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ADNP-Related Disorder

Synonyms: Helsmoortel-Van der Aa Syndrome, *ADNP*-Related ID/ASD

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Summary

Clinical characteristics

ADNP-related disorder is characterized by hypotonia, severe speech and motor delay, mild-to-severe intellectual disability, and characteristic facial features (prominent forehead, high anterior hairline, wide and depressed nasal bridge, and short nose with full, upturned nasal tip) based on a cohort of 78 individuals. Features of autism spectrum disorder are common (stereotypic behavior, impaired social interaction). Other common findings include additional behavioral problems, sleep disturbance, brain abnormalities, seizures, feeding issues, gastrointestinal problems, visual dysfunction (hypermetropia, strabismus, cortical visual impairment), musculoskeletal anomalies, endocrine issues including short stature and hormonal deficiencies, cardiac and urinary tract anomalies, and hearing loss.

Diagnosis/testing

The diagnosis of *ADNP*-related disorder is established by identification of a heterozygous *ADNP* pathogenic variant on molecular genetic testing.

Management

Treatment of manifestations: Treatment is symptomatic and can include: speech, occupational, and physical therapy; specialized learning programs depending on individual needs; treatment of neuropsychiatric features; nutritional support as needed; standard treatment of gastrointestinal, ophthalmologic, musculoskeletal, endocrine, and cardiac findings; standard treatments for hearing loss, seizures, urinary tract anomalies, and recurrent infections.

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Surveillance: At each visit monitor growth and nutrition, occupational and physical therapy needs; assess for seizures, developmental progress, behavioral issues, gastrointestinal issues, and family needs; annual vision assessment.

Genetic counseling

ADNP-related disorder is expressed in an autosomal dominant manner and typically caused by a *de novo ADNP* pathogenic variant, the risk to other family members is presumed to be low. Once an *ADNP* pathogenic variant has been identified in an affected family member, prenatal testing and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

ADNP-related disorder **should be considered** in individuals with the following clinical and MRI findings.

Clinical findings

- Severe speech and motor delay
- Mild-to-severe intellectual disability
- Autism spectrum disorder, additional behavioral problems, and sleep disturbance
- Characteristic facial appearance including prominent forehead, high anterior hairline, downslanted palpebral fissures, prominent eyelashes, ear malformations, wide and depressed nasal bridge, short nose with full, upturned nasal tip, long philtrum, thin vermilion of the upper lip, pointed chin, and widely spaced teeth. See Figure 1.
- Feeding difficulties and gastrointestinal problems (e.g., gastroesophageal reflux disease, lack of satiation, frequent vomiting, constipation)
- Vison issues (e.g., strabismus, cortical visual impairment, hypermetropia) and various ophthalmologic defects
- Musculoskeletal anomalies (e.g., joint laxity, hand and foot anomalies, pectus deformities, plagiocephaly)
- Other features: endocrine manifestations, cardiac and renal anomalies, hearing loss, seizures, recurrent infections

MRI findings include atypical white matter lesions, wide ventricles, corpus callosum underdevelopment, cerebral atrophy, cortical dysplasia, and choroid cysts. Note that these findings are not sufficiently distinct to specifically suggest the diagnosis of *ADNP*-related disorder.

Establishing the Diagnosis

The diagnosis of *ADNP*-related disorder **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *ADNP* identified by molecular genetic testing (see Table 1).

Note: (1) 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. (2) Identification of a heterozygous *ADNP* variant of uncertain significance does not establish or rule out the diagnosis.

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. Single-gene testing (sequence analysis of *ADNP*,

Figure 1. Facial features of individuals with *ADNP* pathogenic variants. Frontal and lateral views. Note the prominent forehead with

high anterior hairline, the wide and depressed nasal bridge, and short nose with full, upturned nasal tip [Van Dijck et al 2019].

followed by gene-targeted deletion/duplication analysis) may be indicated in individuals with the distinctive findings described in Suggestive Findings.

