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NFIA-Related Disorder

Synonym: NFIA Haploinsufficiency

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Summary

Clinical characteristics

For the purposes of this chapter, *NFIA*-related disorder is defined as heterozygous inactivation or disruption of only *NFIA* without involvement of adjacent or surrounding genes. *NFIA*-related disorder comprises central nervous system abnormalities (most commonly abnormalities of the corpus callosum) with or without urinary tract defects, such as unilateral or bilateral vesicoureteral reflux and hydronephrosis. Additional features include macrocephaly, seizures, developmental delay and/or cognitive impairment, nonspecific dysmorphic features, ventriculomegaly, and hypotonia, which can exacerbate motor delay and feeding issues in infancy. Rarer features may include strabismus, cutis marmorata, or craniosynostosis of the metopic, lambdoid, or sagittal suture.

Diagnosis/testing

The diagnosis of *NFIA*-related disorder is established in a proband by detection of one of the following: a heterozygous intragenic *NFIA* pathogenic variant; a heterozygous deletion of the 1p31.3 region that includes part or all of *NFIA* with surrounding genes intact; or a chromosome translocation/other rearrangement with a 1p31.3 breakpoint that disrupts *NFIA*.

Management

Treatment of manifestations: Standard treatment of seizure disorder, tethered spinal cord, recurrent urinary tract infections, hydronephrosis, strabismus, craniosynostosis, and developmental delays.

Surveillance: Affected individuals should be followed by the appropriate specialists (e.g., neurologist, urologist, and/or clinical geneticist) as needed based on their particular features.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual by molecular genetic testing for the genetic alteration identified

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in the proband in order to identify as early as possible those who would benefit from prompt initiation of treatment.

Genetic counseling

NFIA-related disorder is inherited in an autosomal dominant manner. Each child of an individual with *NFIA*-related disorder has a 50% chance of inheriting the causative genetic alteration. The proportion of *NFIA*-related disorder caused by *de novo* variants is approximately 75%-80%. Prenatal diagnosis for a pregnancy at increased risk is possible if the causative genetic alteration in an affected family member is known.

Diagnosis

NFIA-related disorder is defined here as heterozygous inactivation or disruption of only *NFIA*; larger, nonrecurrent chromosome 1p32-p31 deletions are discussed in Genetically Related Disorders.

Suggestive Findings

An *NFIA*-related disorder **should be suspected** in individuals with the following clinical and radiographic findings.

Clinical features

- Macrocephaly
- Seizures including:
  - Generalized tonic-clonic
  - Pseudo-seizures
  - Nonspecific seizure disorders
- Hypotonia (generalized/neonatal)
- Developmental delay
- Frequent urinary tract infections
- Nonspecific dysmorphic features (See Clinical Characteristics.)
- Other, less common findings, including eye abnormalities (e.g., strabismus) or cutis marmorata

Radiographic abnormalities

- **Brain**
  - Abnormalities of the corpus callosum including agenesis or hypoplasia of the corpus callosum
  - Ventriculomegaly (typically non-progressive)
  - Hydrocephalus
  - Less commonly, Chiari type I malformation and/or subarachnoid hemorrhage
- **Urinary tract**
  - Vesicoureteral reflux
  - Hydronephrosis
  - Renal cysts
- **Spine.** Tethered spinal cord
- **Skull.** Rarely, craniosynostosis, which may involve the metopic, lambdoid, or sagittal sutures

Establishing the Diagnosis

The diagnosis of *NFIA*-related disorder (defined here as heterozygous inactivation or disruption of only *NFIA*) **is established** in a proband by detection of one of the following (see Table 1):

- Heterozygous intragenic *NFIA* pathogenic (or likely pathogenic) variant

- Heterozygous deletion of the 1p31.3 region that includes part or all of *NFIA* with surrounding genes intact
- Chromosome translocation / other rearrangement with a 1p31.3 breakpoint that disrupts *NFIA*

Note: (1) Molecular testing by CMA or karyotyping may detect a large and/or complex heterozygous rearrangement that inactivates *NFIA* and one or more (often adjacent) genes. Because individuals with such rearrangements (sometimes termed the chromosome 1p32-p31 deletion syndrome) have additional features, they are not the focus of this *GeneReview* and are described in Genetically Related Disorders. (2) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (3) Identification of a heterozygous *NFIA* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **chromosomal microarray analysis (CMA)**, a **multigene panel**, and **exome** or **genome sequencing**:

