Archival Report

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Clinical Presentation of a Complex Neurodevelopmental Disorder Caused by Mutations in *ADNP*

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ABSTRACT

BACKGROUND: In genome-wide screening studies for de novo mutations underlying autism and intellectual disability, mutations in the *ADNP* gene are consistently reported among the most frequent. *ADNP* mutations have been identified in children with autism spectrum disorder comorbid with intellectual disability, distinctive facial features, and deficits in multiple organ systems. However, a comprehensive clinical description of the Helsmoortel-Van der Aa syndrome is lacking.

METHODS: We identified a worldwide cohort of 78 individuals with likely disruptive mutations in *ADNP* from January 2014 to October 2016 through systematic literature search, by contacting collaborators, and through direct interaction with parents. Clinicians filled in a structured questionnaire on genetic and clinical findings to enable correlations between genotype and phenotype. Clinical photographs and specialist reports were gathered. Parents were interviewed to complement the written questionnaires.

RESULTS: We report on the detailed clinical characterization of a large cohort of individuals with an *ADNP* mutation and demonstrate a distinctive combination of clinical features, including mild to severe intellectual disability, autism, severe speech and motor delay, and common facial characteristics. Brain abnormalities, behavioral problems, sleep disturbance, epilepsy, hypotonia, visual problems, congenital heart defects, gastrointestinal problems, short stature, and hormonal deficiencies are common comorbidities. Strikingly, individuals with the recurrent p.Tyr719* mutation were more severely affected.

CONCLUSIONS: This overview defines the full clinical spectrum of individuals with *ADNP* mutations, a specific autism subtype. We show that individuals with mutations in *ADNP* have many overlapping clinical features that are distinctive from those of other autism and/or intellectual disability syndromes. In addition, our data show preliminary evidence of a correlation between genotype and phenotype.

Keywords: *ADNP*, Autism, Genetics, Helsmoortel-Van der Aa syndrome, Intellectual disability, Neurodevelopmental disorder

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Autism spectrum disorder (ASD) is a condition defined by deficits in social interaction, communication, and selected behaviors (1). Each aspect of the disorder may vary in presentation, range, and severity, cumulating in a broad clinical spectrum. The frequency of the disorder is under continuous debate, but ASD may affect up to 1.5% of the population (2). Although a genetic contribution to its etiology has been firmly demonstrated (3), it took the introduction of trio-based whole-exome sequencing to truly accelerate substantially the identification of ASD genes. In these studies, individuals are screened along with their parents, enabling the unbiased detection of de novo mutations in large ASD cohorts (4–6). These initiatives are complemented by targeted resequencing of larger cohorts (7). Studies in ASD cohorts comorbid with intellectual disability (ID) collectively demonstrate an unprecedented genetic heterogeneity of ASD, with no single gene responsible for more than a fraction of the total population. Several of the identified genes appear to cluster in a subset of cellular networks, including networks enriched for chromatin remodeling and synaptic functioning (5,8). Overlap between ASD genes and genes causative for other neurodevelopmental disorders, including ID and seizures, is common (9,10).

Despite the high heterogeneity and observed molecular overlap, there is preliminary evidence for the existence of

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clinical ASD subtypes. For instance, mutations in the chromatin remodeler *CHD8* cause an ASD/ID subtype with specific physical characteristics, such as macrocephaly and significant gastrointestinal problems (11,12). In contrast, individuals with a mutation in *DYRK1A*, a gene duplicated in Down syndrome, have ASD/ID, microcephaly, intrauterine growth retardation, febrile seizures in infancy, impaired speech, stereotypic behavior, hypertonia, and a distinctive facial gestalt (13). Yet the clinical delineation of ASD/ID syndromes has lagged behind their respective molecular definition. Because possible future treatment may be based on targeting the underlying molecular defect rather than on the basis of the clinical presentation, it is of primary importance to define autism subtypes correctly at the molecular level (14).

ADNP was one of the most frequently mutated genes across multiple recent whole-exome sequencing and targeted molecular inversion probe sequencing studies in ASD/ID cohorts (6,7). The *ADNP* gene plays a role in embryonic development, especially during the time of neuronal tube closure, and is involved in chromatin remodeling (15–18). Based on the first 10 individuals identified with *ADNP*-related ASD/ID, *ADNP* mutations were estimated to explain one or two per 1000 ASD/ID cases. Some shared clinical features were suggested (19). Since that time, a number of case reports have expanded the phenotype of the Helsmoortel-Van der Aa syndrome (Online Mendelian Inheritance in Man [OMIM] identification 615873) (20–23). Here, we describe the clinical details of a cohort of 78 individuals from 16 countries with a likely disruptive mutation in *ADNP.* We define a novel subtype of ASD/ID, and at the same time we present evidence for a significant genotype-phenotype correlation.

