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

Supplemental Information

Supplemental Tables

Table S1. Parameters used for statistical analyses

Epidemiology
Country of lab
Country of Origin
Gender
Age (months) - last observation
Age father (years) - at time of birth
Age mother (years) - at time of birth
Part of twin
Growth
At birth: duration gestation (weeks)
Weight, g
Weight, SD
Length, cm
Length, SD
OFC, cm
OFC, SD
Post-natal - age last measurements (yr)
Weight, SD
Height, SD
OFC, SD
BMI
Short stature (< -2SD)
Development
Delay/ ID : severe; moderate; mild
Motor delay
Sitting (months)
Walking independently
Walking independently from the age of (months)
Speech delay
No speech (nonverbal child)
Speech - first words (months)
Loss of skills
Autism
ADHD
Behavioral problems
Mood disorder

Aggressive behavior
Self-injurious behavior
Temper tantrums
Obsessive compulsive behavior
Social behavior
Asocial behavior (reserved, avoids people)
Friendly behavior
Feeding problems
Gastrointestinal problems
Feeding G-Tube
GERD or Reflux
Oral movement difficulties
Oral drinking liquid problems
Satiety problems: does not seem to "get full"
Aspiration difficulties
Obesity
Frequent vomiting
Constipation
Hypotonia
Hypertonia
Seizures
Ear-Nose-Throat
Hearing loss
Narrow hearing canal
Hearing tubes
Frequent otitis media
Eye defects
Hypermetropia
Strabismus
Ptosis
Hypertelorism
CVI
Myopia
Nystagmus
Craniofacial features
Coarse face
High hairline
Low hairline
Abnormal hair thickness
Prominent forehead
Eversion/notch eyelid
Prominent eyelashes
Thick eyebrows
Sagging periorbital skin
Narrow palpebral fissures
Upward slant palpebral fissures
Downward slant palpebral fissures
Small chin

Pointed chin
Wide nasal bridge
Narrow nasal bridge
Low nasal bridge
Upturned nasal tip (anteverted nares)
Broad nasal tip
Broad nasal base
Short nose
Broad philtrum
Long philtrum
Short philtrum
Smooth philtrum
Large mouth
Thin upper vermillion
Thick lower vermillion
Drooping lower lip
Cleft palate / submucous cleft
Widely spaced teeth
Teeth problems
Low set or posteriorly rotated ears
Malformed ears
Small ears
Trunc and limbs
Thick neck
Scoliosis
Widely spaced nipples
Pectus
Cryptorchidism (uni/bilateral)
Small genitalia
Umbilical/inguinal hernia
Hand abnormalities
Single palmar crease
Thumb abnormalities
Finger abnormalities
Broad fingers
Broad halluces
Fetal finger pads
Brachydactyly
Fetal finger pads
Hyperlaxity
Sandal gap
Nail anomalies
Feet abnormalities
Toe abnormalities
Flat feet
Cardiac abnormalities
Cardiac

Atrial Septal Defect
Mitral Valve Prolapse
Ventricular Septal Defect
Patent Foramen Ovale at birth
Patent Ductus Arteriosus at birth
Tetralogy of Fallot
Other cardiac defect
Neuroradiology
MRI brain abnormality
Delayed myelination
Wide ventricles
Callosal body underdevelopment
Cerebral atrophy
White matter lesions
Cortical dysplasia
Other MRI brain abnormalities
Brain abnormalities including seizures
Therapy
Speech therapy
Physical therapy
Opposite effects of medication
Antiepileptic therapy
Other
Renal anomalies
Dentition (normal; delayed prim / delayed permanent)
Early teeth
Early puberty
Frequent infections
Sleep problems
Obstructive Sleep Apnea Syndrome
Bladder training delay
Hormonal deficiencies
Insensitivity to pain
Sensory Processing Disorder
Growth hormone deficiency
Thyroid hormone problems
Orthopedic and muscular system abnormalities
Skull abnormalities
Hip problems

