RE(ACT)CONGRESS

7-10 March 2018 BOLOGNA

The lesson of Rare Neurologic Diseases to clinical neurologists and neuroscientists for understanding normal and pathological nervous system functions

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Università degli Studi di Siena

Iscriversi e studiare a Siena

Rare Diseases

NEUROLOGICAL

More than 60%

NON NEUROLOGICAL

40%

The neurologist has a key role in the diagnosis and treatment of rare diseases

John William Waterhouse *Pandora* (1896)

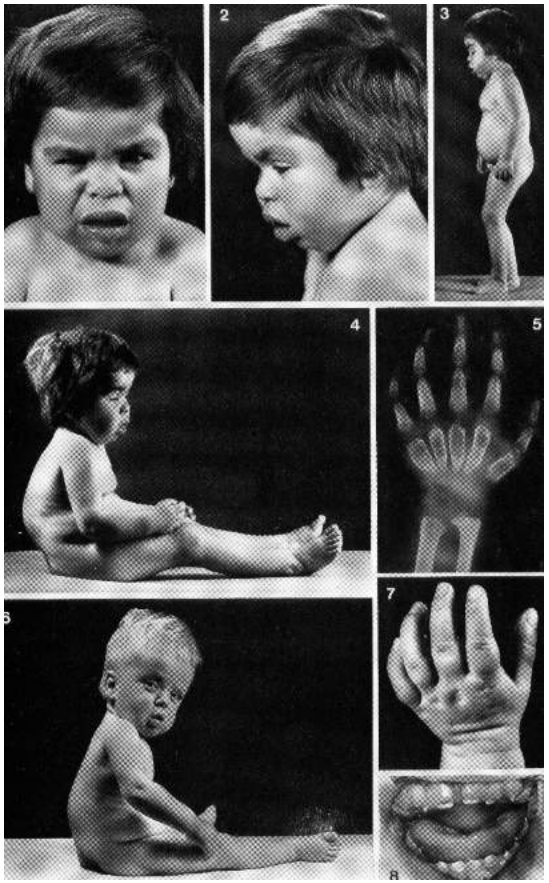
Rare Neurological Diseases:

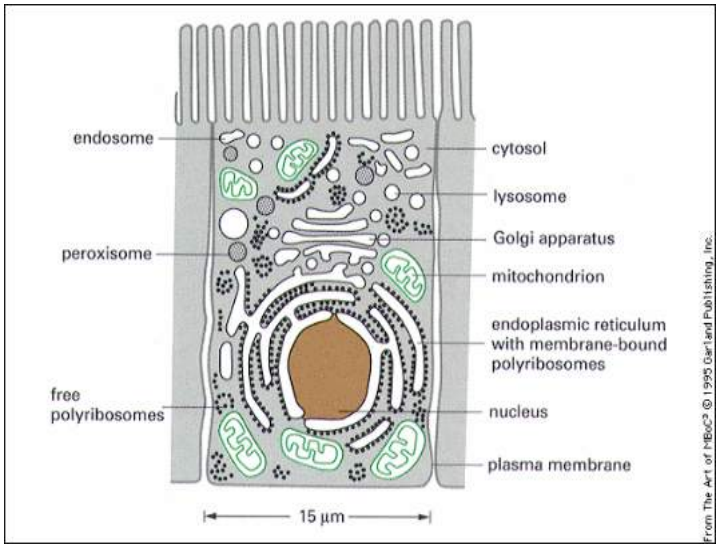
a Pandora's box for Neurology

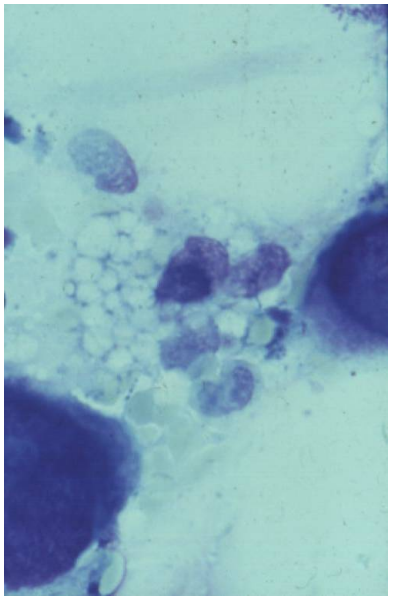
and

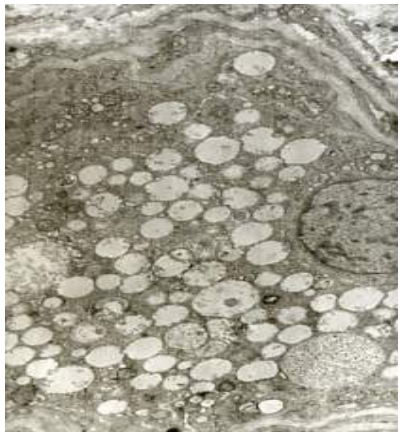
Neurosciences

Lysosomal diseases and lysosomes



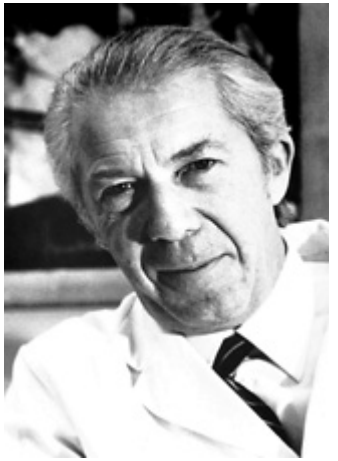




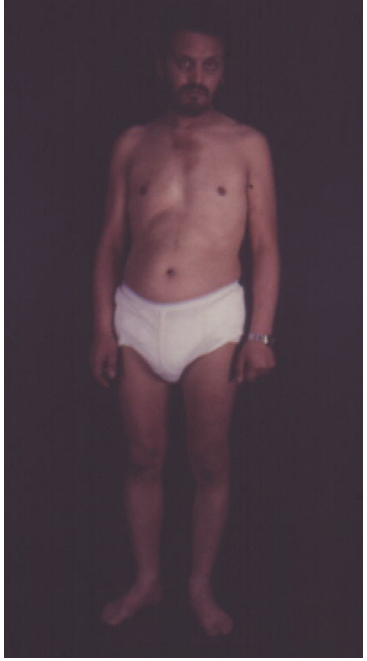


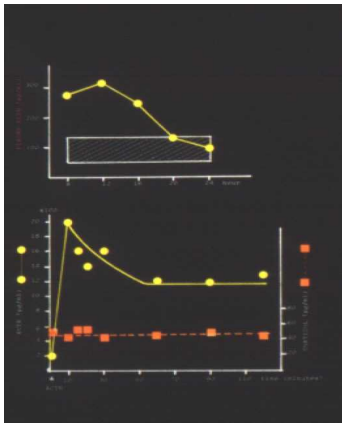
1965: De Duve

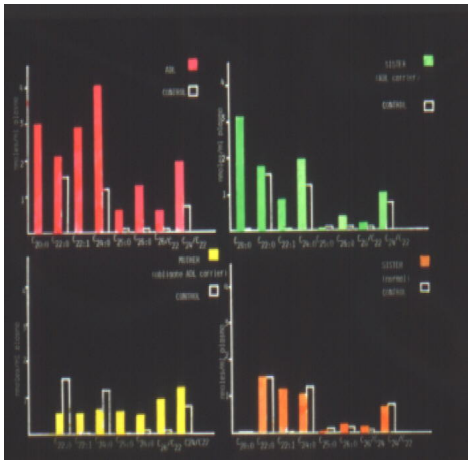
1974: Nobel Prize

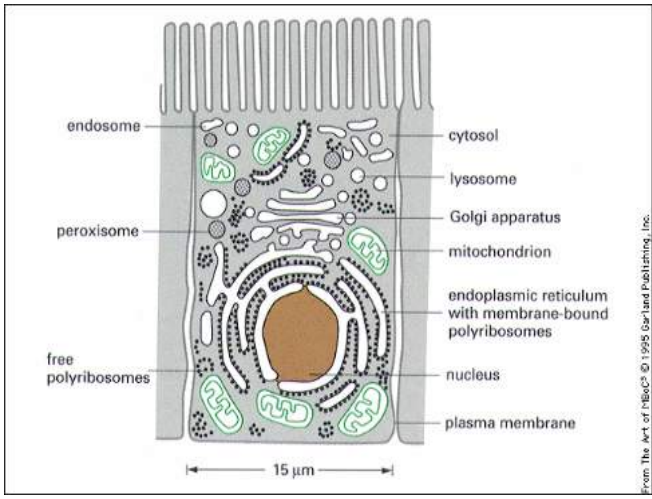


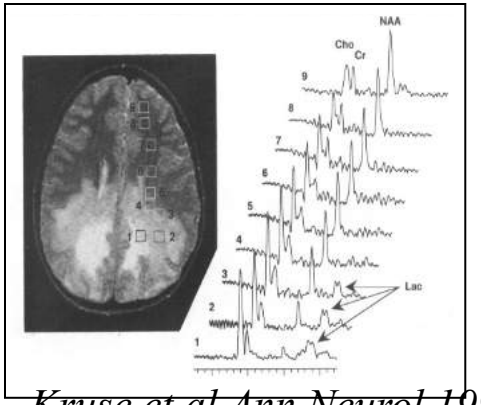
Adrenoleucodystrophy





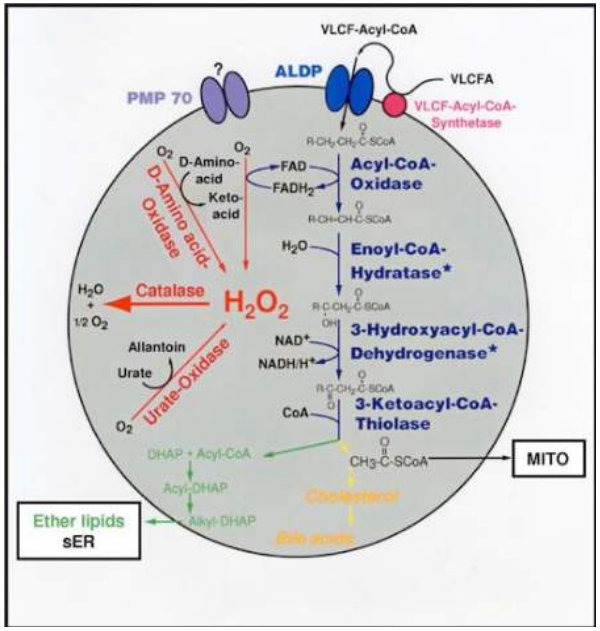






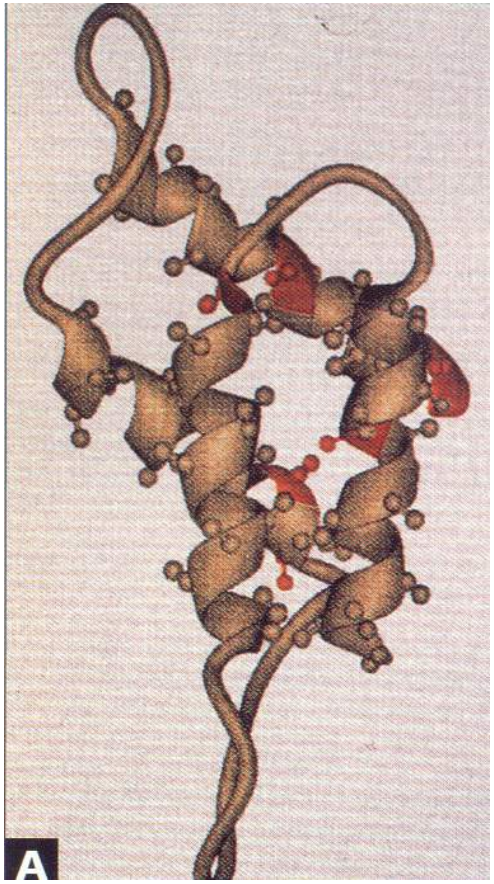
Kruse et al Ann Neurol 1994

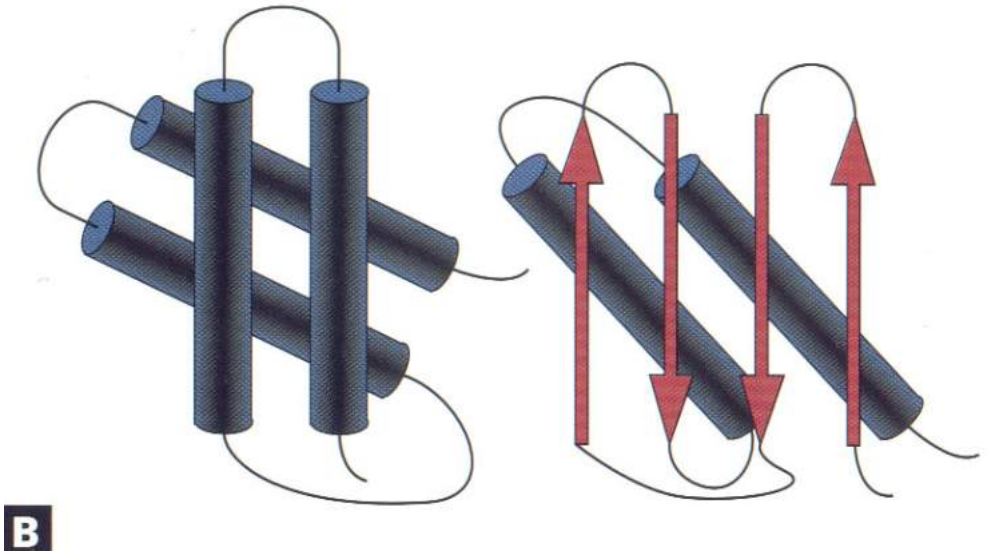
- **ADL gene codifies for a protein, one of the 4th carriers linked to the structure of ATP, localized on the peroxysomal membrane**
- **More than 300 mutations have been detected (www.x-adl-nh.com)**