- If not already performed, **CMA** may be obtained to detect genome-wide deletions that include *NFIA*. The ability to determine the size of the deletion depends on the type of microarray used, the density of the probes in the 1p31.3 region, and the size cutoff for reporting. The genomic size of the *NFIA* locus is 380 kb.
- **A multigene panel** that includes *NFIA* and other genes of interest (see Differential Diagnosis) may be considered. 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*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.
- More comprehensive genomic testing (when available) including **exome sequencing** and **genome sequencing** may be considered. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

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

Karyotype. If clinical suspicion is high and other molecular genetic testing methods have not identified a pathogenic variant involving *NFIA*, a high-resolution karyotype to detect a balanced chromosomal rearrangement involving the 1p31 region, followed by custom MLPA to confirm deletion of *NFIA*, or sequencing of the breakpoints to confirm disruption of *NFIA*, could be considered.

Table 1. Molecular Genetic Testing Used in *NFIA*-Related Disorder

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
NFIA	Sequence analysis [3]	5/13 [4, 5]
	Gene-targeted deletion/duplication analysis [6]	See footnotes 7 & 8.
	CMA [9]	5/13 [5, 10]
	Karyotype [11]	3/13 [12]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on 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 missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Iossifov et al [2012], Negishi et al [2015], Revah-Politi et al [2017]
5. The number of probands is 13; some probands have other affected family members. The total number of individuals reported with *NFIA*-related disorder is 20 (see Revah-Politi et al [2017], Table 2).
6. 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.
7. Intragenic deletions that affect one or multiple exons within NFIA but disrupt no other genes have been identified in five probands [Mikhail et al 2011, Rao et al 2014, Nyboe et al 2015, Bayat et al 2017, Hollenbeck et al 2017].
8. Gene-targeted methods will detect single-exon up to whole-gene deletions; however, breakpoints of large deletions and/or deletion of adjacent genes may not be determined.
9. Chromosomal microarray analysis (CMA) using oligonucleotide arrays or SNP arrays. CMA designs in current clinical use typically cover the 1p31.3 region.
10. Lu et al [2007], Mikhail et al [2011], Rao et al [2014], Nyboe et al [2015], Coci et al [2016], Bayat et al [2017], Hollenbeck et al [2017]
11. Karyotype can detect balanced chromosome rearrangements that are not detectable through chromosomal microarray analysis.
12. Chromosome rearrangements, including translocations and inversions, which disrupt *NFIA* (in some cases, shown to result in deletions at the breakpoints), have been identified in three probands [Lu et al 2007, Coci et al 2016].

Note: For *NFIA* somatic variants, see Genetically Related Disorders, **Cancer and benign tumors**.

Clinical Characteristics

Clinical Description

NFIA-related disorder comprises central nervous system abnormalities (see Suggestive Findings) with or without urinary tract defects. Additional features include macrocephaly, seizures, developmental delay, dysmorphic features (see below), ventriculomegaly, and hypotonia.

Central nervous system (CNS) abnormalities. Abnormalities of the corpus callosum are the most consistent feature of this disorder, present in virtually all affected individuals (all but one published individual to date). These abnormalities can include agenesis of the corpus callosum, hypoplasia of the corpus callosum, or other defects (including dysgenesis of the corpus callosum, agenesis of the rostral part of the corpus callosum, or thin corpus callosum). Other CNS phenotypes that may be present include non-progressive ventriculomegaly, hydrocephalus, Chiari type I malformation, and tethered spinal cord. Less common CNS findings include polymicrogyria and decreased periventricular white matter. There appears to be variable expressivity of the CNS phenotype, with no one affected individual presenting with all of the different features listed here.

Seizures are present in approximately half of reported individuals. The types of seizures range from tonic-clonic seizures [Lu et al 2007] to pseudo-seizures [Revah-Politi et al 2017] to nonspecific seizure disorders [Lu et al 2007, Revah-Politi et al 2017].

Developmental delay, ranging from mild to severe, includes both motor and speech delays. Some affected individuals also have **hypotonia**, which can exacerbate motor delays and feeding issues (particularly in infancy). Despite early delays, most affected individuals are able to walk and use verbal language to communicate. The oldest reported affected individual was a male age 42 years (father of the proband in Nyboe et al [2015]) who was not reported to have any developmental delays. Of probands with developmental delay, the oldest reported individual was a female age 25 years, who at the time of evaluation was experiencing some cognitive delays and behavioral issues [Mikhail et al 2011]. Behavioral abnormalities reported in affected individuals include autism [Iossifov et al 2012, Revah-Politi et al 2017] and bipolar disorder / depression [Mikhail et al 2011, Revah-Politi et al 2017]. Intellectual disability (which may be mild) has also been reported [Mikhail et al 2011, Coci et al 2016, Hollenbeck et al 2017].

