



Research in Ataxia: SP15 and Cerebral Palsy

Euro HSP and Ataxia Meeting, 23rd Aug 2025

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Short CV and disclosures

CV

- 1995, Medical Doctor, Kaunas Medical Academy in Lithuania
- 2006, Certified paediatrician, Denmark
- 2013, Certified neuropaediatrician
- 2015, PhD, Aarhus University
- 2020, Chair of CPOP, Cerebral Palsy Follow-Up Programme
- 2021-2025, Ass. clinical professor, Aarhus University
- 2025, Senior Consultant in Neuropaediatrics, Royal Hospital, Copenhagen

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- Elsass Foundation
- Aarhus University
- Central Denmark Region Research Foundation
- Augustinus Foundation
- Dagmar Marshalls Foundation
- Civil engineer Frode V. Nyegaard and wife's Foundation



Aarhus University Hospital

Ataxic cerebral palsy

- European project (FR, DE, SE, Spain, NO, DK, ...)
- Clinical study of 5-8 years old children
- SCPE register-study

Hereditary Spastic Paraplegia vs. Cerebral Palsy

- Should everyone with CP be re-examined to rule out HSP?

Melpida Gene Therapy

- Treatment of HSP (SPG50) at Copenhagen Royal Hospital

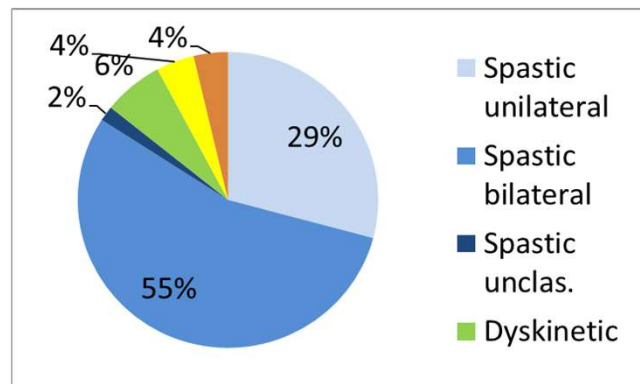
Ataxic cerebral palsy

Ataxic cerebral palsy

= early onset ataxia without progressive disease

1 of 550 children in Denmark has cerebral palsy, -> 100 children/ birth year

4% of CP is ataxic -> 4 children/birth year in DK





Ataxic cerebral palsy

European multicenter register study*

679 children with ataxic CP:

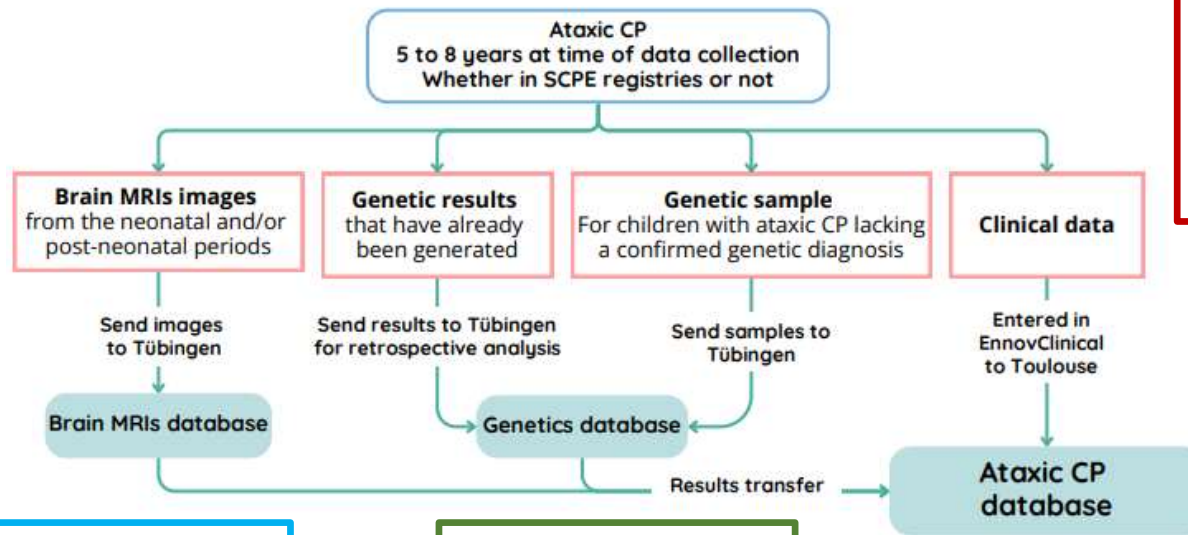
- 79% born at term vs. less than 50% in spastic CP
- 70% able to walk unaided
- 40% severe intellectual impairment
- brain imaging differs from other CP types
- only 9% had genetic syndromes in birth years 1980-2010

