Clinical Insights and Emerging Therapeutic Perspectives in Helsmoortel-Van der Aa syndrome

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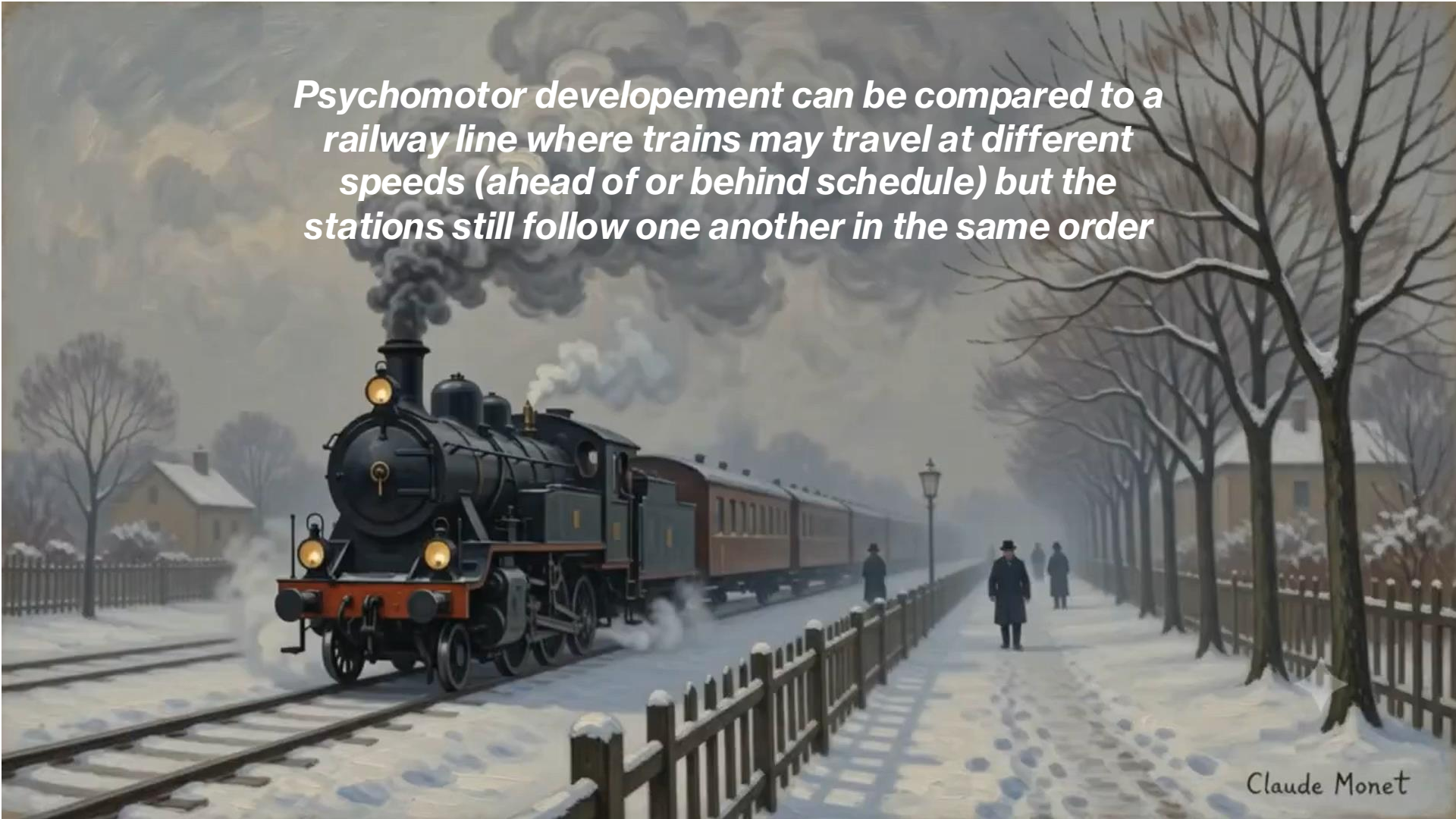
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ADNP

is a rare neurodevelopmental disorder




Psychomotor developement can be compared to a railway line where trains may travel at different speeds (ahead of or behind schedule) but the stations still follow one another in the same order
Claude Monet

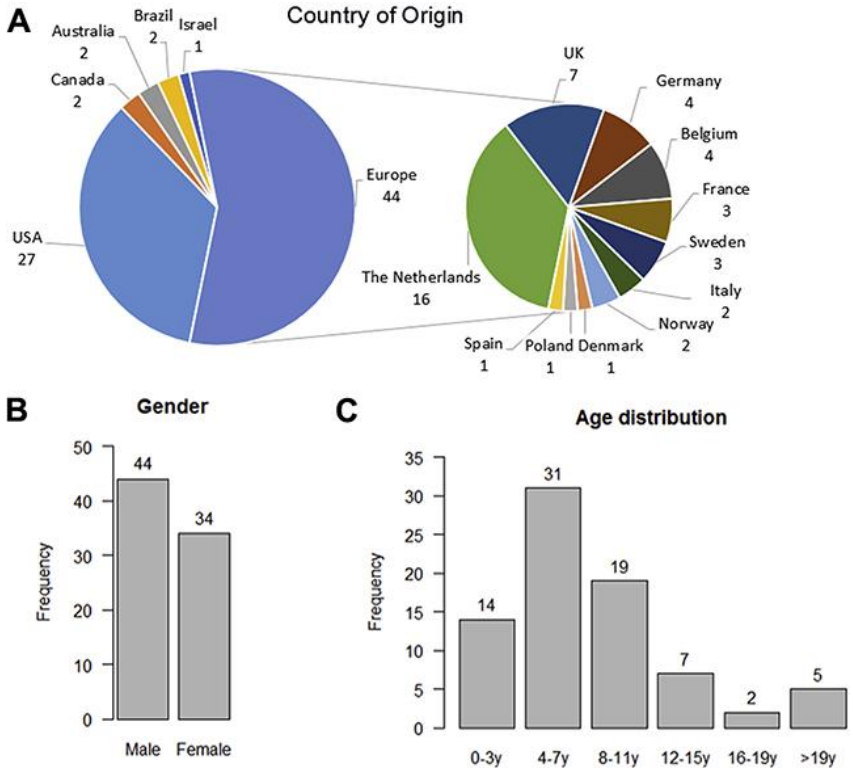
ultra-RARE DISEASE

1 child/27,000
in the United States and Europe Worldwide

Approximately 45 patients have been diagnosed with ADNP syndrome in Italy.

