Salla disease – rare but diverse. A 13-Year Follow-Up study of a Finnish Patient Sample

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Frambu Competence Center for Rare Disorders

Liisa Paavola
PhD, specialized in neuropsychology

Salla district, north-eastern Lapland, Finland

Rare diseases

- A disease is considered rare when it affects a small amount of people compared with the general population, in Europe one affected person per 2000 (http://www.eucerd.eu/)
- There are thousands of rare diseases in the world (http://rarediseases.info.nih.gov/)
  - often chronic and progressive
  - characterized by a broad diversity of disorders and symptoms that vary from disease to disease, and also from patient to patient suffering from the same disease (www.eurordis.org)
  - Salla disease (SD, OMIM 604369) is a particularly rare lysosomal storage disease, belonging to the Finnish disease heritage, FDH

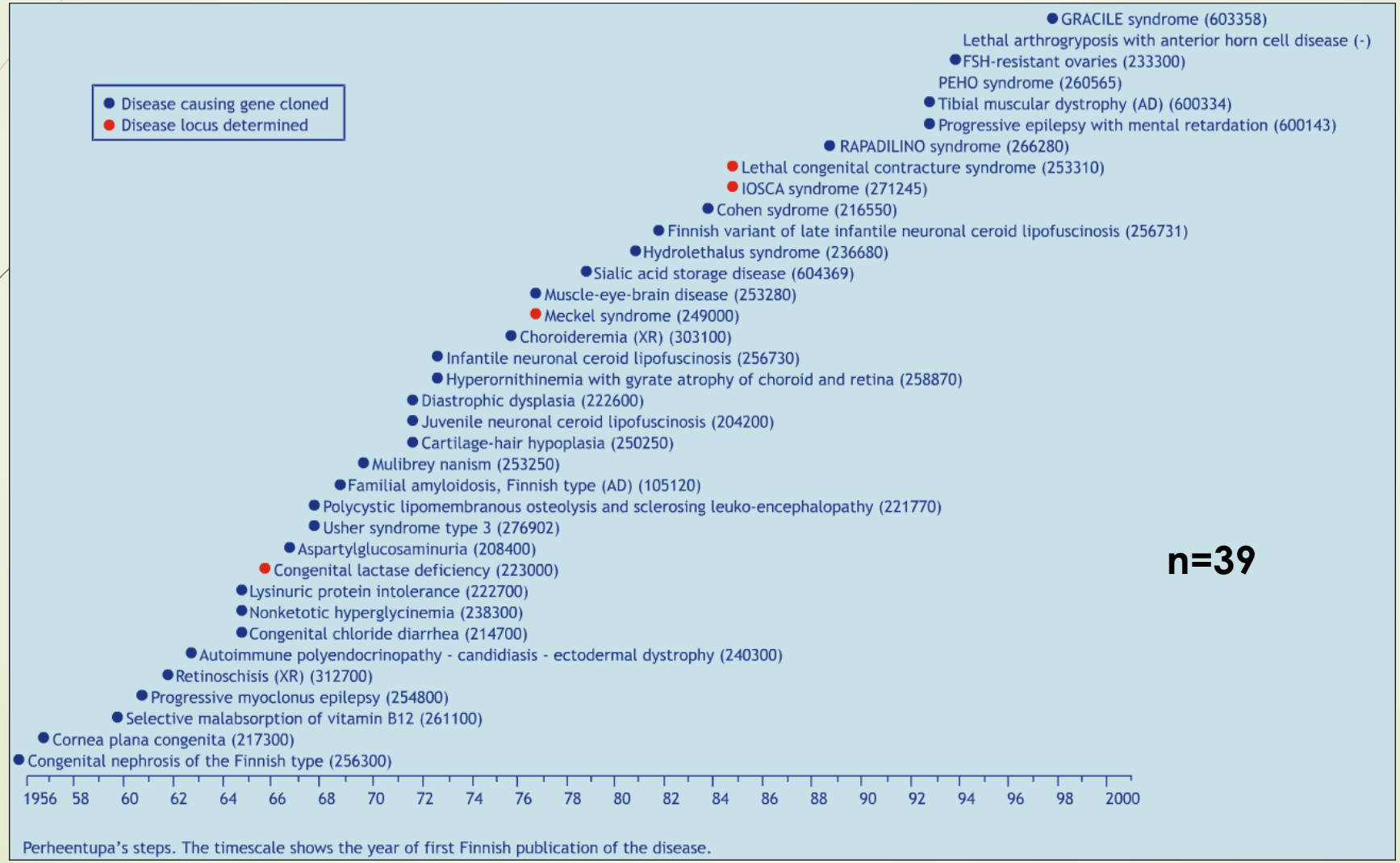
Finnish Disease Heritage (FDH)

- consists of almost forty rare hereditary diseases that are clearly more prevalent in Finland than elsewhere in the world
- these all are particularly rare diseases
- the concept of Finnish disease heritage reversed means that there are many diseases lacking in Finland that are common elsewhere in the world
- FDH was presented in print for the first time in Finnish in 1972 (Perheentupa 1972) and in English in 1973 (Norio et al. 1973)

