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A Brief Overview on SYNGAP1 Gene Related Autism

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

Mutations in genes encoding synaptic proteins are autism spectrum disorders in nearly half of the cases of SYNGAP syndrome. Premature development of dendritic spine synapses in the early postnatal period led to increased excitability in the hippocampus and behavioral abnormalities. Mutations in SYNGAP1 have minimal impact on spine synapse function when induced after critical developmental windows closed, and repairing these mutations in adulthood did not improve behavior and cognition. SYNGAP protein plays an important role in regulating neural excitability during development, influencing cognitive abilities throughout life. The timing of dendritic spine synapse maturation in early life is crucial for normal intellectual development. SYNGAP 1 gene is a high-risk gene for autism spectrum disorder. In this brief overview we focus on the relationship between mutations in the SYNGAP gene and autism spectrum disorders in childhood.

Keywords: SYNGAP; mutation; child, autism; premature.

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1. INTRODUCTION

The SYNGAP syndrome, also known as SYNGAP1 syndrome, is a very rare congenital disorder. In the past, the condition was also referred to as mental retardation 5 (MRD5) and classified as a non-syndromic, autosomal dominant mental retardation (Gamache et al. 2020). The collection of symptoms is now referred to as a syndrome. According to the Bridge the Gap Foundation, approximately 1-2% of intellectually disabled individuals are affected by the SYNGAP syndrome. With a total of 420,000 intellectually disabled individuals in Germany, the frequency is estimated to be about 1:10,000 to 1:20,000. The underlying cause is a mutation in the SYNGAP1 gene, located on the short arm (p-arm) of chromosome 6, which encodes a RasGTPase activating synaptic protein (Holder JL et al. 2019, Araki Y et al. 2024, Jeyabalan et al. 2016). In 1998, Richard Huganir and his team at Johns Hopkins University School of Medicine discovered the SYNGAP1 gene. Synaptic Ras GTPase-activating protein 1, also known as synaptic Ras-GAP 1 or SYNGAP1, is a protein encoded by the SYNGAP1 gene in humans. SYNGAP1 is a ras GTPase-activating protein that plays a critical role in cognition development and proper synapse function. Mutations in humans can lead to intellectual disability, epilepsy, autism, and sensory processing deficits. SynGAP1 is a complex protein with various functions that may be regulated temporally through different isoforms. One of its well-documented functions involves NMDA receptor-mediated synaptic plasticity and the membrane insertion of AMPA receptors by suppressing upstream signaling pathways. Additionally, SynGAP1 has been shown to work with Unc51.1 in axon formation. It affects these processes through the MAP kinase signaling pathway by attenuating Ras signaling. Alternative splicing and multiple translational start sites can have opposing effects, highlighting the importance of multiple functional domains within the protein. For example, the expression of different c-terminal variants of SynGAP1 can either increase or decrease synaptic strength. Overall, SynGAP1 is crucial for development and survival, as knockout mice die shortly after birth. SynGAP1 localizes at the postsynaptic density on dendritic spines of excitatory synapses. Cultured neurons from SynGAP knockout mice show accelerated maturation of dendritic spines, leading to larger spine size and more mature shapes. This is due to increased phosphorylation of cofilin, resulting in decreased F-actin severing and turnover. The larger dendritic spines also have more membrane-bound AMPARs or fewer silent synapses, leading to higher frequency and larger amplitudes of miniature excitatory postsynaptic potentials. Mice models with specific mutations exhibit neonatal hyperactivity in the hippocampal circuit, with the most significant impact during the first 3 weeks of development. Reversing mutations in adults does not improve behavior and cognition. The genetic detection of pathogenic SYNGAP1 variants or microdeletions of chromosome 6p21.32 (aCGH) confirms the diagnosis (Bloomfield et al. 2024, Wang et al. 2013, Wiltrout et al. 2024, Katsanevaki et al. 2024, Jeyabalan 2016). The main symptoms of the SYNGAP syndrome include global developmental delay or developmental disorder and motor development (Kilinc et al. 2018, Zhao et al. 2023). SYNGAP patients typically reach developmental milestones later than normally developing children. SYNGAP1-related intellectual disability is classified as an autosomal dominant condition, which means that having one copy of the altered gene in each cell is enough to cause the disorder. Most cases are due to new mutations in the gene and occur in individuals with no family history of the disorder. This is often noticed by parents and pediatricians in the first year of life due to muscle hypotonia. As a result, motor development is significantly delayed, and affected children learn to walk later. They often exhibit a wide-legged, clumsy gait. Fine motor skills are also greatly impaired, with many children showing pronounced dyspraxia. Poor oral motor skills are evident in newborns, such as feeding difficulties and reduced vocalization. Betrothed children also exhibit a temporary protrusion of the tongue between the lips – a result of hypotonia of the mouth muscles. Previously acquired sounds and syllables are often forgotten. In later years, a verbal development dyspraxia or apraxia is often diagnosed. Most SYNGAP patients are non-verbal or have a very limited vocabulary of only a few words or syllables (Xing et al. 2016). Eating and chewing induced seizures are well known in children with SYNGAP mutations (von Stülpnagel et al. 2019). Some children, however, are able to learn simple written communication. To express their needs, affected individuals use both their own body language and means of supported communication. Some children show a slowed cognitive development in early developmental tests, which is later referred to as mental retardation in medical reports. In later intelligence tests, patients fall within the range of moderate to