NEW multicenter study starts in 2025

** Horber V, Andersen GL, Arnaud C, et al. Prevalence, Clinical Features, Neuroimaging, and Genetic Findings in Children With Ataxic Cerebral Palsy in Europe. Neurology. 2023;101(24):e2509-e2521. doi:10.1212/WNL.0000000000207851*



ARTEMIS, clinical cohort



Aim: to collect detailed information about 50 children with ataxic CP

Aim: to improve classification of MRI findings in ataxic CP

Aim: to genetic diagnostics in ataxic CP

Hereditary Spastic Paraplegia vs. Cerebral Palsy

- Should everyone with CP be re-examined to rule out HSP?
- Should everyone with CP be re-examined to rule out spinocerebellar ataxia?
- Should everyone with CP be re-examined to rule out a genetic cause?

CP Mimics

HSP vs. CP



Cerebral Palsy is a group of disorders of movement and/or posture and of motor function, which are due to a non-progressive lesion or abnormality of the immature brain.

Brain injury is permanent and does not progress over time

SCPE, Surveillance of Cerebral Palsy in Europe

Cans et al., Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. Dev Med Child Neurol, 2000. 42: 816-824

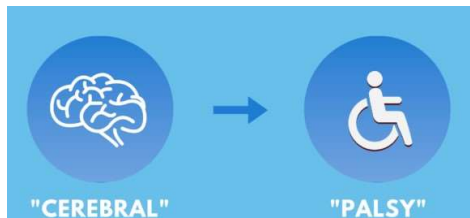
Brain imaging (MRI) is normal in 3-10% *

Impaired motor function

Clinical picture is changing due to development of the brain and child's growth

* Larsen ML et al. Continuing Decline in the Prevalence of Cerebral Palsy in Denmark for Birth Years 2008–2013. EPN journal 30 (2021): 155–161.

HSP vs. CP



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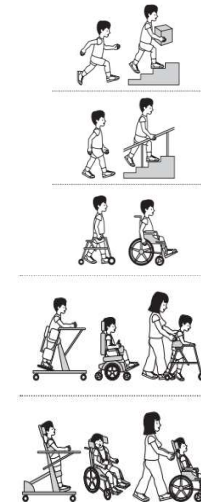
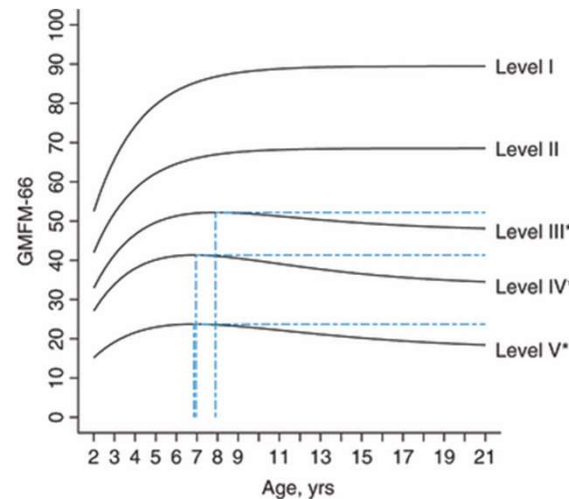
Clinical picture is changing due to development of the brain and child's growth

Changing clinical picture – is it CP Mimics?

