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Gabriele-de Vries Syndrome

Synonym: *YY1* Intellectual Disability Syndrome

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Summary

Clinical characteristics

Gabriele-de Vries syndrome is characterized by mild-to-profound developmental delay / intellectual disability (DD/ID) in all affected individuals and a wide spectrum of functional and morphologic abnormalities. Intrauterine growth restriction or low birth weight and feeding difficulties are common. Congenital brain, eye, heart, kidney, genital, and/or skeletal system anomalies have also been reported. About half of affected individuals have neurologic manifestations, including hypotonia and gait abnormalities. Behavioral issues can include attention-deficit/hyperactivity disorder, anxiety, autism or autistic behavior, and schizoaffective disorder.

Diagnosis/testing

The diagnosis of Gabriele-de Vries syndrome is established in a proband by the identification of a heterozygous pathogenic variant involving *YY1* or a heterozygous deletion of 14q32.2 involving only *YY1*.

Management

Treatment of manifestations: Developmental delay / intellectual disability, craniofacial anomalies (Pierre Robin sequence, cleft palate, craniosynostosis, abnormalities of the lacrimal duct), feeding difficulties, gastroesophageal reflux, constipation, seizures, behavioral manifestations, strabismus, refractive error, congenital heart defects, renal anomalies, cryptorchidism, and skeletal anomalies are treated per standard practice.

Surveillance: Of clinical manifestations as clinically indicated.

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Genetic counseling

Gabriele-de Vries syndrome is inherited in an autosomal dominant manner. All probands reported to date with Gabriele-de Vries syndrome whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo YY1* pathogenic variant or deletion. Risk to future pregnancies is presumed to be low as the proband most likely has a *de novo YY1* pathogenic variant or deletion; however, given the theoretic possibility of parental germline mosaicism, recurrence risk to sibs is estimated at 1%, and thus prenatal and preimplantation genetic testing may be considered.

Diagnosis

No formal clinical diagnostic criteria exist for Gabriele-de Vries syndrome.

Suggestive Findings

The clinical spectrum of Gabriele-de Vries syndrome is variable. Gabriele-de Vries syndrome **should be considered** in individuals presenting with the following clinical findings.

Clinical findings

- Mild-to-profound developmental delay **and/or** intellectual disability; AND
- Any of the following features presenting in infancy or childhood:
  - Craniofacial dysmorphisms (See Clinical Description.)
  - Intrauterine growth restriction / low birth weight
  - Feeding difficulties
  - Neurologic abnormalities (hypotonia, abnormalities of movement, gait abnormalities)
  - Behavioral problems (attention-deficit/hyperactivity disorder, anxiety, autism or autistic behavior, schizoaffective disorder)
  - Congenital brain, eye, heart, kidney, genital, and/or skeletal system anomalies (See Clinical Description.)

Establishing the Diagnosis

The diagnosis of Gabriele-de Vries syndrome **is established** in a proband who has **one of the following** on molecular genetic testing (see Table 1):

- A heterozygous pathogenic (or likely pathogenic) variant involving *YY1*
- A heterozygous deletion of 14q32.2 involving *YY1* only

Note: (1) See Genetically Related Disorders for information about deletions of 14q32.2 that involve *YY1* and other, adjacent genes. (2) Per ACMG 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. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants.

Molecular genetic testing in a child with developmental delay or an older individual with intellectual disability 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*YY1*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **Chromosomal microarray analysis (CMA)** uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *YY1*) that cannot be detected by sequence analysis.

Note: To date, most individuals with a *YY1* deletion have been identified by CMA performed in the context of evaluation for developmental delay, intellectual disability, or autism spectrum disorder; however, many CMA platforms do not include sufficient coverage for this region and thus a *YY1* deletion may not be detected.

- **An intellectual disability (ID) multigene panel** that includes *YY1* 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*. Of note, given the rarity of *YY1*, some panels for ID may not include this gene. (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, yields results similar to an ID multigene panel but has two advantages: (1) a multigene panel may not include all rare genes recently identified as causing ID; and (2) exome sequencing may be able to detect pathogenic variants in genes that – for technical reasons – do not sequence well.

