Hereditær Spastisk Paraparese

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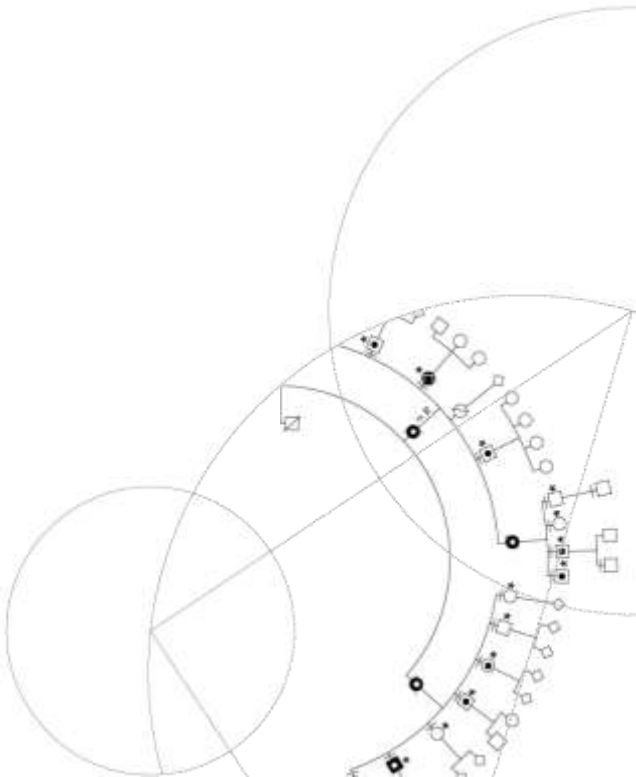

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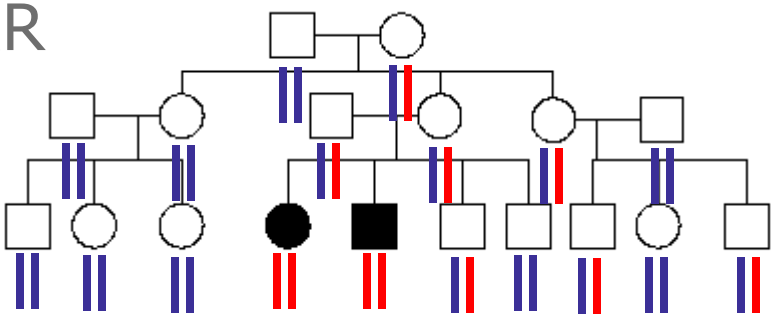
Hereditær Spastisk Paraparese (HSP)

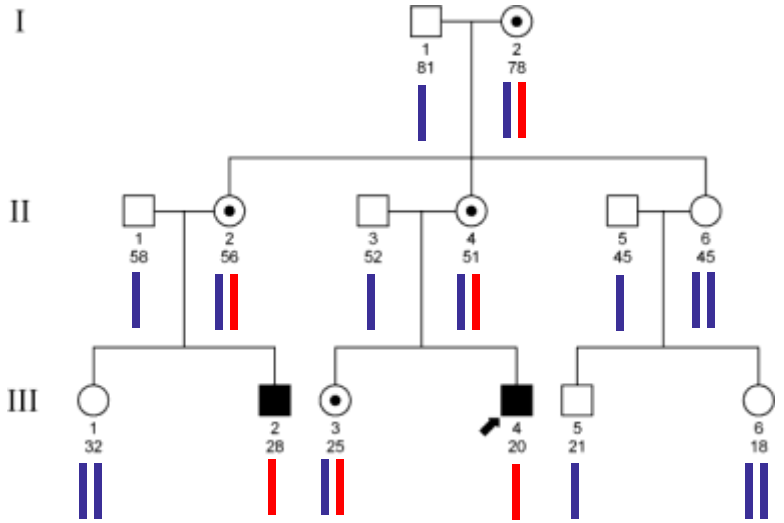
- En gruppe af sjældne arvelige neurodegenrative sygdomme
- Forekomst: 7.4/100,000 målt i Norge
- Symptomer: Kluntet gang, langsomt progredierende stivhed og svaghed i benene, vandladningsgener
- Neurologisk undersøgelse: Spasticitet i benene, nedsat kraft og for kraftige reflekser.
- Klassifiseres efter arvegang, dvs autosomal dominant, autosomal recessiv eller X-bundet
- Klassificeres som "ren" or "kompleks" (AE Harding, 1983)
- Symptomatisk behandling