HSP vs. CP

Gross Motor Function in 2-21-year-old children and adults with CP

GMFM-66
Gross Motor Function
Measurement by 66 items:
head control, , standing,
walking, jumping...

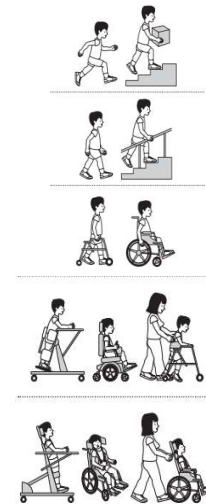
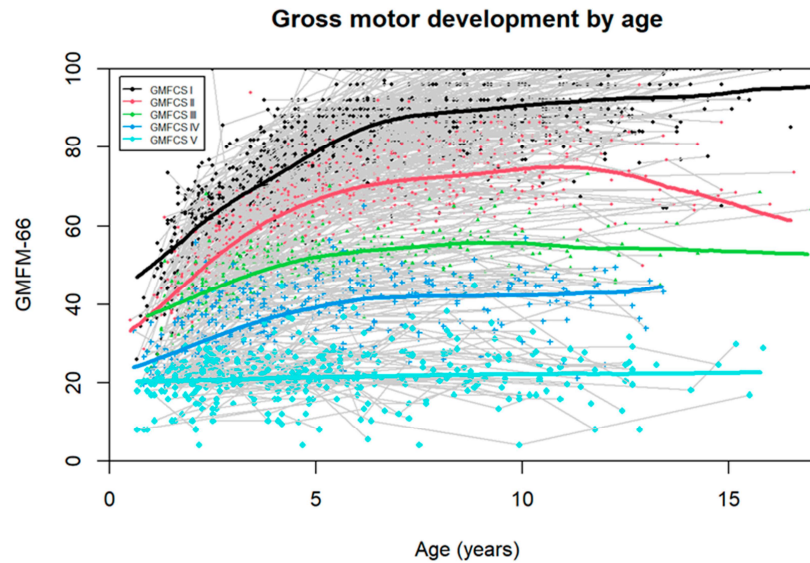


Healthy 5-year-old child will score 100 in GMFM-66

Palisano et al. Stability and decline in gross motor function among children and youth with cerebral palsy aged 2 to 21 years. Dev Med Child Neurol, 2009

HSP vs. CP

GMFM-66
Gross Motor Function
Measurement by 66 items:
head control, standing,
walking, jumping...



Norwegian CPOP data, 2025

Jahnsen, R. B., Weedon-Fekjar, H., Myklebust, G., & Storvold, G. V. (2025). Gross Motor Development by Age and Functional Level in Children with Cerebral Palsy from 6 Months to 17 Years—A Norwegian Population-Based Registry Study. *Journal of Clinical Medicine*, 14(1), 178. <https://doi.org/10.3390/jcm14010178>

Cerebral Palsy Mimics

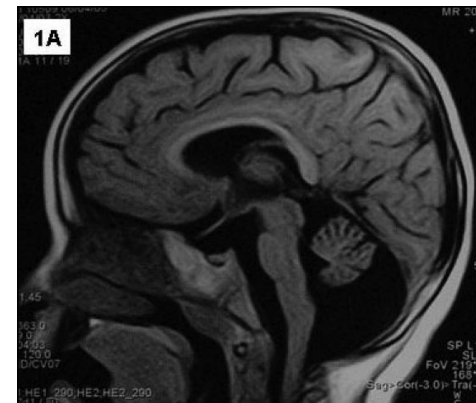
- Diplegic CP mimics hereditary spastic paraplegia
- Ataxic CP mimics spinocerebellar ataxia