METHODS AND MATERIALS

Participants

The study was performed at the University of Antwerp, Belgium. Individuals were identified through exome sequencing in our own center or gathered from genetic centers worldwide that offer exome-wide or targeted genetic screening in a clinical or a research setting. Additional individuals were collected on the website http://humandiseasegenes.nl/adnp/. A minority of the individuals were previously described in case reports (19–23). All individuals were enrolled between January 1, 2014, and October 1, 2016. Inclusion required a clinical geneticist-confirmed diagnosis of a nonsense or frameshift mutation in the *ADNP* gene and presence of clinical information in at least three of the following domains: demographics, development, craniofacial features, and behavior. Essentially all mutations were identified by next-generation sequencing of individuals with autism and/or developmental delay, often in combination with additional syndromic features. In part, the *ADNP* mutations were identified in individuals in preassembled ASD/ID cohorts that were subjected to trio-based whole-exome sequencing or targeted molecular inversion probe sequencing as described in Helsmoortel *et al.* (19). The remainder of our cohort was assembled from the individuals in whom an *ADNP* mutation was diagnosed after genetic testing using either neurodevelopmental gene panels or trio-based whole-exome sequencing. After the identification of a causative *ADNP* mutation in an individual, the patient's clinical geneticist asked for consent to be included in this study. In each case, the mutation that was identified using next-generation sequencing was independently verified using Sanger sequencing either in our own or in the referring laboratory. Individuals carrying a missense mutation in *ADNP* were excluded from this study. All gene annotations have been made according to reference sequence NM_015339.2 (human genome version 19). Approval for this study was obtained from the Ethics Committee of the Antwerp University Hospital. Pictures were published only if the parents provided written informed consent on behalf of their child.

Procedures

Collaborating physicians were asked to fill out an extensive questionnaire with clinical and molecular information about the

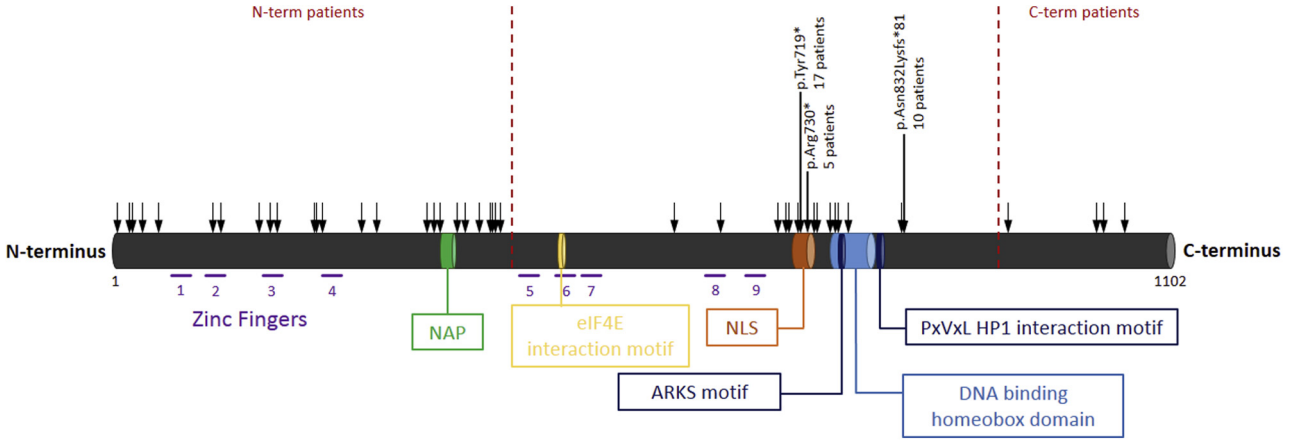

Figure 1. Schematic illustration of *ADNP* and its functional domains. *ADNP* consists of five exons and 14 domains, including nine zinc fingers, NAP (a short octapeptide sequence, single letter code, NAPVSIPQ), an eIF4E interaction motif, a nuclear localization signal (NLS), an alanine-arginine-lysine-serine (ARKS) motif, a DNA-binding homeobox domain, and a PxVxL motif (15,17,30). Zinc fingers: AA 74–97, 107–129, 165–188, 221–244, 447–469, 489–510, 512–535, 622–647, 662–686; NAP amino acid (AA) 354–361; eIF4E NAP AA 490–499; NLS AA 716–733; ARKS motif AA 765–768; DNA-binding homeobox domain AA 754–814; PxVxL heterochromatin protein 1 (HP1) interaction motif AA 819–823. Black arrows indicate the location of the mutations in the reported individuals, highlighting the three most frequent mutations.

individuals they had identified and assessed. We specifically asked for the results of the test the individuals had been given, including but not limited to IQ test and Autism Diagnostic Observation Schedule. Medical specialist reports and magnetic resonance imaging data were collected and systematically reevaluated to refine the interpretation of the findings. To compare the data that were collected in various parts of the world, which did not in all cases use the same tests and terminology, we curated all incoming data and recontacted the collaborating clinicians to harmonize the medical information. The *ADNP*kids Facebook community (24) helped us contact clinicians and parents so we could complete and verify the details of the clinical information.