Urinary tract defects described in individuals with *NFIA*-related disorder most commonly include vesicoureteral reflux and hydronephrosis (which may be unilateral or bilateral); additional phenotypes include pyelonephritis, ureterovesical junction diverticulum, dysplastic kidneys, and renal cysts. Sometimes the defects manifest as recurrent urinary tract infections. Urinary tract defects are present in approximately half of affected individuals [Revah-Politi et al 2017], with reported intrafamilial variation [Nyboe et al 2015, Revah-Politi et al 2017].

Dysmorphic features associated with *NFIA*-related disorder are typically described as mild and have variable penetrance. Recurrent features include relative macrocephaly, frontal bossing / prominent forehead, low-set ears, and proximally placed first digits [Revah-Politi et al 2017].

Eye abnormalities have been reported in rare instances and include strabismus divergens in two individuals [Coci et al 2016], ptosis in two individuals [Coci et al 2016, Hollenbeck et al 2017], and esotropia in one individual [Hollenbeck et al 2017].

Dermatologic findings. Cutis marmorata has been reported in one individual with an intragenic deletion of *NFIA* [Rao et al 2014].

Note: Cutis marmorata has been described in multiple individuals with deletions that include *NFIA* and surrounding genes (see Genetically Related Disorders), suggesting the existence of another rare phenotype associated with NFIA haploinsufficiency.

Craniosynostosis has been seen in a minority of individuals with *NFIA* pathogenic variants [Rao et al 2014, Nyboe et al 2015]. Types of craniosynostosis reported include metopic, lambdoid, and sagittal.

Prognosis. It is unknown if life span in *NF1A*-related disorder is abnormal. One reported individual is alive at age 42 years [Nyboe et al 2015], 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 genotype-phenotype correlations have been identified to date, with the exception of individuals who have larger, nonrecurrent 1p31.3 deletions that include *NFIA* and other, often adjacent, genes (see Genetically Related Disorders) [Lu et al 2007, Koehler et al 2010, Chen et al 2011, Ji et al 2014, Labonne et al 2016].

Nomenclature

Early reports that identified deletions affecting *NFIA* referred to the phenotypic presentation as "chromosome 1p32-p31 deletion syndrome" or "chromosome 1p31 deletion." The identification of intragenic deletions and single-nucleotide variants within *NFIA* that lead to a similar phenotypic presentation have demonstrated that loss of function of *NFIA* is responsible for most of the phenotypes associated with the 1p31 deletion.

NFIA-related disorder is referred to as "brain malformations with or without urinary tract defects" (BRMUTD) in OMIM (613735).

Prevalence

NFIA-related disorder is rare, having been described in only 13 families representing 20 affected individuals.

Genetically Related (Allelic) Disorders

Chromosome 1p32-p31 deletion syndrome. Individuals with larger deletions of the 1p32-p31 region that involve *NFIA* and other, often adjacent, genes have been reported (see, e.g., Chen et al [2011], Ji et al [2014]). Additional reported features not seen in those with *NFIA*-related disorder may include congenital heart defects [Ji et al 2014], ambiguous external genitalia [Chen et al 2011], attention-deficit/hyperactivity disorder [Lu et al 2007, Labonne et al 2016], congenital hip dysplasia [Lu et al 2007], short limbs [Lu et al 2007], cutis marmorata, and syringomyelia [Campbell et al 2002, Lu et al 2007]. However, given the many overlapping phenotypes between individuals with the 1p32-p31 deletion syndrome and those with *NFIA* pathogenic variants, *NFIA* has been proposed to be the critical gene within this deletion syndrome region [Revah-Politi et al 2017].

Cancer and benign tumors. Sporadic tumors occurring as single tumors in the absence of any other findings of *NFIA*-related disorder may contain a somatic nucleotide variant in *NFIA* that is not present in the germline. Per the COSMIC database (last accessed 2-28-19), 171 different tumor samples (including many different tumor types) have been reported to have pathogenic variants in *NFIA*. However, given the limited number of individuals with *NFIA*-related disorder, the natural history of this disorder is still evolving. An increased risk for cancer predisposition has not been observed in individuals with *NFIA*-related disorder but cannot be excluded.