The age distribution is skewed toward the developmental age, as affected adults who remain undiagnosed or were born before 2014 elude epidemiological analysis

The clinical incidence of the syndrome is **identical between sexes** (1:1), but the genetic mutation operates through distinct, sex-specific molecular pathways, (selectively impairing the unfolded protein response (UPR) in males and mitochondrial function/mt-ATP6 in females)



ADNP Kids Research Foundation

FUTURE OUTLOOK

In recent years there has been growing interest in the genetics of ADNP syndrome and the **phenotypic traits of intellectual and motor disability** due to their significant impact on patients' quality of life (QoL)

Awareness of the disability's impact has increased alongside growing confidence in preclinical studies of NAP (Davunetide) to correct cellular defects caused by ADNP deficiency in both sexes

However, access to **rehabilitative interventions** is becoming less frequent and the effectiveness of these therapies remains unclear given the rarity of the disease



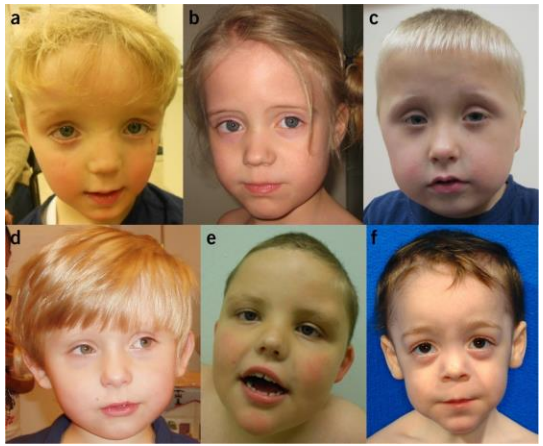
ADNP-RELATED HELSMOORTEL-VAN DER AA SYNDROME

- *De novo* variants in the Activity-Dependent Neuroprotective Protein (ADNP) cause syndromic autism-intellectual disability, termed Helsmoortel-Van der Aa syndrome (OMIM 615873)

nature genetics

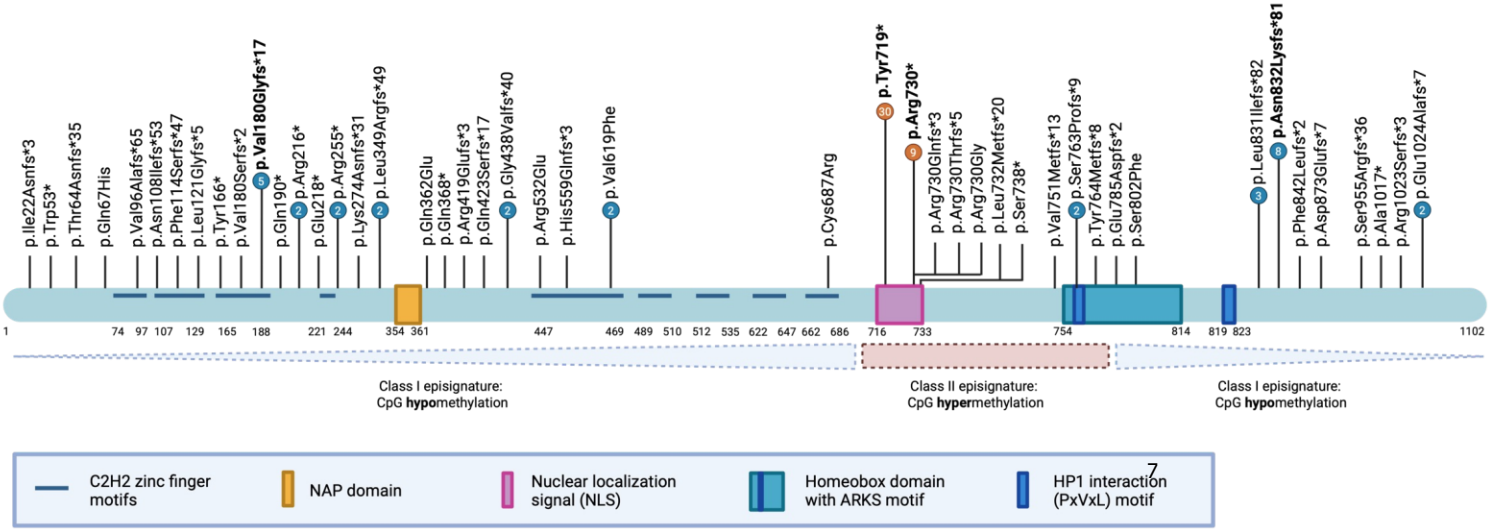
A SWI/SNF-related autism syndrome caused by *de novo* mutations in *ADNP*

Céline Helsmoortel[1], Anneke T Vulto-van Silfhout[2,16], Bradley P Coe[3,4,16], Geert Vandeweyer[1,5], Liesbeth Rooms[1], Jenneke van den Ende[6], Janneke H M Schuurs-Hoeijmakers[2], Carlo L Marcelis[2], Marjolein H Willemsen[2], Lisenka E L M Vissers[2], Helger G Yntema[2], Madhura Bakshi[7], Meredith Wilson[8], Kali T Witherspoon[3,4], Helena Malmgren[9], Ann Nordgren[9], Göran Annerén[10], Marco Fichera[11,12], Paolo Bosco[13], Corrado Romano[14], Bert B A de Vries[2,15], Tjitske Kleefstra[2,15], R Frank Kooy[1], Evan E Eichler[3,4] & Nathalie Van der Aa[1,6]