FDH

- a great proportion of the genes of FDH are known
  - 32 are autosomal recessive, two autosomal dominant and two X-chromosomal
  - almost 1/3 of these diseases cause intellectual disabilities and visual handicap
  - also epileptic and deteriorating neurological diseases are represented
  - genital malformations, bone disorders, hearing loss, metabolic disturbances, blood disorders and multisystemic syndromes are reported
  - one major mutation has been identified for all the diseases belonging to FDH (Peltonen et al. 1999)
  - other mutations are usually found as compound heterozygotes, together with the major mutation (Norio 2003a)
  - long-term genetic drift and gene flow may also explain the factors behind the FDH and regional differences related to Finnish population (Norio 2003a, 2003b, Palo et al. 2009)

FDH


Disease causing gene cloned
Disease locus determined
GRACILE syndrome (603358)
Lethal arthrogryposis with anterior horn cell disease (-)
FSH-resistant ovaries (233300)
PEHO syndrome (260565)
Tibial muscular dystrophy (AD) (600334)
Progressive epilepsy with mental retardation (600143)
RAPADILINO syndrome (266280)
Lethal congenital contracture syndrome (253310)
IOSCA syndrome (271245)
Cohen sydrome (216550)
Finnish variant of late infantile neuronal ceroid lipofuscinosis (256731)
Hydrolethalus syndrome (236680)
Sialic acid storage disease (604369)
Muscle-eye-brain disease (253280)
Meckel syndrome (249000)
Choroideremia (XR) (303100)
Infantile neuronal ceroid lipofuscinosis (256730)
Hyperornithinemia with gyrate atrophy of choroid and retina (258870)
Diastrophic dysplasia (222600)
Juvenile neuronal ceroid lipofuscinosis (204200)
Cartilage-hair hypoplasia (250250)
Mulibrey nanism (253250)
Familial amyloidosis, Finnish type (AD) (105120)
Polycystic lipomembranous osteolysis and sclerosing leuko-encephalopathy (221770)
Usher syndrome type 3 (276902)
Aspartylglucosaminuria (208400)
Congenital lactase deficiency (223000)
Lysinuric protein intolerance (222700)
Nonketotic hyperglycinemia (238300)
Congenital chloride diarrhea (214700)
Autoimmune polyendocrinopathy - candidiasis - ectodermal dystrophy (240300)
Retinoschisis (XR) (312700)
Progressive myoclonus epilepsy (254800)
Selective malabsorption of vitamin B12 (261100)
Cornea plana congenita (217300)
Congenital nephrosis of the Finnish type (256300)
1956 58 60 62 64 66 68 70 72 74 76 78 80 82 84 86 88 90 92 94 96 98 2000
Perheentupa's steps. The timescale shows the year of first Finnish publication of the disease.

n=39

Neurodevelopmental characters of SD

Table 1. Methods used in neuropsychological evaluation.

Abbreviation	Full name of test	Reference	Focus of test / chosen parts	Baseline study	Follow-up study
WISC-R	Wechsler Intelligence Scale for Children-R	Wechsler (1984)	Verbal and perceptual cognitive skills	X	
WISC-III	Wechsler Intelligence Scale for Children-III	Wechsler (1991)	Verbal and perceptual cognitive skills		X
NEPSY	Children´s Neuropsychological Test Battery (3-6 years)	Korkman (1988), Korkman *et al.* (1997)	*Comprehension of Instructions		X
			*Oromotor Sequences		X
			*Repetition of Nonsense Words		X
			*Handedness	X	
			*Fingertip Tapping	X	
VMI	Visual-Motor-Integrating task	Beery (1989)	Visual-motor development	X	
BSID-II	Bayley Scales of Infant Development 2nd ed.	Bayley (1997)	Motor and mental skills	X	X
PANESS	Physical and Neurological Examination for Soft Signs	Denckla (1985), Roeder *et al.* (2008)	Corpus callosum dysfunctions		X
CEREBELLAR tests	Static and Dynamic Cerebellar Tests	Fawcett *et al.* (2001)	Dysfunctions of cerebellum		X
TUG-test	Timed Up and Go-test	Williams *et al.* (2005)	The basic and functional mobility		X

(Paavola et al., 2012)