Table S2. List of mutations identified in the reported individuals (NM_015339.2 (hg19))

cDNA	Protein	gDNA	CADD score*	Patient ID	Frequency
c.1A>G	p.Met1?	g.49520533T>C	24.6	48	1
c.118C>T	p.Gln40*	g.49518637G>A	37	11	1
c.190dupA	p.Thr64Asnfs*35	g.49518565insT	34	64	1
c.339delC	p.Phe114Serfs*47	g.49510912delG	21.2	21	1
c.372_373delGT	p.Ile125*	g.49510878_49510879delAC	33	54	1
c.484C>T	p.Gln162*	g.49510767G>A	36	47	1
c.517C>T	p.Arg173*	g.49510734G>A	36	17	1
c.539_542delTTAG	p.Val180Glyfs*17	g.49510709_49510712delCTAA	34	28, 39	2
c.646 C>T	p.Arg216*	g.49510605G>A	36	20	1
c.651_655delAGAGA	p.Glu218*	g.49510596_49510600delTCTCT	29	68	1
c.673C>T	p.Arg225*	g.49510578G>A	35	42, 66	2
c.790C>T	p.Arg264*	g.49510461G>A	36	73	1
c.819delC	p.Lys274Asnfs*31	g.49510432delG	25.2	62	1
c.1026_1027insT	p.Val343Cysfs*56	g.49510224_49510225insA	33	23	1
c.1033C>T	p.Gln345*	g.49510218G>A	37	65	1
c.1046_1047delTG	p.Leu349Argfs*49	g.49510204_49510205delCA	32	13	1
c.1102C>T	p.Gln368*	g.49510149G>A	37	80	1
c.1134T>G	p.Tyr378*	g.49510117A>C	23.5	50	1
c.1184_1190delAGTCTGC	p.Gln395Leufs*11	g.49510061_49510067delGCAGACT	34	60	1
c.1211C>A	p.Ser404*	g.49510040G>T	37	2	1
c.1216delC	p.Gln406Serfs*2	g.49510035delG	33	59	1
c.1222_1223delAA	p.Lys408Valfs*31	g.49510028_49510029delTT	32	3	1
c.1235delT	p.Leu412Profs*10	g.49510016delA	31	52	1
c.1754dupA	p.Asn585Lysfs*2	g.49509497dupT	26.5	75	1
c.1930C>T	p.Arg644*	g.49509321G>A	37	9	1

cDNA	Protein	gDNA	CADD score*	Patient ID	Frequency
c.2089C>T	p.Gln697*	g.49509162G>A	39	36	1
c.2129delC	p.Pro710Glnfs*6	g.49509122del	35	41	1
c.2129dupC	p.Ser711Lysfs*24	g.49509122dupG	34	29	1
c.2153_2165delCTTACGAGCAAAT	p.Thr718Argfs*6	g.49509086_49509098delATTTGCTCGTAAG	35	4	1
c.2156dup	p.Tyr719*	g.49509095dupT	32	5, 10, 27, 38, 44, 55, 70, 79	8
c.2157C>A	p.Tyr719*	g.49509094G>T	22.9	57, 58, 63	3
c.2157C>G	p.Tyr719*	g.49509094G>C	21.9	12, 16, 26, 34, 49, 56,	6
c.2188C>T	p.Arg730*	g.49509063G>A	36	18, 25, 45, 69, 74	5
c.2206dupA	p.Ser736Lysfs*2	g.49509045dupT	28.4	51	1
c.2213C>G	p.Ser738*	g.49509038G>C	43	71	1
c.2251delGinsTAAA	p.Val751*	g.49509000delCinsTTTA	38	31	1
c.2268_2269insT	p.Lys757*	g.49508982_49508983insA	35	53	1
c.2287delT	p.Ser763Profs*9	g.49508964delA	35	46	1
c.2310delT	p.Leu771*	g.49508941delA	32	33	1
c.2491_2494delTTAA	p.Leu831Ilefs*82	g.49508757_49508760delTTAA	35	6, 8, 15, 78	4
c.2495_2499delATAAA	p.Asn832Serfs*4	g.49508752_49508756delTTTAT	35	61	1
c.2496_2499delTAAA	p.Asn832Lysfs*81	g.49508752_49508755delTTTA	35	1, 14, 19, 24, 30, 32, 35, 40, 67, 72	10
c.2808delC	p.Tyr936*	g.49508443delG	16.42	7	1
c.3047dupA	p.Ala1017Glyfs*6	g.49508204dupT	35	37	1
c.3069_3072delAGAG	p.Arg1023Serfs*3	g.49508179_49508182delCTCT	35	43	1
c.3170T>A	p.Leu1057*	g.49508081A>T	47	22	1