Helsmoortel et al. 2014 Nature Genetics

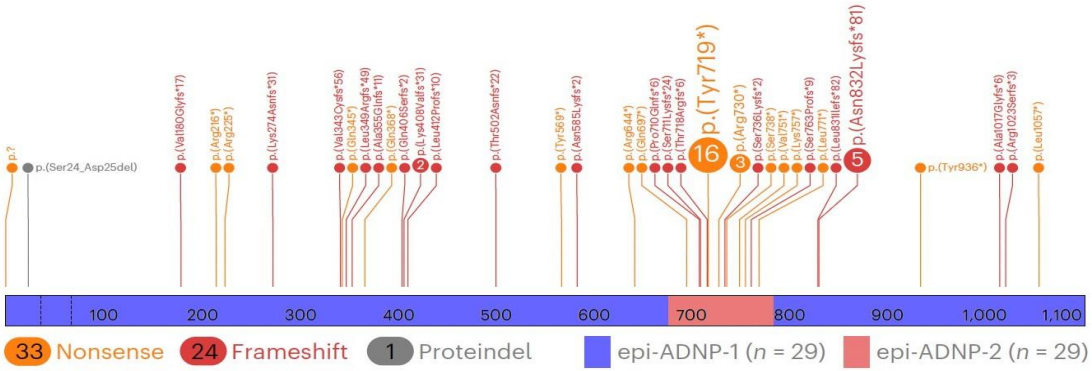
MAPPING OF REPORTED ADNP VARIANTS IN 105 INDIVIDUALS

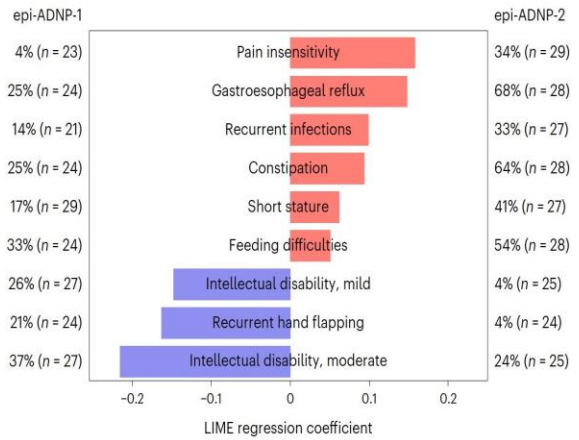


locus 20q13.13

GENOTYPE-PHENOTYPE CORRELATION FOLLOWING DISCOVERY OF DUAL METHYLATION PATTERNS

- Variants located in N- or C-terminal of *ADNP* → **Genome-wide hypo**methylation
  - Less severe clinical picture in general
- Variants located at the center of *ADNP* → **Genome-wide hyper**methylation
  - More severe clinical picture in general



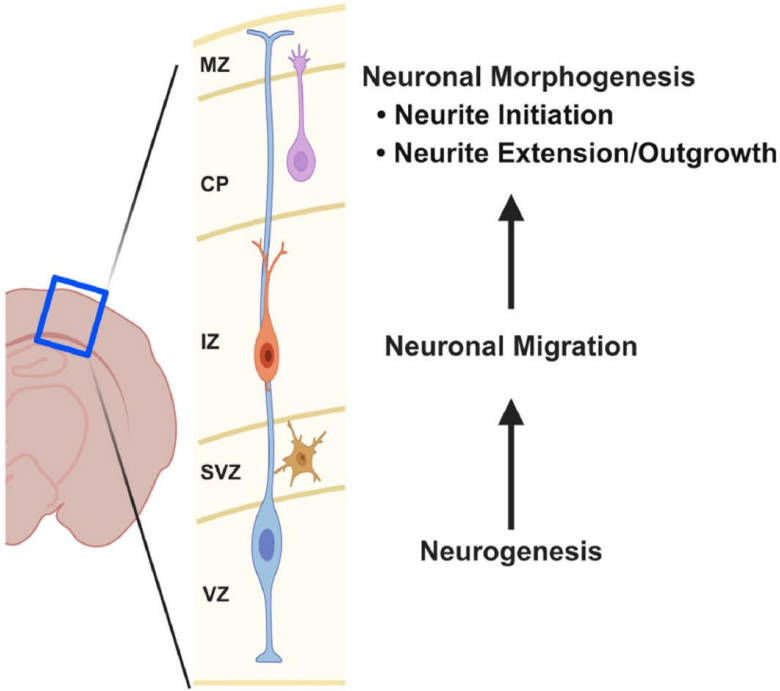


The most frequent mutations are STOP-GAIN and FRAMESHIFT mutations, which produce a truncated protein that doesn't interact with the SWI/SNF complex responsible for chromatin remodeling

Dingemans et al., 2023

ADNP GENE (ACTIVITY-DEPENDENT NEUROPROTECTIVE PROTEIN) :

encodes a putative transcription factor with differential interactions with proteins involved in chromatin remodeling.
It is essential for the neocortical neurogenesis and contributes to neuronal differentiation



Stage-specific ADNP Functions

ADNP in Neuronal Morphogenesis
- Neurite Initiation
  - Cytoplasmic ADNP is required to initiate neurite initiation
  - Knockdown accelerates neurite initiation
- Neurite Extension/Outgrowth
  - NAP accelerates neurite outgrowth
  - ADNP loss increases axon length

ADNP in Neuronal Migration
- Knockdown did not cause issues
- ADNP might be involved in neuronal migration by regulating MT dynamics and stabilization by binding to EB1/EB3 and Tau.

ADNP in Neurogenesis
- ADNP loss causes neural tube defects, resulting in embryonic lethal.
- ChAHP complex regulates gene expression

It is still unclear how specific ADNP mutations differentially affect nuclear and cytoplasmic functions and **whether transcriptional** and **cytoskeletal dysregulation** is the primary cause of ADNP syndrome phenotypes