Statistical Analysis

Associations between reported clinical features were systematically tested in a pairwise analysis using one-way analysis of variance (ANOVA), Pearson correlation, and Fisher's exact tests, depending on the nature of the variables. A listing of all 170 variables included in our analysis is provided in Supplemental Table S1. For one-way ANOVA, features for which only a single level was available were excluded. If ANOVA resulted in significant results ($p < .05$), post hoc Tukey honest significant difference testing was applied to identify significant differences in mean. For Fisher's exact tests, a minimum of two levels per tested category and >10 records per tested condition were required. If either category contained three or more levels, p values were calculated via a Monte Carlo simulation using 10,000 replicates. The association between demographic features, including gender, age, and clinical features, was analyzed similarly. Additionally, we evaluated the presence of genotype-phenotype correlations. First, the three most frequent mutations were analyzed separately: p.Tyr719* (17 individuals), p.Leu831Ilefs*82/p.Asn832Lysfs*81 (14 individuals), and p.Arg730* (5 individuals). Subsequently, mutations were grouped according to gene location: in the N terminus (25 individuals), at the center of the gene (49 individuals), and in the C terminus (4 individuals). Finally, we analyzed mutations per domain. For each analysis, prevalence or extent of all individual clinical features was compared between the selected subcohort and the remaining individuals. Multiple testing correction was performed via the false discovery rate method [Qvalue add-on package in R, version 2.6.0 (25)]. All calculations were performed in the software package in R version 3.3.1 (26). Significant correlations are indicated at the appropriate Results section.

RESULTS

We included 78 individuals with a disruptive mutation in *ADNP*, including 44 male subjects and 34 female subjects (Figures 1 and 2). The mean age of our cohort is 8 years 2 months, with a range of 1 to 40 years. Individuals were from 44 clinics in 16 countries. Parental consanguinity was not reported, and no sibling was diagnosed with a mutation in *ADNP*. Five individuals have nonidentical healthy twin siblings. We found 46 unique mutations on the DNA level, of which 25 were nonsense and 21 frameshift (Supplemental Table S2). All but three mutations were located in the fifth and last exon of the *ADNP* gene

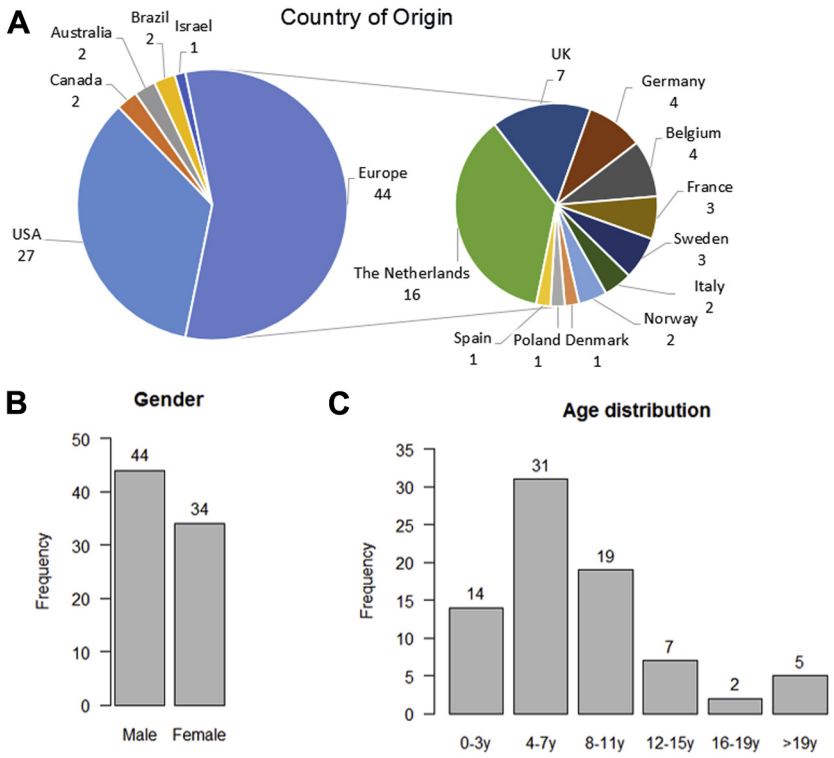

Figure 2. Demographic data of the reported individuals: **(A)** country of origin, **(B)** gender, and **(C)** age distribution.

