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SYNGAP1-Related Intellectual Disability

Synonym: *SYNGAP1*-Related Developmental and Epileptic Encephalopathy

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Summary

Clinical characteristics

SYNGAP1-related intellectual disability (*SYNGAP1*-ID) is characterized by developmental delay (DD) or intellectual disability (ID) (100% of affected individuals), generalized epilepsy (~84%), and autism spectrum disorder (ASD) and other behavioral abnormalities (≤50%). To date more than 50 individuals with *SYNGAP1*-ID have been reported. In the majority DD/ID was moderate to severe; in some it was mild. The epilepsy is generalized; a subset of individuals with epilepsy have myoclonic astatic epilepsy (Doose syndrome) or epilepsy with myoclonic absences. Behavioral abnormalities can include stereotypic behaviors (e.g., hand flapping, obsessions with certain objects) as well as poor social development. Feeding difficulties can be significant in some.

Diagnosis/testing

The diagnosis of *SYNGAP1*-ID is established in a proband with developmental delay or intellectual disability in whom molecular genetic testing identifies either a heterozygous pathogenic variant in *SYNGAP1* (~89%) or a deletion of 6p21.3 (~11%).

Management

Treatment of manifestations: DD/ID are managed as per standard practice. No guidelines are available regarding choice of specific anti-seizure medications (ASMs). In about 50% of patients, the epilepsy responds to a single ASM; in the remainder it is pharmacoresistant. Children may qualify for and benefit from interventions used in treatment of ASD. Consultation with a developmental pediatrician may guide parents through appropriate behavioral management strategies and/or provide prescription medications when necessary. Nasogastric/gastrostomy feeding may be required for individuals with persistent feeding issues.

Surveillance: Monitor seizure manifestations and control; behavioral issues; developmental progress and educational needs.

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Genetic counseling

SYNGAP1-ID is inherited in an autosomal dominant manner. To date almost all probands with *SYNGAP1*-ID whose parents have undergone molecular genetic testing have had a *de novo* germline pathogenic variant; however, vertical transmission (from a mildly affected, mosaic parent to the proband) has been reported in one family. Thus, while the risk to sibs appears to be low, it is presumed to be greater than in the general population because of the possibility of germline mosaicism in a parent. Once the *SYNGAP1* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

No formal diagnostic criteria have been published for *SYNGAP1*-related intellectual disability.

Suggestive Findings

SYNGAP1-related intellectual disability (*SYNGAP1*-ID) **should be considered** in individuals with developmental delay or intellectual disability with or without:

- Generalized epilepsy;

  and/or

- Autism spectrum disorder (ASD).

Establishing the Diagnosis

The diagnosis of *SYNGAP1*-ID **is established** in a proband with developmental delay (DD) or intellectual disability (ID) in whom molecular genetic testing (see Table 1) identifies either:

- A heterozygous pathogenic (or likely pathogenic) variant in *SYNGAP1* (~89%);

  or

- A deletion of 6p21.3 (~11%).

Note: Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants.

Molecular genetic testing in a child with DD or an older individual with ID typically begins with chromosomal microarray analysis (CMA). If CMA is not diagnostic, the next step is typically either a multigene panel or exome sequencing. Note: Single-gene testing (sequence analysis of *SYNGAP1*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

CMA uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *SYNGAP1*) that cannot be detected by sequence analysis. Note: The ability to determine the size of the deletion/duplication depends on the type of microarray used and the density of probes in the 6p21.32 region.

An ID multigene panel that includes *SYNGAP1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition in a person with a nondiagnostic CMA while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include

genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder, an ID multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Exome sequencing, which does not require the clinician to determine which gene is likely involved, has the advantage over an ID multigene panel of detecting variants in recently identified rare genes not yet included in some ID multigene panels.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *SYNGAP1*-Related Intellectual Disability

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method [3]
SYNGAP1	Sequence analysis [4]	49/55 (89%)
	Gene-targeted deletion/duplication analysis [5]	Unknown; see footnote 6.
	Chromosomal microarray analysis [7]	6/55 (11%)