- **Chromosomal microarray analysis (CMA)** uses oligonucleotide or SNP array to detect genome-wide large deletions/duplications (including *ADNP*) that cannot be detected by sequence analysis.
- **Single-gene testing.** Sequence analysis of *ADNP* can be performed to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- **A multigene panel** that includes *ADNP* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause 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 an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.
- **Comprehensive genomic testing** does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used and yields results similar to a multigene panel with the additional advantage that exome sequencing includes genes recently identified as causing intellectual disability whereas some multigene panels may not. **Genome sequencing** is also possible.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.
- **Epigenetic signature analysis / methylation array.** Two distinctive epigenetic signatures (disorder-specific genome-wide changes in DNA methylation profiles) in peripheral blood leukocytes have been identified in individuals with *ADNP*-related disorder [Aref-Eshghi et al 2020]. Individuals with an *ADNP* pathogenic variant located outside the region between nucleotides 2000 and 2340 have a distinct epigenetic signature, whereas individuals with an *ADNP* pathogenic variant located between nucleotides 2000 and 2340 have a different epigenetic signature [Bend et al 2019, Breen et al 2020]. Epigenetic signature analysis of a peripheral blood sample or DNA banked from a blood sample can therefore be considered to clarify the diagnosis in individuals with clinical findings of *ADNP*-related disorder and a variant of uncertain clinical significance identified by molecular genetic testing. For an introduction to epigenetic signature analysis click here.

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

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
ADNP	Sequence analysis [3]	99% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported
	CMA [6]	1 individual [7]

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 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. Coe et al [2014], De Rubeis et al [2014], Helsmoortel et al [2014], Pescosolido et al [2014], Vandeweyer et al [2014], Deciphering Developmental Disorders Study Group [2015], and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
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. Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including ADNP) that cannot be detected by sequence analysis. The ability to determine the size of the deletion/duplication depends on the type of microarray used and the density of probes in the 20q13.13 region. CMA designs in current clinical use target the 20q13.13 region.
7. One individual with a heterozygous 20q13.13 deletion that encompassed *ADNP* and *DPM1* presented with features consistent with *ADNP*-related disorder [Huynh et al 2018].

Clinical Characteristics

Clinical Description

The following clinical description is based on a published report of a large cohort of 78 individuals in whom a pathogenic variant in *ADNP* has been identified [Van Dijck et al 2019].

Of note, the oldest individual known to the authors to date is age 40 years [Author, personal observation].

Table 2. Select Features of *ADNP*-Related Disorder

Feature	% of Persons w/ Feature	Comment
DD/ID	100%	Mild (in 12%), moderate (36%), or severe (52%) ID; ASD & other behavior disorders are common.
Characteristic facial features	97%	Prominent forehead, high anterior hairline, downslanted palpebral fissures, prominent eyelashes, ear malformations, wide & depressed nasal bridge, short nose w/full, upturned nasal tip, long philtrum, thin upper lip, pointed chin, widely spaced teeth
Gastrointestinal/ feeding issues	83%	Gastroesophageal reflux disease, constipation, oral movement problems, lack of satiation, swallowing problems, frequent vomiting
Vision issues	74%	Strabismus, cortical visual impairment, hypermetropia, ptosis, nystagmus, myopia
Hand & foot abnormalities	62%	Digit abnormalities, single palmar crease, nail anomalies, sandal gap
Musculoskeletal features	55%	Joint hypermobility, scoliosis, hip problems, pectus deformities, skull deformities
Endocrine issues	25%	Early puberty, thyroid hormone problems, growth hormone deficiency

Table 2. continued from previous page.

Feature	% of Persons w/ Feature	Comment
Short stature	23%	<−2 SD
Truncal obesity	8%	
Congenital heart anomalies	38%	Atrial septal defect, patent ductus arteriosus, mitral valve prolapse, patent foramen ovale, ventricular septal defect
Hearing loss	32%	Narrow auditory canal, frequent otitis media, hearing loss
Seizures	16%	Absence seizures, focal seizures w/reduced awareness, epilepsy w/continuous spike & waves during slow-wave sleep
Urinary tract anomalies	13%	Narrow ureters, bilateral vesicoureteral reflux

ASD = autism spectrum disorder; DD = developmental delay; ID = intellectual disability

Development. Infants often have hypotonia. Developmental milestones are delayed: the average age to sit independently is 13 months, and the average walking age is 2.5 years. Speech impairment is prominent, with expressive language ranging from no words to sentences. Bladder training is delayed in half of affected individuals.

All have mild-to-severe intellectual disability.