Baseline Study

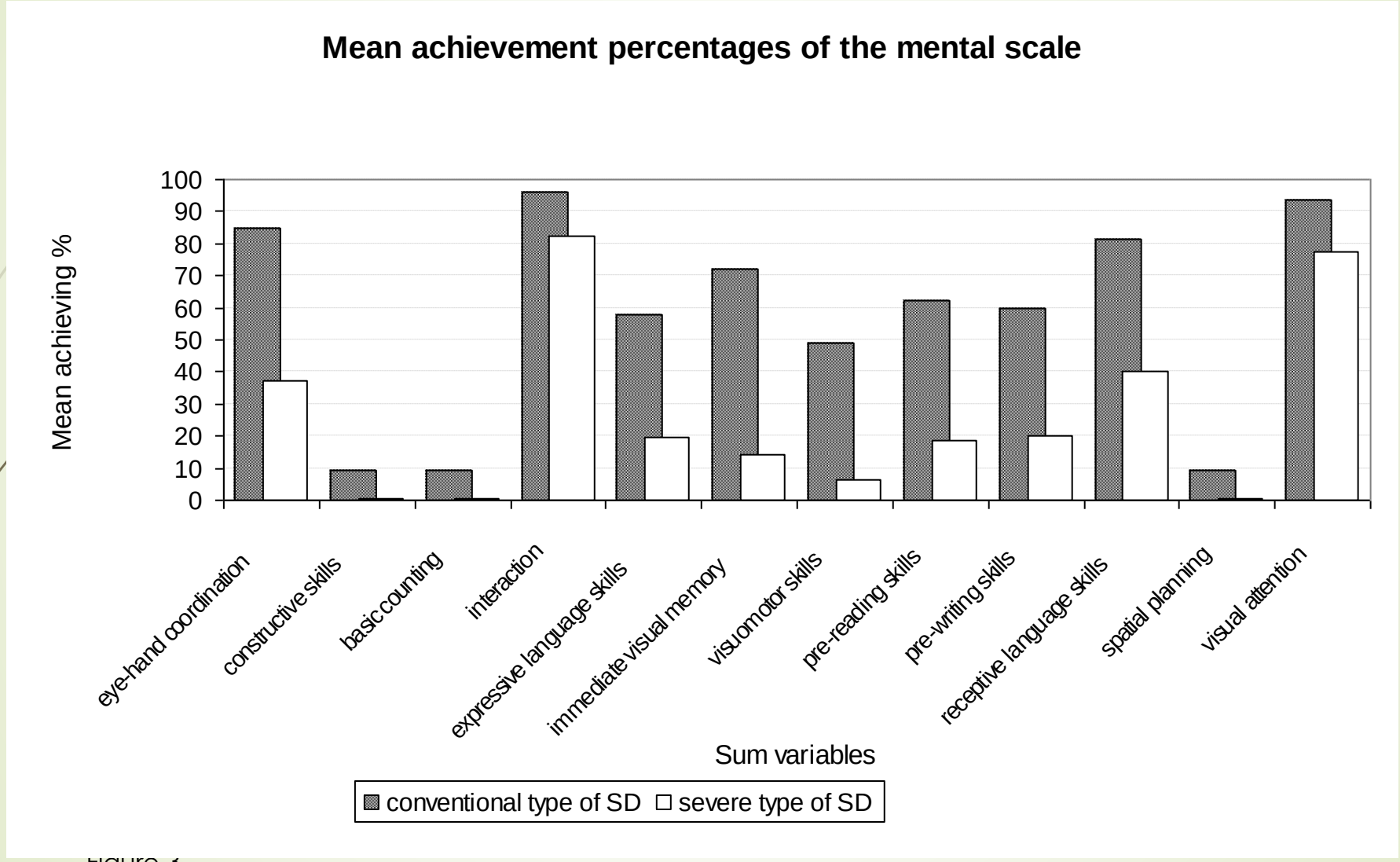


Figure 3.

(Alajoki et al., 2004)