Arvegang

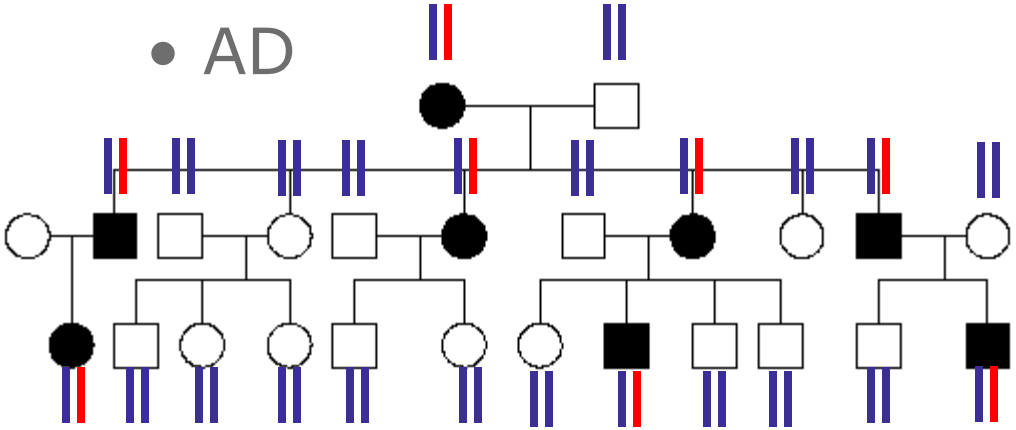
- AR



- X-bundet

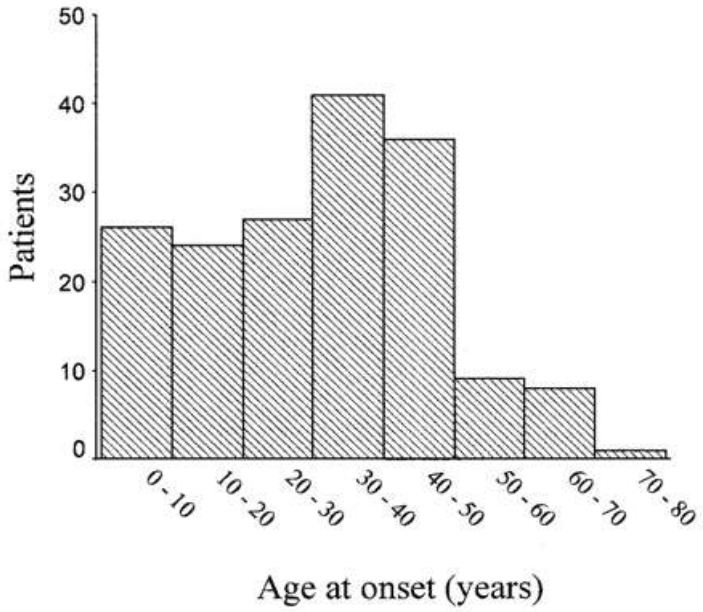


- AD



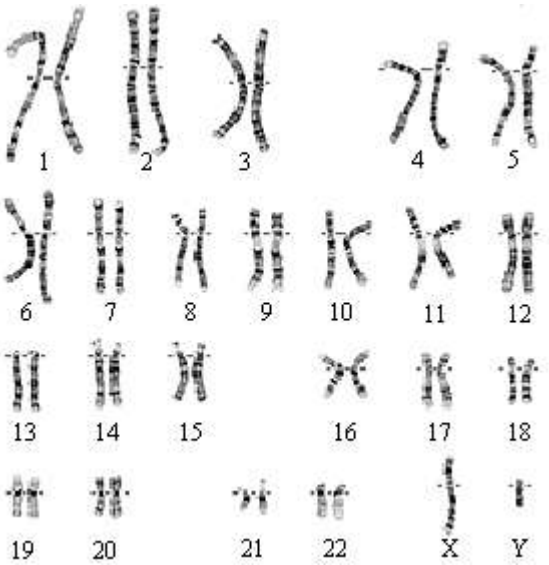
Variation ved HSP

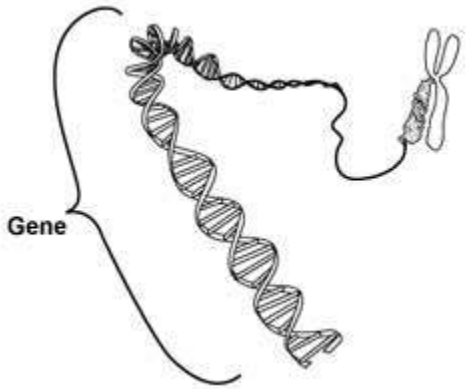
- Debutalder 1-74 år, de fleste 30-40 år
- Debutsymptomer
- Hastighed af forværring
- Sygdomsgraden
- Mønsteret af symptomer
- Andre neurologiske fund:
  Ataxi, mental retardering, hørenedsættelse, nethinde-sygdom, neuropati)
- Stor variation mellem familier med samme type og indenfor familier



Fonknechten et al, Hum Mol Genet 2000

Hurtigt genetik overblik





<u>44 kendte lokalisationer på kromosomerne (SPG1, SPG2 etc)</u>

- 19 med AD arvegang
- 21 med AR arvegang
- 4 med X-bunden arvegang

<u>20 identificerede gener</u>

- 10 i AD HSP
- 8 i AR HSP
- 2 i X-bunden HSP

Inheritance	Locus	Chromosome region	Gene (protein)	Features	Age of onset	Frequency
X-linked	SPG1	Xq28	*L1CAM*	Complex	Infancy	Rare
	SPG2	Xq22	*PLP1*	Complex/pure	0 to18	Rare
	SPG16	Xq11.2	Unknown	Complex	Infancy	1 family
	SPG34	Xq25	Unknown	Pure	12 to 25	1 family
AD	SPG3	14q11-q21	*SPG3A*	Pure/complex	1 to 68	10%
	SPG4	2p22-p21	*SPAST* (Spastin)	Pure/complex	1 to 74	40%
	SPG6	15q11.1	*NIPA1*	Pure	9 to 35	9 families
	SPG8	8q24.13	*KIAA0196* (Strumpellin)	Pure	Adulthood	6 families
	SPG9	10q23.3-q24.1	Unknown	Complex	1 to 37	1 family
	SPG10	12q13	*KIF5A*	Pure	8 to40	7 families
	SPG12	19q.13	Unknown	Pure	Mean 14	1 family