Autism spectrum disorder (ASD), characterized by stereotypic behavior and impaired social interaction, is reported in 67% of the children. Children have a strong sensory interest (sensory processing disorder). A high pain threshold is common.

Additional behavior problems may include anxiety, obsessive compulsive disorder, aggressive behavior, temper tantrums, attention-deficient/hyperactivity disorder, and sleep problems.

Characteristic facial features include a prominent forehead, high anterior hairline, ptosis, downslanted palpebral fissures, prominent eyelashes, wide and depressed nasal bridge, short nose with full, upturned nasal tip, a long philtrum, thin vermilion of the upper lip, widely spaced teeth, pointed chin, and ear abnormalities including small low-set ears and protruding cup-shaped ears.

Gastrointestinal/feeding. Feeding difficulties and gastrointestinal problems are common, including decreased sucking or chewing, gastroesophageal reflux disease, lack of satiation, frequent vomiting, and constipation. Some individuals required a gastrostomy tube.

Vision issues. More than half have visual problems, most commonly hypermetropia or strabismus. Forty-one percent have cortical visual impairment. Ophthalmologic defects are diverse: ectropion, coloboma, congenital cataracts, nystagmus, everted or notched eyelid, or mild ptosis.

Hand abnormalities are present, including clinodactyly, polydactyly, small fifth fingers, fetal fingertip pads, prominent interphalangeal joints and distal phalanges, a single palmar crease, and nail anomalies.

Foot abnormalities include toe malformations, flat feet, and sandal gap.

Additional muscular skeletal features include joint laxity (38%), pectus deformities (22%) such as pectus excavatum, pectus carinatum or narrow thorax, or skull deformity (14%) including plagiocephaly, trigonocephaly, or brachycephaly.

Endocrine manifestations include thyroid hormone problems (15%, mainly hypothyroidism) and/or growth hormone deficiency. Some have signs of early pubertal development.

Growth. Birth weight, length, and occipitofrontal circumference are within the normal range. Several develop truncal obesity. Twenty-three percent of the individuals have short stature (height <-2 SD in individuals reported with age range of 2-23 years). Growth hormone deficiency is present in 11%.

Cardiac anomalies. Atrial septal defect is the most common. Less frequent cardiac defects include: patent ductus arteriosus, patent foramen ovale, mitral valve prolapse, ventricular septal defect, and other cardiovascular malformations.

Seizures. Some children have seizures (16%) including absence seizures, focal seizures with reduced awareness, and epilepsy with continuous spike and waves during slow-wave sleep.

Renal. Renal anomalies include narrow ureters or bilateral vesicoureteral reflux.

Recurrent infections. Most children have recurrent infections, including upper respiratory and urinary tract infections (51%).

Other

- Submucous cleft palate (1 individual)
- Metopic craniosynostosis (2 individuals)

Genotype-Phenotype Correlations

There is no evidence for a clinically relevant impact of a specific pathogenic variant on the clinical presentation. However, it was noticed that individuals with a p.Tyr719Ter pathogenic variant walked later and had a higher pain threshold than those with other *ADNP* pathogenic variants [Van Dijck et al 2019].

Penetrance

Penetrance is less than 100%; In two families reported to date, probands diagnosed with *ADNP*-related disorder inherited a pathogenic variant from an unaffected parent [Van Dijck et al 2019].

Prevalence

The prevalence of pathogenic variants in *ADNP* is estimated at 0.17% of individuals with ASD (95% binomial confidence interval: 0.083%-0.32%). It is one of the most common known single-gene causes of ASD [Helsmoortel et al 2014].

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Phenotypic features associated with *ADNP* pathogenic variants are not sufficient to diagnose *ADNP*-related disorder. All genes known to be associated with intellectual disability * should be included in the differential diagnosis of *ADNP*-related disorder.

* More than 200 have been identified; see OMIM Autosomal Dominant, Autosomal Recessive, Nonsyndromic X-Linked, and Syndromic X-Linked Intellectual Developmental Disorder Phenotypic Series.