1. See Table A. Genes and Databases for chromosome locus and protein.
2. Based on a review of published series and case reports
3. Krepischi et al [2010], Pinto et al [2010], Vissers et al [2010], Hamdan et al [2011a], Hamdan et al [2011b], Klitten et al [2011], Zollino et al [2011], de Ligt et al [2012], Rauch et al [2012], Berryer et al [2013], Carvill et al [2013], Writzl & Knegt [2013], Redin et al [2014], Parker et al [2015], Mignot et al [2016], Prchalova et al [2017]
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Gene-targeted methods will detect deletions of a single exon up to a whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes may not be determined. If a whole-gene deletion is detected by a gene-targeted deletion/duplication assay, CMA is needed to determine the size of the deletion.
7. Chromosomal microarray analysis (CMA) using oligonucleotide arrays or SNP arrays. CMA designs in current clinical use target the 6p21.3 region; however, some 6p21.3 deletions may not have been detectable by older oligonucleotide or BAC platforms.

Clinical Characteristics

Clinical Description

Since the original description of *SYNGAP1*-related intellectual disability (*SYNGAP1*-ID) in three individuals [Hamdan et al 2009], more than 50 affected individuals with detailed clinical information have been reported [Krepischi et al 2010, Pinto et al 2010, Vissers et al 2010, Hamdan et al 2011a, Hamdan et al 2011b, Klitten et al 2011, Zollino et al 2011, de Ligt et al 2012, Rauch et al 2012, Berryer et al 2013, Carvill et al 2013, Writzl & Knegt 2013, Redin et al 2014, Parker et al 2015, Mignot et al 2016, Prchalova et al 2017]. The following description of the phenotypic features associated with this condition is based on these reports.

Developmental delay and intellectual disability. The great majority of affected children present with developmental delay or intellectual disability that is typically moderate to severe but can be mild.

Early motor development is characterized by hypotonia. The average age at walking was 26 months (range: 10.5 months to 5 years). A subset of these children had an ataxic gait that remained stable or improved over time.

Language is generally impaired; a third of individuals age five years or more remain nonverbal. In those who are verbal, language development ranges from use of single words only to four-to-five-word sentences.

Epilepsy. Approximately 84% of individuals with *SYNGAP1*-ID have generalized epilepsy; a subset of these were diagnosed with myoclonic astatic epilepsy (Doose syndrome) or epilepsy with myoclonic absences [Mignot et al 2016].

While the epilepsy responds to a single anti-seizure medication in approximately half of affected individuals, it is pharmacoresistant in the remainder. Children with refractory seizures may be diagnosed with epileptic encephalopathy (i.e., refractory seizures and cognitive slowing or regression associated with frequent ongoing epileptiform activity).

- **Age at onset of seizures** varies between six months and seven years; mean age of seizure onset was 3.5 years in one study [Mignot et al 2016].
- **Seizure types** include typical or atypical seizures, myoclonic jerks with or without falls, eyelid myoclonia, tonic-clonic seizures, myoclonic absences, and atonic seizures. In one study, Doose syndrome (myoclonic astatic epilepsy) was diagnosed in three of 17 individuals [Mignot et al 2016].
- **Electroencephalography** typically shows generalized epileptic activity, frequently with a posterior predominance. Photosensitivity and fixation-off phenomenon have been observed in a number of individuals.
- **Brain MRI** is typically normal; in rare cases, brain atrophy or delayed myelination has been reported.

Autism spectrum disorder (ASD) and other behavioral abnormalities. The occurrence of ASD could be as high as 50%. This includes stereotypic behaviors such as hand flapping, obsessions with certain objects, and poor social development. In addition, inattention, impulsivity, self-directed and other-directed aggressive behavior, elevated pain threshold, hyperacusis, and sleep disorders have been observed.

Other associated features include the following:

- **Acquired microcephaly** observed in a minority of affected individuals
- **Eye abnormalities** including strabismus
- **Musculoskeletal disorders** including hip rotation or dysplasia, kyphoscoliosis, and *pes planus*
- **Hypertrichosis** (predominantly on the limbs and lower spine) occasionally described
- **Gastrointestinal dysfunction** (including constipation requiring medical intervention) frequently reported; swallowing difficulties rarely reported
- **Craniofacial features.** Although some authors have suggested a subtle but consistent facial appearance (almond-shaped palpebral fissures, mildly myopathic and open-mouthed appearance) [Parker et al 2015], it is unclear if these changes are distinct enough to allow a clinician to suspect the condition in a child.