	SPG13	2q33.1	*HSPD1* (HSP60)	Pure	17-68	2 families
	SPG17	11q13	*BSCL2* (Seipin)	Complex	8 to63	Several
	SPG19	9q	Unknown	Pure	36 to 55	1 family
	SPG29	1p31.1-p21.1	Unknown	Complex		1 family
	SPG31	2p11.2	*REEP1*	Pure/complex	10 to 30	3%
	SPG33	10q24.2	*ZFYVE27*	Pure	50	1 family
	SPG37	8p21.1-q13.3	Unknown	Pure	8 to 60	1 family
	SPG38	4p16-p15	Unknown	Complex	Mean 16 years	1 family
	SPG41	11p14.1-p11.2	Unknown	Pure	Mean 16 years	1 family
	SPG42	3q24-q26	*SLC33A1*	Pure	4 to 42	1 family
AR	SPG5	8q21.3	*CYP7B1*	Pure	1 to 47	<20 families
	SPG7	16q24.3	*SPG7* (Paraplegin)	Complex/pure	10 to 42	1-4%
	SPG11	15q21.1	*SPG11* (Spatacsin)	Complex	4 to 31	21%
	SPG14	3q27-q28	Unknown	Complex	Mean 30	1 family
	SPG15	14q22-q24	*ZFYVE26* (Spaticin)	Complex	8 to 36	15%
	SPG20	13q12.3	*SPG20* (Spartin)	Complex	Early childhood	Amish
	SPG21	15q21-q22	*SPG21* (Maspardin)	Complex	1 to 40	Amish
	SPG23	1q24-q32	Unknown	Complex	Childhood	1 family
	SPG24	13q14	Unknown	Pure	1	1 family
	SPG25	6q23-q24.1	Unknown	Complex	30 to 46	1 family
	SPG26	12p11.1-q14	Unknown	Complex	8	2 families
	SPG27	10q22.1-q24.1	Unknown	Complex	25 to 45	2 families
	SPG28	14q21.3-q22.3	Unknown	Pure	6 to15	1 family
	SPG30	2q37.3	Unknown	Complex	12 to 21	1 family
	SPG32	14q12-q21	Unknown	Complex	6 to 7	1 family
	SPG35	16q21-q23	Unknown	Complex	6 to 11	1 family
	SPG39	19p.13	*PNPLA6*	Complex	Childhood	2 families
	SPG44	1q41-q42	*GJC2*	Complex	Adult	1 family