Cerebral Palsy can be genetic / a part of genetic syndrome

Example:

Pontocerebellar hypoplasia

- Microcephaly
- Severe developmental delay
- Spasticity
- Dyskinesia
- Epilepsy



Genetics: 15 types, mRNA and tRNA mutations

Cerebral Palsy can be genetic / a part of genetic syndrome

Scientific review April 2024:*

55 genes in at least 2 CP patients

79 genes in 1 CP patient

*JAMA Pediatrics 2025**:*

243 genes, incl. 58 genes with actionable treatment options

Poster in EACD 2025, phd stud. Signe V. Pedersen et al., DK:

378 genes are “pathogenic” or “likely pathogenic”

* Janzing, Anna M. et al. *Clinical Characteristics Suggestive of a Genetic Cause in Cerebral Palsy: A Systematic Review. Pediatric Neurology, April 2024.*

** Lewis SA, Chopra M, Cohen JS, et al. *Clinical Actionability of Genetic Findings in Cerebral Palsy: A Systematic Review and Meta-Analysis. JAMA Pediatr. 2025;179(2):137-144. doi:10.1001/jamapediatrics.2024.5059*

Genetics and Neuro-functional Examinations to Support Individualized Solutions for Cerebral Palsy Prognosis (**GENESIS-CP**)

PhD. study by MD. Jesper Kayser
University of Copenhagen



Supervisors and collaborators:

Prof. Jens Bo Nielsen, neuroscience
Prof. Jørgen Erik Nielsen, clinical neuroscience
Prof. Jakob Lorentzen, neurorehabilitation
Tua Vinther-Jensen, PhD, MD
Prof. Elsebet Østergaard, clinical genetics
Gija Rackauskaite, PhD, MD, neuropediatrician

GENESIS-CP

Aims:

- to identify genetic, structural, and neurofunctional causes of Cerebral Palsy (CP) in Danish adults;
- to explore correlation between genetics and clinical features;
- to explore correlation between brain imaging and clinical features

Study 1. Registry-based study of 800-1000 adults with CP in DK

- Epidemiology
- Clinical symptoms (from medical files)
- Genetic testing (registry data)
- Brain Imaging (registry data)

Study 2 & 3. Clinical study of 100 adults with CP

- Neurological examination
- Cognitive and motor assessments
- Brain imaging
- Whole exome sequencing and copy number variant testing

**Correlation of genetics and imaging
with clinical and functional features**

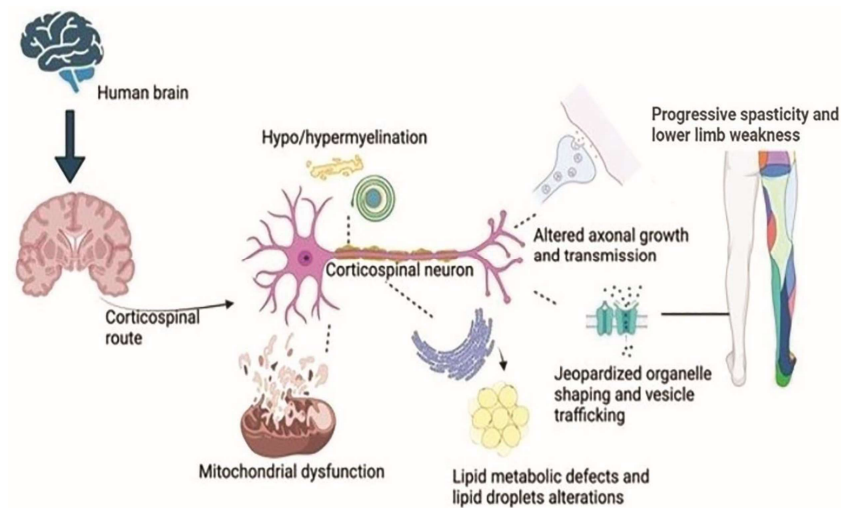
Melpida Gene Therapy

Treatment of HSP (SPG50) at Copenhagen Royal Hospital

SPG50

- What do we know?
- What do we need to know?
- Research trial at Copenhagen Royal Hospital