Table 1. Clinical Features of the Reported Individuals With Mutation in the *ADNP* Gene

Clinical Features		Sample *n*/ Total *N*
General Information		
Age at examination, range (mean)	1–40 years (8 years 2 mo)	78/78
Gender, female:male, *n*	34:44	78/78
Gestational age, weeks	38.7	70/70
Age of father at time of birth, years	32.1	65/65
Age of mother at time of birth, years	29.8	67/67
Mutation Information, %		
De novo *ADNP* mutation	97.1	68/70
Nonsense mutation	56.4	44/78
Frameshift mutation	43.6	34/78
Growth		
Short stature, < -2 SD, %	23.2	16/69
Neurodevelopmental Features		
Developmental delay/ID, %	100.0	73/73
Mild ID	12.3	9/73
Moderate ID	35.6	26/73
Severe ID	52.1	38/73
Motor delay, %	95.9	71/74
Age at sitting independently, years, mean	1.1	58/58
Walking independently, %	86.8	66/76
Age at walking independently, years, mean	2.5	64/64
Speech delay, %	98.6	70/71
Age at first words, years, mean	2.5	49/49
No speech, %	19.4	14/72
Autism spectrum disorder including autistic features, %	92.8	64/69
Attention-deficit/hyperactivity disorder, %	43.9	25/57
Loss of skills, %	20.3	12/59
Bladder training delay, %	81.1	43/53
Feeding and Gastrointestinal Problems, %	83.3	60/72
Gastroesophageal reflux (disease)	58.5	38/65
Constipation	49.3	34/69
Oral movement problems	45.6	26/57
Lack of satiation	41.5	22/53
Problems swallowing liquids	32.2	19/59
Frequent vomiting	29.5	18/61
Aspiration difficulties	21.4	12/56
Gastrostomy tube	12.7	8/63
Obesity	7.5	5/67
Neurological Problems and Behavior, %		
Hypotonia	78.3	54/69
Hypertonia	3.8	3/78
Seizures	16.2	12/74
Cerebral imaging—structural brain abnormalities	55.9	33/59
Wide ventricles	29.4	15/51
Corpus callosum underdevelopment	18.4	9/49
Cerebral atrophy	17.8	8/45
Delayed myelination	8.9	4/45
White matter lesions	7.5	4/53
Cortical dysplasia	3.8	2/52
MRI brain abnormalities, unspecified	36.2	17/46
Behavioral problems	77.6	38/49
Temper tantrums/aggression	83.3	20/24
Obsessive-compulsive behavior	64.0	16/25
Mood disorder	56.3	9/16
Self-injurious behavior	20.0	2/10
Insensitivity to pain	63.6	35/55
Sensory processing disorder	66.7	28/42
Sleep problems	65.2	45/69
Visual System, %	73.6	53/72
Strabismus	49.2	31/63
Cerebral visual impairment	41.2	14/34
Hypermetropia	40.3	25/62
Ptosis	24.2	15/62
Nystagmus	11.7	9/77
Myopia	7.9	5/63
Colobomata	5.6	4/72
Ear-Nose-Throat System, %	32.1	25/78
Narrow hearing canal	87.5	7/8
Frequent otitis media	85.7	12/14
Hearing tubes	73.3	11/15
Hearing loss	11.7	7/60
Obstructive sleep apnea syndrome	6.6	5/76
Cardiovascular System, %	37.7	26/69
Atrial septal defect	15.9	11/69
Patent ductus arteriosus	8.7	6/69
Mitral valve prolapse	5.8	4/69
Patent foramen ovale	5.8	4/69
Ventricular septal defect	4.3	3/69
Tetralogy of Fallot	1.4	1/69
Cardiac defect, unspecified	8.7	6/69
Urogenital System, %	28.0	21/75
Cryptorchidism	34.3	12/35
Renal anomalies	12.5	6/48
Small genitalia	5.4	4/74
Endocrine System, %	24.5	12/49
Early puberty	30.0	3/10
Thyroid hormone problems	15.2	7/46
Growth hormone deficiency	10.9	5/46
Musculoskeletal System, %	54.9	39/71
Joint hypermobility	37.7	23/61
Scoliosis	17.2	11/64
Hip problems (hip dysplasia, Perthes' disease, dislocated hips)	7.5	4/53
Thorax abnormalities	22.2	12/54
Pectus excavatum	14.8	8/54
Pectus carinatum	5.6	3/54
Narrow thorax	1.9	1/54

Table 1. Continued

Clinical Features		Sample *n*/ Total *N*
Abnormal skull shape	13.9	10/72
Plagiocephaly	8.3	6/72
Trigonocephaly	2.8	2/72
Brachycephaly	4.2	3/72
Hand and Foot Abnormalities, %	62.3	43/69
Finger abnormalities (prominent distal phalanges, prominent interphalangeal joints, polydactyly, interdigital webbing, 2–3 toe syndactyly, fifth finger clinodactyly, small fifth finger or absent distal phalanx of fifth finger, tapering fingers, brachydactyly, broad fingers, fetal fingertip pads)	46.3	31/67
Single palmar crease	10.8	7/65
Nail anomalies	25.0	14/56
Sandal gap	19.6	11/56
Toe abnormalities (broad halluces, 2–3 toe syndactyly, brachydactyly)	10.8	7/65
Other, %		
Early teeth	71.1	32/45
Frequent infections	50.7	35/69
Widely spaced nipples	20.4	11/54
Umbilical/inguinal hernia	8.5	5/59

ID, intellectual disability; MRI, magnetic resonance imaging.

and were predicted to escape nonsense-mediated decay. On the protein level, three mutations, including the p.Tyr719* mutation, were present in ≥5 individuals. Sixty-eight mutations in our cohort were confirmed de novo, eight mutations were of unknown inheritance, and two C-terminal mutations were inherited.