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

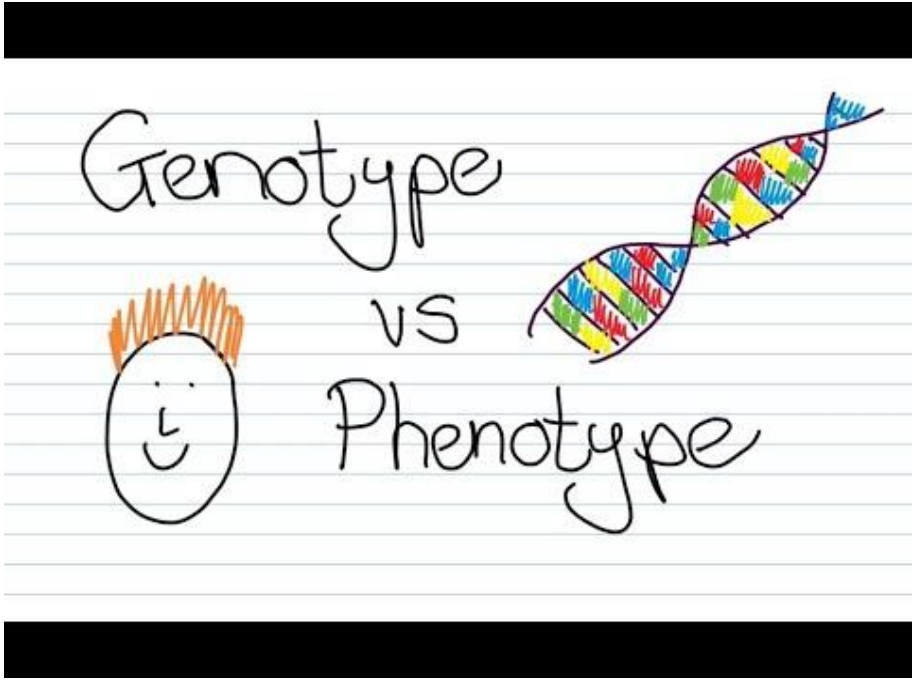
Van Dijck et al. 2019 Biological Psychiatry

- Intellectual disability (mild to severe) **100%**
- Language delay (mixed receptive-expressive and oral language) **98.6%**
- Motor delay and gross and fine motor impairment **95.8%**
- Autism spectrum disorder **92.8%**
- Hypotonia **78.3%**
- Sensory processing disorder **91%**
- Attention-deficit/hyperactivity disorder **43.9%**
- Obsessive-compulsive disorder **77%**
- Visual disorders (CVI, strabismus, myopia, astigmatism) **74%**
- Epilepsy **16.2%**





Phenotypic spectrum continues to expand → HVDAS = continuum of neurodevelopmental and systemic features

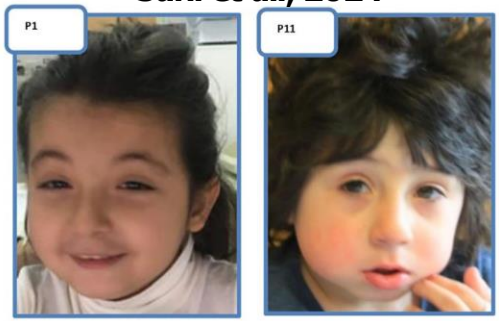


Emerging diagnostic approaches: methylation patterns & AI-based facial phenotyping

UNDER REPORTED/ UNDER COVERED CLINICAL FEATURES

- Blepharophimosis (n = 5/5)
  - Narrow opening of the eye

Sarli et al., 2024



- Hypertelorism (n = 5/6)
  - Increased distance between the eyes



Pascolini et al., 2024

Activity-Dependent Neuroprotective Protein (ADNP): An Overview of Its Role in the Eye

International Journal of Molecular Sciences, 2022

- In ADNP the combination of strabismus and CVI deeply impairs spatial awareness, leading directly to an unstable, wide-based gait
- We cannot fix the walk without treating the sight – a combined neuro-visual and physical therapy is mandatory
- ***Visual correction must precede or run parallel to gait training***





MUSCULOSKELETAL ABNORMALITIES

54.9%

Hand and foot digit abnormalities include:

- Fetal fingertip pads, clinodactyly
- Small fifth finger,
- Brachydactyly, single palmar crease
- Flat foot
- Long or broad great toes
- Syndactyly of the second and third toes
- Nail hypoplasia

- Scoliosis
- Pectus excavatum
- Pectus carinatum
- Combined excavatum/carinatum deformity

MUSCULOSKELETAL ABNORMALITIES AND GAIT IMPAIRMENTS

50%-75%







Mean age of independent gait acquisition is 30 months, varying by specific ADNP mutation

Van Dijck 2019

Costa-Bertani angle



Costa-Bertani angle (R: 135°, L: 151°)







Hypometria of the 4th metatarsals and left 3rd metatarsal
Hypermetria of the 1st and 2nd phalanges.
Bilateral MTP valgus of the 1st and 2nd rays.
Bilateral 5th digit clinodactyly

SCOLIOSIS

17,2%

The clinical symptoms of ADNP syndrome show partial overlap with other genetic syndromes that include developmental delay and autism spectrum disorders, such as Prader-Willi syndrome

High Prevalence of Scoliosis in a Large Cohort of Patients with Prader-Willi Syndrome
Armando M. J Clin Med March 2022

















It is an irregular spinal curvature caused by disorders of the brain, spinal cord, and muscular system; it is associated with pelvic obliquity and with kyphosis; it reduces capacity for trunk motor control; it compromises postural stability, sitting balance and ambulation. The deformity continues after skeletal maturity

Helsmoortel-Van der Aa syndrome [OMIM] 615873

The clinical symptoms of Helsmoortel-Van der Aa syndrome partially overlap with other genetic syndromes that include developmental delay and autism spectrum disorders, such as **Angelman**, **Prader-Willi**, **Kleefstra**, **Smith-Magenis** or **Rett syndrome**







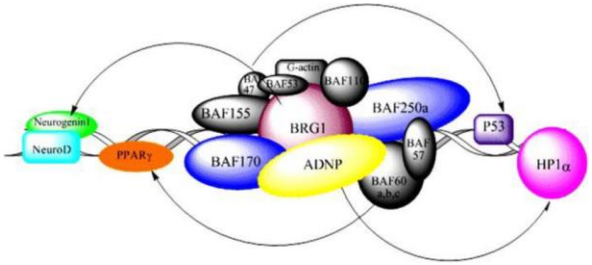
HYPOTONIA

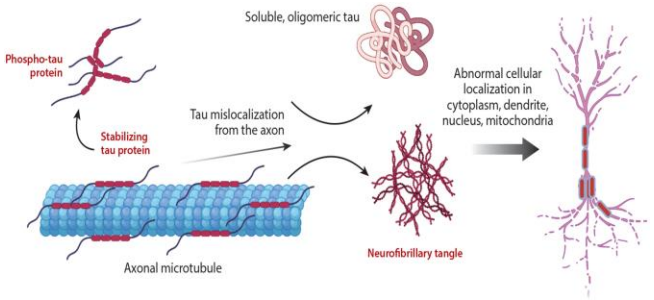
78,3%

Hypotonia in ADNP

Hypotonia is a neurological disorder of central origin, not a primary muscular defect.

