System (mini-MACS), Manual Ability Classification System (MACS), and Communication Function Classification System (CFCS) (all originating in the cerebral palsy field) The interrater reliability and stability in longitudinal assessments varied from 73.8% to 77.3% in their agreement and from 0.62 to 0.94 in Test-retest

stability scores which is considered appropriate for use in research trials despite not being as accurate as in CP.

The other finding of this study was that gross motor function is least affected while Language function is most affected for both conditions(STXBP1-RD and SYNGAP1) and their conclusion was was that the above functional rating scales can be used to inform care, aid in identifying subgroups based on phenotypic features, and to classify individuals in future intervention trials.

Additional paper related to evaluation tools for research in the STXBP1 population is by **JM Orlando et al from Phyladelphia published in its pre peer review form in MedRvix and describes the Quantification of neuromotor control in STXBP1-Related Disorders with wearable sensors**

The researchers used inertial sensors put on the upper arms and forearms of 31 children with STXBP-1 in order to characterize motor control abnormalities . This tool was used to quantify the prevalence and clinical features of tremor and other motor control impairments and found significant tremor in 64.5% of the patients studied. The prevalence of tremor in the study group exceeds by fivefold what has been reported in other genetic neurodevelopmental disorders, suggesting that tremor may be heavily underreported in historical, retrospective datasets on STXBP1 -RD. They also demonstrated slower reaching time, decreased arm acceleration intensity, less smooth reaching, and tremor frequency characteristics consistent with an unstable or irregular rhythmic movement pattern. The reaching task required from the patients was feasible for most participants (83.9%) and the patterns observed are indicative of disorganized or unstable rhythmic movements, consistent with features of rhythmic myoclonus.

The study also showed strong correlations between motor control measures and developmental function using the STXBP1-Clinical Severity Assessment (S-CSA) tool. The correlation found enables the use of the data collected from this easily managed wearable sensor tool as biomarkers for future clinical trials.

Two additional posters in the AES meeting 2025 are related to real world clinical interventions in STXBP1-RD population : the first one is by **K. Barbourthe et al from the Scripps Research Translational Institute and other centres and is related to the Clinical Responses to Off-Label Use of Phenylbutyrate for STXBP1 :**

18 children (median age of 6 years) and median treatment duration of 6 months were assessed by parents interviews : in five children (nonverbal and non ambulatory at baseline) parents claim that they Initiating more social interactions and communicated their wants and needs more . Seven children (ambulatory and nonverbal at baseline) showed more eye contact, joint attention, and improved ability to follow simple instructions, show more complex communication (combining signed words, new word approximation) and in addition improvements in mood, attention, and behavior . In 6 children (ambulatory and verbal at baseline) parents reported increased vocabulary and more complex phrases or sentences, improvements in following instructions and again improvements in mood, attention, and behavior. 13/14 children who continued phenylbutyrate experienced resolution of side effects within 2-10 days of the dosing period (starting or increasing), except for one with persistent constipation managed with a laxative.

The observations is worth reporting but it should be emphasized that they rely only on subjective recollections of the parents

A poster presented by **Dr M Gia from MediClub Georgia Medical Center, Tbilisi, Georgia and reported clinical observation of 4 patients with STXBP1-RD treated with Acetazolamide in neurology clinics from Georgia ,US and Italy .**

Four unrelated patients with STXBP1-RD and drug resistant epilepsy received adjunctive acetazolamide (17–25 mg/kg/day) following failure of multiple antiseizure medications .Clinical outcomes included seizure frequency, EEG changes, motor/ataxia symptoms and developmental progress. According to their report 3 patients achieved complete seizure freedom within two weeks, and one showed dramatic EEG improvement with cessation of spasms and normalization of EEG background activity. Two patients experienced striking improvements in ataxia, tremor, motor abilities, and social interaction. This is the first report of acetazolamide use in STXBP1-related disorder suggesting that this drug should be considered as a therapeutic option for both epileptic and motor manifestations in STXBP1-related NDD, warranting systematic evaluation in larger cohorts.

The final reviewed paper from the last 3 months is related to the involvement of Munc -18 (STXBP1 related protein) in dementia. " **Munc 18–1 is a multifaceted therapeutic target for dementia by KS singh et al. Aging Research Reviews 112 (2025**)

This paper is a comprehensive review of the role of Munc-18-1 (Stxbp1 protein) in dementia pathogenesis by the influence of the protein in amyloid precursor protein (APP) processing, modulation of Tau phosphorylation through CDK5, and acting as a molecular chaperone for α-synuclein, all related to the neurodegenerative processes of aging and dementia. Notably, reductions or mutations in Munc18–1 have been consistently associated with increased neuronal apoptosis and cognitive decline in various dementia models. Several studies have reported alterations in Munc18–1 levels in brain tissues and cerebrospinal fluid (CSF) of patients with dementia and Alzhaeimer disease (AD) and in Post-mortem analyses of AD brains. The effect is primarily presynaptic and shown in both glutamatergic and cholinergic neurons. The authors of this review claim that Munc18–1 serves as a master regulator in the multifactorial landscape of dementia, due to its interface with major pathogenic processes including : SNARE-mediated synaptic vesicle fusion, amyloid precursor protein (APP) processing, α-synuclein aggregation, maintenance of synaptic integrity and neurotransmission, Tau hyperphosphorylation, neuroinflammatory signalling, and BDNF-TrkB- mediated synaptic modulation. All these findings makes this protein an interesting target for dementia therapy which puts STXBP1 gene in focus not only in STXBP1-RD but also in the much more common field of dementia.

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