Pre- and Perinatal Observations and Congenital Abnormalities

Most children were born at term (mean gestational age 38.7 weeks, range 30–42 weeks). Mean maternal and paternal ages at birth were 30 and 32 years, respectively. Intrauterine growth retardation was not reported. Overall, birth weight, height, and head circumference were within normal ranges (Supplemental Table S3, Supplemental Figure S1A–C).

Six individuals (12.5%) were born with renal anomalies (narrow ureters, bilateral vesicoureteral reflux that was surgically repaired) (Table 1). Reported hand and feet abnormalities were nonspecific; they included fetal finger pads, clinodactyly, small fifth fingers, brachydactyly, single palmar crease, sandal gap, pes planus, long or broad halluces, and syndactyly of the second and third toes. Twenty-five percent had nail abnormalities such as thin or small nails, or hypoplastic nails of the fifth digit. Some had widely spaced nipples, pectus excavatum, pectus carinatum, or combined excavatum/carinatum deformity. One child had a submucous cleft palate. Two of the children were born with metopic craniosynostosis, and 1 of them needed surgery. Six children had plagiocephaly, of whom 3 wore a cranial-molding helmet.

Failure to thrive in early childhood was noted in a number of individuals. Some of them appeared to have severe cardiac problems, requiring open heart surgery. Thirty-eight percent had one or more congenital cardiac defects. These were diverse: atrial septal defect, patent ductus arteriosus, patent foramen ovale, mitral valve prolapse, ventricular septal defect, and other cardiovascular malformations such as a right aortic arch, dysplastic aortic valve, tetralogy of Fallot, ductus arteriosus aneurysm, quadricuspidal aortic valve, aortic ectasia, and a mild pulmonary valve stenosis were found (Figure 3A).

Facial Appearance

Individuals shared similar facial features, including a prominent forehead with a high anterior hairline, a wide and depressed nasal bridge, and a short nose with full, upturned nasal tip (Figure 4, Supplemental Table S4). One third of the individuals had downslanted palpebral fissures and prominent eyelashes. Ear malformations were observed in nearly half of individuals. Abnormalities included small or dysplastic, low-set, and posteriorly rotated ears. The philtrum was long in 39.3% of study cohort. Seventy percent of individuals had a thin upper lip, often combined with an everted lower lip and a pointed chin that appeared more pronounced at younger age (Figure 5). One third have widely spaced teeth.

Growth and Endocrine System

Twenty-three percent of the individuals had short stature (height < -2 SD, range 2–23 years old) (Supplemental Table S3, Supplemental Figure S1E). Nine individuals had hormonal deficiencies (Table 1). Of these, 2 had isolated growth hormone deficiency, 4 had hypothyroidism, and 3 a combination of both hormonal deficiencies. One 29-year-old woman had a narrow thorax with breast hypoplasia. Signs of early puberty were present in 3 of 10 individuals older than 6 years for whom information was available; 1 boy and 1 girl had pubic hair growth at the age of 7 and 8 years, respectively, and 1 girl had menarche at 8 years of age.

Development and Neurology

Fifty-two percent of the individuals in this cohort presented with severe ID at the age of assessment, 36% had a moderate disability, and 12% had a mild disability. Developmental delay was present in all individuals, with motor delay being one of the key features. The average age to sit up independently was 12.8 months [cohort range 6–60 months, normal range 4–9 months (27)] (Supplemental Figure S2A). Delayed age of walking independently [after 18 months of age (27)] (Supplemental Figure S2B) was observed in 86.8% of the children, with an average age of 2 years 5.5 months (cohort range 15–72 months).

Interestingly, individuals with a p.Tyr719* mutation started walking at a mean of 3.5 years, significantly later than the 2 years 2 months of the remainder of the cohort ($p < .0001$, one-way ANOVA). Seventy-eight percent of the children had hypotonia, while hypertonia was present in 3 children. Standing unassisted for long periods of time or walking long distances is difficult for many of the children. The walking pattern can be