* CADD score is Phred-scaled

Table S3. Growth in individuals with Helsmoortel-Van der Aa syndrome

Growth													
	Mean		**Mean z-score**		**z-score < -2 (%)**			**z-score > +2 (%)**			**Number of patients**		
	F	**M**	**F**	**M**	**F**	**M**	**Total**	**F**	**M**	**Total**	**F**	**M**	**Total**
Birth weight (g)	2965.8	3155.5	-0.3	0.4	10.0%	6.1%	7.9%	0.0%	9.1%	4.8%	30	33	63
Birth length (cm)	48.9	49.5	-0.2	0.3	12.5%	0.0%	6.3%	0.0%	0.0%	0.0%	24	24	48
Birth OFC (cm)	34.7	34.5	0.5	0.1	12.5%	0.0%	6.5%	0.0%	0.0%	0.0%	16	15	31
Weight at last observation	NA	NA	0.4	0.7	0.0%	5.9%	3.2%	10.3%	5.9%	7.9%	29	34	63
Length at last observation	NA	NA	-0.4	-0.8	22.6%	23.7%	23.2%	0.0%	2.6%	1.4%	31	38	69
OFC at last observation	NA	NA	-0.4	-0.3	10.7%	5.9%	8.1%	0.0%	0.0%	0.0%	28	34	62

Growth parameters at birth and at last observation. OFC = Occipital Frontal Circumference; F = Female; M = Male

Table S4. Facial features of the reported individuals with mutation in the *ADNP* gene

Facial feature	Frequency	Total
Thin upper vermillion	70.3%	45/64
Prominent forehead	65.6%	42/64
Wide nasal bridge	50.0%	33/66
High hairline	50.0%	33/66
Short nose	49.2%	31/63
Malformed ears	48.5%	32/66
Upturned nasal tip	46.7%	28/60
Everted lower lip	45.5%	25/55
Long philtrum	39.3%	22/56
Thick lower vermillion	36.4%	20/55
Downward slant palpebral fissures	33.3%	20/60
Widely spaced teeth	34.6%	18/52
Broad nasal base	29.6%	16/54
Broad nasal tip	26.3%	15/57
Teeth problems	24.5%	13/53
Narrow palpebral fissures	24.1%	14/58
Large mouth	23.2%	13/56
Low nasal bridge	20.6%	13/63
Eversion/notch eyelid	19.0%	12/63
thick eyebrows	18.3%	11/60
Coarse face	16.9%	11/65
Prominent eyelashes	16.7%	10/60
Broad philtrum	16.1%	9/56
Low-set or posteriorly rotated ears	14.7%	10/68
Abnormal hair thickness	14.0%	8/57
Sagging periorbital skin	13.6%	8/59
Small ears	11.6%	8/69
Thick alae nasi	11.3%	6/53