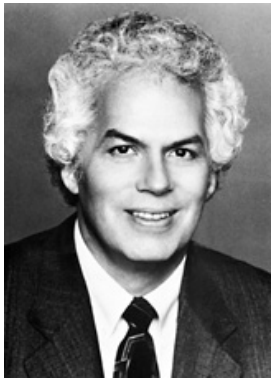


15 enzymes
- Oxidase and cathalase
- Very long chain fatty acids Beta-oxidation (C24-C26)
- Plasmalogen Synthesis (Myelin phospholipids)

Prionic encephalopathies and prions

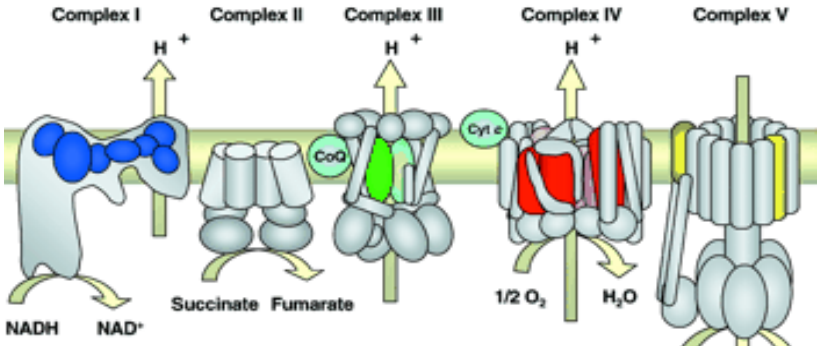


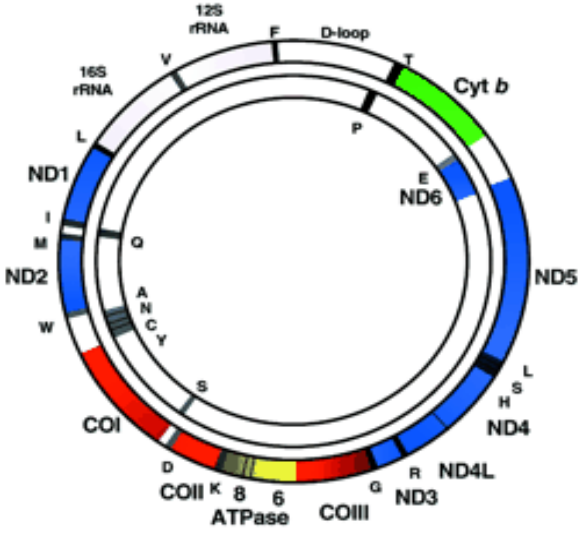


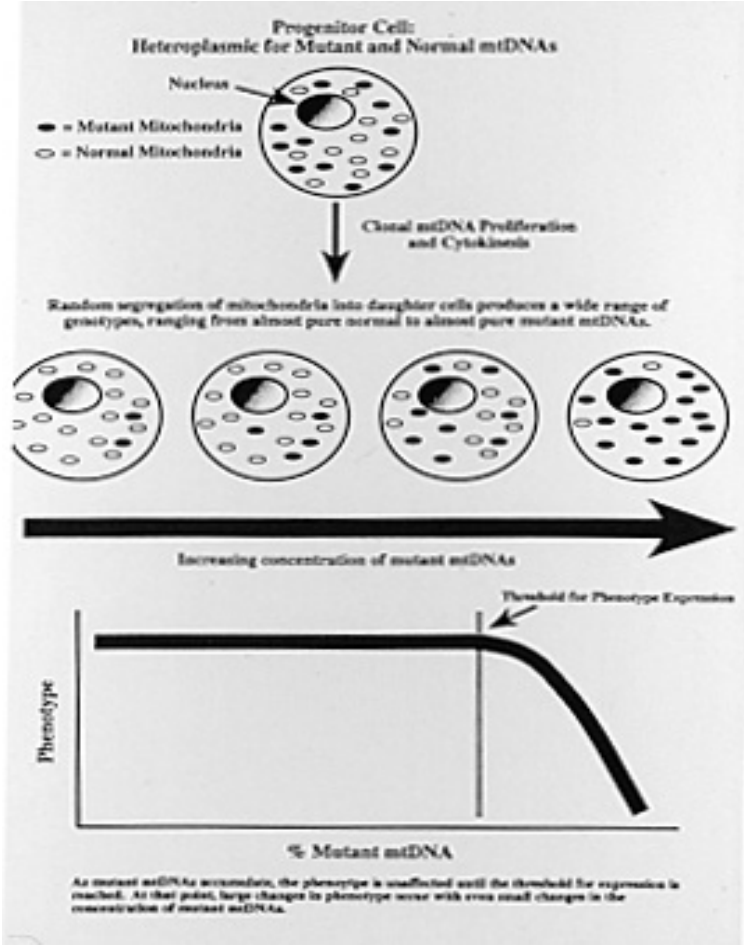


S. Prusiner,

Nobel Prize 1997



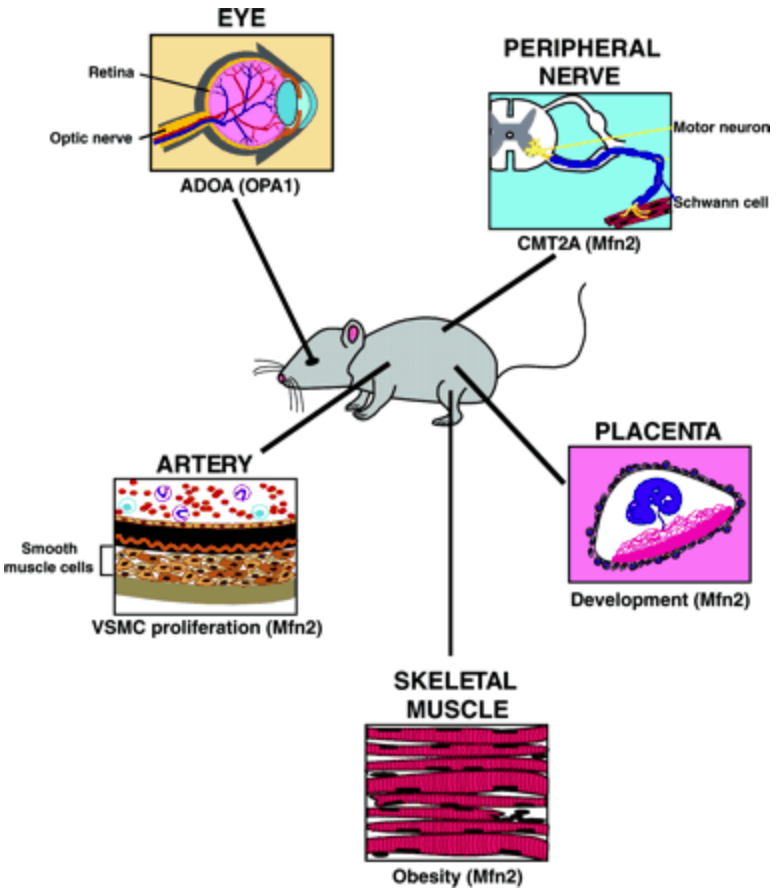


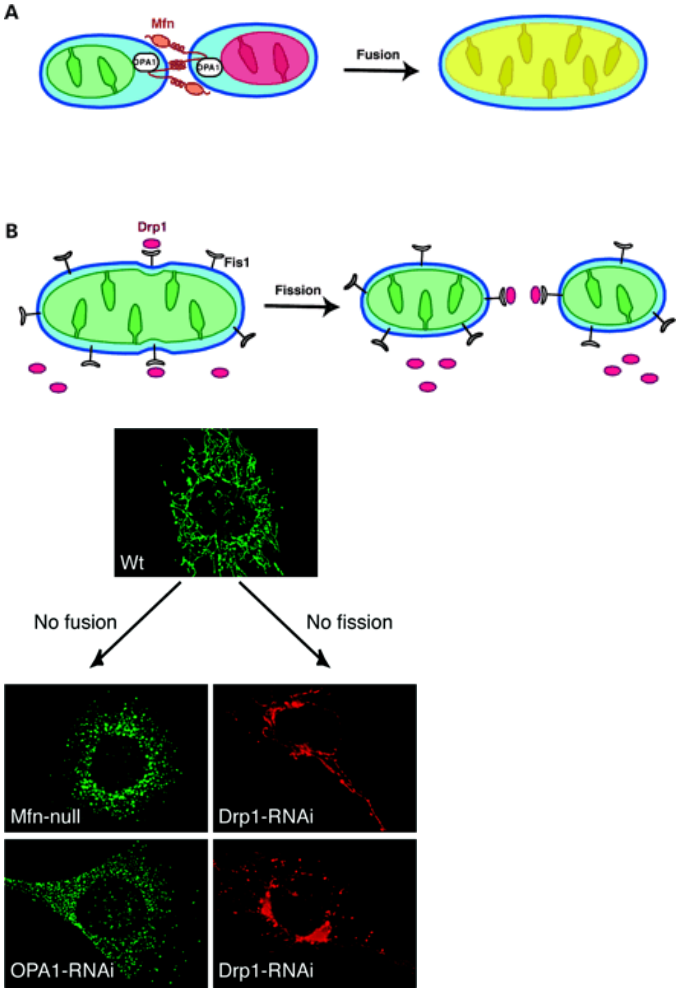


Reddy PH, Beal MF.
Amyloid beta, mitochondrial dysfunction and synaptic damage: implications for cognitive decline in aging and Alzheimer's disease.
Trends Mol Med. 2008 Feb;14(2):45-53.

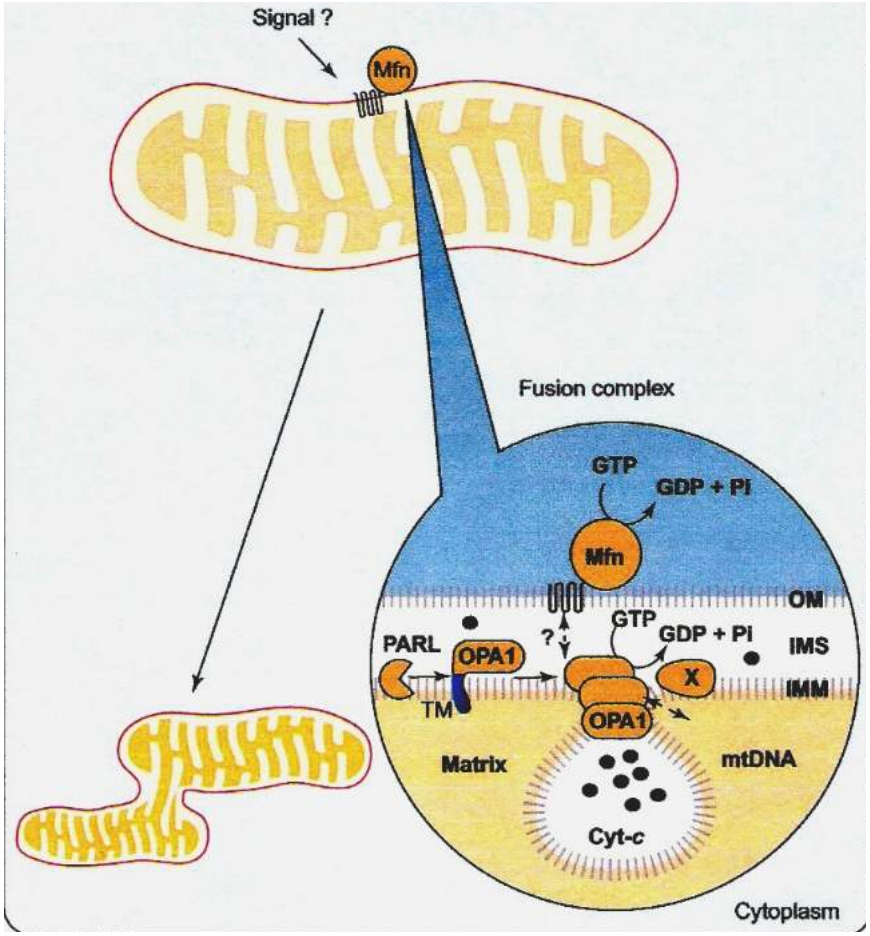
Chung KW, et al. Early onset severe and late-onset mild Charcot-Marie-Tooth disease with mitofusin 2 (MFN2) mutations.
Brain. 2006 Aug;129(Pt 8):2103-18