Modified from Stevanin et al, 2009

Mål

- Finde mutationer hos patienter og finde ud af om de er sygdomsfremkaldende
- Finde sammenhæng mellem mutationer og bestemte sygdomstræk
- Finde nye gener for HSP
- Belyse funktionen af generne og proteinerne
- Finde sammenhængen mellem generne for HSP
- Finde muligheder for behandling
- Afprøve behandling

Udvalgte publikationer

PLoS Biol. 2010 Jun 29;8(6)

A genome-scale DNA repair RNAi screen identifies SPG48 as a novel gene associated with hereditary spastic paraplegia.

Słabicki M, Theis M, Krastev DB, Samsonov S, Mundwiller E, Junqueira M, Paszkowski-Rogacz M, Teyra J, Heninger AK, Poser I, Prieur F, Truchetto J, Confavreux C, Marelli C, Durr A, Camdessanche JP, Brice A, Shevchenko A, Pisabarro MT, Stevanin G, Buchholz F.

J Neurol Neurosurg Psychiatry. 2010 Oct;81(10). Epub 2010 Jun 20.

Hereditary spastic paraplegia due to SPAST mutations in 151 Dutch patients: new clinical aspects and 27 novel mutations.

de Bot ST, van den Elzen RT, Mensenkamp AR, Schelhaas HJ, Willemsen MA, Knoers NV, Kremer HP, van de Warrenburg BP, Scheffer H.

Department of Neurology, Radboud University Nijmegen Medical Centre, Donders Centre for Brain Cognition and Behaviour, Nijmegen, The Netherlands.
st.bot@neuro.umcn.nl

Flere udvalgte

Spinal Cord. 2010 May 25. [Epub ahead of print]

Health-related quality of life in patients with hereditary spastic paraplegia in Estonia.

Braschinsky M, Rannikmäe K, Krikmann U, Lüüs SM, Raidvee A, Gross-Paju K, Haldre S.

Department of Neurology, University of Tartu, Tartu, Estonia.

Eur J Hum Genet. 2010 Sep;18(9):1065-7. Epub 2010 May 12.

A total of 220 patients with autosomal dominant spastic paraplegia do not display mutations in the SLC33A1 gene (SPG42).

Schlipf NA, Beetz C, Schüle R, Stevanin G, Erichsen AK, Forlani S, Zaros C, Karle K, Klebe S, Klimpe S, Durr A, Otto S, Tallaksen CM, Riess O, Brice A, Bauer P, Schöls L.

Department of Medical Genetics, Institute of Human Genetics, Tübingen, Germany.

Prenat Diagn. 2010 May;30(5):485-6.

Prenatal diagnosis of autosomal dominant hereditary spastic paraplegia (SPG42) caused by SLC33A1 mutation in a Chinese kindred.

Lin P, Mao F, Liu Q, Shao C, Yan C, Gong Y.

Nat Genet. 2010 Apr;42(4):313-21. Epub 2010 Mar 7.

Mutations in the mitochondrial protease gene AFG3L2 cause dominant hereditary ataxia SCA28.

Di Bella D, Lazzaro F, Brusco A, Plumari M, Battaglia G, Pastore A, Finardi A, Cagnoli C, Tempia F, Frontali M, Veneziano L, Sacco T, Boda E, Brussino A, Bonn F, Castellotti B, Baratta S, Mariotti C, Gellera C, Fracasso V, Magri S, Langer T, Plevani P, Di Donato S, Muzi-Falconi M, Taroni F.

Unit of Genetics of Neurodegenerative and Metabolic Diseases, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy.

Brain. 2010 Feb;133(Pt 2):591-8. Epub 2010 Jan 28.

SPATACSIN mutations cause autosomal recessive juvenile amyotrophic lateral sclerosis.

