

ADNP Related Syndrome

<https://www.ncbi.nlm.nih.gov/books/NBK355518/>

SummaryClinical 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.**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.

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. 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)
Vision 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

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]. (more...)

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, 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 and/or 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	Method	Proportion of Probands with a Pathogenic Variant Detectable by Method
ADNP	Sequence analysis	399%
	Gene-targeted deletion/duplication analysis	None reported
	CMA	61 individual

ADNP

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].

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)
Vision 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

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]. (more...) 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.

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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, 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 and/or 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](#).

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Gene	Method	Proportion of Probands with a Pathogenic Variant Detectable by Method
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Clinical CharacteristicsClinical DescriptionThe 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 DisorderView in own

windowFeature% of Persons w/FeatureCommentDD/ID100%Mild (in 12%), moderate (36%), or severe (52%) ID; ASD & other behavior disorders are common.Characteristic facial

features97%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 teethGastrointestinal/feeding

issues83%Gastroesophageal reflux disease, constipation, oral movement problems, lack of satiation, swallowing problems, frequent vomitingVision issues74%Strabismus, cortical visual

impairment, hypermetropia, ptosis, nystagmus, myopiaHand & foot abnormalities62%Digit abnormalities, single palmar crease, nail anomalies, sandal gapMusculoskeletal features55%Joint

hypermobility, scoliosis, hip problems, pectus deformitiesEndocrine issues25%Early puberty, thyroid hormone problems, growth hormone deficiencyShort

stature23%<#8210;2 SDTruncal obesity8%Congenital heart anomalies38%Atrial septal defect, patent ductus arteriosus, mitral valve prolapse, patent foramen ovale, ventricular septal

defectHearing loss32%Narrow auditory canal, frequent otitis media, hearing

lossSeizures16%Absence seizures, focal seizures w/reduced awareness, epilepsy w/continuous spike & waves during slow-wave sleepUrinary tract anomalies13%Narrow ureters, bilateral

vesicoureteral refluxASD = autism spectrum disorder; DD = developmental delay; ID = intellectual disabilityDevelopment. 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].

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 View in own window 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 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)

Table 2. Select Features of ADNP-Related Disorder	
Feature	% of Persons
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
 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

Select Features of ADNP-Related Disorder

Feature	% of Persons w/Feature	Comment	DD/ID
Mild (in 12%), moderate (36%), or severe (52%) ID; ASD & other behavior disorders are common.	100%		
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	
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

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

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 disability¹⁶⁰;* should be included in the differential diagnosis of ADNP-related disorder.*¹⁶⁰More 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 View in own window System/Concern Evaluation Comment

Development

Comprehensive developmental assessment To incl: motor, adaptive, cognitive, & speech/language eval; testing for ASD & ID; eval for early intervention¹⁶⁰;/ 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

Gastroenterology¹⁶⁰;/ nutrition¹⁶⁰;/ 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 professionals¹To inform affected persons & their families re nature, MOI, & implications of ADNP-related disorder in order to facilitate medical & personal decision making

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 View in own window 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

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.
Table 5. Recommended Surveillance for Individuals with ADNP-Related Disorder
View in own window
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 (NAPVSP1Q), 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.

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			
View in own window	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

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By genetics professionals¹ To inform affected persons & their families re nature, MOI, & implications of ADNP-related disorder in order to facilitate medical & personal decision making

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

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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

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Audiology eval; referral to ENT if indicated

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Recommended Evaluations Following Initial Diagnosis in Individuals with ADNP-Related Disorder

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Consider eval for gastric tube placement in those w/dysphagia &/or aspiration risk.

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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)

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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

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.

Table 4. Treatment of Manifestations in Individuals with ADNP-Related Disorder
View in own window
Manifestation/Concern Treatment Considerations/Other

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Treatment of Manifestations in Individuals with ADNP-Related Disorder

Manifestation/Concern	Treatment	Considerations/Other
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Speech, OT, PT; specialized learning programs depending on individual needs		
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Psychiatric/		
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Behavioral		
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Poor weight gain /		
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Failure to thrive		
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Nutritional support if needed		
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Gastrointestinal		
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SurveillanceTable 5. Recommended Surveillance for Individuals with ADNP-Related DisorderView
in own windowManifestation/ConcernTreatmentFrequency

Feeding

Measurement of growth parametersEval 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 assessmentAnnually

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

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

View in own window	Manifestation/Concern	Treatment	Frequency
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Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior

Eyes

Visual assessment
Annually

Gastrointestinal

Monitor for constipation & signs/symptoms of gastrointestinal reflux.
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Manifestation/Concern	Treatment	Frequency
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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/respice care, home nursing, other local resources) & care coordination.

Measurement of growth parameters

Eval of nutritional status & safety of oral intake

Monitor those w/seizures as clinically indicated.

Assess for new manifestations (e.g., seizures, changes in tone, movement disorders).

OT = occupational therapy; PT = physical therapy

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

Therapies Under InvestigationAdministration 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*^{+/Δ} 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.

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

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.

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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

BelgiumEmail: adnpkids.hvdasbelgium@gmail.com

www.trefpuntstan.be/adnp-kids

Amis de ADNP France

FranceEmail: caroleherman2012@gmail.com

www.alliance-maladies-rares.org/association/amis-de-adnp-france

American Association on Intellectual and Developmental Disabilities (AAIDD)

Phone: 202-387-1968Fax: 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

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

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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 View in own window GeneChromosome LocusProteinLocus-Specific DatabasesHGMDClinVar

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) View in own window

611386ACTIVITY-DEPENDENT NEUROPROTECTOR HOMEBOX; ADNP

615873HELSMOORTELVAN DER AA SYNDROME; HVDAS
Molecular PathogenesisADNP

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 VariantsView in own windowReference SequencesDNA Nucleotide
ChangePredictedProtein ChangeComment [Reference]

NM_015339​.5

NP_056154​.1

c.2157C>Gp.Tyr719TerPathogenic variant in exon 4; assoc w/late onset of walking & higher pain threshold than other ADNP pathogenic variants [Van Dijck et al

2019]c.2491_2494delTTAAp.Leu831IlefsTer82All 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_2499delTAAAp.Asn832LysfsTer81c.2188C>Tp.Arg730TerCommon pathogenic variantVariants 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.

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Table B.OMIM Entries for ADNP-Related Disorder (View All in OMIM) [View in own window](#)

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Notable ADNP Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
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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.
Acknowledgments
We thank the families with individuals affected by an ADNP pathogenic variant who are participating in our research programs.
Author History
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Geert Vandeweyer, PhD (2016-present)
Revision History
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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