Jahani-Asl A, et al. Mitofusin 2 protects cerebellar granule neurons against injury-induced cell death J Biol Chem. 2007 Aug 17;282(33):23788-98

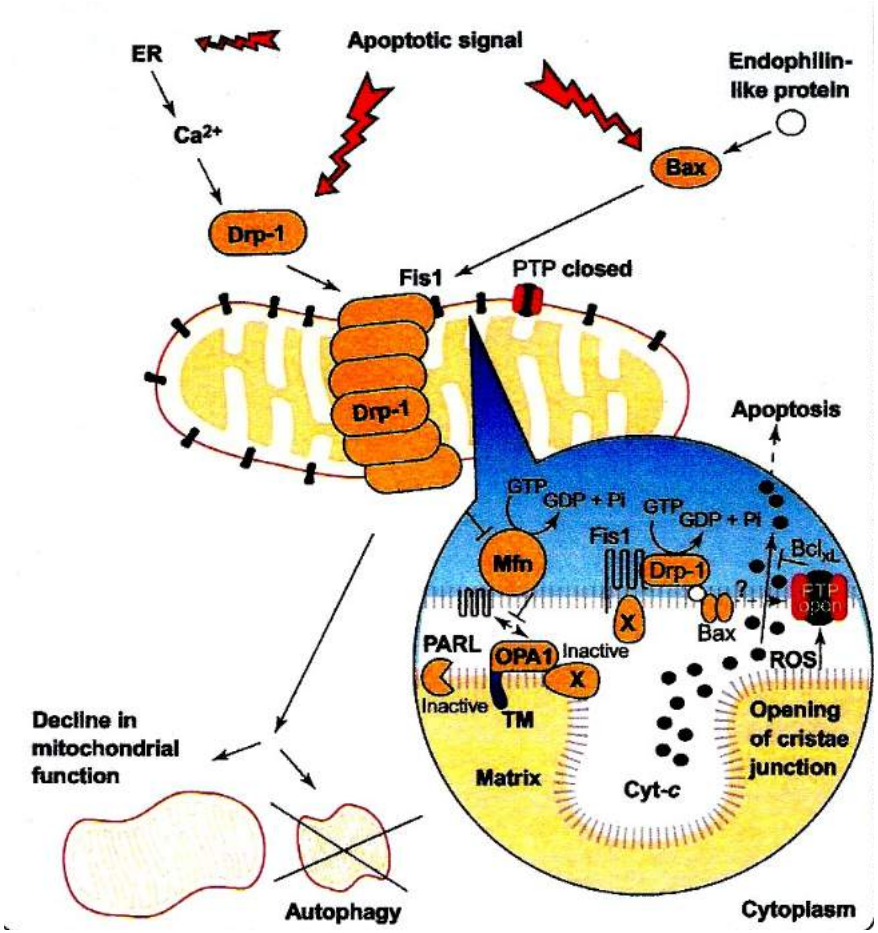




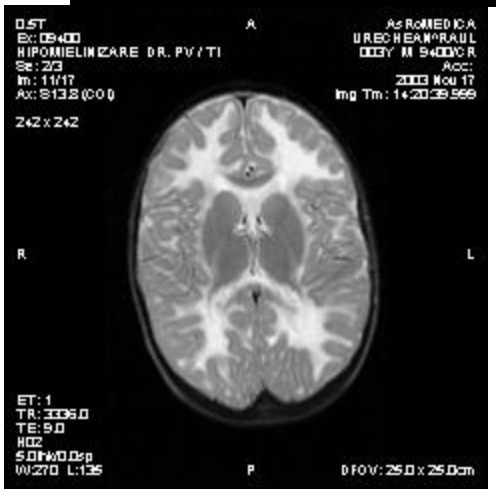
Mitochondrial fusion

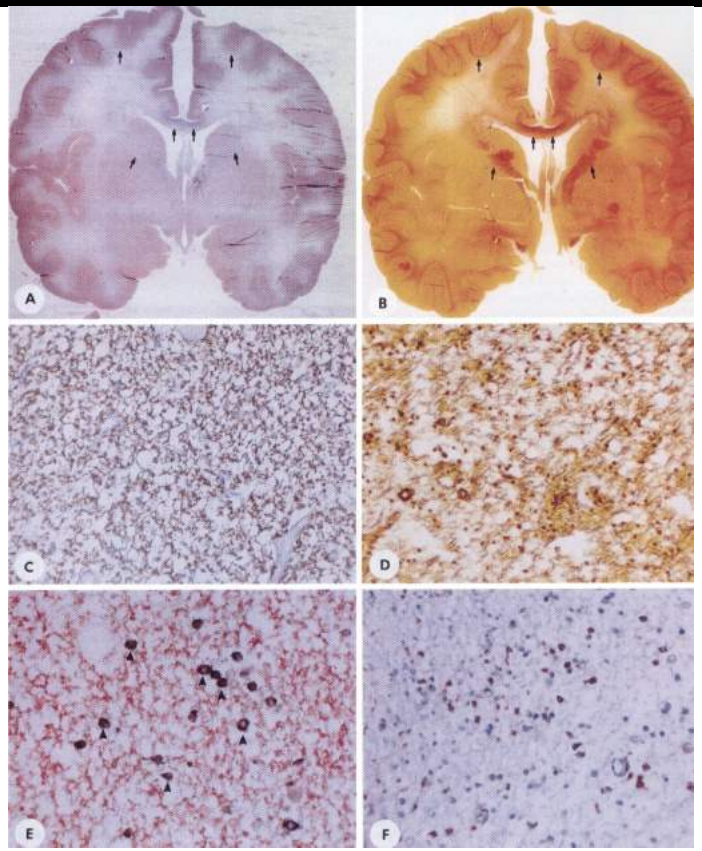


Mitochondrial fission



Vanishing white matter disease, eIF2B and stress



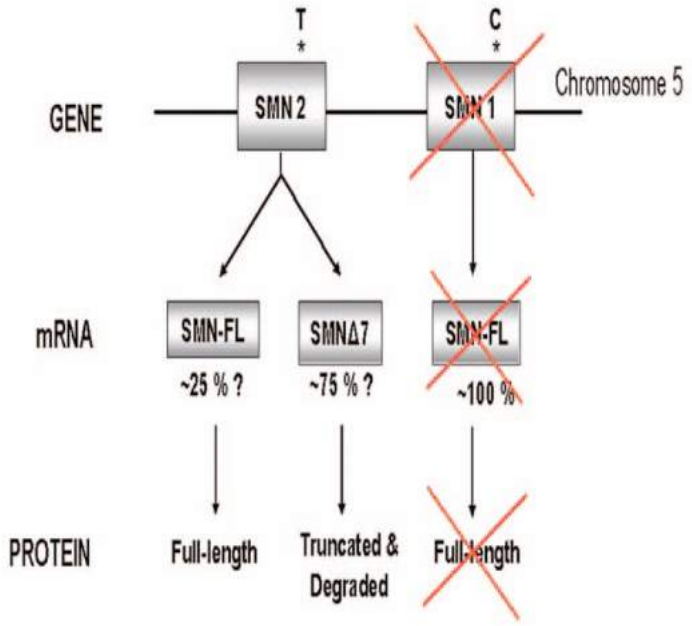


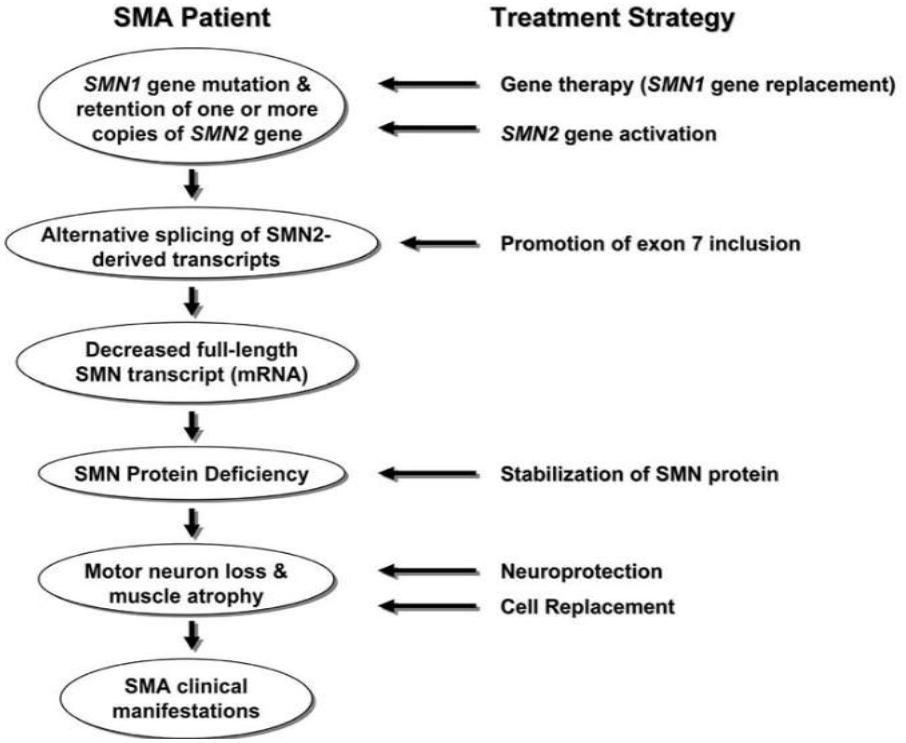
- The responsible gene in this area is EIF2B5, encoding the epsilon-subunit of eukaryotic translation initiation factor (eIF), eIF2B (Leegwater et al, 2001)

Under a variety of stress conditions protein synthesis is decreased. Stress may lead to misfolding and denaturation of proteins, contributing to cell death.

The inhibition of normal RNA translation during stress is thought to enhance cell survival by limiting the accumulation of denaturated proteins.

Spinal Muscular Atrophy and SMNp

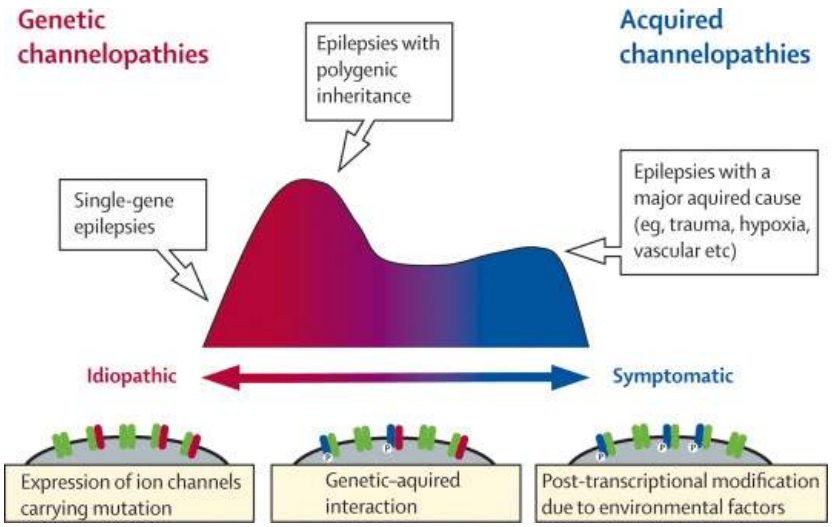




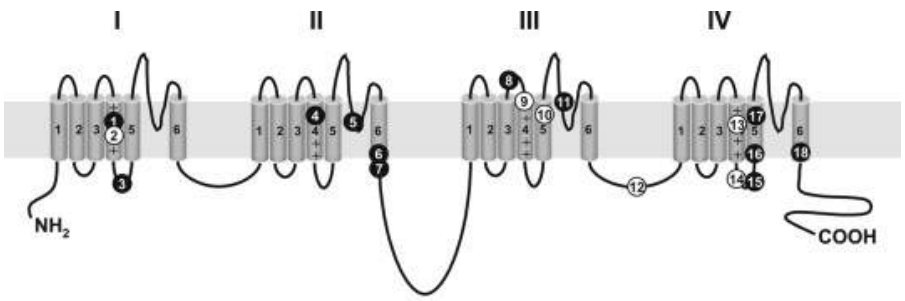
This SMN complex interacts with several other proteins, many of which are components of various **ribonucleoprotein complexes that are involved in distinct aspects of RNA processing**.
The SMN complex may, therefore, play a role in diverse aspects of RNA metabolism, including pre-RNA splicing, transcription, and metabolism of ribosomal RNAs.
Presently, the best-characterized function of the SMN complex is regulating the assembly of a specific class of RNA-protein complexes, the uridine-rich small nuclear ribonucleoproteins.