Orlacchio A, Babalini C, Borreca A, Patrono C, Massa R, Basaran S, Munhoz RP, Rogaeva EA, St George-Hyslop PH, Bernardi G, Kawarai T.

Centro Europeo di Ricerca sul Cervello -Istituto di Ricovero e Cura a Carattere Scientifico Santa Lucia, 64 Via del Fosso di Fiorano, Rome 00143, Italy. a.orlacchio@hsantalucia.it

Hum Mutat. 2010 Apr;31(4):E1251-60.

Mutation of FA2H underlies a complicated form of hereditary spastic paraplegia (SPG35).

Dick KJ, Eckhardt M, Paisán-Ruiz C, Alshehhi AA, Proukakis C, Sibtain NA, Maier H, Sharifi R, Patton MA, Bashir W, Koul R, Raeburn S, Gieselmann V, Houlden H, Crosby AH.

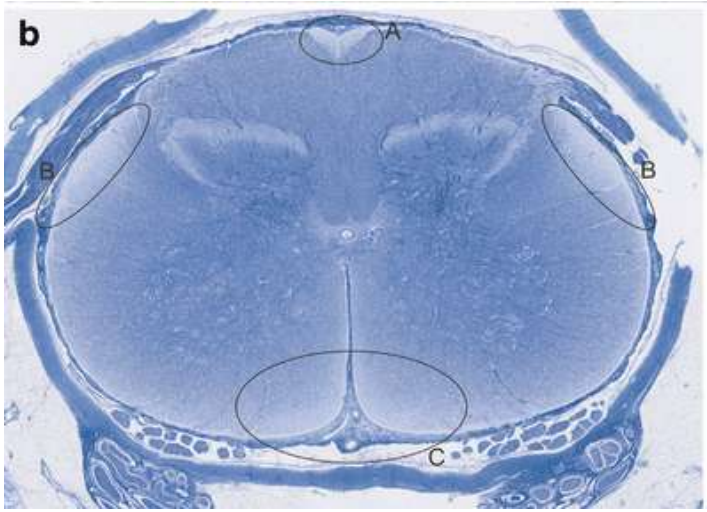
Medical Genetics, Clinical Developmental Sciences, St George's University of London, London, UK.

Neurogenetics. 2010 May;11(2):175-83. Epub 2009 Aug 28.

Congenital bovine spinal dysmyelination is caused by a missense mutation in the SPAST gene.

Thomsen B, Nissen PH, Agerholm JS, Bendixen C.

Department of Genetics and Biotechnology, Faculty of Agricultural Sciences, University of Aarhus, Tjele, Denmark. bo.thomsen@agrsci.dk