Life span. It is unknown if life span in *SYNGAP1*-ID is abnormal. One reported individual is alive at age 31 years [Prchalova et al 2017], demonstrating that survival into adulthood is possible. Since many adults with disabilities have not undergone advanced genetic testing, it is likely that adults with this condition are underrecognized and underreported.

Genotype-Phenotype Correlations

No definitive phenotype-genotype correlation between the type of *SYNGAP1* pathogenic variant (missense, truncating, large intragenic deletion) and cognitive abilities or the occurrence of comorbidities has been observed.

Penetrance

Penetrance is 100%. All individuals with germline pathogenic variants in *SYNGAP1* have developmental delay, cognitive dysfunction, intellectual disability, and/or epilepsy.

Prevalence

The prevalence of *SYNGAP1* pathogenic variants in two studies was:

- 1% in a series of 500 individuals with epileptic encephalopathy [Carvill et al 2013];
- 0.75% in a large series of 931 unrelated children with intellectual disability [Fitzgerald et al 2015].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *SYNGAP1*.

Differential Diagnosis

The phenotype associated with *SYNGAP1*-related intellectual disability (ID) overlaps with that of other disorders of ID and epileptic encephalopathy.

Most genes known to be associated with ID (see OMIM Autosomal Dominant Intellectual Developmental Disorder Phenotypic Series) and epileptic encephalopathy (see OMIM Epileptic Encephalopathy, Early Infantile Phenotypic Series) if compatible with walking should be included in the differential diagnosis.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *SYNGAP1*-related intellectual disability, the evaluations summarized in Table 2 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 2. Recommended Evaluations Following Initial Diagnosis in Individuals with *SYNGAP1*-Related Intellectual Disability

System/Concern	Evaluation	Comment
Eyes	Ophthalmologic eval	Evidence of strabismus
Gastrointestinal/ Feeding	Baseline eval for reflux &/or constipation; assessment for feeding problems	Refer to gastroenterologist &/or feeding therapist for treatment if indicated.
Musculoskeletal	Assessment for hip rotation/dysplasia, kyphoscoliosis, *pes planus*	
Neurologic	Neurologic eval	Incl EEG & brain MRI if seizures are suspected
Psychiatric/ Behavioral	Neuropsychiatric eval	Screen persons age >12 mos for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD.
Miscellaneous/ Other	Developmental assessment	Incl motor, speech/language eval, general cognitive, & vocational skills.
	Consultation w/clinical geneticist &/or genetic counselor	

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder

Treatment of Manifestations

Table 3. Treatment of Manifestations in Individuals with *SYNGAP1*-Related Intellectual Disability

Manifestation/Concern	Treatment	Considerations/Other
Strabismus	Standard treatment(s) as recommended by ophthalmologist	
Swallowing dysfunction	Nasogastric/gastrostomy feeding may be required for persistent feeding issues.	
Constipation	Standard treatment as recommended by gastroenterologist	Gastroenterology consultation, if severe
Hip rotation/dysplasia, kyphoscoliosis, & *pes planus*	Standard treatment as recommended by orthopedist	Orthopedic consultation may be considered.
Epilepsy	Standardized treatment w/ASMs by experienced neurologist	• To date, no guidelines on choice of specific ASMs • Anecdotal reports of improved seizure control w/ketogenic diet in some persons

ASMs = anti-seizure medications

Education of parents regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for parents or caregivers of children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy. In the US, early intervention is a federally funded program available in all states.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed.

Ages 5-21 years

- In the US, an IEP based on the individual's level of function should be developed by the local public school district. Affected children are permitted to remain in the public school district until age 21.
- Discussion about transition plans including financial, vocation/employment, and medical arrangements should begin at age 12 years. Developmental pediatricians can provide assistance with transition to adulthood.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies and to support parents in maximizing quality of life.

Consideration of private supportive therapies based on the affected individual's needs is recommended. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

In the US:

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction. Assuming that the individual is safe to eat by mouth, feeding therapy – typically from an occupational or speech therapist – is recommended for affected individuals who have difficulty feeding because of poor oral motor control.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and is typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

Monitor those with seizures as clinically indicated.

Assess as needed for anxiety, attention, and aggressive or self-injurious behavior.