  If exome sequencing is not diagnostic – and particularly when evidence supports autosomal dominant inheritance – exome array (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

  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 Gabriele-de Vries Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
YY1	Sequence analysis [3]	10/10 [4]
	Gene-targeted deletion/duplication analysis [5, 6]	None reported [4, 7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. 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.
4. Gabriele et al [2017]
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. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (e.g., those described by Gabriele et al [2017]) may not be detected by these methods.
6. Targeted deletion testing is not appropriate for an individual in whom a pathogenic *YY1* deletion was not detected by CMA designed to target chr14:100,705,102-100,745,371 region (GRCh37).
7. Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including*YY1*) that cannot be detected by sequence analysis. Approximately 13 individuals who have larger deletions of 14q32.2 that include *YY1* and other, adjacent genes have been identified through CMA analysis (see Genetically Related Disorders) [Gabriele et al 2017].

Clinical Characteristics

Clinical Description

To date, ten individuals with a *de novo* pathogenic *YY1* variant have been described with an overlapping phenotype [Vissers et al 2010, Gabriele et al 2017]. *De novo YY1* variants result in syndromic ID with a wide spectrum of functional and morphologic abnormalities, in particular intrauterine growth restriction or low birth weight, feeding difficulties, congenital anomalies, nonspecific craniofacial dysmorphism, and neurologic and behavioral abnormalities.

Developmental delay (DD) and intellectual disability (ID). All individuals with a *YY1* intragenic pathogenic variant had DD/ID, which was usually mild (IQ 50-70) to moderate (IQ 35-49). One individual with a *de novo YY1* pathogenic variant manifested severe ID.

- **Gross motor skills.** The majority of individuals with a *de novo YY1* pathogenic variant (8/10) had motor delay and started walking independently between age 15 months and 6.5 years (median age: 2 years). Three affected individuals sat alone at 12 months. Gait disturbances were noticed in two affected individuals, specifically toe walking and waddling gait.
- **Language development** was delayed in half of the children with a pathogenic *YY1* variant (5/10). Severity varied between individuals; while two children had mild speech delay, one child used two- to three-word sentences at age seven years and another child, age nine years, did not use verbal communication.

Craniofacial features. All individuals described have facial dysmorphisms. The facial gestalt in most of the individuals with a *de novo YY1* variant includes the following:

- Generalized facial asymmetry, with mild discrepancy in the size of one side of the face compared to the other
- Broad forehead
- Fullness of upper eyelids

- Downslanted palpebral fissures
- Bulbous nose
- Malar flattening
- Indentation of the vermilion of the upper lip resembling a ginkgo leaf
- Thick vermilion of the lower lip
- Pointed chin

External ear malformations are common and include the following:

- Abnormally shaped ears
- Simple ears
- Posteriorly rotated ears
- Low-set ears
- Protruding ears

Rare craniofacial findings have included the following:

- Abnormalities of the lacrimal duct, specifically lacrimal duct stenosis and hypoplastic lacrimal duct
- Craniosynostosis in one affected individual (suture not specified)
- Pierre Robin sequence with a cleft palate in one affected individual

Growth. Low birth weight was reported in approximately half of newborns with a *YY1* pathogenic variant (5/9). Later weight was recovered and only two of these individuals maintained persistently low body weight. Short stature was observed in two affected individuals with a pathogenic *YY1* variant.

Feeding difficulties / gastrointestinal abnormalities. Feeding difficulties occurred often. Oral-pharyngeal dysphagia with chewing and swallowing difficulty may be seen and some individuals require G-tube insertion for feeding problems.

Neurologic abnormalities. About half of affected individuals had neurologic problems, including hypotonia, abnormalities of movement (1 affected individual with tremor and 2 with progressive dystonia, including torsion dystonia), gait abnormalities, and, rarely, febrile seizures.

Behavioral phenotype. Approximately half of the individuals with a pathogenic *YY1* variant had behavioral problems (5/9), which included attention-deficit/hyperactivity disorder, anxiety, autism or autistic behavior, and schizoaffective disorder. Sleeping problems were described in a minority of affected individuals (2/9).