Management

Evaluations Following Initial Diagnosis

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

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

System/Concern	Evaluation	Comment
Development	Comprehensive developmental assessment	To incl: motor, adaptive, cognitive, & speech/language eval; testing for ASD & ID; eval for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval if behavioral problems are present	For persons age >12 mos: screen for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD.
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastric tube placement in those w/ dysphagia &/or aspiration risk.
Vision	Ophthalmologic exam & vision assessment	Incl electrophysiologic & visual perception exam to detect cortical visual impairment
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Joint hypermobility • Mobility, activities of daily living, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Growth	Measurement of growth parameters	To evaluate for growth deficiency, short stature, obesity
Endocrine	Assess for: • Thyroid problems; • Growth hormone deficiency in those w/ short stature.	
Cardiac	Echocardiogram	
Hearing	Audiology eval; referral to ENT if indicated	
Neurologic	Neurologic exam	• Consider EEG if seizures a concern. • To incl brain MRI to detect brain abnormalities
Urinary tract	Assess for frequent urinary tract infections	
Immunology	Assess for recurrent infections	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *ADNP*-related disorder in order to facilitate medical & personal decision making

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; ENT = ear, nose, and throat specialist; ID = intellectual disability; MOI= mode of inheritance; OT = occupational therapy; PT = physical therapy.
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Treatment is symptomatic; no specific therapy is available. Routine medical care by a pediatrician or primary care physician is recommended.

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

Manifestation/Concern	Treatment	Considerations/Other
Development	Speech, OT, PT; specialized learning programs depending on individual needs	
Psychiatric/ Behavioral	Treatment of any neuropsychiatric features incl sleep disorders, &/or behavioral problems	
Poor weight gain / Failure to thrive	Nutritional support if needed	
Gastrointestinal	Standard treatment for constipation & gastrointestinal reflux	
Abnormal vision &/or strabismus	Standard treatment(s) as recommended by ophthalmologist	Community vision services through early intervention or school district
Central visual impairment	No specific treatment; early intervention to stimulate visual development	
Plagiocephaly / Other musculoskeletal issues	Standard treatment	
Hypothyroidism	Standard treatment	
Cardiac anomalies	Standard treatment(s) as recommended by cardiologist	
Hearing loss	Standard treatments	
Seizures	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
Urinary tract anomalies	Standard treatment	
Recurrent infections	Standard treatment	

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; OT = occupational therapy; PT = physical therapy
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Surveillance

Table 5. Recommended Surveillance for Individuals with *ADNP*-Related Disorder

Manifestation/Concern	Treatment	Frequency
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	At each visit
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations (e.g., seizures, changes in tone, movement disorders).	
Development	Monitor developmental progress & educational needs.	
Psychiatric/Behavioral	Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior	
Eyes	Visual assessment	Annually
Gastrointestinal	Monitor for constipation & signs/symptoms of gastrointestinal reflux.	At each visit
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	

OT = occupational therapy; PT = physical therapy

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Administration of NAP, a neuroprotective octapeptide (NAPVSPIQ), has been reported to ameliorate some of the cognitive abnormalities observed in a knockout mouse model [Bassan et al 1999, Vulih-Shultzman et al 2007]. It restores learning and memory and reduces neurodegeneration in *Adnp*$^{+/-}$ mice. The drug name for NAP is davunetide, a candidate for treatment of multiple selected neurologic disorders. Intranasal and intravenous formulations of the drug have been shown to cross the blood-brain barrier. Phase II and Phase III clinical trials showed good tolerance without significant side effects. Although it is not known whether the disease is the result of a loss of function of *ADNP* and although the knockout mouse model has not been evaluated for autistic traits, the observations raise hope for treatment in individuals with *ADNP*-related disorder [Vandeweyer et al 2014].

A Phase II trial with the drug ketamine in children with *ADNP*-related disorder is currently recruiting.

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.

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

ADNP-related disorder is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- Most probands reported to date with *ADNP*-related disorder whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo ADNP* pathogenic variant.
- In two families reported to date, probands diagnosed with *ADNP*-related disorder inherited a pathogenic variant from an unaffected parent [Van Dijck et al 2019].
- Molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism.

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

- If the *ADNP* 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].
- If a parent of the proband is known to have the *ADNP* pathogenic variant identified in the proband, the risk to the sibs of inheriting the variant is 50%.

Offspring of a proband

- Each child of an individual with *ADNP*-related disorder has a 50% chance of inheriting the *ADNP* pathogenic variant.
- Individuals with *ADNP*-related syndromic autism are not known to reproduce.