Baseline Study

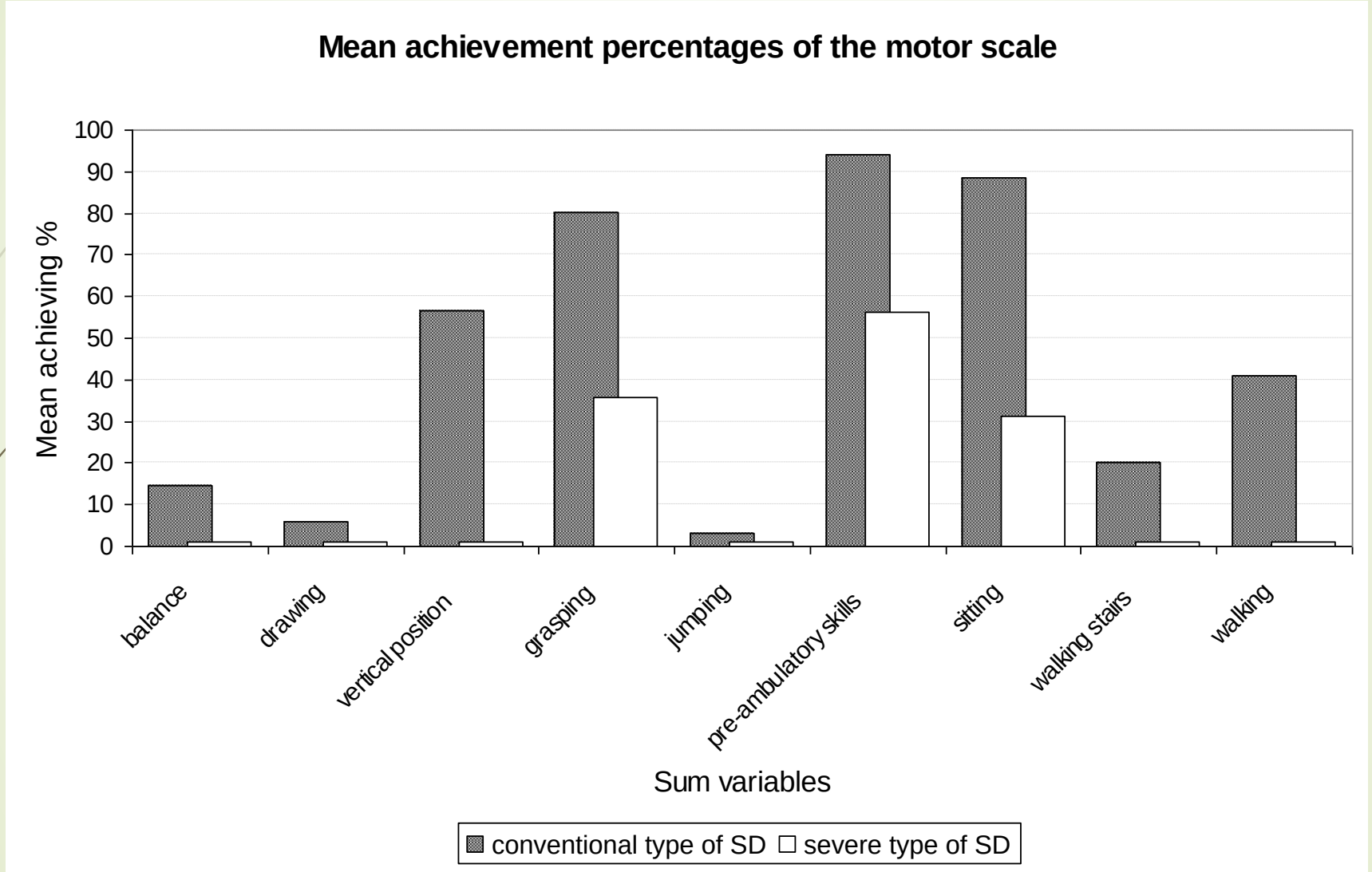
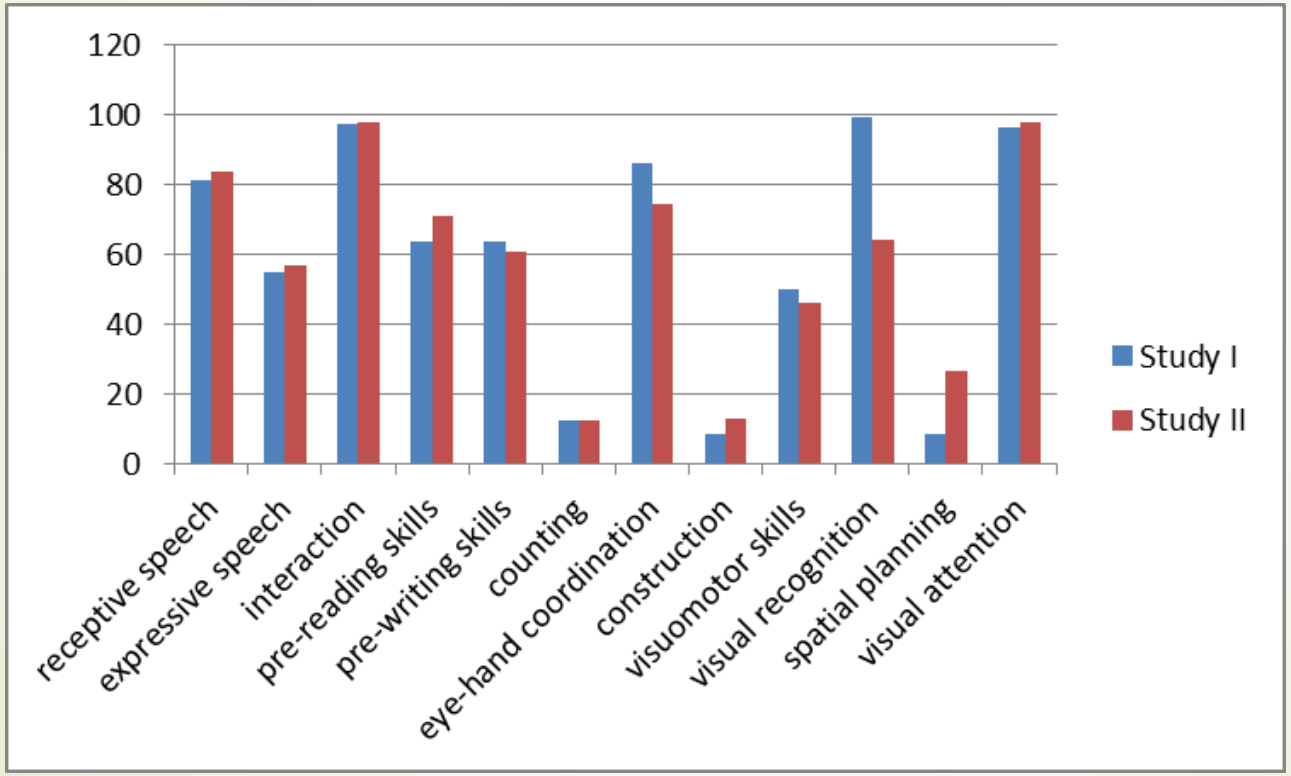