Neuroimaging abnormalities. A variety of nonspecific morphologic abnormalities of the central nervous system (CNS) have been described, including the following:

- Abnormalities of the subarachnoid space (widened subarachnoid space)
- Delayed myelination
- Frontal gliosis
- Cortical dysplasia
- Focal areas of encephalomalacia
- Unilateral and/or bilateral dilatation of the lateral ventricles
- Abnormalities of cerebral white matter (cerebral white matter atrophy, subcortical bifrontal white matter foci)
- Abnormalities of the corpus callosum (ranging from hypoplasia of the corpus callosum to agenesis of corpus callosum)

Each of the reported CNS morphologic abnormalities was observed in one or two individuals (occurring alone or concomitantly with another neuroimaging abnormality) and is not exclusive to Gabriele-de Vries syndrome.

Congenital anomalies. A variety of structural malformations have been described:

- **Eye abnormalities.** Strabismus and abnormalities of refraction (hypermetropia and astigmatism) were present in more than half of affected individuals.
- **Heart abnormalities.** Patent foramen ovale and small aorto-pulmonary collateral has been described in one individual and Ebstein's anomaly of the tricuspid valve in another.
- **Renal abnormalities.** Hydronephrosis (2/7), occurring concomitantly or not with ureteropelvic junction stenosis (1/7), was reported in a minority of affected individuals.
- **Genital abnormalities.** Bilateral cryptorchidism was unusual, being reported in only one individual (1/5).
- **Skeletal abnormalities.** The majority of affected individuals manifested abnormalities of the extremities, which varied greatly in location and severity. The following anomalies were present in no more than one individual each:
  - Unilateral hemihypotrophy of lower limb
  - Patella luxations
  - Increased laxity of fingers
  - Long fingers
  - Sydney crease *
  - Sandal gap
  - Hallux valgus
  - Distal arthrogryposis

* Note: The Sydney crease is a proximal transverse (5-finger) crease that starts on the radial side of the hand near the base of the index finger and extends completely to the ulnar margin of the palm.

Endocrine abnormalities were reported in three affected individuals and included hypothyroidism in two and growth hormone deficiency in one.

Other. The following features have been observed in one affected individual each, and therefore it is unclear if the finding is related to the diagnosis of Gabriele-de Vries syndrome or is a coincidental finding:

- Recurrent infections
- Breast hypoplasia
- Hyperextensible skin
- Childhood-onset neuroblastoma

Genotype-Phenotype Correlations

Given the small number of affected individuals reported in the literature, no genotype-phenotype correlations are currently known.

Prevalence

Gabriele-de Vries syndrome is a rare condition. So far, ten affected individuals worldwide have been described in the medical literature with a *de novo* intragenic *YY1* variant.

The prevalence of Gabriele-de Vries syndrome is yet to be determined. To date, *de novo* pathogenic variants in *YY1* were identified in 0.03%-1% of individuals with unexplained intellectual disability in diverse studied cohorts with estimates of prevalence varying in different subsets of individuals tested [Vissers et al 2010, Gabriele et al 2017].

Since individuals have been recruited via large exome sequencing projects, it is expected that more affected individuals will be diagnosed with Gabriele-de Vries syndrome as the use of genomic testing increases.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic intragenic variants in *YY1*.

Contiguous gene deletions encompassing *YY1* and adjacent genes. Non-recurrent significantly larger deletions encompassing all or part of *YY1* and adjacent genes have been described in 13 individuals, resulting in syndromic intellectual disability [Vissers et al 2010, Gabriele et al 2017].

The phenotype of those with contiguous gene deletions including *YY1* depends on the size of the deletion and the specific gene content. Overlapping clinical characteristics observed in individuals with chromosomal deletions encompassing *YY1* and adjacent genes and those who have solely *YY1* pathogenic variants include feeding difficulties, congenital anomalies, nonspecific craniofacial dysmorphism, ophthalmologic abnormalities, and neurologic and behavioral abnormalities. Nevertheless, because of the involvement of numerous additional genes occasionally comprising the UPD(14) gene cluster, **larger deletions of 14q32.3 that include *YY1*** result in a clinically distinct phenotype, including the following:

- **Prenatal abnormalities.** Therapeutic abortion was performed in two pregnancies of fetuses with multiple congenital anomalies and larger deletions of 14q32.3 encompassing *YY1*. One fetus presented with partial esophageal atresia, clubfeet, congenital heart disease (tricuspid regurgitation and right ventricle thickness), and fetal cystic hygroma and the other with agenesis of corpus callosum, enlarged kidneys, and a single umbilical artery. Intrauterine growth restriction was further observed in almost half of individuals (5/11) with larger 14q32.3 deletions that include *YY1*.
- **Craniofacial features.** Craniosynostosis (sutures not specified) was seen in four affected individuals, one of whom also had a cleft palate.
- **Growth.** Short stature was observed in two individuals. Head circumference was generally within the normal range; microcephaly occurred in one person.
- **Neurologic abnormalities.** Hypotonia was observed in approximately half of the individuals. One affected individual manifested spasticity.
- **Behavioral phenotype.** Two individuals were diagnosed with attention-deficit/hyperactivity disorder.
- **Heart abnormalities.** Two individuals exhibited abnormalities of the cardiac septa, specifically atrial septal defect and atrioventricular septal defect with a hypoplastic aortic arch. One other individual manifested right ventricle thickness and tricuspid regurgitation.
- **Renal abnormalities.** Duplex kidney, ureteral duplication with vesicoureteric reflux, and enlarged kidneys were detected in three individuals.
- **Genital abnormalities.** Micropenis was observed in two individuals with a pathogenic deletion involving *YY1* and adjacent genes. One of these individuals also had scrotal hypoplasia.

Sporadic tumors (including insulinomas) occurring as single tumors in the absence of any other findings of Gabriele-de Vries syndrome frequently harbor somatic pathogenic variants in *YY1* that are **not** present in the germline. In these circumstances predisposition to these tumors is not heritable. For more information, see Cancer and Benign Tumors.

Differential Diagnosis

The phenotypic features associated with Gabriele-de Vries syndrome are not sufficient to diagnose this condition clinically; therefore, all disorders with intellectual disability and congenital anomalies should be considered in the differential diagnosis. See OMIM Autosomal Dominant, Autosomal Recessive, and Syndromic X-Linked Intellectual Developmental Disorder Phenotypic Series.

Management

Evaluations and Referrals Following Initial Diagnosis

Evaluation by a multidisciplinary team can be beneficial.

To establish the extent of disease and needs in an individual diagnosed with Gabriele-de Vries syndrome, the evaluations summarized Table 2 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Note: Some evaluations are age dependent and may not be relevant at the time of initial diagnosis.

Table 2. Recommended Evaluations Following Initial Diagnosis of Gabriele-de Vries Syndrome

System/Concern	Evaluation	Comment
Neurodevelopmental	Developmental assessment	To incl eval of motor, speech/language, general cognitive, & vocational skills
Craniofacial	Clinical eval for cleft palate &/or micrognathia	Refer to multidisciplinary craniofacial team if cleft palate &/or micrognathia present. [1]
	Clinical assessment for craniosynostosis	Refer to multidisciplinary craniofacial team for facial asymmetry / abnormal head shape or size.
Constitutional	Assessment of growth parameters to identify children w/low birth weight &/or short stature	Consider endocrinologic eval, incl thyroid function tests & growth hormone assessment.
Gastrointestinal	Assessment of feeding difficulties	• Refer to occupational or speech therapist for feeding therapy. • Consider referral to gastroenterologist, if severe, to assess need for gastrostomy tube.
	Assessment for gastroesophageal reflux disease & constipation	Consider referral to gastroenterologist, if severe.
Neurologic	Neurologic eval [2]	• W/consideration of EEG &/or brain MRI • Consider referral to pediatric neurologist.
Behavioral/ Psychiatric	Consider neuropsychiatric eval.	Screen persons age >12 mos for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD.
Ophthalmologic	Consider referral to ophthalmologist.	For eval of strabismus &/or refraction errors
Cardiac	Consider echocardiography to evaluate for congenital heart defects.	Refer to pediatric cardiologist.
Renal	Consider baseline renal ultrasound.	To assess for renal anomalies
Genital	Clinical eval of cryptorchidism or other penile or scrotal anomalies in boys	Consider referral to pediatric urologist if cryptorchidism present.
Musculoskeletal	Clinical eval for skeletal abnormalities	Consider referral to an orthopedist if abnormalities present.
Miscellaneous/Other	Consultation w/clinical geneticist &/or genetic counselor	