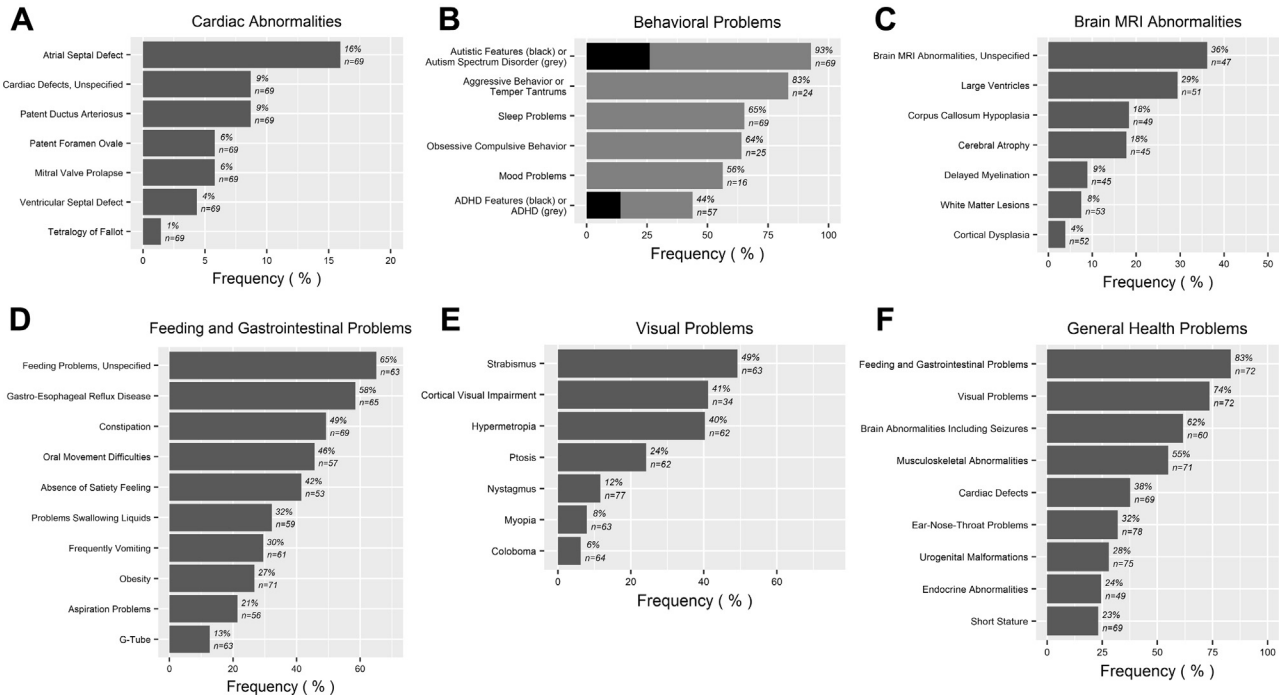

Figure 3. Clinical features reported in individuals with *ADNP* mutation: **(A)** cardiac abnormalities, **(B)** behavioral problems, **(C)** brain magnetic resonance imaging (MRI) abnormalities, **(D)** feeding and gastrointestinal problems, **(E)** visual problems, and **(F)** general health problems. ADHD, attention-deficit/hyperactivity disorder.

abnormal (e.g., broad-based or tiptoe gait, foot slap). Six children learned to walk with support between 5.5 and 8 years of age, after many years of physiotherapy. A minority were not able to walk at the time of last evaluation.

Another key feature was speech delay, which presented in 98.6% of individuals. The mean age of first words was 30 months (cohort range 7–72 months, as opposed to a normal range of 12–18 months) (Supplemental Figure S2C). Nineteen percent had no language development at all. Apparent loss of acquired abilities was reported in 12 children for skills such as speaking, counting, riding a bicycle, or being toilet trained. Eighty-one percent of the children had a considerable delay in bladder training and many were still not toilet trained when approaching puberty.

Sixteen percent had seizures, including absence seizures, focal seizures with reduced awareness, epilepsy with continuous spike and waves during slow-wave sleep, or unclassified seizures. At least 5 children were reported to have breath-holding spells. Some of them were hospitalized for multiple cyanotic episodes causing an acute life-threatening event.

Autistic Features, Behavior, and Sleep

Ninety-three percent of the individuals presented with autistic features (Figure 3B). Sixty-seven percent of them were reported to have a clinical diagnosis of ASD. They had a strong sensory interest, illustrated by putting fingers or objects in their mouth or being attracted to lights or water. Repetitive use of objects, hand and finger mannerisms, and stereotyped movements such as rocking back and forth or hand flapping were common. Some presented with echolalia. Sixty-seven percent had also been diagnosed with sensory processing disorder. A high pain threshold was reported in 63.6% of individuals. Interestingly, all individuals with a p.Tyr719* mutation are included in this group (p = 0.0003, Fisher's exact test).

Although parents report that 88% of the children were overall happy and friendly, behavioral problems were reported in 77.6% of them. Several presented with obsessive-compulsive behavior, mood disorder, a high anxiety level, temper tantrums, self-injurious behavior, and (verbally) aggressive behavior. Forty-four percent of the individuals were hyperactive or easily distracted. About one third of them had a diagnosis of attention-deficit/hyperactivity disorder. Several individuals were taking behavior-regulating medication such as methylphenidate or atypical antipsychotics such as risperidone or olanzapine to help control behavioral disturbances, particularly aggression.

Sleep problems were present in 65.2%. Some individuals were extremely anxious, with struggles falling asleep and frequent nighttime awakenings. Some were treated with melatonin. Many individuals had a low daytime activity level or excessive daytime sleepiness; a minority had sleep apnea.