Epilepsy and ion channels

	Monogenic disorders	Susceptibility genes	Gene product
Autosomal dominant seizure syndromes of the first year of life			
Benign familial neonatal seizures	*KCNQ2* *KCNQ3*		Neuronal voltage-gated potassium channel subunits, responsible for M-current
Benign familial neonatal-infantile seizures	*SCN2A*		Neuronal voltage-gated sodium channel subunit
Febrile seizures, GEFS+, and Dravet syndrome			
GEFS+, febrile seizures, Dravet syndrome	*SCN1A*		Neuronal voltage-gated sodium channel, α1 subunit
GEFS+	*SCN1B*		Neuronal voltage-gated sodium channel, β1-subunit
GEFS+, febrile seizures, Dravet syndrome	*GABRG2*		γ2-subunit of the neuronal $GABA_A$ receptor
GEFS+		*GABRD*	δ-subunit of the $GABA_A$ receptor
Idiopathic generalised epilepsy			
Childhood absence epilepsy	*GABRG2*†‡		γ2-subunit of the neuronal $GABA_A$ receptor
Juvenile myoclonic epilepsy	*GABRA1*§		α1-subunit of the neuronal $GABA_A$ receptor
Various phenotypes	*CLCN2*†		Voltage-gated chloride channel
Childhood absence epilepsy		*CACNA1H*¶	Neuronal voltage-gated T-type calcium channel subunit
Juvenile myoclonic epilepsy		*EFHC1*‖	Protein of unknown function with Ca^{2+}-binding EF-hand motifs

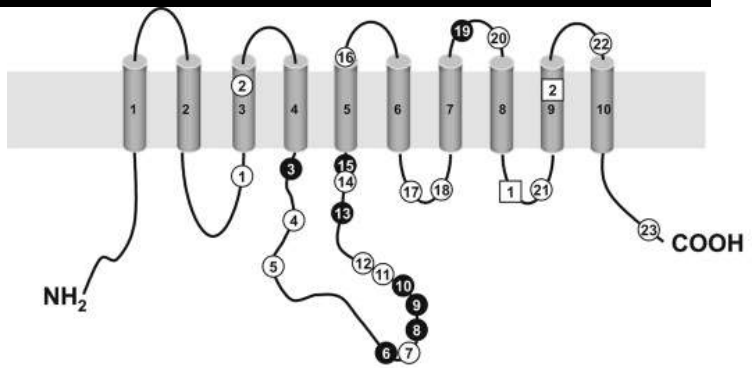


Familial Haemiplegic Migraine, Ca Channel and K-Na ATPase



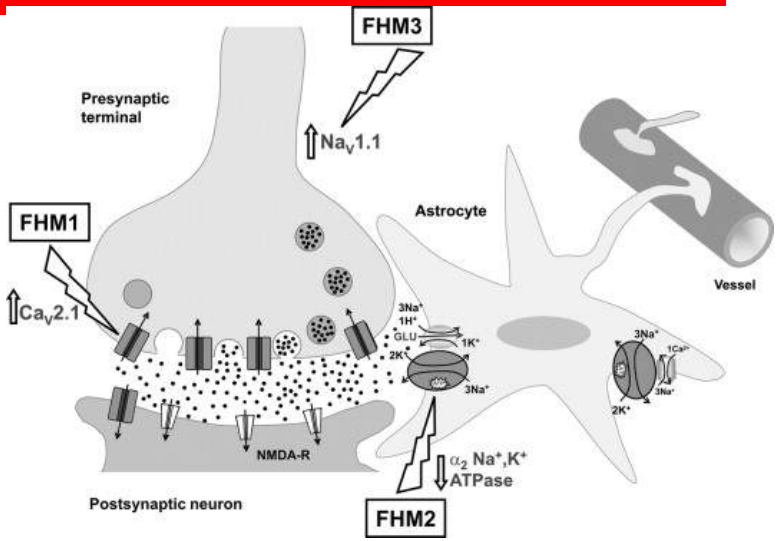
1 R192Q	5 T666M	9 R1347Q	13 R1667W	17 I1710T
2 R195K	6 V714A	10 Y1385C	14 L1682P	18 I1811L
3 S218L	7 D715E	11 V1457L	15 W1684R	
4 R583Q	8 K1336E	12 C1534S	16 V1696I	

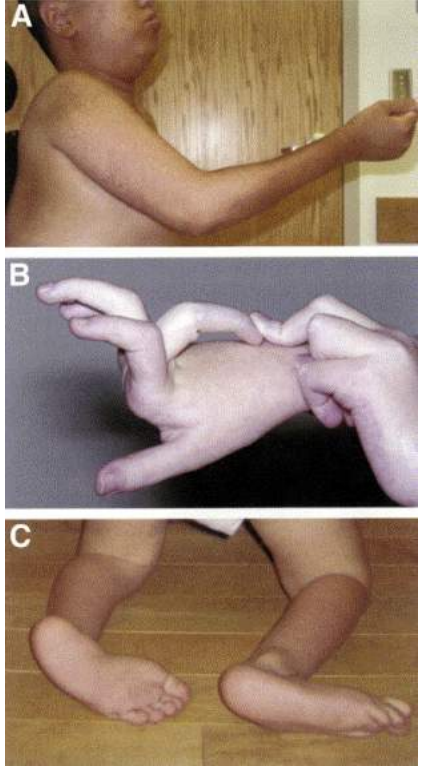
Secondary structure of the Cav2.1 α1 subunit and location of the familial hemiplegic migraine 1 mutations identified so far



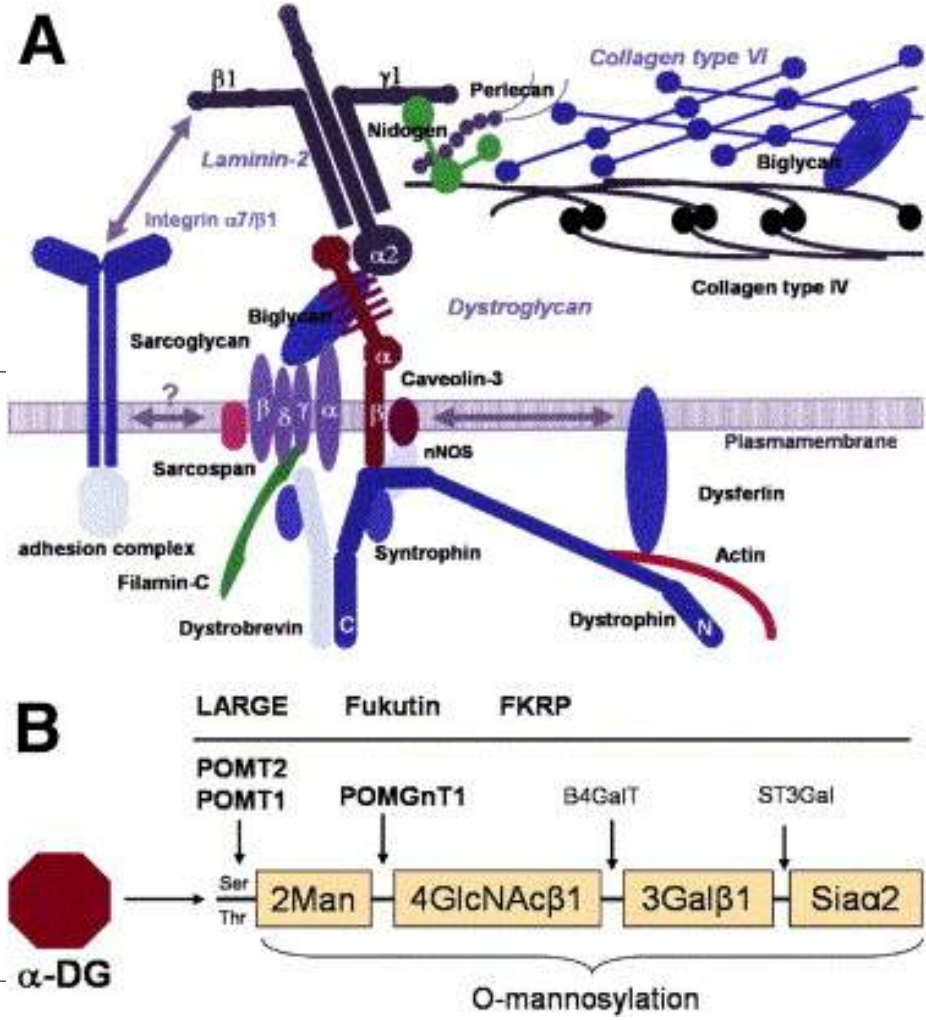
1 T263M	6 R593W	11 E700K	16 P796R	21 R937P
2 G301R	7 A606T	12 D718N	17 M829R	22 P979L
3 T345A	8 G615R	13 M731T	18 R834Q	23 X1021R
4 T376M	9 V628M	14 R763H	19 W887R	1 del 5aa ins I
5 R383H	10 R689Q	15 L764P	20 E902K	2 del CT (S966fs)

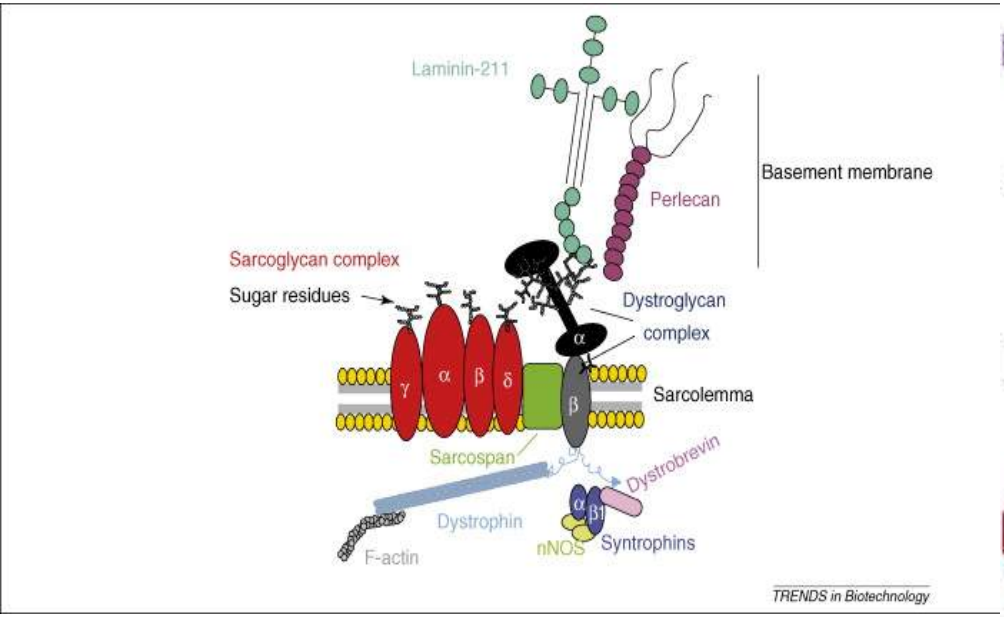
Secondary structure of the Na+,K+-ATPase α2 subunit and location of the familial hemiplegic migraine 2 mutations





From congenital muscle dystrophies to muscle protein functions





Minor clinical findings in heterozygous carriers in recessive diseases

- The finding that heterozygous carriers of Gaucher's mutations may have an higher incidence of Parkinson's diseases and that glucocerebrosidase activity interacts with synuclein in the brain has been reported from several years.
- Similarly, Nieman Pick type C patients have protein tau and amyloid deposits in the brain similar to Alzheimer disease and increase of susceptibility for dementia is present in heterozygous subjects.
- Several other neurometabolic genetic diseases have shown evidences that low enzyme activity in carrier range may be a susceptible factor for minor pathological conditions.

Clin Genet. 1984 May;25(5):381-415.

Clinical consequences of heterozygosity for autosomal-recessive diseases.

Vogel F.

Abstract

Heterozygotes of autosomal-recessive diseases can often be recognized by special heterozygote tests, since enzyme activities are normally reduced in comparison with the normal homozygote state. In Drosophila, the majority of recessive lethal mutations shows a reduction of fitness in heterozygotes, whereas in a strong minority fitness of heterozygotes is increased. This review will be devoted to a consideration of the extent to which heterozygotes for a wide variety of nominally recessive diseases are subject either to an increased liability for common diseases or slight shifts of behavioral characteristics. The available evidence has been collected and will be discussed in three steps: Most studies are available for phenylketonuria. For this group of diseases, **a slight reduction of average--especially verbal--I.Q. in heterozygotes has been reported together with signs of a slightly increased cerebral irritability, a possible slight increase of risk for mental disease, and an increase of blood phenylalanine levels in stress situations.** The PKU example is used to discuss methodological problems involved in such studies. Other conditions for which relevant deviations in heterozygotes are possible or even likely include among others **lipid storage diseases, microcephaly, myoclonus epilepsy, Wilson's disease, galaktokinase deficiency, homocystinuria, recessive myotonia and ataxia- teleangiectasia (increased cancer risk)**. Since heterozygotes for autosomal recessive diseases are common, it is possible that an appreciable fraction of "multifactorial" genetic liabilities for common, "constitutional" or mental disease might simply be due to heterozygosity for genes whose homozygous affects are already well known. By the same token, much of the "normal" genetic variability influencing cognitive performance (I.Q.)--especially in the lower range--and personality characteristics could also be caused by recessive genes in the heterozygous state.

Clin Genet. 2006 Oct;70(4):275-82.

Heterozygosity for a Mendelian disorder as a risk factor for complex disease.

Sidransky E[1].

Abstract

While genetic diseases are generally classified as being either 'simple' monogenic or 'complex' polygenic, the distinction between Mendelian and complex disorders is becoming increasingly blurred. Mendelian disorders may demonstrate qualities more typical of multifactorial diseases through shared clinical presentations, the effect of genetic modifiers, moonlighting proteins, synergistic heterozygosity, disease manifestations in heterozygotes and situations where heterozygosity for a 'simple' disorder proves to be a risk factor for seemingly unrelated complex diseases. A recent example of the last instance is the observation that mutations in glucocerebrosidase, the enzyme deficient in Gaucher disease, may be a risk factor for the development of Parkinson disease and other synucleinopathies. Insights gleaned from the study of Mendelian disorders may ultimately lead to a better understanding of factors influencing complex diseases.

