Letter to the Editor

SYNGAP-Disorders and Autism Pathogenesis

EDITORIAL

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. In children with autism spectrum disorder, nearly 50 per cent have SYNGAP 1 disorder. SYNGAP 1 gene is a high-risk gene for autism spectrum disorder. In this review we focus on the relationship between mutations in the SYNGAP gene and autism spectrum disorders in childhood.

Keywords

SYNGAP-Mutation-Child-Autism

**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 (1-21). 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 (2,3,8). The genetic detection of pathogenic SYNGAP1 variants or microdeletions of chromosome 6p21.32 (aCGH) confirms the diagnosis (4-7). The main symptoms of the SYNGAP syndrome include global developmental delay or developmental disorder and motor development (9,10). SYNGAP patients typically reach developmental milestones later than normally developing children. 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 (11). 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 (12). 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 (13,14). 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 (15). 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 (16,17). In human genetics, the SYNGAP1 gene is examined for changes. This analysis is performed using a single gene test through Sanger sequencing. Additionally, various laboratories offer different gene panels that analyze the SYNGAP1 gene using next-generation sequencing (18-20). 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.

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. 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) (21). 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 (21). Furthermore, the mouse model of Syngap1 haploinsufficiency showed an altered progenitor-to-neuron ratio (21). 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.

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