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

1. Including plastic surgeons, neurosurgeons, speech pathologists, geneticists, pediatricians, orthodontists, and other craniofacial specialists

2. Assessment of hypotonia, movement disorders, gait abnormalities, and history of possible seizures

Treatment of Manifestations

Table 3. Treatment of Manifestations in Individuals with Gabriele-de Vries Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Cleft palate	Surgical repair	Per multidisciplinary craniofacial team [1]
Craniosynostosis	Surgical repair, as needed	Per a multidisciplinary craniofacial team [1]
Feeding difficulties	Feeding therapy &/or dietary measures	Gastrostomy tube placement may be required for persistent feeding problems.
Gastroesophageal reflux disease &/or constipation	Standard mgmt & treatment(s)	Consider referral to a gastroenterologist, if severe.
Seizures	Standardized treatment w/ASMs by experienced neurologist [2]	Many ASMs may be effective; none has been demonstrated effective specifically for this disorder.
Behavioral/psychiatric abnormalities	Appropriate behavior mgmt strategies &/or psychotropic medications, per psychiatrist	
Strabismus &/or refraction abnormalities	Routine mgmt for ophthalmologic problems	
Congenital heart defects	Routine treatment for cardiac abnormalities	
Renal structural anomalies	Routine mgmt for renal abnormalities	
Cryptorchidism	Routine mgmt for cryptorchidism	
Skeletal anomalies	Standard treatment as recommended by orthopedist	

ASM = anti-seizure medication

1. Including plastic surgeons, pediatricians, orthodontists, and other craniofacial specialists

2. 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.

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.
- 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 as a result 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, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Surveillance

A developmental pediatrician or a geneticist should coordinate the follow up of a child with Gabriele-de Vries syndrome. Surveillance of gastrointestinal, craniofacial, cardiac, renal, genital, skeletal, and endocrine abnormalities should be tailored to the affected individual according to the specific problems identified at diagnosis.

Long-term follow up by other specialists is also recommended and includes the following.

Table 4. Recommended Surveillance for Individuals with Gabriele-de Vries Syndrome

System/Concern	Evaluation	Frequency
Constitutional	Measurement of growth parameters	At each visit until adulthood
At each visit beginning in childhood	Monitor those w/seizures	As clinically indicated
	Assessment of neurologic disease progression	
Psychiatric	Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior	
Ophthalmologic	Ophthalmologic evaluation	As needed based on symptoms

Table 4. continued from previous page.

System/Concern	Evaluation	Frequency
Miscellaneous/ Other	Monitor developmental progress & educational needs	At each visit

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

Gabriele-de Vries syndrome 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

- All probands reported to date with Gabriele-de Vries syndrome whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo YY1* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the *YY1* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the pathogenic variant most likely occurred *de novo* in the proband. Another possible explanation is that the proband inherited a pathogenic variant from a parent with germline mosaicism. Although theoretically possible, no instances of germline mosaicism have been reported to date.
- Theoretically, if the parent is the individual in whom the *YY1* pathogenic variant first occurred, the parent may have somatic mosaicism for the variant and may be mildly/minimally affected.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents: if the *YY1* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

Offspring of a proband. Individuals with Gabriele-de Vries syndrome are not known to reproduce.

Other family members. Given that all probands with Gabriele-de Vries syndrome reported to date have the disorder as a result of a *de novo YY1* 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

Risk to future pregnancies is presumed to be low as the proband most likely has a *de novo YY1* pathogenic variant. There is, however, a recurrence risk (~1%) to sibs based on the theoretic possibility of parental germline mosaicism [Rahbari et al 2016]. Given this risk, prenatal and preimplantation genetic testing may be considered.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. 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.

- **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
- **MedlinePlus**
  Intellectual Disability
- **VOR: Speaking out for people with intellectual and developmental disabilities**
  Phone: 877-399-4867
  Email: info@vor.net
  www.vor.net

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. Gabriele-de Vries Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar

Table A. continued from previous page.