Cerebral Imaging

In this cohort, magnetic resonance imaging of the brain was performed in 75.6% of the individuals. Fifty-six percent of them appeared to have cerebral abnormalities, including atypical white matter lesions, delayed myelination, cortical dysplasia or atrophy, perinatal hypoxic ischemic encephalopathy, hydrocephalus, and hippocampal hypoplasticity (Figure 3C).

Figure 4. Facial features of individuals with mutations in *ADNP*. 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. Informed consent has been obtained for publication of all images present in this paper. (Individual numbers from Supplemental Table S2 corresponding to the pictures: A = 49, B = 34, C = 44, D = 21, E = 17, F = 63, G = 28, H = 29, I = 45, J = 11, K = 38, L = 15, M = 48, N = 50, O = 60, P = 36, Q = 58, R = 33, S = 51, T = 39, U = 42, V = 31, W = 41, X = 10, Y = 70, Z = 27).

Magnetic resonance images of 5 individuals were studied in detail. The following abnormalities were seen in multiple individuals: underdevelopment of the frontal lobes with simplified gyral pattern of the cortex and occasional hypoplasia of the bulbus olfactorius and chiasma opticum; a thin and/or short, underdeveloped corpus callosum and inferior vermis hypoplasia; abnormal, often asymmetric opercularization of the Sylvian fissure with sometimes abnormal overlying cortex; dilatation of the lateral ventricles, mostly in the frontal areas; and dilated perivascular spaces of Virchow-Robin in the cerebral white matter (Figure 6).

Gastrointestinal Problems

Eighty-three percent of the individuals had feeding or gastrointestinal problems, mainly gastroesophageal reflux, frequent vomiting, and constipation (Figure 3D). A few had excessive appetite. At the age of assessment, 20.9% of the individuals were overweight and 7.5% were obese, according to standard World Health Organization classification (28). Two individuals had Crohn's disease, 1 of them with a positive familial history. Oral movement problems, with implications for feeding and speech, were common (45.6%) and were significantly more common in individuals with mutations in the nuclear localization signal and C terminal of this domain (p = .0004, Fisher's exact test). Problems with drinking liquids or aspiration difficulties were frequent. Eight individuals were fed by gastrostomy tube in early childhood. The individuals suffering from gastrointestinal problems presented more often with sleep disturbances (p = .0005, Fisher's exact test).

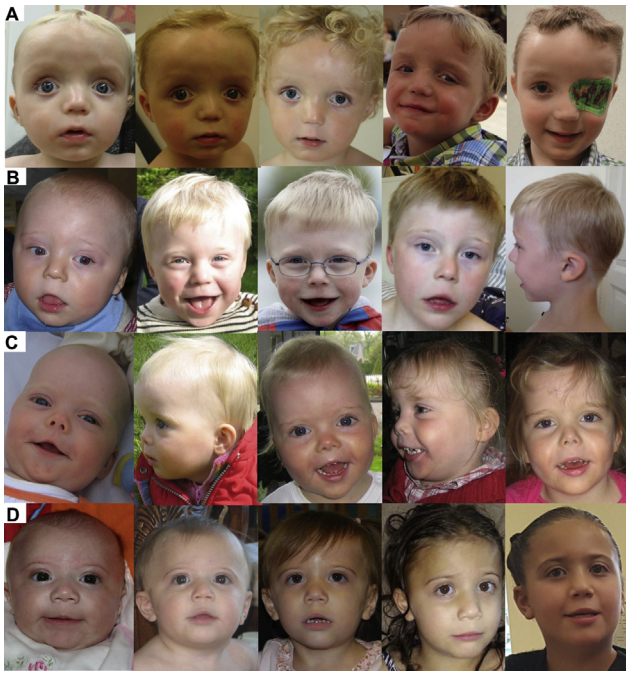

Figure 5. Individuals at different ages showing evolution with age. **(A)** Individual 1 at 10 months, 15 months, 29 months, 4 years, and 6 years of age; **(B)** individual 32 at 13 months, 26 months, 3 years 10 months, 5 years 11 months, 5 years 11 months of age; **(C)** individual 40 at 4 months, 13 months, 13 months, 3 years 6 months, 3 years 6 months of age; **(D)** individual 65 at 3 months, 10 months, 24 months, 4 years 9 months, 8 years 9 months of age. Informed consent has been obtained for publication of all images present in this paper.

Visual Problems

In 73.6% of the individuals, visual problems, especially hypermetropia (40.3%) and strabismus (49.2%), but also myopia and astigmatism, were present (Figure 3E). Many of these individuals were prescribed eyeglasses. Forty-one percent of the individuals had a diagnosis of cerebral visual impairment. Ophthalmologic defects were diverse: ectropion, coloboma, congenital cataracts, nystagmus. Some had an everted or notched eyelid, or mild ptosis, the latter observed particularly in individuals with mutations in the nuclear localization signal and C terminal of this domain (p = .0004, Fisher's exact test).