severe intellectual disability. Parents typically become aware of epileptic seizures around the age of 2-3 years. However, they often realize in hindsight that signs of seizures were present in the first year of life. These seizures manifest as atypical absences, eyelid myoclonus, myoclonic-astatic seizures and drop attacks. The seizures resemble those of Doose syndrome. In EEG, the seizures start in the visual center and then generalize. This is often manifested clinically by a distinctive gaze followed by loss of tone. In many cases, the EEG remains nonspecific. Triggers are epileptic seizures are mainly triggered by fatigue, stress, and sensory stimuli. Particularly noticeable in SYNGAP patients are seizures triggered by eating (Llamosas et al. 2020). These short, usually lasting only a few seconds, seizures are often recognized as epilepsy too late and are misinterpreted as fatigue or enjoyable eating, especially in younger children. Therefore, parents of SYNGAP children should try to capture the eating situation on video for the treating pediatrician or neurologist. In EEG, especially in a sleep EEG, these patients may appear completely normal, or the EEG may be described as abnormal but not pathological (Paasch et al. 2023, Hong et al. 2025). However, if they are given something to eat during a wake EEG, many patients show a typical EEG pattern. Approximately half of SYNGAP patients have a diagnosed autism spectrum disorder. According to the classical classification, the autistic symptoms would likely be classified as atypical autism (Haetzel et al. 2024). However, the actual number of individuals affected by autism is likely higher, as diagnosing autism in nonverbal, intellectually disabled individuals with dyspraxia is not straightforward. Additionally, behavioral issues such as impulsivity and aggression may occur. Obsessive behaviors are particularly noticeable. SYNGAP children are especially fond of water and music, but also objects like fans, elevators, escalators, switches, glass roofs, and spatial perspective in motion. When they feel the need for these, they appear unusually motivated. However, if access to the desired object is denied, due to the lack of language, they use all physical means to assert their will. The diagnosis of SYNGAP syndrome can only be made through a genetic test (Frazier et al. 2023, Beversdorf et al. 2023). Mutation analysis of SYNGAP1 gene can be done by conventional technology or by next generation sequencing technology. Usually SYNGAP1 gene is included in an NGS panel such as autism panel/ whole exome. Additionally, various laboratories offer different gene panels that analyze the SYNGAP1 gene using next-generation sequencing (Frazier et al. 2024, Harris et al. 2021, Meili et al. 2021). Depending on the laboratory, this may be a gene panel for developmental disorders, mental retardation, epilepsy, epileptic encephalopathy, or autism. A causal therapy was successfully performed using statins. Statins inhibit the overactive RAS cascade in SYNGAP syndrome. Since July 2023, therapies for SYNGAP syndrome are being researched in the EURAS project, funded by the European Union. The main differential diagnosis is Angelman syndrome (Berryer, et al., 2013; Hamdan, et al., 2011).

2. CONCLUSION

Genes linked to synaptic function are prevalent in individuals with autism spectrum disorder due to rare genetic variants. While disrupted cortical neurogenesis is a key factor in ASD, the role of 'synaptic' ASD risk genes in early brain development remains unclear (von Stülpnagel et al. 2019). A recent study focused on the synaptic Ras GTPase-activating protein 1 (SYNGAP1), a prominent ASD risk gene, which is expressed in human radial glia cells (hRGCs) (Birtele et al. 2023). Using a human cortical organoid model of SYNGAP1 haploinsufficiency, researchers observed abnormalities in cytoskeletal dynamics affecting hRGC scaffolding and division, leading to impaired cortical layering and accelerated maturation of neurons (Birtele et al. 2023). Furthermore, the mouse model of Syngap1 haploinsufficiency showed an altered progenitor-to-neuron ratio (Birtele et al. 2023). The findings of the study suggest that SYNGAP1-related brain disorders may involve non-synaptic mechanisms, underscoring the importance of studying NDD-associated genes in various human cell types and developmental stages.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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