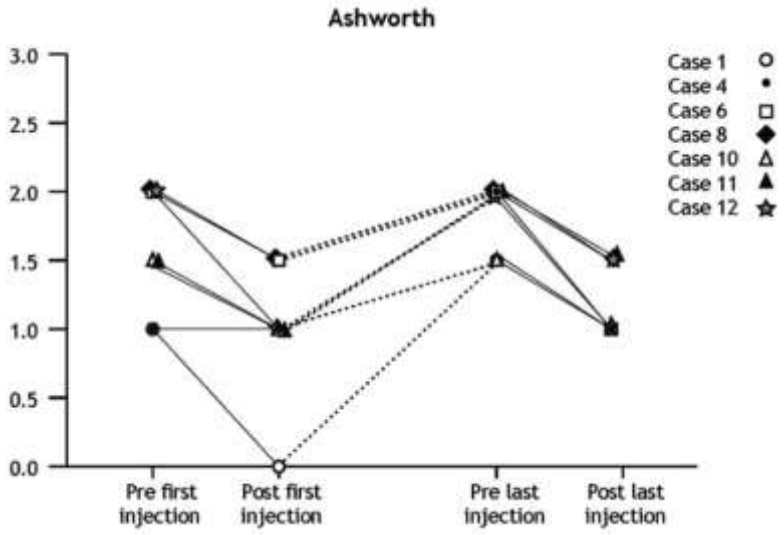
Behandling

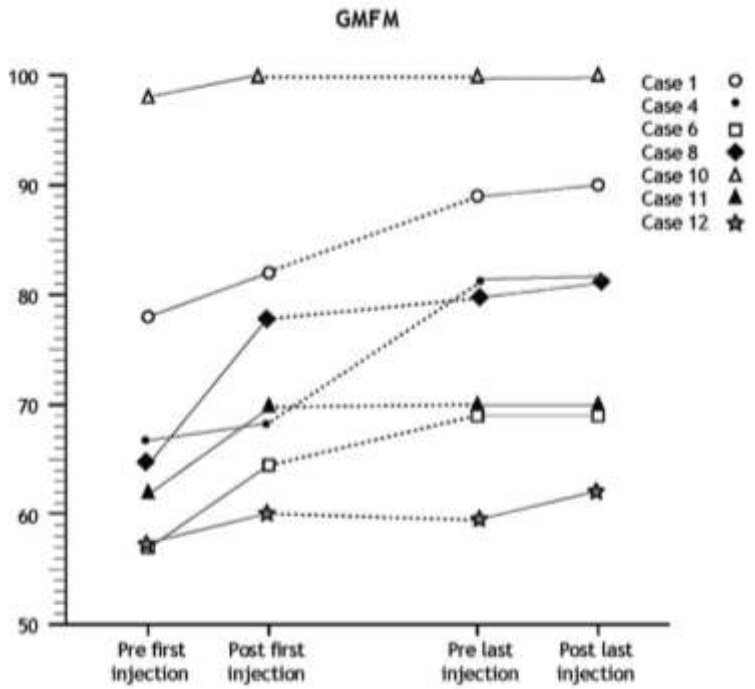
J Child Neurol. 2010 Aug;25(8):969-75. Epub 2010 Apr 20.

Botulinum toxin injections for pediatric patients with hereditary spastic paraparesis.

Geva-Dayan K, Domenievitz D, Zahalka R, Fattal-Valevski A.

Pediatric Neurology Unit, Tel Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.





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Mov Disord. 2008 Jan 30;23(2):228-33.

Botulinum neurotoxin type A injections reduce spasticity in mild to moderate hereditary spastic paraplegia--report of 19 cases.

Hecht MJ, Stolze H, Auf dem Brinke M, Giess R, Treig T, Winterholler M, Wissel J; German Spasticity Education Group.

Department of Neurology, University of Erlangen-Nuremberg, Erlangen, Germany.

Double-blind crossover trial of gabapentin in SPG4-linked hereditary spastic paraplegia.

Scheuer KH, Svenstrup K, Jennum P, Rogvi-Hansen B, Werdelin L, Fenger K, Nielsen JE.

Department of Neurology, Hillerød Hospital, Denmark.

Igangværende projekter

- REEP1 (SPG31)
- Sporadisk HSP – identifikation af mutationer
- SPG11
- SPG13

- Det mere molekylære

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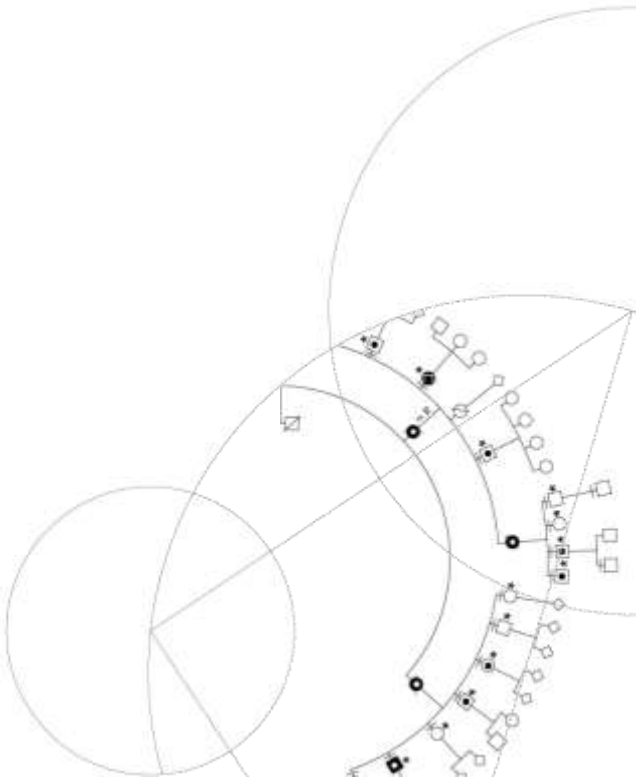

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