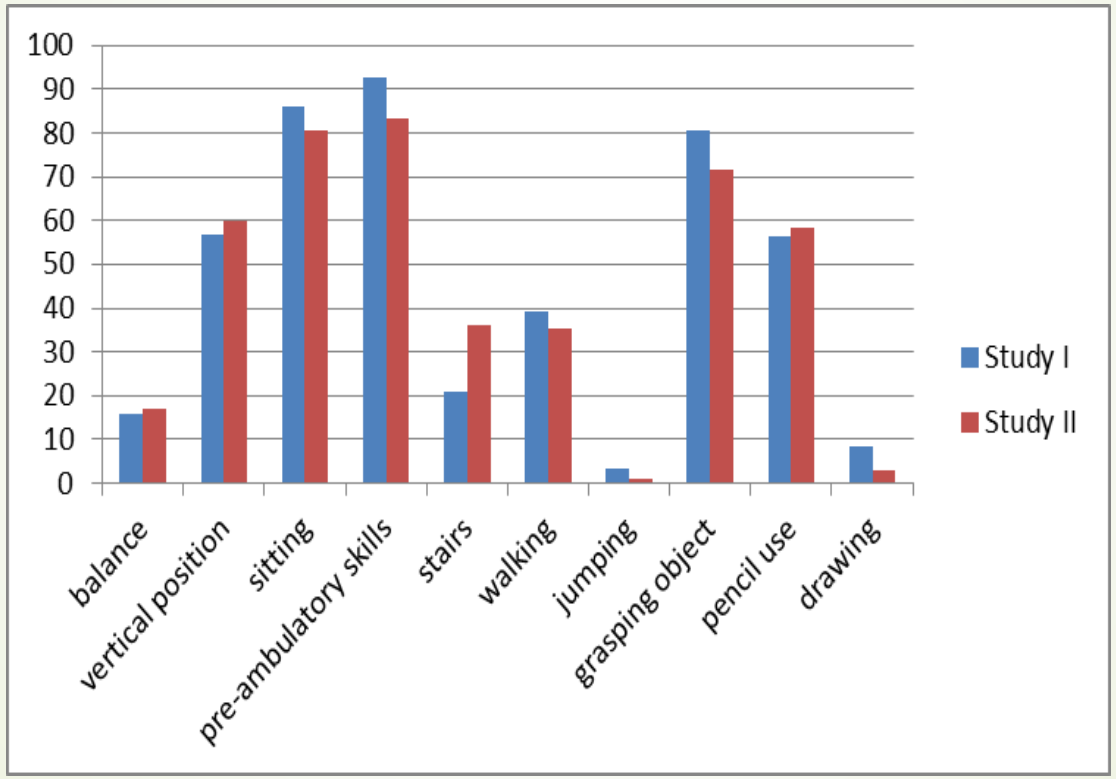
Figure 2.

(Alajoki et al., 2004)

BSID-II mental scale



BSID-II motor scale



Neurodevelopmental characters of SD

- the neurocognitive deficits of SD are clear in childhood, but the disease does not have a rapid progressive nature after the teens
- the motor handicap is severe but the cognitive skills related to verbal comprehension and interactive skills do not deteriorate in adulthood
  - right-handedness is typical in SD
- four neurodevelopmental periods in SD can be outlined
  - 1) The perinatal history and the first months after birth are normal in most of the patients. Mature myelination is seen in the brain stem, hemispheres, cerebellar peduncles and stria medullaris thalami. The myelination seems to cease between the birth and the first months (Haataja et al. 2004a)
  - 2) The first symptoms, typically hypotonia and delayed motor development, are present from the first year of life. Slow but positive development continues to puberty. During this developmental stage ataxia will decline and disappear
  - 3) A quite constant period of neurocognitive skills and neurological findings can be seen between 15– 40 years. The development of neurocognitive skills is slow but positive till age 40 years
  - 4) The progressive decline in mental abilities starts after 40 years of age. After age 20 years there is an apparent decline in motor skills.

Neurodevelopmental findings in SD

Table 3. Frequency of deficits in language and fine motor skills of 27 SD patients.

Test	No deficits (%)	Mild-moderate deficits (%)	Clear deficits (%)
NEPSY			
*Comprehension of instructions	63	10	27
*Oromotor sequences	3	7	90
*Repetition of nonsense words	10	3	87
Dynamic cerebellar tests			
*Finger to thumb	3	4	93
*Toe tapping	33	20	47
*Pegboard task	0	43	57
*Bead threading	13	24	63
TUG-test	10	38	52

(Paavola et al., 2012)

A unique neurodevelopmental profile of a woman with the SallaFIN mutation

- Diagnosed at the age of 3 years
- Mild ataxia and athetosis in early childhood
- Very active and verbally talented from early childhood
- Cognitive development mildly slow but positive
- Active rehabilitation team

- School years in a special class
- Can read and write
- Many hobbies (sports, theater, arts, dance, swimming)