- De novo mutations lead to ADNP haploinsufficiency that disrupts chromatin accessibility, destabilizes the neuronal cytoskeleton by impairing microtubule regulation.





- ADNP protein deficiency compromises Tau interaction and synaptic plasticity.
- These molecular defects combined with delayed myelinitation compromise central motor pathways manifesting as the generalized hypotonia that delays early postural milestones







Motor problems are poorly explored and their potential effect on gait and the resulting mobility problems, activity limitations and participation restrictions are not well understood

(Dravet 2011, Gozes 2012, Van Dijck 2019)



Investigation of Gait Characteristics and Kinematic Deviations in Rare Genetic Disorders with Instrumented Gait Analysis

J Intellect Disabil Res. 2025, Esra Kinaci Biber et al

37 patients aged 16–22 (Dravet syndrome, Down syndrome and Tuberous Sclerosis, including 12 ADNP)
Conclusions: in ADNP walking at lower speed with reduced step length and greater step angle width is due to biomechanical impairment

Open questions
Gait abnormalities depend on:

Responsible genetic defect?

Each gene encodes proteins that determine functional deficits in a specific cellular pathway, including channelopathies, transport disorders, synaptopathies associated with the onset of movement disorders (Papandreou 2020, Erro 2017)

General developmental delay?

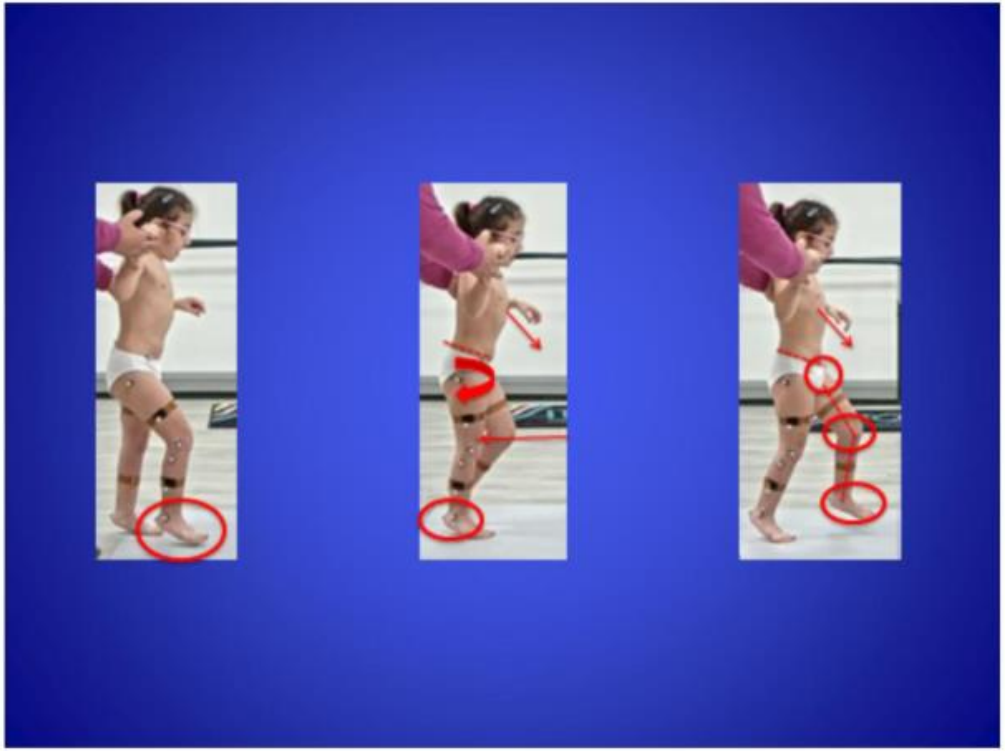
The syndrome is characterized by intellectual disability and behavioral alterations that could influence gait (O'Keefe 2018)

Epilepsy

Has a significant impact on motor developmental outcomes (Kadish 202, Milh 2023)

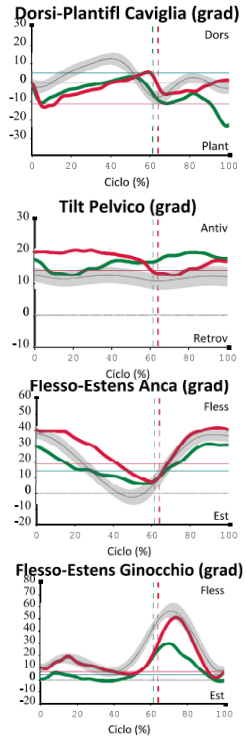
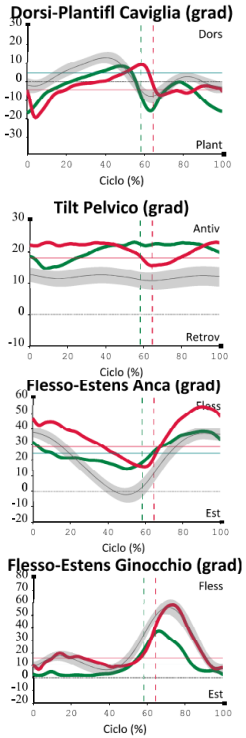
Gait abnormalities in ADNP

- Motor planning deficits & wobbliness
- Lower speed
- Reduced step length
- Greater step angle width



S.C. date of birth 09.10.2014

2 gait analyses 2 years apart

8 Years	10 Years
	

Significant Differences:

"Loss" of the first rocker, limited to the right side

Better swing-phase kinematics (the foot drops less in the first phase of swing)

Minor differences:

Slight increase in pelvic anteversion

Increased left hip flexion

Slight increase in right knee hyperextension during stance phase

8 Years



10 Years



TRANSLATIONAL MEDICINE

ADNP syndrome is a great example of **translational medicine** that converts experimental laboratory data into concrete clinical applications and brings clinical observations back into the research environment to refine therapies for the neurological and behavioral symptoms



CURRENT KNOWLEDGE

Novel ADNP syndrome Mice Reveal Dramatic Sex-specific Peripheral Gene Expression with brain and Tau pathologies (Biol Psychiatry 2022. Karmon G, Gozes I. et al)