Other family members

- The risk to other family members depends on the genetic status of the proband's parents: if a parent has the *ADNP* pathogenic variant, the parent's family members may be at risk.
- Given that most probands with *ADNP*-related disorder reported to date have the disorder as a result of a *de novo ADNP* 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 the parents of an affected individual.

Prenatal Testing and Preimplantation Genetic Testing

Once the *ADNP* 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.

- **ADNP Kids**
  www.adnpkids.com
- **ADNP Kids Research Foundation**
  Email: ADMIN@adnpfoundation.org
  www.adnpfoundation.org
- **ADNP Kids-HVDAS Belgium**
  Belgium
  Email: adnpkids.hvdasbelgium@gmail.com
  www.trefpuntstan.be/adnp-kids
- **Amis de ADNP France**
  France
  Email: caroleherman2012@gmail.com
  www.alliance-maladies-rares.org/association/amis-de-adnp-france
- **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
- **Simons Searchlight Registry**
  Simons Searchlight aims to further the understanding of rare genetic neurodevelopmental disorders.
  Phone: 855-329-5638
  Fax: 570-214-7327
  Email: coordinator@simonssearchlight.org
  www.simonssearchlight.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. ADNP-Related Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ADNP	20q13.13	Activity-dependent neuroprotector homeobox protein	ADNP database	ADNP	ADNP

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 ADNP-Related Disorder (View All in OMIM)

611386	ACTIVITY-DEPENDENT NEUROPROTECTOR HOMEOBOX; ADNP
615873	HELSMOORTEL-VAN DER AA SYNDROME; HVDAS

Molecular Pathogenesis

ADNP contains five exons, the last three of which are translated. The protein contains nine zinc fingers and three other functional domains, including NAP, an 8-amino-acid neuroprotectant peptide (NAPVSIPQ), a DNA-binding homeobox domain, and a HP1-binding motif.

ADNP is a vasoactive intestinal peptide (VIP)-responsive gene. VIP, a neuroprotective peptide, is active during embryonic development, in particular during the time of neuronal tube closure. It protects damaged nerve cells from cell death by inducing glia-derived, survival-promoting substances [Helsmoortel et al 2014].

Wild type ADNP directly binds genomic DNA and mediates the recruitment of the BAF complex through its C-terminal end. The C-terminal end is truncated in all individuals with an *ADNP*-related disorder. It has been hypothesized that the mutated protein still binds to the DNA, but is no longer capable of recruiting the BAF complex, leading to diminished functionality of the complex as a whole and ultimately to deregulation of several cellular processes [Helsmoortel et al 2014]. ADNP has also been shown to interact with the chromatin-remodeling gene *CHD4* [Ostapcuk et al 2018].

Mechanism of disease causation. The mutational mechanism is not known, but it has been hypothesized that the mutated ADNP protein competes with the wild type protein to bind with the BAF complexes (the functional

eukaryotic equivalent of the SWI/SNF complex that is involved in the regulation of gene expression in yeast) [Helsmoortel et al 2014].

Table 6. Notable *ADNP* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_015339.5 NP_056154.1	c.2157C>G	p.Tyr719Ter	Pathogenic variant in exon 4; assoc w/later onset of walking & higher pain threshold than other *ADNP* pathogenic variants [Van Dijck et al 2019]
	c.2491_2494delTTAA	p.Leu831IlefsTer82	All other pathogenic variants are heterozygous frameshift or nonsense variants in the 3′ end of 5th (last) exon of *ADNP* & predict a premature termination [Helsmoortel et al 2014].
	c.2496_2499delTAAA	p.Asn832LysfsTer81	
	c.2188C>T	p.Arg730Ter	Common pathogenic variant

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

Author Notes

The research group Cognitive Genetics is part of the research cluster Medical Genetics of the Faculty of Pharmaceutical, Biomedical, and Veterinary Sciences of the University of Antwerp. Our mission is to identify genetic causes of cognitive disorders and to study the molecular defects in order to eventually develop rational therapy.

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- 6 October 2022 (sw) Revision: epigenetic signature analysis (Establishing the Diagnosis)
- 15 April 2021 (sw) Comprehensive update posted live
- 7 April 2016 (bp) Review posted live
- 18 December 2015 (avd) Original submission

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