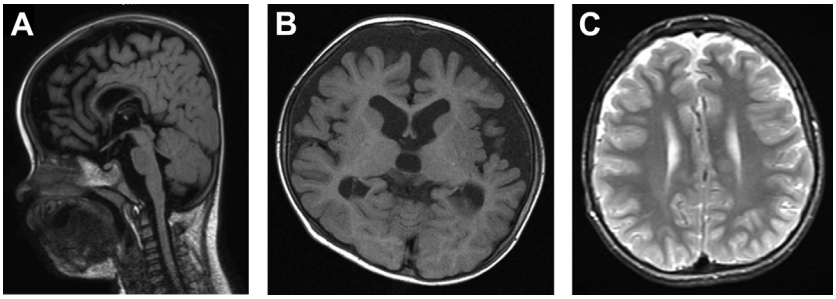

Figure 6. Brain magnetic resonance imaging of a child with a mutation in the *ADNP* gene. **(A)** Brain magnetic resonance image of individual 49 performed at 13 months of age, showing generalized and frontal cortical atrophy and a gracile corpus callosum (sagittal, T2 weighted fluid-attenuated inversion recovery). **(B)** Brain magnetic resonance image of individual 49 performed at 19 months of age, showing frontotemporal atrophy (axial, T1-weighted). **(C)** Brain magnetic resonance image of individual 45 performed at 12 years of age, showing mild frontal atrophy (axial, T2-weighted).

Additional Problems

Musculoskeletal problems were common (Figure 3F). In addition to joint hypermobility, mild scoliosis was present in some individuals. Four had hip problems. Thirty-four percent of the male individuals had unilateral or bilateral cryptorchidism; 2 had bilateral inguinal hernias. Fifty-one percent of the individuals had recurrent infections. Many of the children experienced chronic otitis media requiring ventilation tubes. Some individuals (11.7%) were diagnosed with mild hearing loss in childhood. Two children had hearing aids for sensorineural hearing loss. Ear-nose-throat problems, including narrow ear canals, laryngomalacia, and sleep apnea, were present in 32.1% of the individuals.

DISCUSSION

Individuals with mutations in *ADNP* present with mild to severe ID, autistic features, and a delay in language and motor development (Table 1). In addition, the syndrome may be accompanied by a wide range of medical conditions, including very frequent (>75%) gastrointestinal and feeding problems, hypotonia, and behavioral disturbances. Frequent comorbidities (50%–75%) include visual problems, brain malformations, sleep disturbances, hand/foot and musculoskeletal abnormalities, and frequent infections. Common (25%–50%) associated features include congenital heart disease, otorhinolaryngologic problems, and urogenital defects. Up to 25% of individuals have hormonal deficiencies, short stature, or seizures. The clinical symptoms of Helsmoortel-Van der Aa syndrome show partial overlap with other genetic syndromes that include developmental delay and ASD, as evidenced by genetic testing of our cohort for disorders such as Angelman, Prader-Willi, Kleefstra, Smith-Magenis, or Rett syndromes prior to the diagnosis of an *ADNP* mutation. As we did not have access to the full clinical data of all individuals in the screening cohorts from which our cohort was assembled, we cannot determine to what extent a possible ascertainment bias has influenced the clinical presentation of the syndrome.

A striking element is the presence of mutational hot spots. The p.Tyr719*, p.Leu831Ilefs*82/p.Asn832Lysfs*81, and p.Arg730* mutations each occurred independently in ≥5 individuals. Interestingly, we found evidence for a genotype-phenotype correlation. We noticed, for instance, that individuals with a p.Tyr719* mutation walked later and had a higher pain threshold than the individuals with other mutations. Individuals with mutations in the C terminal of the nuclear localization signal domain more often had ptosis or oral movement problems than individuals with mutation elsewhere in the gene. Our findings encourage further investigations on larger study cohorts to unveil possible additional genotype-phenotype correlations. We did not find any evidence for gender-, IQ-level- or age-specific correlations.

Social media is increasingly used by parents to connect with one another and with scientists. This has been the case for this syndrome (24). These interactions helped us to collect genetic and clinical information and the parents' experiences, providing us with important new insights into symptoms, daily struggles, and challenges. While consensus has to grow to determine what level of evidence is required to include parental observations of this type in a scientific publication, some of these hypotheses have been successfully tested in follow-up studies. As an example, the recently reported early teething in individuals with an *ADNP* mutation started as a parental observation (29).

Conclusions

Through a careful and structured comparison of the clinical symptoms of 78 individuals with a mutation in the *ADNP* gene, we delineated the clinical presentation of this specific subtype of autism. Our synthesis is indispensable in the decision-making process for caretakers and relatives. Moreover, it will significantly improve the interpretation of the clinical relevance of novel rare variants in the gene. The main limitation of our study is the relatively young age of our study cohort. Long-term follow-up studies are necessary to define the developmental path of individuals with a mutation in *ADNP*. While to date most cases have been found on a genotype-first basis, a specific combination of features such as ID, ASD, speech and motor delay, and additional problems may emerge to screen for *ADNP* mutations in cohorts including older individuals. Finally, this clinical delineation can be used to monitor effects of potential future treatment, when available.

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