Monitor developmental progress and educational needs.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

SYNGAP1-related intellectual disability (*SYNGAP1*-ID) is inherited in an autosomal dominant manner and is typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- Almost all probands with *SYNGAP1*-ID reported to date whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo* germline pathogenic variant.
- Vertical transmission (from a mildly affected, mosaic parent to the proband) has been reported in one family to date [Berryer et al 2013].
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the proband most likely has a *de novo* pathogenic variant. Parental germline mosaicism is also a possible explanation; paternal somatic and germline mosaicism has been reported in one family [Berryer et al 2013].
- Note: If the parent is the individual in whom the pathogenic variant first occurred, the parent may have both somatic and germline mosaicism for the variant and may be mildly affected [Berryer et al 2013].

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents.
- Most affected individuals reported to date have had a *de novo SYNGAP1* pathogenic variant, suggesting a low risk to sibs. However, because of the possibility of germline mosaicism in a parent, the risk is presumed to be greater than in the general population [Berryer et al 2013].

Offspring of a proband. Individuals with *SYNGAP1*-ID are not known to reproduce; the theoretic risk to offspring of mildly affected mosaic individuals [Berryer et al 2013] is up to 50%.

Other family members. Given that most probands with *SYNGAP1*-ID reported to date have the disorder as a result of a *de novo* pathogenic variant, the risk to other family members is presumed to be low.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to parents of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *SYNGAP1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**
  Intellectual Disability
- **SYNGAP1 Foundation**
  Phone: 240-347-0302
  Email: admin@syngap1foundation.org
  www.syngap1foundation.org
- **VOR: Speaking out for people with intellectual and developmental disabilities**
  Phone: 877-399-4867
  Email: info@vor.net
  www.vor.net
- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  Fax: 202-387-2193
  www.aaidd.org
- **CDC - Developmental Disabilities**
  Phone: 800-CDC-INFO
  Email: cdcinfo@cdc.gov
  Intellectual Disability
- **VOR: Speaking out for people with intellectual and developmental disabilities**
  Phone: 877-399-4867
  Email: info@vor.net
  www.vor.net
- **SYNGAP1 (MRD5) Patient Registry**
  www.syngap1registry.iamrare.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. SYNGAP1-Related Intellectual Disability: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SYNGAP1	6p21.32	Ras/Rap GTPase-activating protein SynGAP	SYNGAP1 database	SYNGAP1	SYNGAP1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for SYNGAP1-Related Intellectual Disability (View All in OMIM)

603384	SYNAPTIC RAS-GTPase-ACTIVATING PROTEIN 1; SYNGAP1
612621	INTELLECTUAL DEVELOPMENTAL DISORDER, AUTOSOMAL DOMINANT 5; MRD5

Gene structure. To date two NCBI reference sequences for human *SYNGAP1* have been reported:

- NM_006772.2 (isoform 1) consists of 19 exons and encodes a protein of 1,343 amino acids (NP_006763.2).
- NM_001130066.1 (isoform 2) consists of 18 exons resulting in a protein of 1,292 amino acids (NP_001123538.1).

Molecular genetic testing for *SYNGAP1* pathogenic variants should include all 19 exons present in its largest reference sequence isoform (NM_006772.2).

By comparing human and rodent *SYNGAP1* cDNAs, Mignot et al [2016] have recently identified potential additional *SYNGAP1* isoforms that could arise from alternative splicing.

Pathogenic variants. The majority of pathogenic *SYNGAP1* variants are large deletions or heterozygous loss-of-function alleles such as nonsense and splice variants, frameshift insertions/deletions, and exon deletions; in addition, pathogenic heterozygous missense variants have been reported in a few instances (see review by Mignot et al [2016]). Most pathogenic variants occur *de novo*.

Normal gene product. The longest *SYNGAP1* isoform (NM_006772.2) encodes a protein of 1,343 amino acids that contains pleckstrin homology (PH), C2, RASGAP, SH3-binding, and coiled-coiled domains. Isoform 2 (NM_001130066.1) encodes a protein of 1,292 amino acids that contains the same domains as isoform 1 but has a different C-terminus that includes a QTRV motif required for postsynaptic scaffold protein interaction.

Abnormal gene product. *SYNGAP1*-ID is caused by haploinsufficiency of SYNGAP1. Pathogenic variants include those likely to result in complete loss of SYNGAP1 protein expression as well as those predicted to cause truncated or misfolded nonfunctional SYNGAP1.

Chapter Notes

Revision History

- 21 February 2019 (bp) Review posted live
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