Examples of blurred boundaries between Mendelian and complex disorders

- Mendelian disorders manifesting as common complex diseases
- Heterozygotes expressing disease manifestations under stress conditions
- Expressing females in X-linked disorders
- The influence of genetic modifiers
- Heterozygote mothers carrying an affected fetus at risk
- Synergistic heterozygosity
- Involvement of contiguous genes resulting from a chromosomal rearrangement or deletion
- Moonlighting' enzymes
- Heterozygotes being at increased risk for other diseases

Heterozygosity for a Mendelian disorder as a risk factor for complex disease

Mutations in the gene for:	May increase the risk of:
Methylenetetrahydrofolate reductase	Atherothrombotic disease
Factor V and prothrombin	Stroke, recurrent miscarriages
Alpha-1-antitrypsin	Chronic obstructive pulmonary disease
CFTR	Obstructive azoospermia,chronic pancreatitis
Glycerol kinase	Diabetes
Glucocerebrosidase	Parkinson disease
Ataxia-teleangiectasia	Tumors
Galactosemia	Cataracts

- CFTR, cystic fibrosis transmembrane regulator.

Mutations for Gaucher disease confer high susceptibility to Parkinson disease.

Mitsui J, Mizuta I, Toyoda A, Ashida R, Takahashi Y, Goto J, Fukuda Y, Date H, Iwata A, Yamamoto M, Hattori N, Murata M, Toda T, Tsuji S.

Arch Neurol. 2009 May;66(5):571-6

The p.L302P mutation in the lysosomal enzyme gene *SMPD1* is a risk factor for Parkinson disease

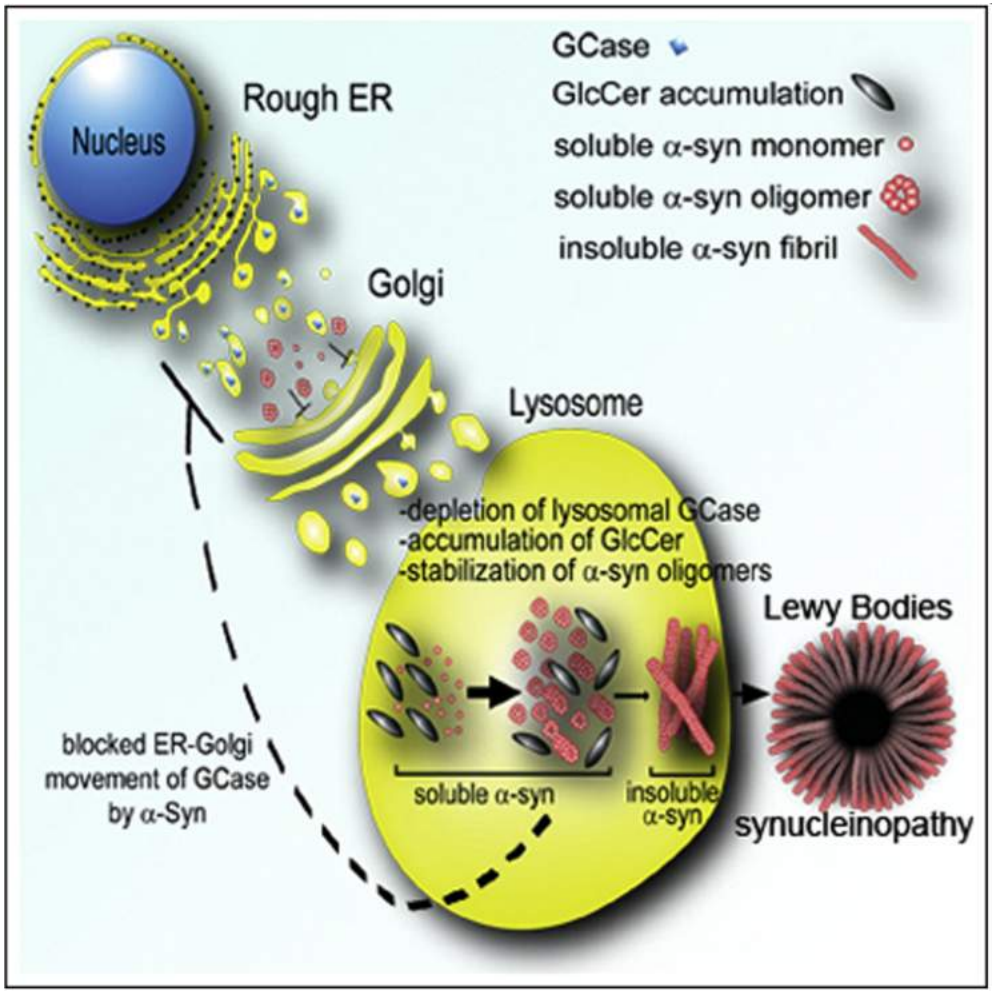
Ziv Gan-Or et al

Neurology, April 23, 2013 80:1606-1610

Cell. 2011 Jul 8;146(1):37-52.

Gaucher disease glucocerebrosidase and α-synuclein form a bidirectional pathogenic loop in synucleinopathies.

Mazzulli JR, Xu YH, Sun Y, Knight AL, McLean PJ, Caldwell GA, Sidransky E, Grabowski GA, Krainc D



Functional loss of GD-linked glucocerebrosidase (GCase) in primary cultures or human iPS neurons compromises lysosomal protein degradation, causes accumulation of α-synuclein (α-syn), and results in neurotoxicity through aggregation-dependent mechanisms.

Glucosylceramide (GlcCer), the GCase substrate, directly influenced amyloid formation of purified α-syn by stabilizing soluble oligomeric intermediates.

α-syn inhibits the lysosomal activity of normal GCase in neurons and idiopathic PD brain, suggesting that GCase depletion contributes to the pathogenesis of sporadic synucleinopathies.

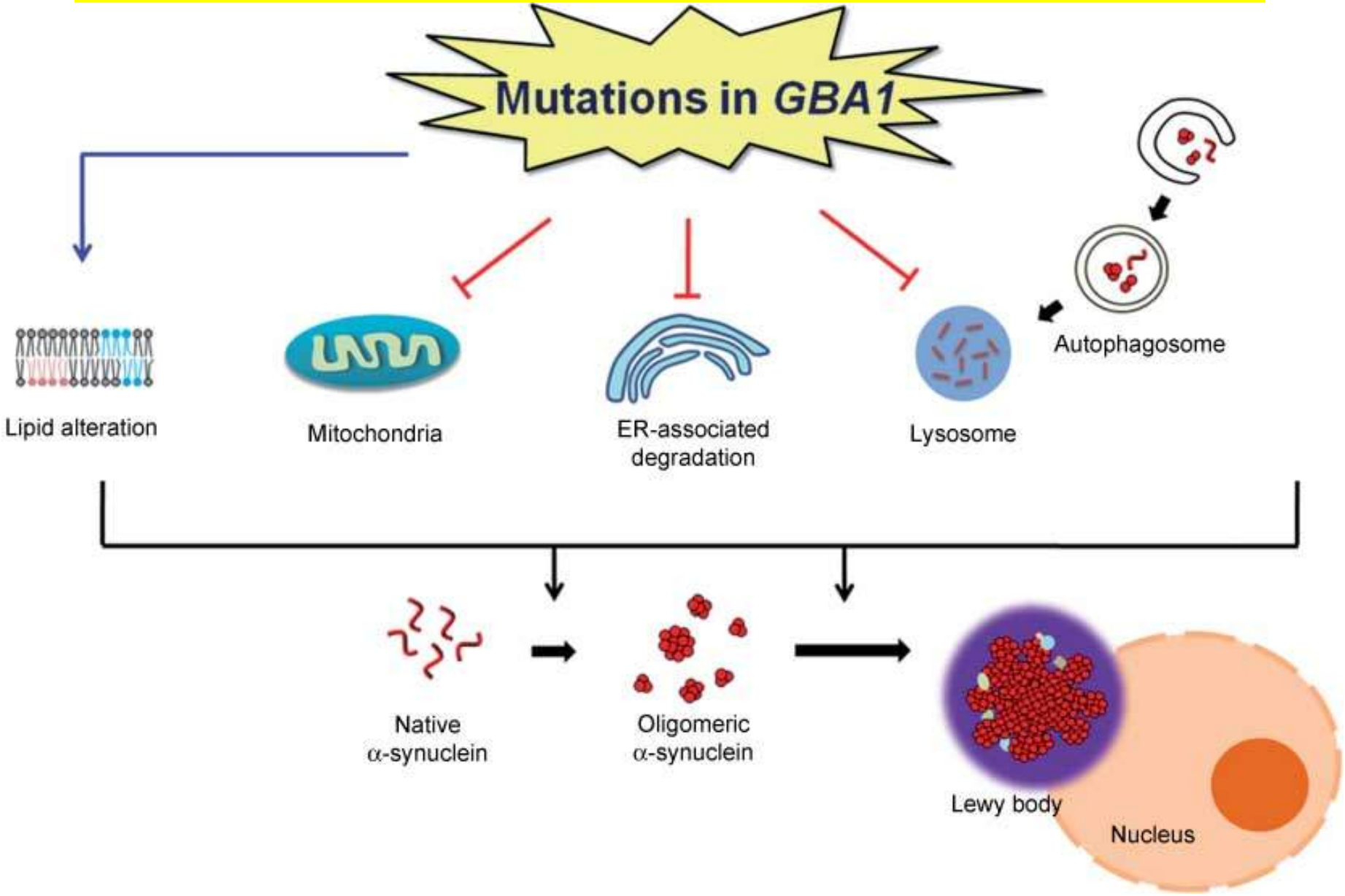
These findings suggest that the bidirectional effect of α-syn and GCase forms a positive feedback loop that may lead to a self-propagating disease.

Therefore, improved targeting of GCase to lysosomes may represent a specific therapeutic approach for PD and other synucleinopathies.

Biol Chem. 2013 Jul;394(7):807-18.

Glucocerebrosidase, a new player changing the old rules in Lewy body diseases.

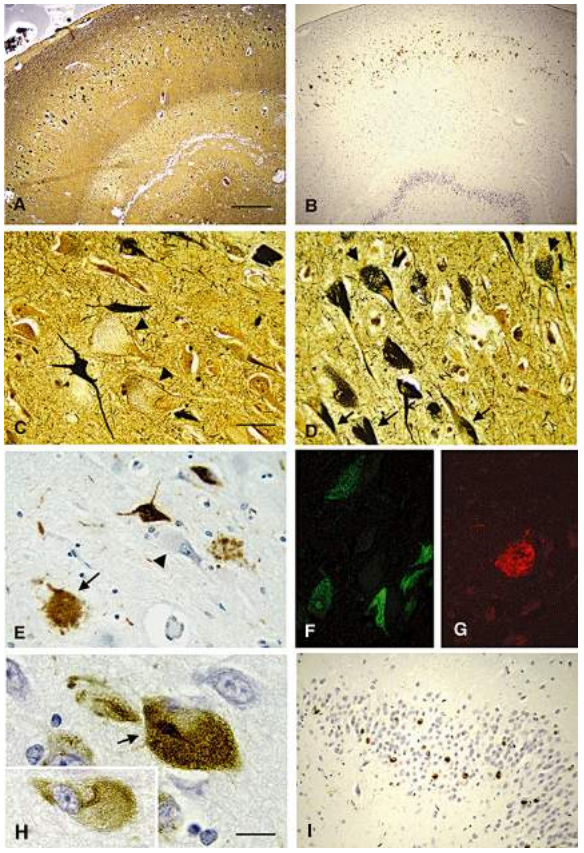
Yang NY[1], Lee YN, Lee HJ, Kim YS, Lee SJ.



Neurofibrillary tangles in Niemann-Pick type C disease

Love S et al, Brain 118: 119-29, 1995

- **The tangles were argyrophillic, fluorescent, strongly reacting with antibody to tau protein; some immunostained for ubiquitin.**
- **They consist ultrastructurally of paired helical filaments identical to those of AD and are related with the abnormal storage material**



{gamma}-Secretase-dependent amyloid-{beta} is increased in Niemann-Pick type C: A cross-sectional study.

Mattsson N, Zetterberg H, Bianconi S, Yanjanin NM, Fu R, Månsson JE, Porter FD, Blennow K.