Biological dysfunction in HSP



Adaptor Protein 4 complex – crucial gatekeeper for protein transport in neurons

AP-4 HSP:
SPG47, SPG50,
SPG51, SPG52

© from Meyyazhagan, A., & Orlacchio, A. (2022). Hereditary Spastic Paraplegia: An Update. *International Journal of Molecular Sciences*, 23(3), 1697. <https://doi.org/10.3390/ijms23031697>

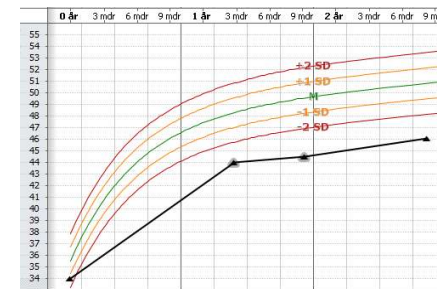
SPG 50

AP4M1 gene, autosomal recessive, < 1 of 50.000

Clinical symptoms:

- Hypotonia / floppy infant
- Early-onset developmental delay
- Post-neonatal microcephaly
- Seizures
- Progressive spastic paraparesis at 2- 6 years
- Urinary and stool incontinence

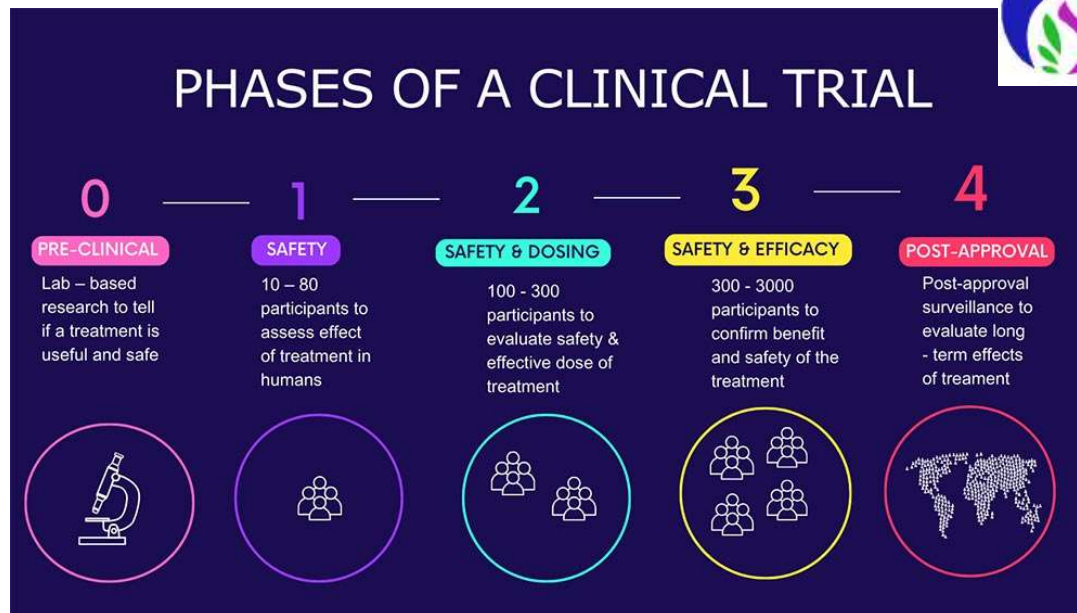
MRI of brain : non-specific reduction of brain volume or structures



Gene therapy for SPG 50

1. Loss-of-function in AP4M1 gene
2. AP4M1 gene be modified by self-complementary adeno-associated virus (scAAV) vector, already used for other progressive CNS disorder
3. Overexpression of gene is assumed not to be harmful
4. Therapeutic window due to relatively slow progression