Developmental ages in WISC-tests

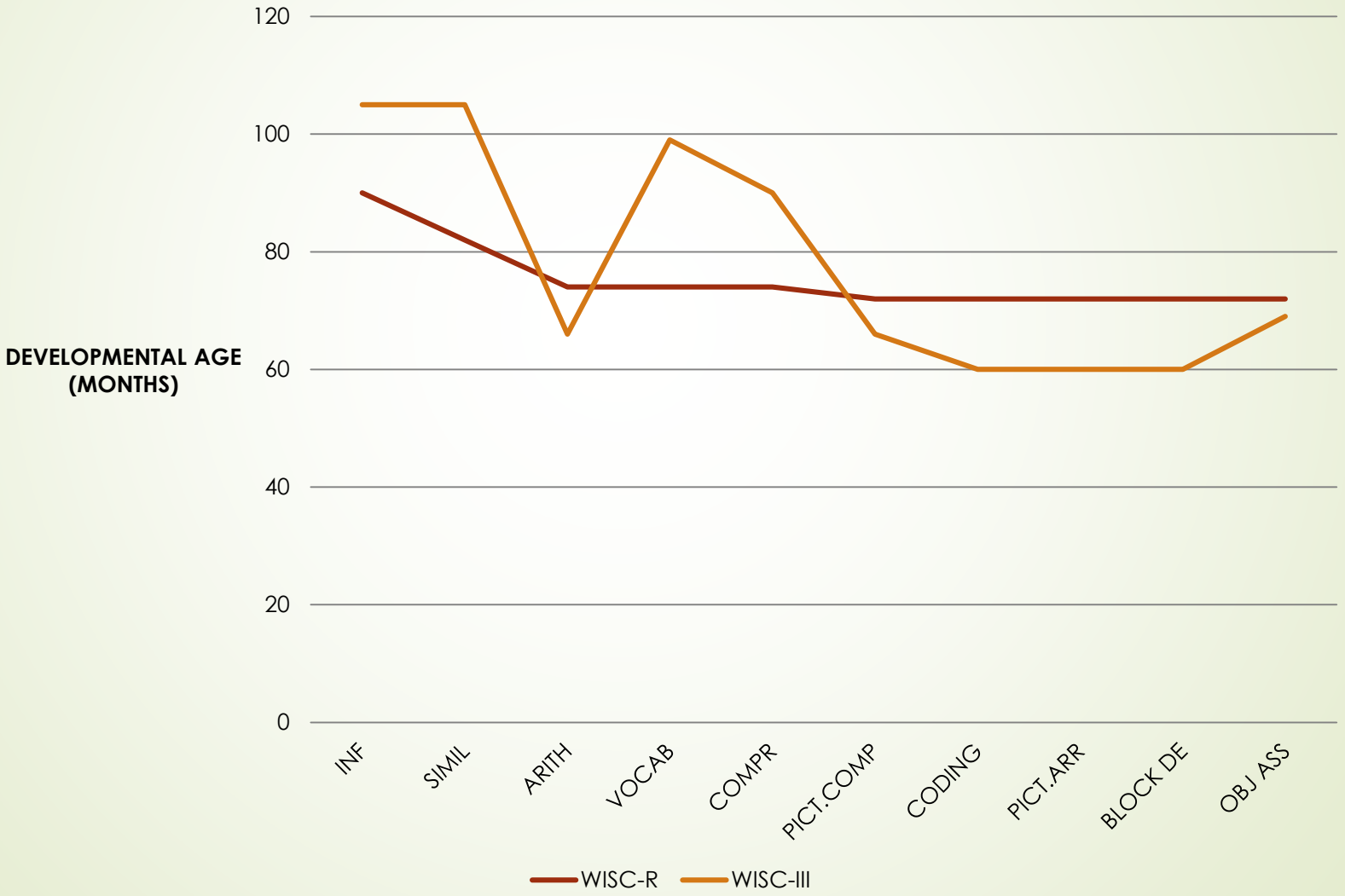
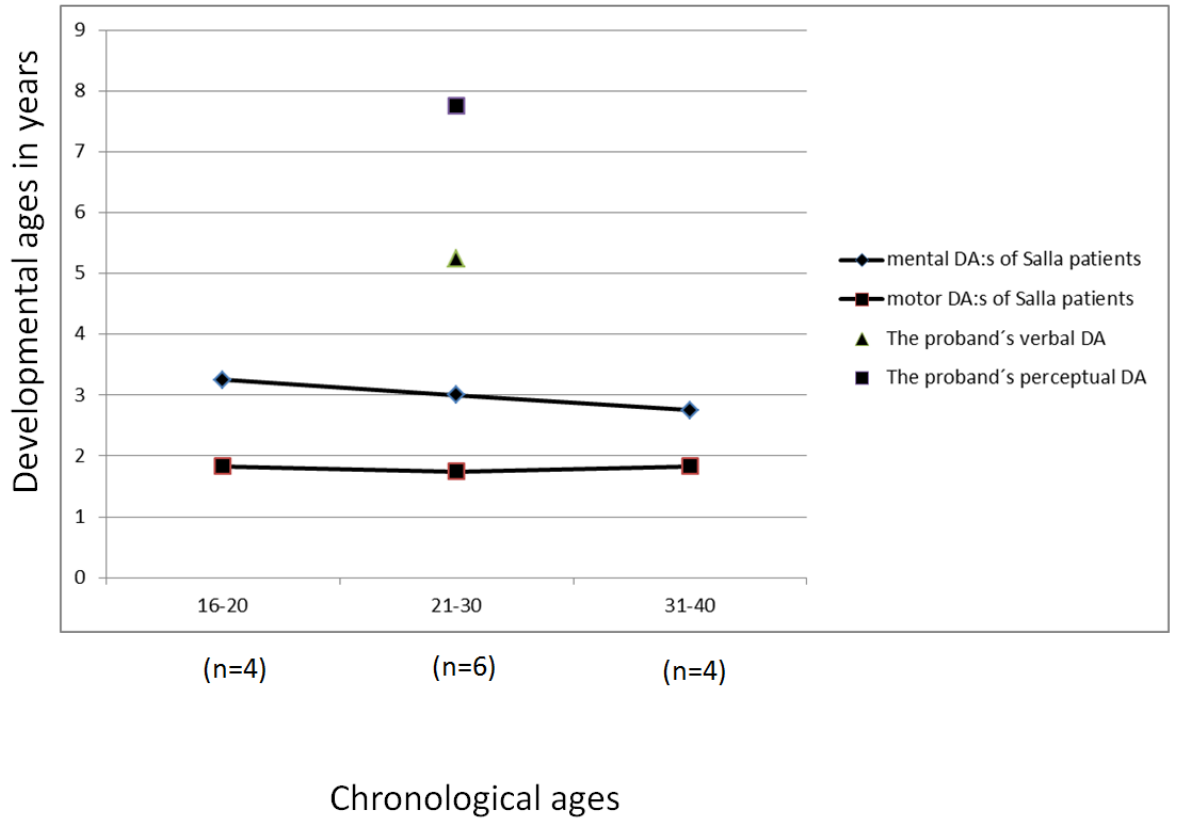