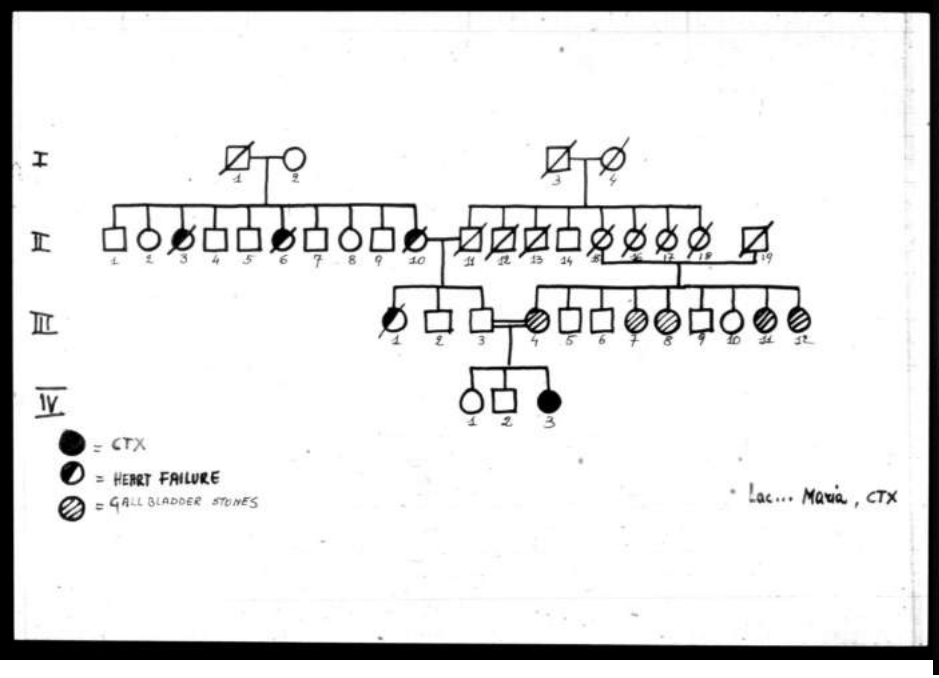
Neurology. 2011 Jan 25;76(4):366-372.

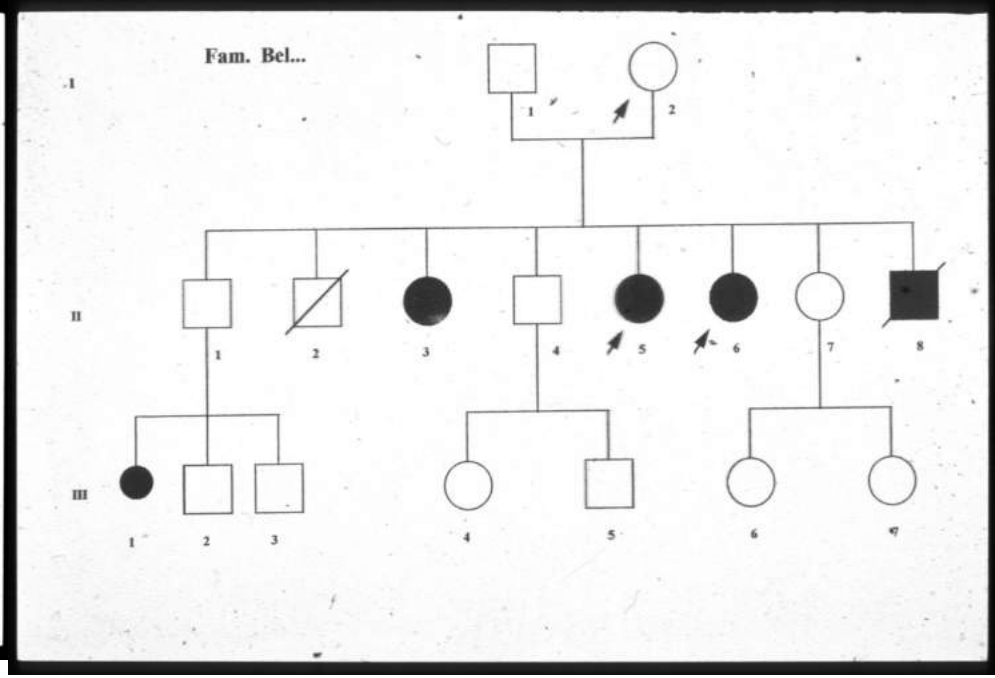
Variation in NPC1, the gene encoding Niemann-Pick C1, a protein involved in intracellular cholesterol transport, is associated with Alzheimer disease and/or aging in the Polish population.

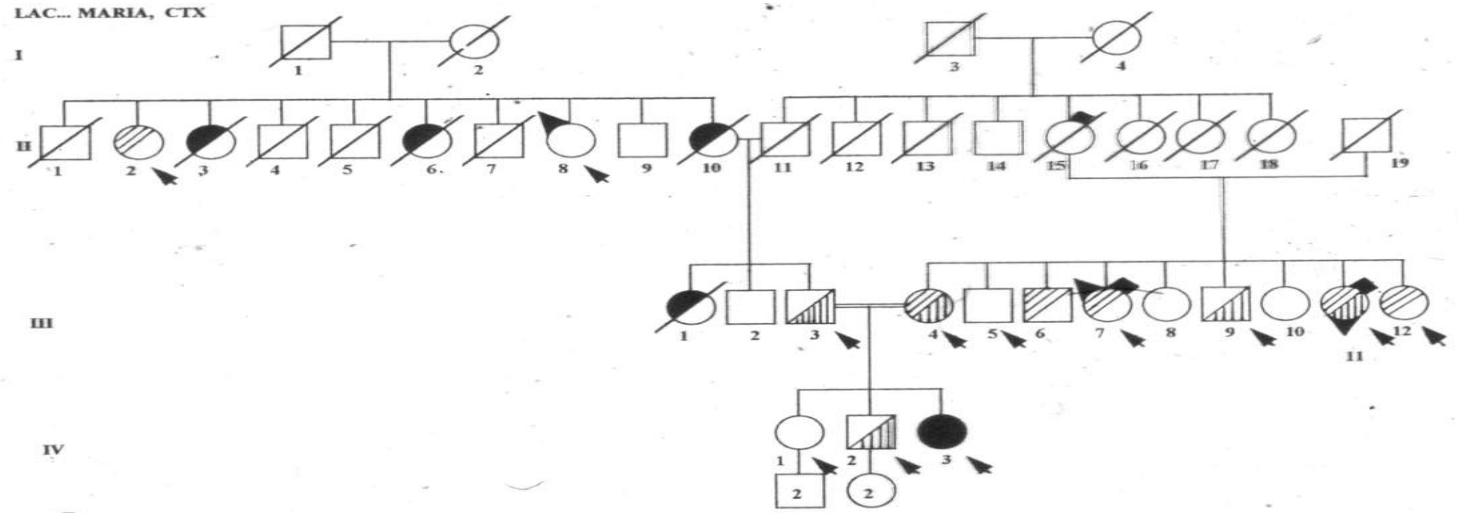
Erickson RP, Larson-Thomé K, Weberg L, Szybinska A, Mossakowska M, Styczynska M, Barcikowska M, Kuznicki J.

Neurosci Lett. 2008 Dec 12;447(2-3):153-7.

- There is abundant evidence that cholesterol metabolism, especially as mediated by the intercellular transporter APOE, is involved in the pathogenesis of sporadic, late-onset Alzheimer disease (SLAD). Identification of other genes involved in SLAD pathogenesis has been hampered since gene association studies, whether individual or genome-wide, experience difficulty in finding appropriate controls in as much as 25% or more of normal adults will develop SLAD.
- Using 152 centenarians as additional controls and 120 "regular", 65-75-year-old controls, an association of genetic variation in NPC1 with SLAD and/or aging has been found. In this preliminary study, we find gradients of two non-synonymous SNP's allele frequencies in NPC1 from centenarians through normal controls to SLAD in this non-stratified Polish population. An intervening intronic SNP is not in Hardy-Weinberg equilibria and differs between centenarians and controls/SLAD. Haplotypes frequencies determined by fastPHASE were somewhat different, and the predicted genotype frequencies were very different between the three groups.
- These findings can also be interpreted as indicating a role for NPC1 in aging, a role also suggested by NPC1's role in Dauer formation (hibernation, a longevity state) in Caenorhabditis elegans.


= CTX
= HEART FAILURE
= GALL BLADDER STONES
Lac... Maria, CTX

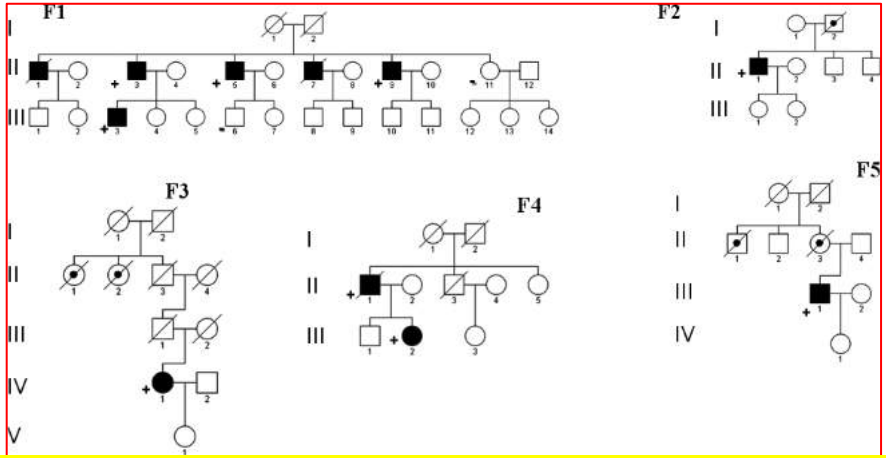

Fam. Bel...

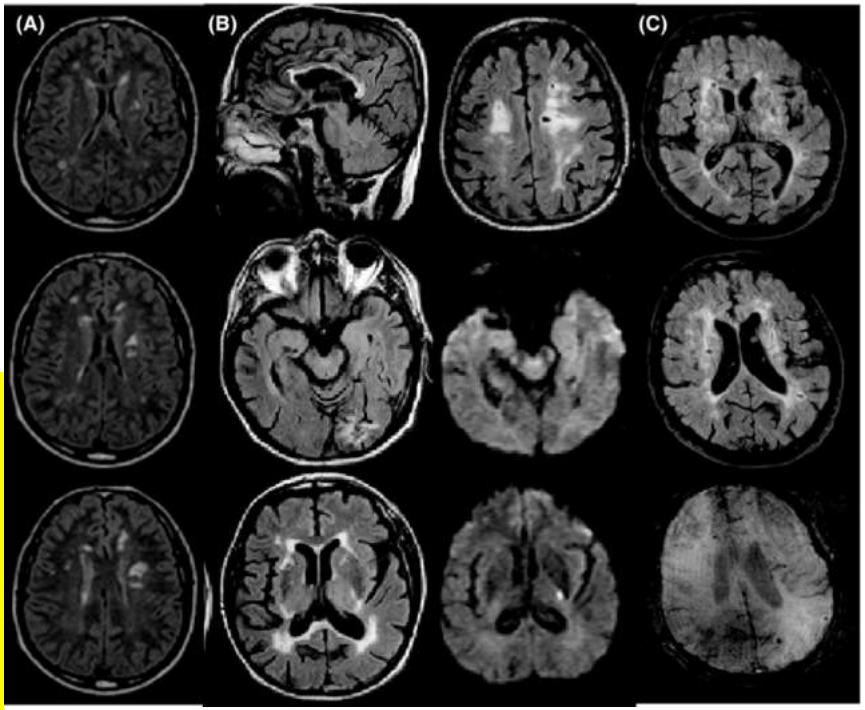

LAC... MARIA, CTX
= CTX
= HEART FAILURE
= GALL BLADDER STONES
= NEPHROLITHIASIS
= CATARACT
= LIPOMA
= PSYCHIATRIC PROBLEMS
III, 4; III, 11; III, 12: THYROID DYSFUNCTION
III, 11; III, 12; IV, 3: XANTELASMA
II , 8; II, 15: DIABETES

Heterozygous mutations of HTRA1 gene in patients with familial cerebral small vessel disease.

Di Donato I, Bianchi S, Gallus GN, Cerase A, Taglia I, Pescini F, Nannucci S, Battisti C, Inzitari D, Pantoni L, Zini A, Federico A, Dotti MT.