Supplemental Figures

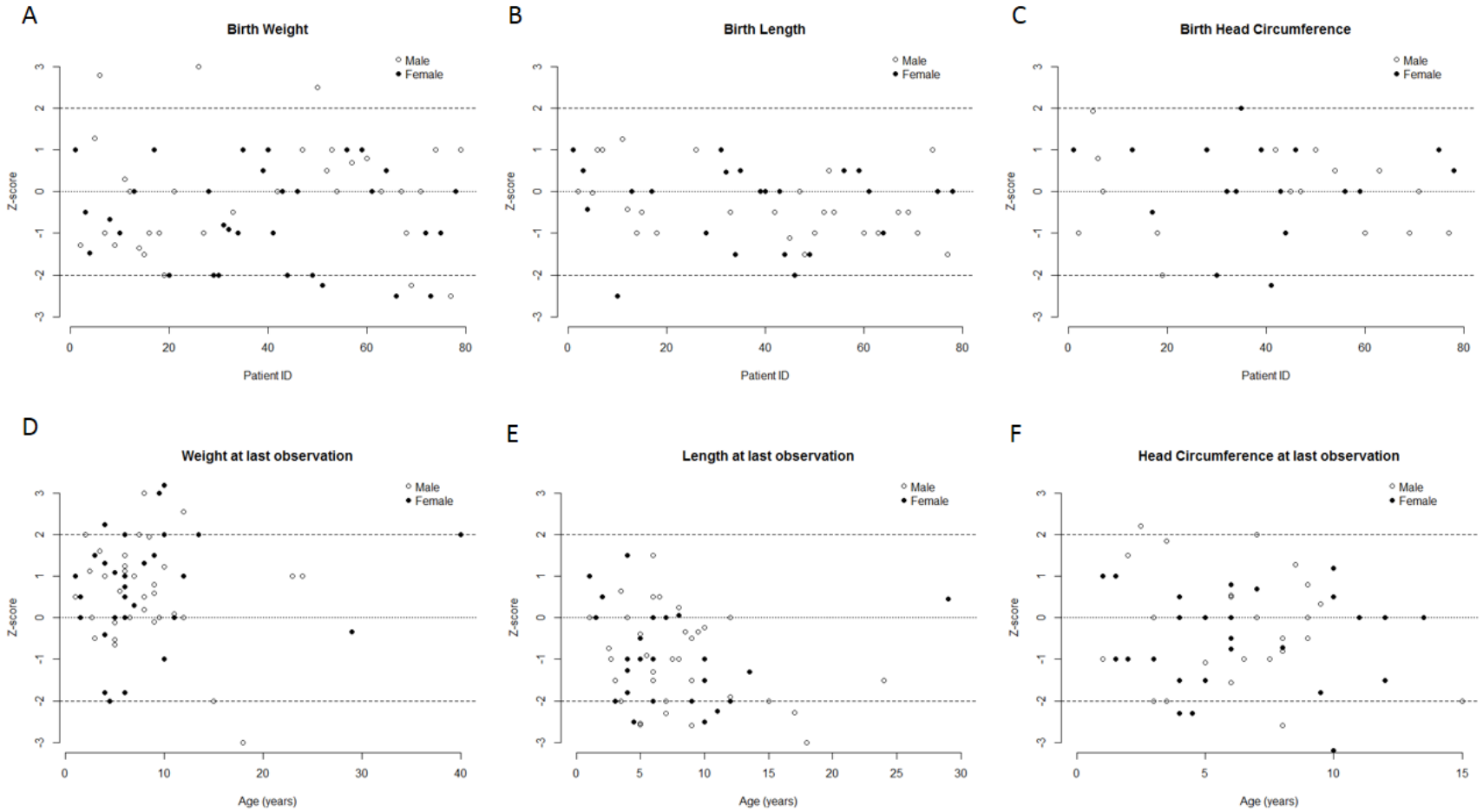

Figure S1. Growth in individuals with Helsmoortel-Van der Aa syndrome

Growth z-scores for height, weight and head circumference in male and female individuals at birth (A-C) and at last observation (D-F).