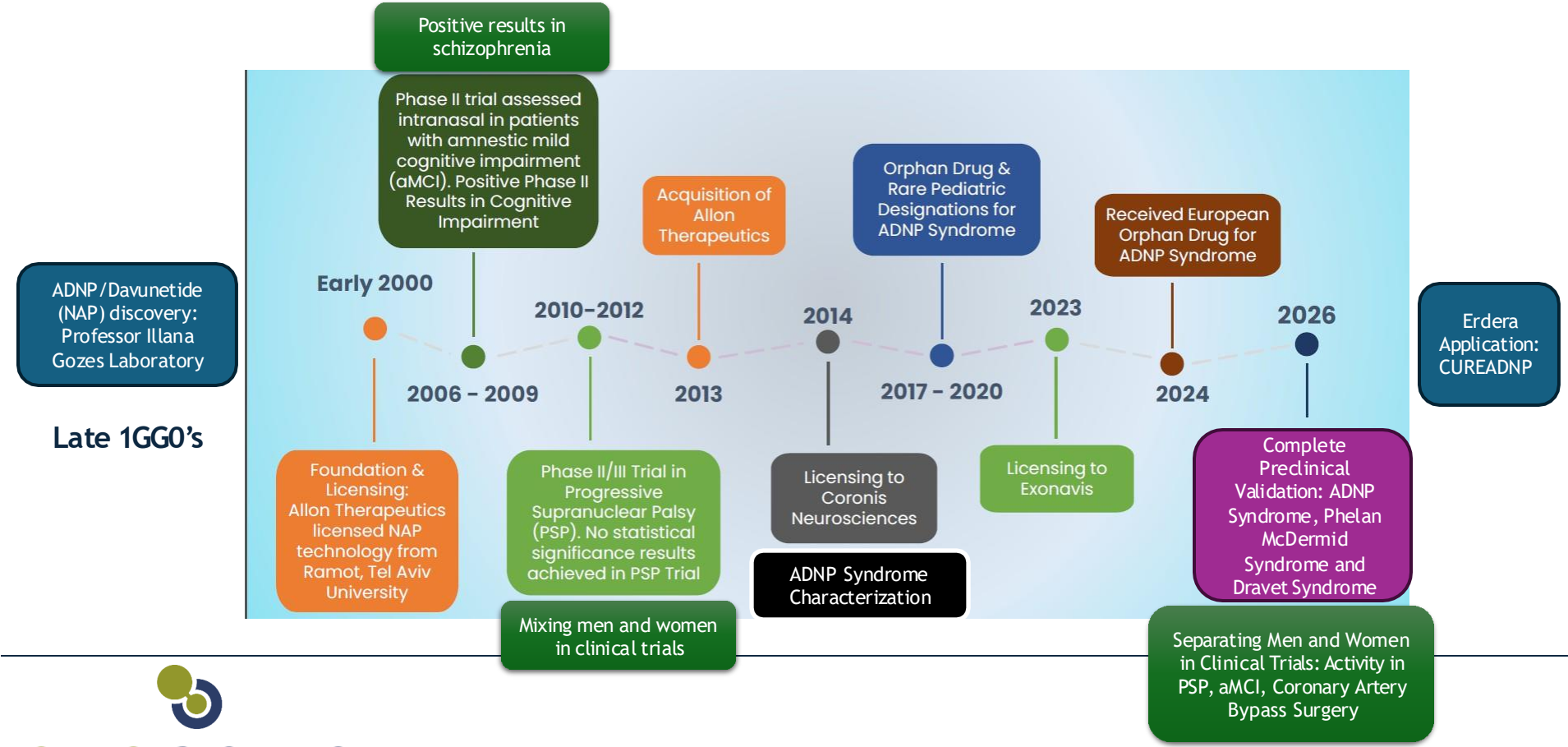
Activity-dependent neuroprotective protein deficiency models synaptic and developmental phenotypes of autism-like syndrome (Clin Invest 2028. Hacohen-Kleiman G , Gozes I et al)

Single Cell ADNP Predictive of Human Muscle Disorders: mouse Knockdown Results in Muscle wasting (Cells 2020. Kapitansky O , Gozes I. et al)

- Phenotypically Tyr mice is similar to patients with ADNP syndrome and exhibited delayed development coupled with sex-dependent gait defects.
- The ADNP protein is essential for human muscle development and holds predictive value for various myopathies.
- Early-onset tauopathy was accentuated in males mimicking humans, and was paralleled by impaired visual evoked potentials.
- All the researches demonstrate that early treatment with the NAP peptide is capable of partially mitigating these synaptic and behavioral alterations emerging as a promising therapeutic candidate.



Davunetide (NAP) Timeline of Development



exonavis

An important recent observation is that sex differences may influence the response to treatment

Davunetide (NAP) Clinical Activity

Study	Davunetide effect	Takeaway
CABG	♀ Neuroprotection ♂ Cognitive protection	Sex-dependent exposure with neuroprotective Benefits in women and neurocognitive benefit in men
aMCI	♂♀ Visual memory ♀ Attention & verbal memory	Cognitive benefit, more comprehensive in women
PSP	♀ Slower deterioration	Protection in women only

The sex in an important factor when evaluating Davunetide efficacy. When the data were analysed according to sex stronger effects were observed in women in some settings including PSP, prodromal Alzheimer's desease and TAU related desease

exonavis

Most importantly, davunetide safety demonstrated in over 560 adults (11 trials).
Protection of activities of daily living and brain conservation was shown in independent clinical trials:

Effect of the neuroprotective peptide **davunetide** (AL-108) on cognition and functional capacity in schizophrenia.
Javitt et al., Schizophr Res. 2012 Apr;136(1-3):25-31. doi: 10.1016/j.schres.2011.11.001. Epub 2011 Dec 12. PMID: 22169248 Clinical Trial.
Effects of **davunetide** on N-acetylaspartate and choline in dorsolateral prefrontal cortex in patients with schizophrenia.
Jarskog LF et all., Neuropsychopharmacology. 2013 Jun;38(7):1245-52. doi: 10.1038/npp.2013.23. Epub 2013 Jan 16. PMID: 23325325 **Free PMC article.** Clinical Trial.