CNS Neurosci Ther. 2017 Sep;23(9):759-765



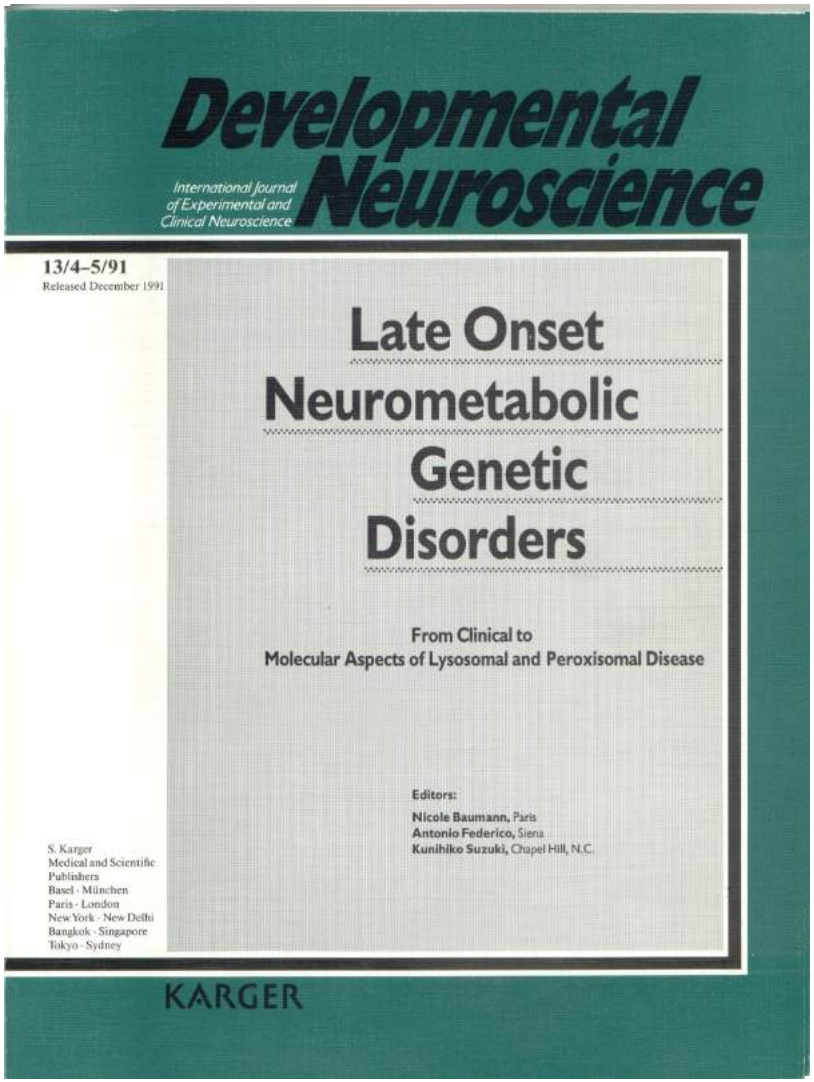


- Brain MRI findings. (A) Periventricular white matter Fazekas grade 1 and deep white matter Fazekas grade 2 involvement including internal capsules (Patient F1-III,3, age 46, serial consecutive axial FLAIR images); (B) Periventricular and deep white matter Fazekas grade 3 involvement including external and internal capsules and corpus callosum, lacunar infarcts, subacute ischemia in the left internal capsule, previous infarction in the left occipital lobe, and supratentorial subcortical atrophy, without involvement of anterior temporal lobes (Patient F1-II,5, age 67, serial nonconsecutive axial FLAIR and DWI images); (C) Periventricular and deep white matter Fazekas grade 3 involvement including external and internal capsule, lacunar infarcts, microbleeds, and supratentorial subcortical atrophy (Patient F5-III,1, age 60, sagittal nonconsecutive axial FLAIR and SWI images

Early and late onset forms

In children, the phenotype of inborn errors of metabolism has well known and the strategy of investigation have been developed from many years

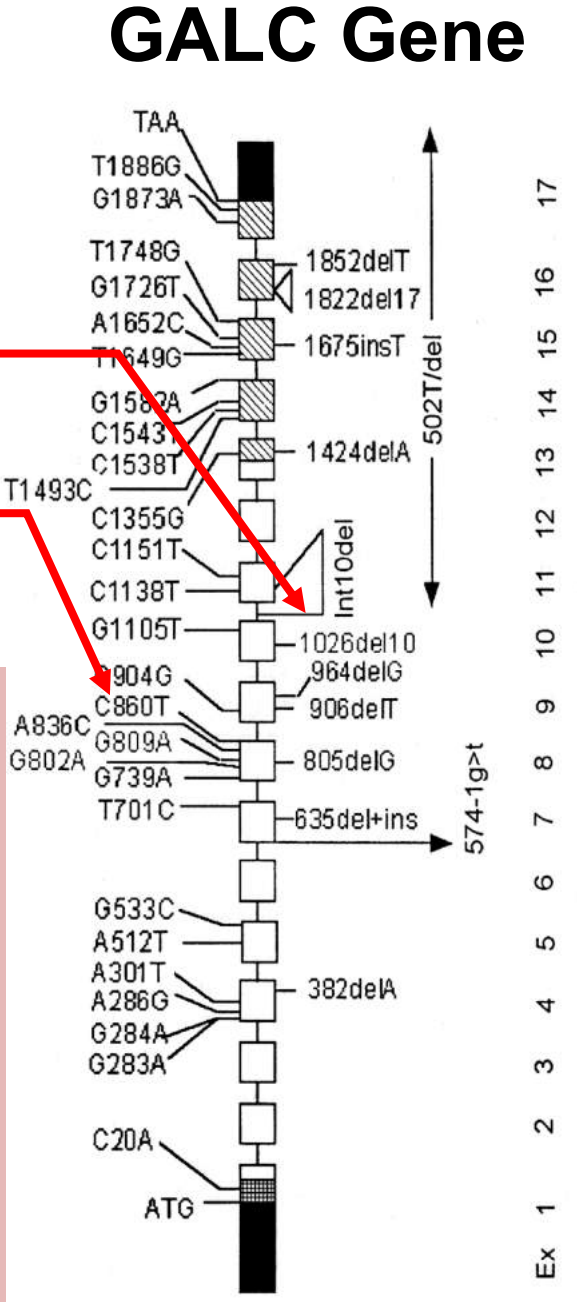
Every known condition presenting in childhood may have a less severe clinical presentation leading to signs only in later ages



Adult-Onset KD GALC Gene Analysis

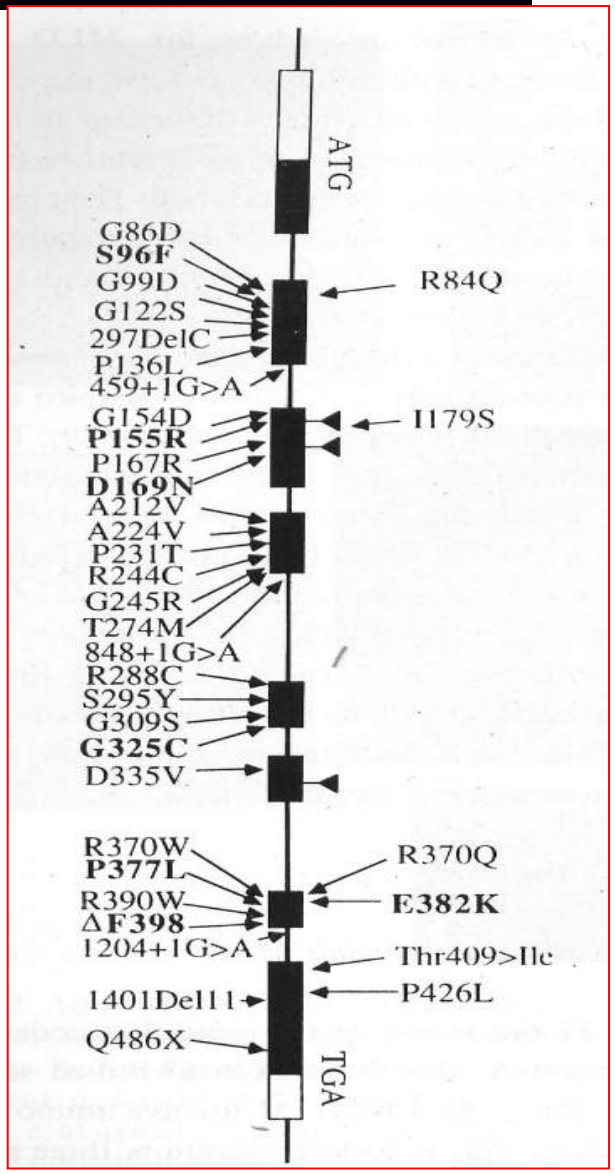
Mutations

- **1026del10**
- **G809A**



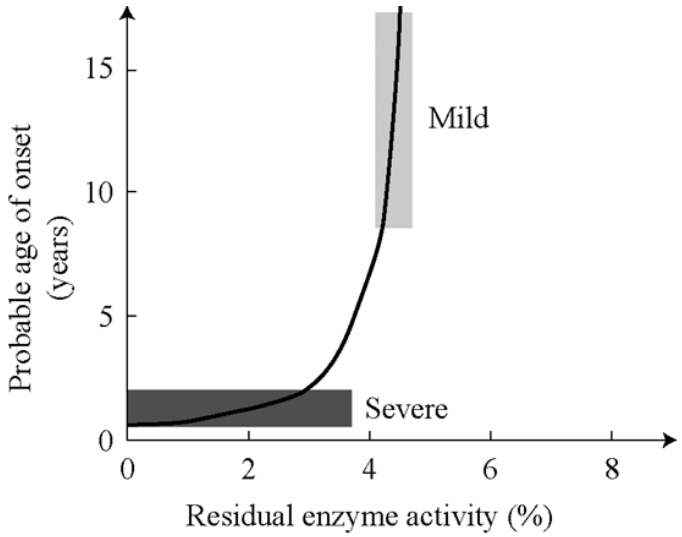
Metachromatic leucodystrophy

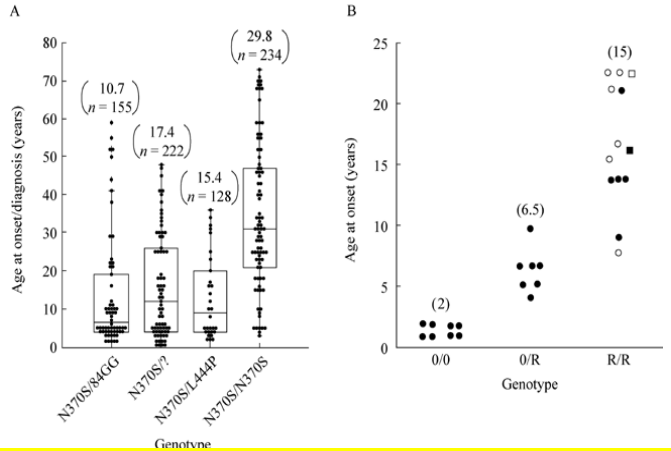
- The three clinical forms are characterized by different levels of ASA activity (severely deficient in early form and with a significant residual activity in adult)
- Variation in residual ASA activity differently regulates substrate storage in lysosomes and consequently influences the clinical evolution



Pathogenesis of Late onset neurometabolic diseases

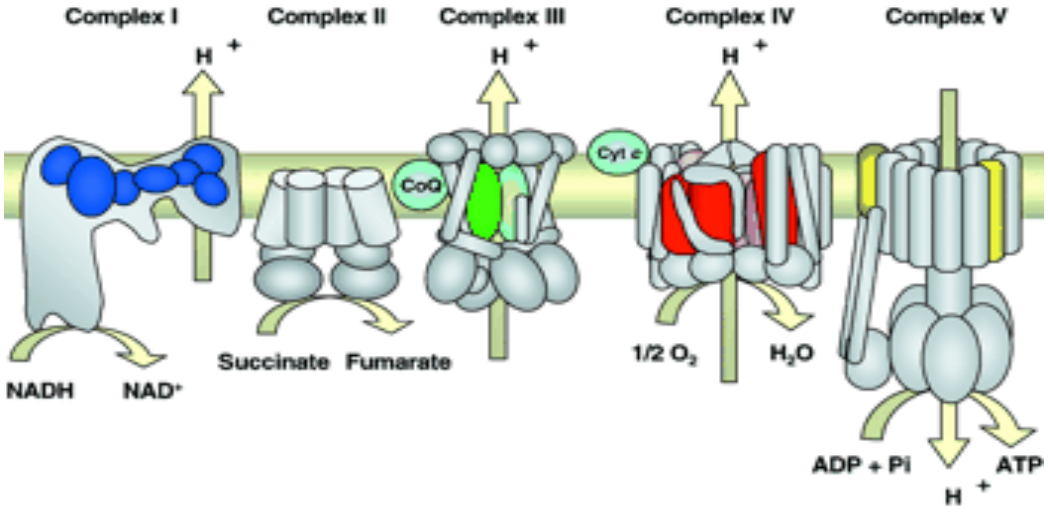
- **The clinical characteristics of the disease would depend on the speed with which the substrate accumulates.**
- **A very severe enzyme deficiency completely arrests metabolism, originating a rapidly progressive disease, with early onset**
- **If there is still some residual enzyme activity (10-30%), it may be sufficient to degrade most of substrates, originating a less severe form, with late onset and slow progression**