Figure 1. Developmental ages (DA) of the proband and the other patients with SallaFIN mutation



A unique neurodevelopmental profile of a woman with the SallaFIN mutation

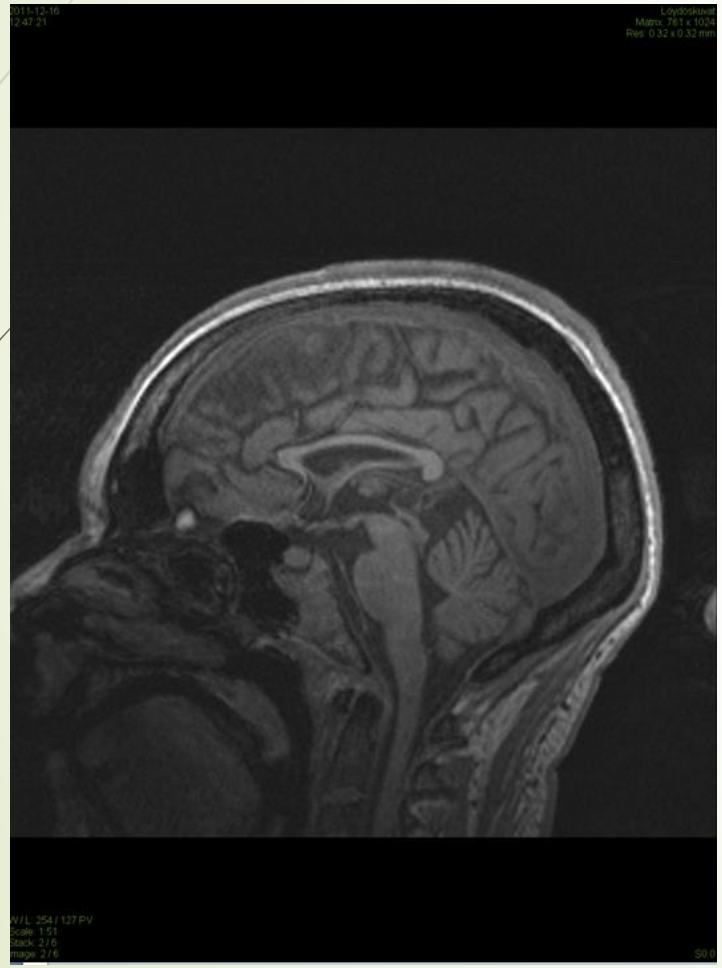
Table 4. Results of neuropsychological evaluation of the female patient with the Salla$_{FIN}$ mutation at 30 years of age.