Differential Diagnosis

Table 2. Disorders to Consider in the Differential Diagnosis of *NFIA*-Related Disorder

Differential Disorder	Gene(s)	MOI	Clinical Features of the Differential Disorder	
			Overlapping w/*NFIA*-related disorder	Distinguishing from *NFIA*-related disorder
Sotos syndrome [1]	*NSD1*	AD	• Macrocephaly • Ventriculomegaly • DD • Brain malformations incl partial-to-complete agenesis of corpus callosum	• No urinary tract defects • Sotos syndrome typically includes distinctive facial appearance & overgrowth.
Acquired macrocephaly w/impaired intellectual development (OMIM 618286)	*NFIB*	AD	• Macrocephaly • DD • Minor dysmorphic features • Brain malformations incl dysgenesis of corpus callosum • Neurodevelopmental phenotypes	No urinary tract defects (in affected individuals reported to date)
NFIX-related Malan syndrome [2]	*NFIX*	AD	• Macrocephaly • Ventriculomegaly • DD • Brain malformations incl hypoplasia of corpus callosum	Individuals w/Malan syndrome generally have an overgrowth phenotype.
Joubert syndrome 9	*CC2D2A*	AR	• Ventriculomegaly w/seizures in some affected individuals • Agenesis of corpus callosum • Hydrocephalus • Kidney disease	• Typically more severe than *NFIA*-related disorder • Characteristic MRI findings ("molar tooth sign") • Eye abnormalities

Table 2. continued from previous page.

Differential Disorder	Gene(s)	MOI	Clinical Features of the Differential Disorder	
			Overlapping w/*NFIA*-related disorder	Distinguishing from *NFIA*-related disorder
Strømme syndrome	*CENPF*	AR	• Hydrocephalus • Agenesis of corpus callosum • Renal abnormalities incl hydronephrosis	• Typically more severe than *NFIA*-related disorder • Intestinal atresia • Ocular abnormalities • Microcephaly • Cardiac involvement

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; MOI = mode of inheritance
1. Because Sotos syndrome and Malan syndrome have overlapping features, Sotos syndrome is sometimes referred to as Sotos syndrome 1.
2. Malan syndrome is also referred to as Sotos syndrome 2.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *NFIA*-related disorder, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *NFIA*-Related Disorder

System/Concern	Evaluation	Comment
Neurologic	Brain MRI	To evaluate for brain anomalies incl Chiari type I malformation
	Spinal imaging [1]	To evaluate for tethered cord
	EEG	If seizures are suspected; referral to neurologist if EEG is abnormal or if strong suspicion of seizures
Development	Developmental assessment	To incl motor, adaptive, cognitive, & speech-language eval
		Eval for early intervention / special education
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	For persons age >12 mos: screen for concerns incl sleep disturbances, ADHD, anxiety, &/or findings suggestive of ASD.
Gastrointestinal/ Feeding	Consider feeding eval for feeding problems related to hypotonia.	1 reported person w/*NFIA*-related disorder was able to tolerate only a soft diet at age 5 yrs but could eat other foods by age 8 yrs. [2]
Genitourinary	Renal ultrasound	To detect renal anomalies
	Consider voiding cystourethrogram.	In those w/suggestive renal ultrasound findings or w/urinary tract infections
Eyes	Ophthalmologic eval	For possible strabismus
Craniofacial	Consider craniofacial 3D CT scanning in those w/abnormal head shape.	Consider referral to craniofacial team if concern for craniosynostosis.
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	To incl genetic counseling
	Family support/resources	Use of community or online resources such as Parent to Parent

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder
1. The choice of imaging depends on the age of the affected individuals. In infants age <3 months, spinal ultrasound may be used. In those age >3 months, typically spinal MRI is required.
2. Shanske et al [2004], Lu et al [2007]

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with NFIA-Related Disorder

Manifestation/Concern	Treatment	Considerations/Other
Seizures	Standard treatment w/ASM by experienced neurologist	Many ASMs may be effective; none has been demonstrated effective specifically for this disorder.
Tethered spinal cord	Standard treatment per neurosurgeon	
Developmental delay / intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Recurrent urinary tract infections &/or hydronephrosis	Standard treatment per urologist	
Strabismus	Standard treatment per ophthalmologist	
Craniosynostosis	Standard treatment	Consider referral to a craniofacial team w/ experience in treating craniosynostosis.

ASM = anti-seizure medication

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States (US); 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.

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. If feeding difficulty is present, particularly in infancy, referral to an occupational or speech therapist for evaluation and treatment, including feeding therapy, is recommended. At least one individual with *NFIA*-related disorder has been reported with a history of feeding issues [Shanske et al 2004, Lu et al 2007].

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 ADHD, when necessary.

Surveillance

Following initial evaluation, affected individuals should be followed by the appropriate specialists (e.g., neurologist, urologist, and/or clinical geneticist) as needed based on their particular features.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual by molecular genetic testing for the genetic alteration identified in the proband in order to identify as early as possible those who would benefit from prompt initiation of treatment.