When analyzing the clinical results by separating men and women, brain protection coupled to cognitive/activities of daily living was further enhanced:

Unexpected gender differences in progressive supranuclear palsy reveal efficacy for davunetide in women.
Gozes I, Shapira G, Lobyntseva A, Shomron N. Transl Psychiatry. 2023 Oct 16;13(1):319. doi: 10.1038/s41398-023-02618-9. PMID: 37845254 **Free PMC article.**
Davunetide sex-dependently boosts memory in prodromal Alzheimer's disease.
Gozes I, Blatt J, Lobyntseva A. Transl Psychiatry. 2024 Oct 2;14(1):412. doi: 10.1038/s41398-024-03118-0. PMID: 39358355 **Free PMC article.** Clinical Trial.
Systemic davunetide provides sex-specific neuroprotection during Coronary Artery Bypass Grafting (CABG).
Gozes I, Blatt J, Guz LS. Transl Psychiatry. 2025 Oct 31;15(1):454. doi: 10.1038/s41398-025-03675-y. PMID: 41173865 **Free PMC article.** Clinical Trial.
Opposite molecular sex correlations in tauopathy paralleled by motor and cognitive efficacy of davunetide in women.
Shapira G, Blatt J, Guz LS, Shomron N, Gozes I. Mol Psychiatry. 2026 Jul 3. doi: 10.1038/s41380-026-03709-x. Online ahead of print. PMID: 42399413

Davunetide Ameliorate Sex-Dependent Deficits Across Mouse Models

	Assessment	Model	Untreated phenotype	NAP effect
Motor	Hanging wire	*Adnp*$^{+/-}$	♂ disrupted	^ ameliorated
	Grip strength	*Adnp*$^{+/-}$	♂ disrupted	^ ameliorated
	Gait	p.Tyr718*	♀ gait abnormalities	^ ameliorated
Memory	Object recognition	*Adnp*$^{+/-}$	♂ ♀ disrupted	^ ameliorated
Social	Social memory	*Adnp*$^{+/-}$	♂ ♀ disrupted	^ ameliorated
	Social recognition	*Adnp*$^{+/-}$	♀ disrupted	^ ameliorated
	Odor discrimination	*Adnp*$^{+/-}$	♀ disrupted	^ ameliorated
Sensory	Visual evoked potentials	p.Tyr718*	♂ impairment	^ ameliorated

Female-predominant social/olfactory deficits

Male-predominant motor impairment

Davunetide-mediated improvement

Dramatic sex differences leading to different brain disease presentation: The requirement for sex-specific medications with ADNP/davunetide as a case study. *Front Neuroendocrinol. 202c Aug 10:101274. doi: 10.101c/j.yfrne.202c.101274. Online ahead of print. PMID: 42575342*

Activity-dependent neuroprotective protein deficiency models synaptic and developmental phenotypes of autism-like syndrome. Hacohen-Kleiman G, Sragovich S, Karmon G, Gao AYL, Grigg I, Pasmanik-Chor M, Le A, Korenková V, McKinney RA, Gozes I. J Clin Invest. 2018 Nov 1;128(11):4656-4666.

Novel ADNP Syndrome Mice Reveal Dramatic Sex-Specific Peripheral Gene Expression With Brain Synaptic and Tau Pathologies. Karmon G, Sragovich S, Hacohen-Kleiman G, Ben-Horin-Hazak I, Kasparek P, Schuster B, Sedlacek R, Pasmanik-Chor M, Theotokis P, Touloumi O, Zoidou S, Huang L, Wu PY, Shi R, Kapitansky O, Lobyntseva A, Giladi E, Shapira G, Shomron N, Bereswill S, Heimesaat MM, Grigoriadis N, McKinney RA, Rubinstein M, **Gozes I.** Biol Psychiatry. 2022 Jul 1;92(1):81-95.

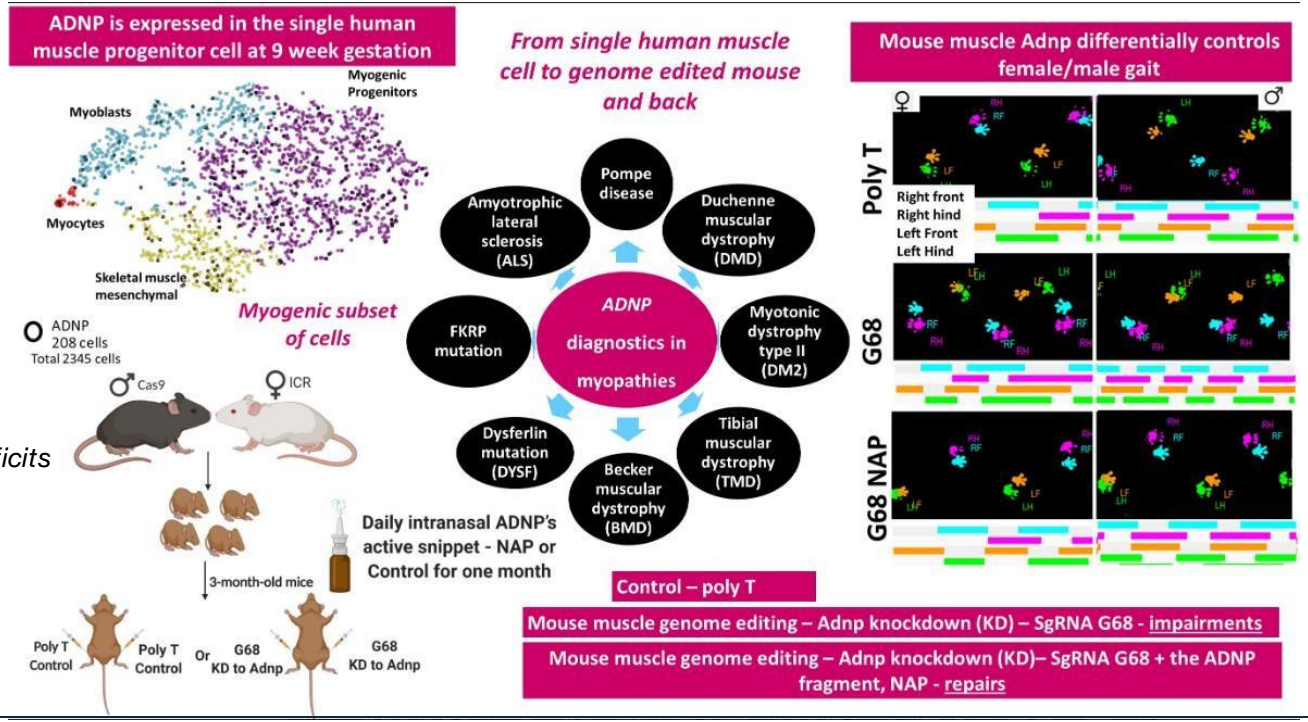
EDITORIAL: Sex and the Brain: Novel ADNP Syndrome Mice Are Protected by NAP **Amal H.** Biol Psychiatry. 2022 Jul 1;92(1):8-9.