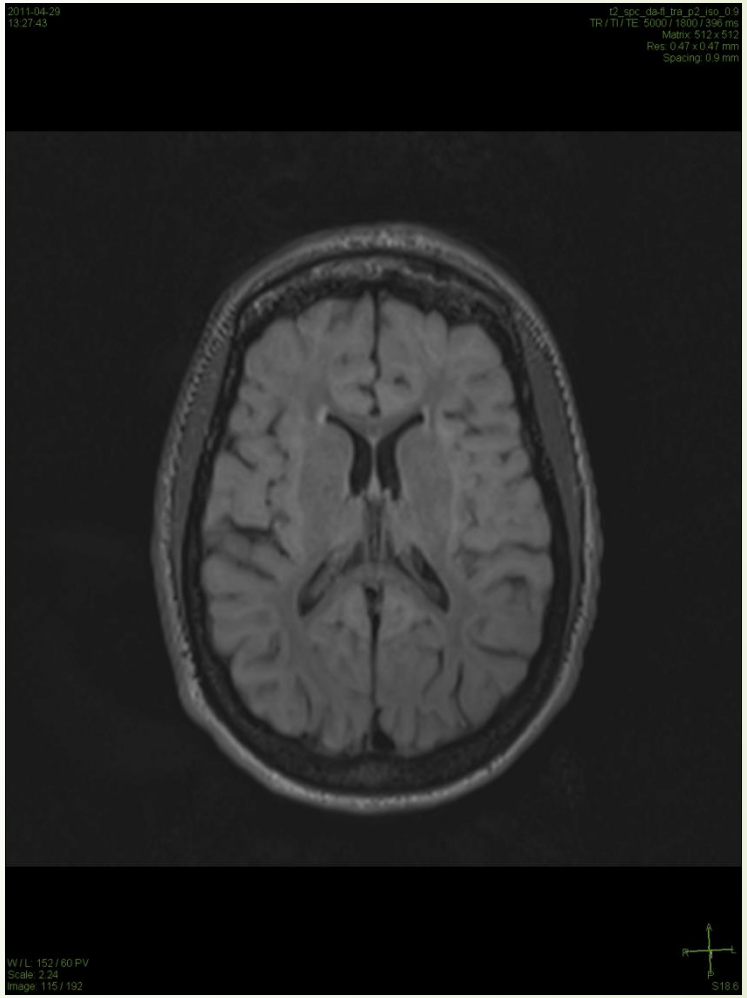
Full name of test	Abbreviation	Reference	Subtests	Performance[a]
Wechsler Intelligence Scale for Children-III	WISC-III	Wechsler (1991)	*Verbal tasks *Perceptual tasks	1 1
Children´s Neuropsychological Test Battery	NEPSY	Korkman *et al.* (1997)	*Comprehension of instructions *Oromotor sequences *Repetition of nonsense words	0 2 2
Physical and Neurological Examination of Soft Signs	PANESS	Denckla 1985)	Tests of corpus callosum dysfunction	2
Static and Dynamic Cerebellar Tests	Cerebellar tests	Fawcett *et al.* (2001)	Tests of cerebellar dysfunctions	1
Timed Up-and-Go-test	TUG-test	Williams *et al.* (2005)	Tests of basic and functional mobility	1

[a]0=among average, 1=mild impairment, 2=severe impairment.

(Alajoki et al., 2004, Paavola et al., 2012)

Case example





Neuropsychologial spectrum

- the patients with SD share some characteristics that are typical in nonverbal learning difficulties (Rourke 1995)
- corpus callosum hypoplasia among patients with SD may partly explain their right hand preference as well as difficulties in mirror movements and left-right differences in timed motor activation test
  - the loss of axons in corpus callosum may be the factor that affects developmental hand preference and cerebral dominance

Neuropsychological spectrum

- severe motor deficits
- the special characters of speech and language development
- strong interactive skills

-> can be seen as a continuum of the exceptional brain maturation and dysmyelination of the CNS

The special role of the Cerebellum

- difficulties and deterioration of speech production skills are partly related to dysarthria and dyspraxia in SD patients

- both of these symptoms are typically related to **cerebellar dysfunctions** (Stoodley & Schmahmann 2009)

The special roles of the Cerecellum

- timing and sequencing both non-motor and motor actions (Xu et al. 2006, Leggio et al. 2008, Molinari et al. 2008)
- organizing motor cognition (Fuentes & Bastian 2007)
- involved in cognitive functions and behavior in many ways (Rapoport et al. 2001, Glickstein & Doron 2008)
  - regulates verbal short term memory functions (Durisko & Fiez 2009, Majerus et al. 2009, Misciagna et al. 2009)
  - organizes language functions (Stoodley & Schmahmann 2009)t
  - there is also evidence for cognitive and motor fronto-cerebro-cerebellar circuits, links or loops in the brain (Krienen & Buckner 2009, Strick et al. 2009, Tavano & Borgatti 2010)

Conclusions and Future Aspects

- individual differences within the SD phenotypes are large
- there is no progression in atrophy or neurocognitive symptoms at 30 years of age
- unknown genetic and environmental variation may explain the individual differences among patients with the SallaFIN mutation
- further studies of these factors in SD are needed
  - the role of epilepsy in SD
  - neuropsychiatric symptoms and dysmyelination
  - cerebellar dysfunctions related to other lysosomal storage disorders

Future aspects

- SD progresses **slowly**
- The streghts within cognitive skills (verbal undeerstanding, interaction, social skills) ground the basis for rehabilitation and learning
- SD patients benefit of rehabilitation throughout the life span
  - Physical activity -> reduction of spasticity
- Neurological follow-ups are needed with adult patients (in Finland the emphasis is on children)
- Hypo- /hypersensitivity (pain, visual and auditory stimulus, sensation)
- Neuropsychiatric symptoms that are typical with SD patients are not well known or documented
  - Behavioral problems, communication deficits, special characters of teenage development