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

NFIA-related disorder is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- The majority of individuals diagnosed with *NFIA*-related disorder have the disorder as a result of a *de novo* genetic alteration.
- Approximately 20%-25% of reported individuals inherited an *NFIA*-related disorder alteration from an affected parent.
- Recommendations for the evaluation of parents of an individual with *NFIA*-related disorder include genetic/genomic testing capable of detecting the genetic alteration identified in the proband.
- If the genetic alteration identified in the proband cannot be detected in either parent, the most likely explanation is that the genetic alteration is *de novo* in the proband. Another possible explanation is parental germline mosaicism (germline mosaicism has not been reported to date).

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband has the genetic alteration identified in the proband, the risk to the sibs is 50%. However, the disorder is known to have variable expressivity; i.e., a sib who inherits the same genetic alteration may not have the same manifestation of the phenotype as the proband. Intrafamilial variation of the phenotype for the same genetic variant has been reported [Nyboe et al 2015, Coci et al 2016, Hollenbeck et al 2017, Revah-Politi et al 2017].
- If a parent of the proband has a chromosome translocation, recurrence risk to sibs depends on the specific structural variant.
- If the genetic alteration identified in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is slightly greater than that of the general population because of the theoretic possibility of parental germline mosaicism. Parental germline mosaicism for *NFIA* genetic alterations has not been reported in the literature thus far.

Offspring of a proband

- Each child of an individual with an *NFIA*-related disorder has a 50% chance of inheriting the genetic alteration.
- Risk to offspring of an individual with a chromosome translocation depends on the specific structural variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the genetic alteration identified in the proband, the parent's family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

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 the parents of an affected child.

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the causative 1p31.3 deletion, *NFIA* intragenic pathogenic variant, or chromosome translocation has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Ultrasound examination. Some features of *NFIA*-related disorder may be identifiable on prenatal ultrasound examination; these include agenesis/hypoplasia of the corpus callosum, ventriculomegaly, and macrocephaly [Negishi et al 2015, Revah-Politi et al 2017]. Poor fetal movement has been described in one case [Shanske et al 2004, Lu et al 2007].

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.

No specific resources for *NFIA*-Related Disorder have been identified by *GeneReviews* staff.

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. NFIA-Related Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
NFIA	1p31.3	Nuclear factor 1 A-type	NFIA	NFIA

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 NFIA-Related Disorder (View All in OMIM)

600727	NUCLEAR FACTOR I/A; NFIA
613735	BRAIN MALFORMATIONS WITH OR WITHOUT URINARY TRACT DEFECTS; BRMUTD

Gene structure. *NFIA* encodes a 554-amino acid protein from a 1.99-kb transcript with 12 exons (based on canonic transcript NM_001145512.1; also ENST00000371189.8).

***NFIA*-specific laboratory technical considerations.** At least four isoforms are produced by alternative splicing. The numbering of pathogenic variants may differ in the literature and in gene/mutation databases. Table 5 may be useful for at least some of the alternative transcripts.

Table 5. *NFIA* Reference Sequences

Ensemble Transcript	NCBI transcript	Predicted Protein	Comments
ENST00000403491.7	NM_001134673.3	509	Longest transcript
ENST00000407417.7	NM_001145511.1	501	Used by ClinVar
ENST00000371189.8	NM_001145512.1	554	Cited as canonic by Ensembl
ENST00000371187.7	NM_005595.4	498	Used by HGMD & ClinVar

Normal gene product. *NFIA* encodes a transcription factor belonging to the nuclear factor I family of dimeric DNA-binding proteins, and includes an N-terminal DNA-binding domain as well as C-terminal transactivation and repression domains.

Abnormal gene product. Haploinsufficiency of the *NFIA* protein causes the phenotypes associated with *NFIA*-related disorder. Animal studies have shown that *NFIA* is essential for normal development of the central nervous system and that it is required in a dose-sensitive manner for ureteral and renal development [Lu et al 2007]. Reduced dosage of *NFIA* may disrupt transcriptional networks important to the development of these organ systems.

Cancer and Benign Tumors

Numerous sporadic tumors (e.g., glioblastoma) occurring as single tumors in the absence of any other findings of *NFIA*-related disorder may contain somatic *NFIA* nucleotide variants and/or show changes in *NFIA* expression that are not present in the germline; thus, predisposition to these tumors is not known to be heritable.

Chapter Notes

Author Notes

Fabiola Quintero-Rivera, MD web page

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