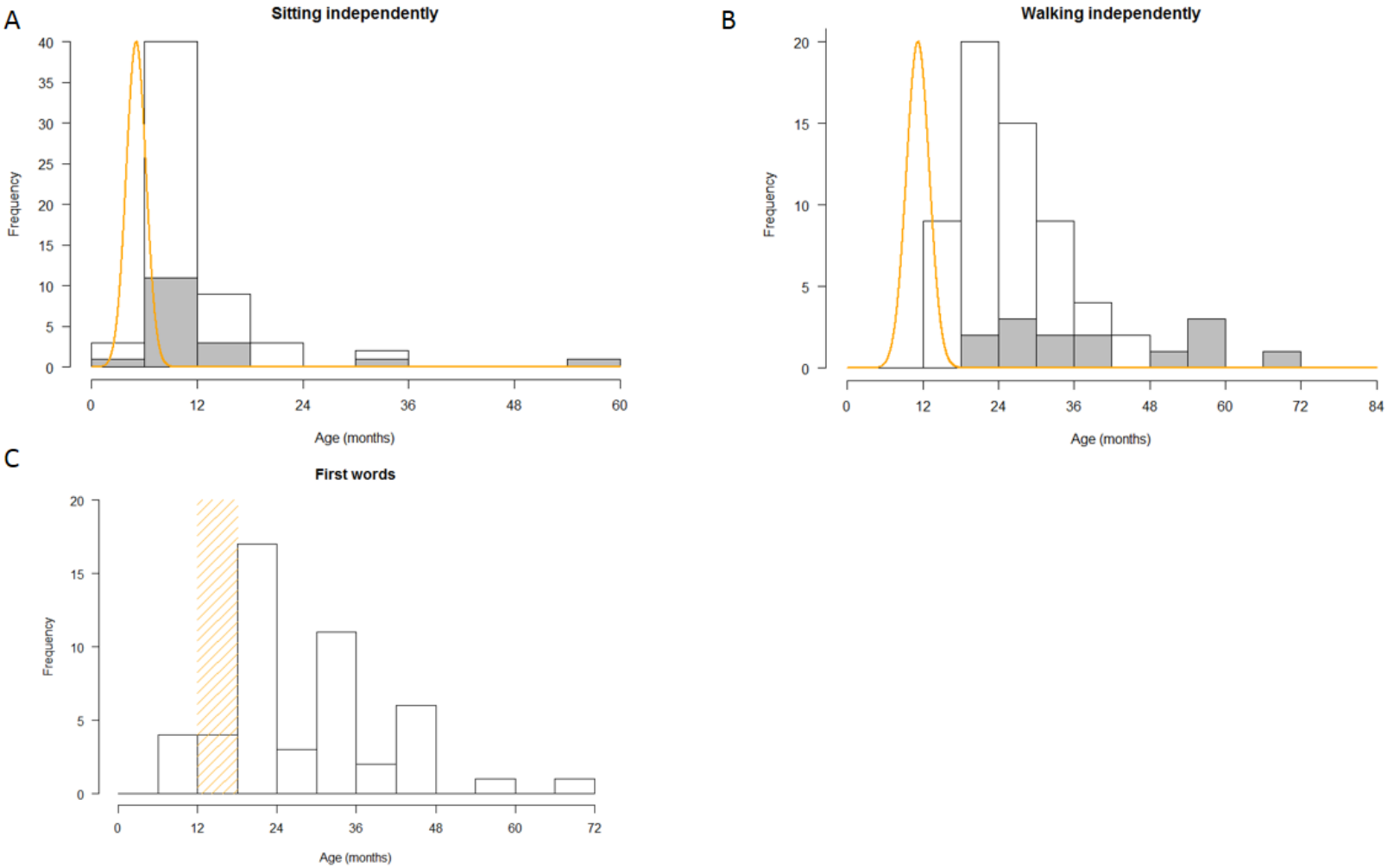

Figure S2. Developmental milestones

(A) Sitting independently. In orange: WHO reference cohort[1]. Grey area: Individuals with p.Tyr719* mutation; (B) Walking independently. In orange: WHO reference cohort[1]. Grey area: Individuals with p.Tyr719* mutation; (C) First words. Shaded area: Typically developing children.

[1] The WHO Child Growth Standards. 2017. http://www.who.int/childgrowth/.