Sex – Dependent Muscle Adnp-Deficient Mouse: Corrected by Davunetide (NAP)

ADNP is essential form muscle development and its deficiency causes myopathy and atrophy Making it a predictive biomarker for several human muscles diseases

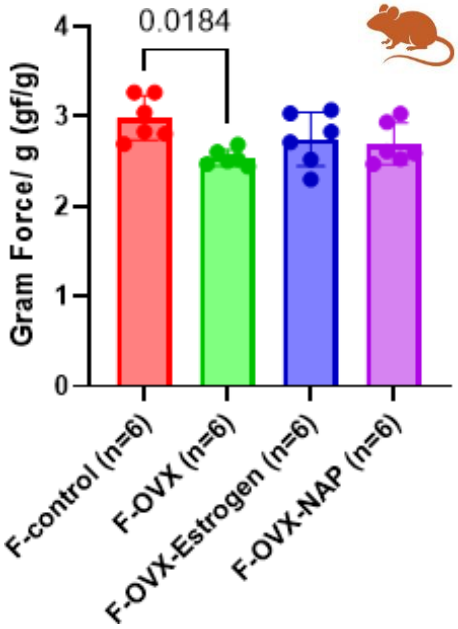
Treatment with Davunetide was able to ameliorate some of these sex-dependent deficits



Single Cell ADNP Predictive of Human Muscle Disorders: Mouse Knockdown Results in Muscle Wasting. Kapitansky O, Karmon G, Sragovich S, Hadar A, Shahoha M, Jaljuli I, Bikovski L, Giladi E, Palovics R, Iram T, Gozes I.Cells. 2020 Oct 19;9(10):2320

Age and Sex-Dependent ADNP Regulation of Muscle Gene Expression Is Correlated with Motor Behavior: Possible Feedback Mechanism with PACAP. Kapitansky O, Sragovich S, Jaljuli I, Hadar A, Giladi E, Gozes I.Int JMol Sci. 2020 Sep 14;21(18):6715. doi: 10.3390/ijms21186715.

Davunetide (NAP) Provides Estrogen Replacement in Mice (it prevents musculoskeletal abnormalities and preserves Grip Strength) & Protects Motor Function in Women Suffering from Progressive Supranuclear Palsy



F-OVX = Ovariectomized females

Sex hormones and sex dependent molecular pathways may influence disease progression and response to Davunetide

Protection by Davunetide in Women and Increasing Effects on the FDA-Recommended Progressive Supranuclear Palsy Rating Scale - PSPRS-10 Individual Outcome Measures

Top PSPRS test statistics for sexXTreatment interaction in week 52

Iten	stat	P
PSPRS-10: Usin knife and fork, b..	-3.255	0.001
Usin knife and fork, buttonin .	-2. 32	0.004
Voluntary left and ri htsaccades	-2.851	0.005
Urinary incontinence	-2.802	0.00
PSPRS-10_S	-2.5 2	0.01
Neck ri idity or dyston	-2.537	0.012
Bradyphrenia	-2.37	0.01G
Disorientation	-2.312	0.022
PSPRS-10: Postural stability (on...	-1.G1	0.058

The table shows top PSPRS test statistics for sexXTreatment interaction in week 52, PSPRS-10: Using knife and fork, b... = knife and fork use, buttoning clothes, washing hands and face; and PSPRS-10: Postural stability on... (backward pull) refers to data re-calculation using only PSPRS-10 (P<0.058) items.

Activity-dependent neuroprotective protein (ADNP) derived peptide NAP prevents musculoskeletal abnormalities in ovariectomized mice. Guz LS, Galushkin A, Gozes I.Front Neurosci. 202c Jul 28;20:18S1428. doi: 10.338S/fnins.202c.18S1428. eCollection 202c.PMID: 42582414

Opposite molecular sex correlations in tauopathy paralleled by motor and cognitive efficacy of davunetide in women. Shapira G, Blatt J, Guz LS, Shomron N, Gozes I.Mol Psychiatry. 202c Jul 3. doi: 10.1038/s41380-02c-0370S-x. PMID: 423SS413

ADNP syndrome is a multisystem disorder that requires a coordinated team of medical specialists and developmental therapists

✓Holistic care pathway

✓In according to ICF-CY
(International Classification of Functioning, disability and Heath for children and Youth)

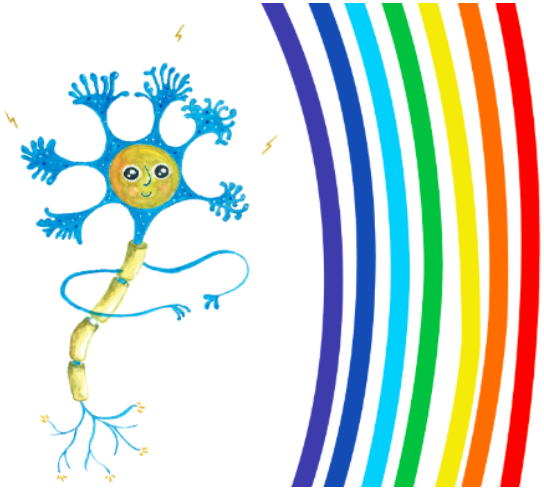
✓Early treatment



Multisystem Management & Building Your Child's Care Team. *Paediatrics June 2026*

In the future of ADNP Syndrome, genetics meets neurorehabilitation: tomorrow's challenge lies in integrating targeted molecular therapies
with early and intensive rehabilitative protocols

Within this framework, the systematic use of gait analysis becomes essential to objectively quantify gait abnormalities and customize intervention patterns



Only by bridging scientific research with precision neuro-motor strategies we can maximize brain plasticity and ensure the highest possible autonomy for our patients

Davunetide thus marks the crucial transition from genetic discovery to therapeutic reality, offering for the first time a concrete path to treat the biological cause of ADNP syndrome and improve patients' lives