YY1	14q32.2	Transcriptional repressor protein YY1	YY1	YY1

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 Gabriele-de Vries Syndrome (View All in OMIM)

600013	TRANSCRIPTION FACTOR YY1; YY1
617557	GABRIELE-DE VRIES SYNDROME; GADEVS

Gene structure. *YY1* is located on chromosome 14:100,705,102-100,745,371 (hg19). The canonic transcript of *YY1*, NM_003403.4 (ENST00000262238.8), has five exons, spanning 6,697 bp and encoding 414 amino acids.

See Table A, **Gene** for a detailed summary of gene and protein information.

Pathogenic variants. Gabriele-de Vries syndrome is caused by haploinsufficiency of *YY1*, which can result from nonsense, missense, or frameshift variants. Large deletions, including whole-gene deletions, have also been reported. Missense variants are so far located in Zinc finger domains.

Normal gene product. YY1 is a Zn-finger protein [Shi et al 1991] that mediates either gene activation or repression in an exquisitely context-dependent manner [Atchison 2014]. It regulates chromatin looping of transcriptional enhancers to their associated promoters [Medvedovic et al 2013, Gerasimova et al 2015, Weintraub et al 2017].

Abnormal gene product. Loss-of-function variants result in halving of YY1 dosage [Gabriele et al 2017]. Disease-associated missense variants in the YY1 Zn finger DNA binding domain completely impair its targeting function, as demonstrated by YY1 chromatin profiles (by ChIPseq) in individuals with either nonsense or missense variants that show the same widespread loss of genome-wide occupancy especially at low-occupancy sites [Gabriele et al 2017].

According to the capability of YY1 to mediate chromatin loops between enhancers and promoters [Medvedovic et al 2013, Gerasimova et al 2015, Weintraub et al 2017], individuals harboring *YY1* pathogenic variants display an extensive loss of H3K27Ac on YY1-bound enhancers, thus characterizing Gabriele-de Vries syndrome as an enhanceropathy. The intellectual disability, a foundational phenotype shared across all individuals with Gabriele-de Vries syndrome, is thus likely caused by failures in orchestrating the stages of neural development that are most sensitive to gene regulation alterations caused by mutations in chromatin and transcriptional regulators [Gabriele et al 2018].

In support of this hypothesis, *YY1* knockdown was shown to negatively affect enhancer-promoter interactions of key genes in neuronal progenitor cells [Beagan et al 2017]. In addition, *YY1* has already been implicated as key regulator in several processes pertaining to nervous system development and function, as extensively reviewed elsewhere [He & Casaccia-Bonnefil 2008]. Notably, the neurodevelopmental phenotype of Gabriele-de Vries syndrome is recapitulated in a *Yy1* heterozygous mouse model, which features growth restriction and neurulation defects [Donohoe et al 1999]. Finally, the myelination deficits observed in patients afford pathophysiologic relevance to the myelination defects that follow conditional *Yy1* ablation in oligodendrocyte as a result of impaired differentiation [He et al 2007].

Cancer and Benign Tumors

YY1 is overexpressed in several sporadic tumors including hepatocellular carcinoma [Zhang et al 2012], breast, ovarian, brain, prostate, colon, and esophagus tumors, as well as osteosarcoma and melanoma, as recently extensively reviewed [Khachigian 2018]. Its upregulation is correlated with poor prognosis [Zaravinos &

Spandidos 2010, Cho & Bonavida 2017, Khachigian 2018]. Moreover, variants in threonine 372 (p.Thr372Arg), which increase its transcriptional activity, have been associated with the onset of sporadic insulinomas [Cao et al 2013, Lichtenauer et al 2015]. Consistent with the pleiotropic and exquisitely context-dependent aspects of its function, YY1 has also been found to promote the expression of tumor suppressors such as BRCA1 and p21 [Khachigian 2018].

Chapter Notes

Author Notes

The authors also recommend the following resource: Human Disease Genes Website Series: *YY1*.

To gain further insight, and expand the clinical phenotype of pathogenic variants within the complete coding region of the *YY1* gene, and to carry on research into the underlying mechanism of this disorder, parents and physicians are encouraged to visit the above-mentioned gene website and submit clinical information on newly diagnosed individuals.

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