Clinical trials



Clinical trials for SPG50




PHASES OF A CLINICAL TRIAL

0

PRE-CLINICAL

Lab – based research to tell if a treatment is useful and safe



1


SAFETY

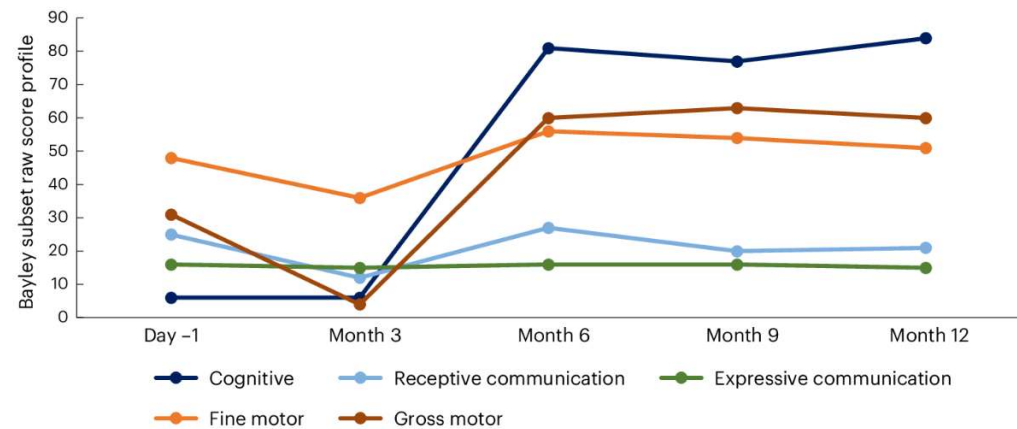
10 participants pass safety of the human

AAV gene therapy for type 50: a phase 1 trial

[James J. Dowling](#), [Terry Pirovolakis](#), [Sahin Darius Ebrahimi-Fakhari](#), [Souad Chen](#), [Berge A. Minassian](#), [Ronald Cohen](#)

Nature Medicine 30, 1882–1887 (2024)





Gene therapy for SPG 50

Recruiting ⓘ

Children's Medical Center Dallas, Texas, USA

Melpida: Recombinant Adeno-associated Virus (serotype 9) Encoding a Codon Optimized Human AP4M1 Transgene (hAP4M1opt)

ClinicalTrials.gov ID ⓘ NCT05518188

Sponsor ⓘ Elpida Therapeutics SPC

Information provided by ⓘ Elpida Therapeutics SPC (Responsible Party)

Last Update Posted ⓘ 2024-10-08

Not yet recruiting ⓘ

No site registered at clinical trials.gov

Phase 3, Open-label Study to Assess the Efficacy and Safety of a Single Lumbar Intrathecal Administration of MELPIDA in Individuals with Hereditary Spastic Paraplegia Type 50 (SPG50) Versus Matched Prospective Concurrent Controls. (SPG50)

ClinicalTrials.gov ID ⓘ NCT06692712

Sponsor ⓘ Elpida Therapeutics SPC

Information provided by ⓘ Elpida Therapeutics SPC (Responsible Party)

Last Update Posted ⓘ 2024-11-18

Compassionate use ?



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Gene therapy for SPG 50

Safety of genetic drug therapy

Experience in AUH & RH

Gene therapies are very expensive

Other financial sources than public health insurance

Immune suppression is needed

Already in use in paediatrics in DK

Intrathecal therapy in general anaesthesia

Already in use

Standardized evaluation before and after

Already in use in paediatrics research in DK

Gene therapy for SPG 50 in DK



Rigshospitalet



Jesper Erdal
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Gija Rackauskaite, M.D, PhD.
Pediatric Neurologist
Aarhus University Hospital



Alfred Peter Born, MD
Pediatric Neurologist
Rigshospitalet

Approvals and
collaboration
agreements in
progress