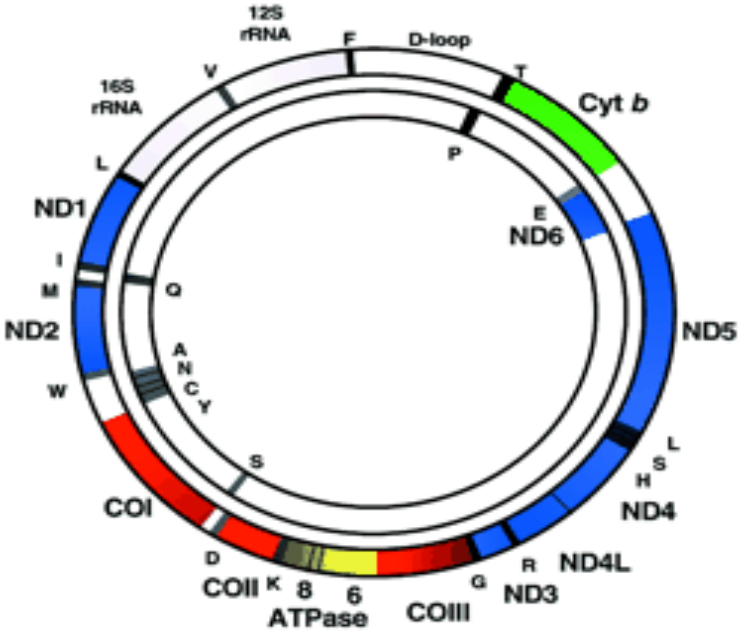


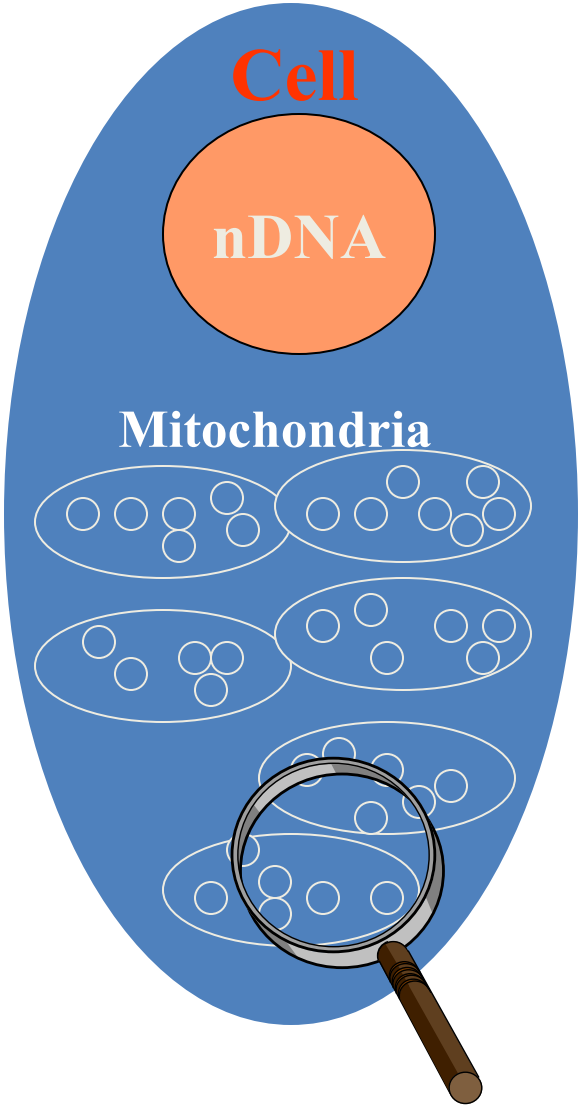


What can cell biology tell us about heterogeneity in lysosomal storage diseases?
V. Gieselmann
Acta Paediatrica, 2005; Vol. 94, (Suppl. 447): pp 80-86

Mitochondrial genome







Pathogenesis of Late onset neurometabolic diseases

- **If a subject is born with an abnormal DNA which give rise to an abnormal genetic product manifestating as a disease, how can the phenomenon of late onset of symptoms be explained?**

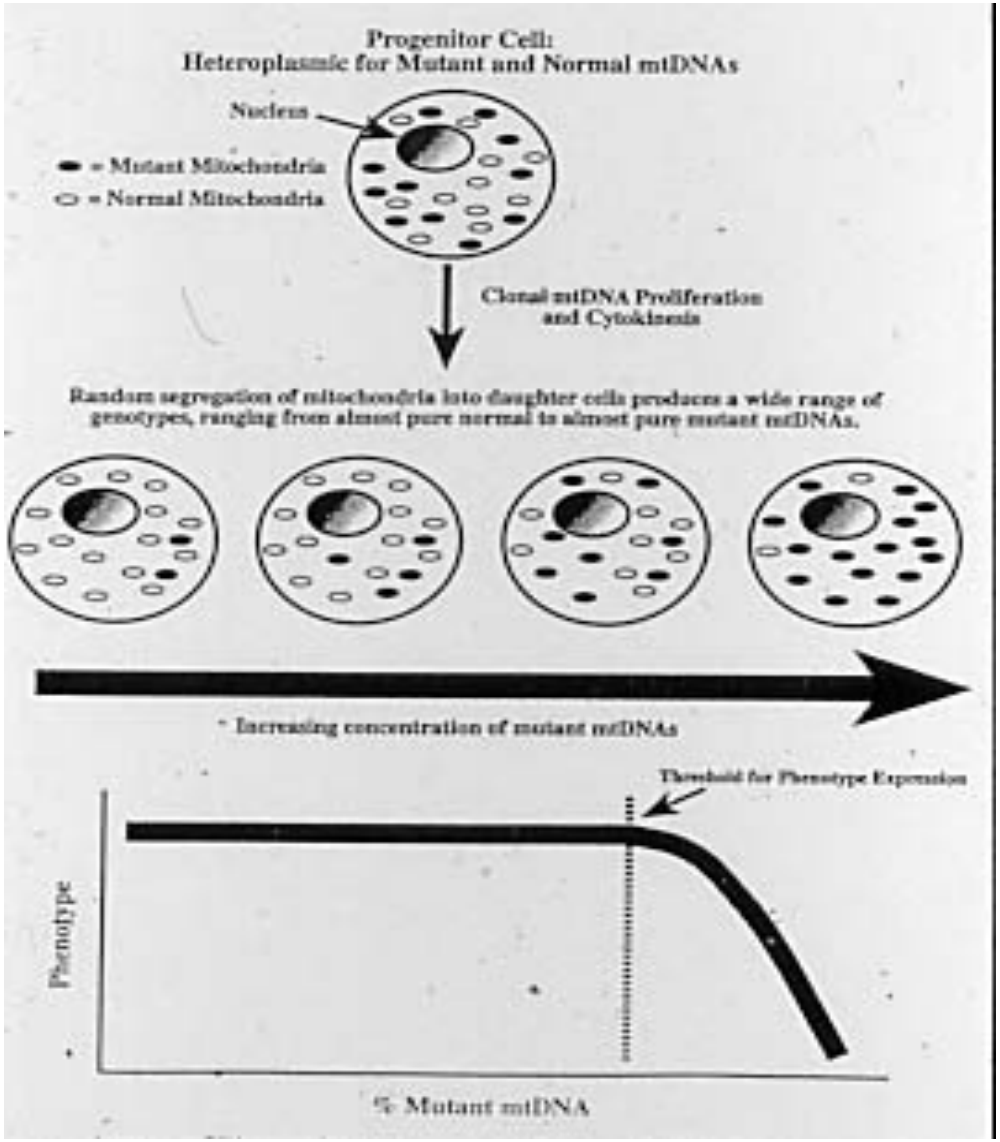
Pathogenesis of Late onset neurometabolic diseases

- **The slow evolution of the adult forms of the neurometabolic diseases may be correlated with a degree of residual enzyme activity sufficient to allow embryonic and post-natal development and nervous system function by manifesting in clinical symptoms only in adulthood.**

Pathogenesis of Late onset neurometabolic diseases

- **This data suggests the existence of a complex system of biochemical and molecular regulation of enzyme activity that may be inpaired in different ways in early and late-onset diseases.**

Heteroplasmy as an explanation of late onset mitochondrial diseases



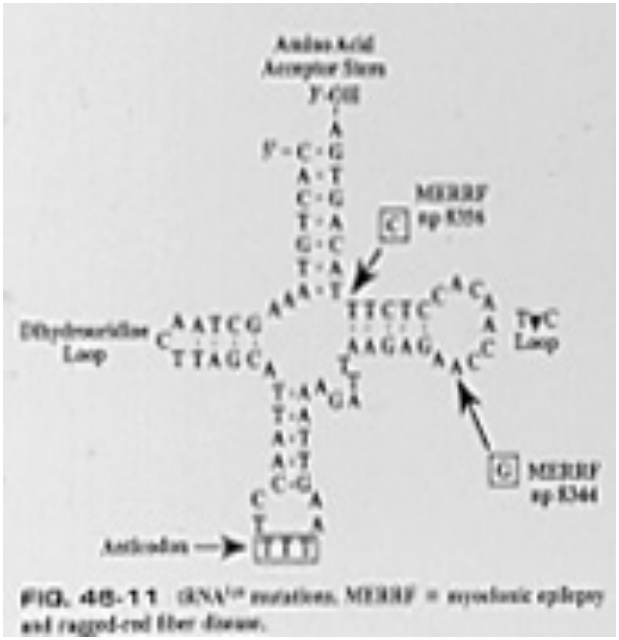
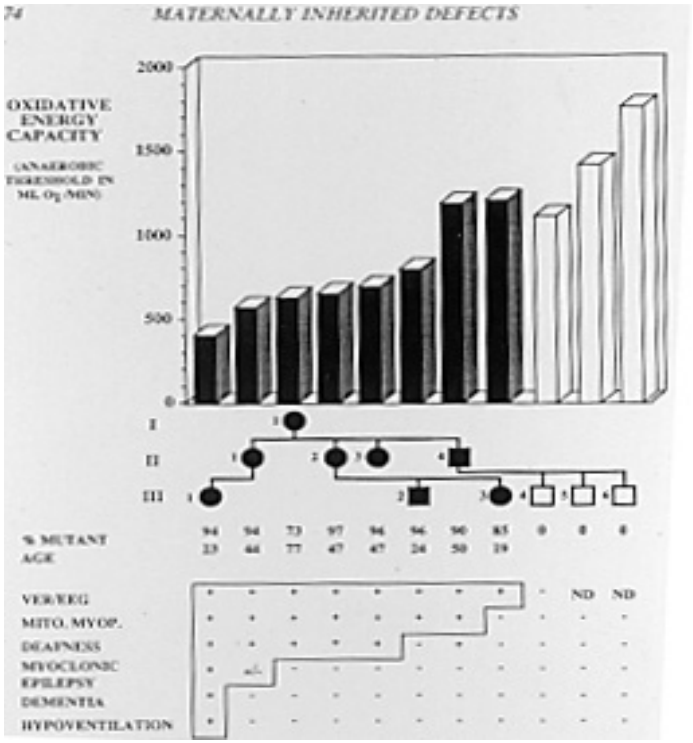
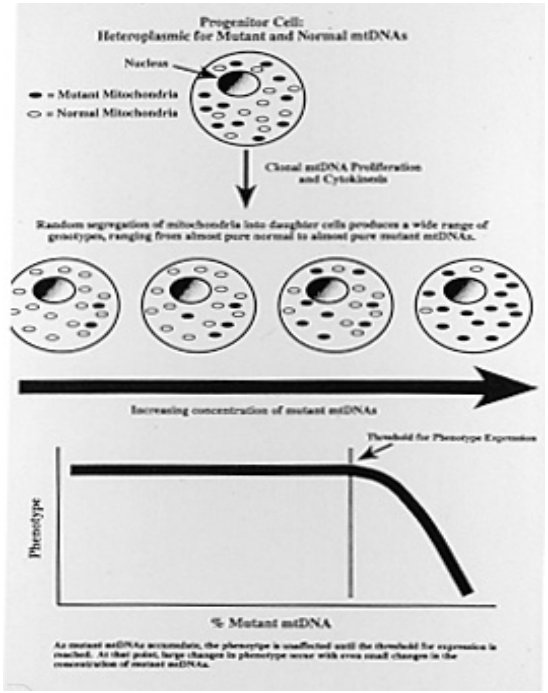


FIG. 48-11 tRNA[Leu] mutations. MERRF = myoclonic epilepsy and ragged-red fiber disease.





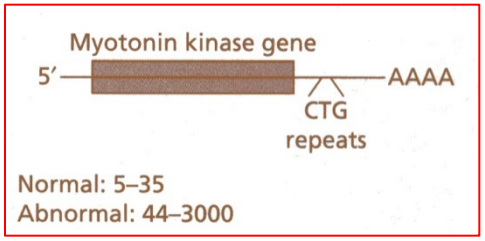
Late onset mitochondrial diseases

- **The number of mitochondria with mutant mitDNA varies with the severity of the clinical symptoms and with age.**
- **With ageing, many hearth, diaphragm and skeletal muscle cells in man and rats loss COX activity, even in absence of pathology.**
- **It seems likely that changes in mitochondrial genome, toghether with other mutations, can play an important role in the phenomena of physiologic aging.**

Late onset mitochondrial diseases

- **MitDNA is more vulnerable than nuclear DNA**
- **It is more exposed to free radicals and does not seem to have adequate repair mechanisms.**
- **Mitochondrial with mutant mitDNA have a greater replication capacity than normal DNA (abnormal mitochondria can replace normal ones)**
- **In mitochondrial diseases and normal ageing, a mosaic distribution of fibrocells with mutant mitDNA in muscle may be caused by the different involvement of specific cell factors which can influence the speed of mutation, replication and repair of mitDNA, leading to the progressive replacement of healthy mitDNA with the mutant variety.**

Myotonic dystrophy



Pathogenesis of Late onset neurometabolic diseases (enzyme function impairement)

- Point mutation of the structural gene, with production of a protein that is not able to easily bind the substrate
- Insertion of a pair of bases or DNA deletion giving rise to protein devoid of catalytic activity
- Changes of proteins associated with maturation of the enzyme leading to the synthesis of a less stable immature form of the enzyme
- Faster degradation of the enzyme
- Enzyme carrier defect
- Abnormality of an enzyme activating factor

Phenotypic heterogeneity in neurometabolic diseases

Globoid cell leucodystrophy: a family with both late infantile and adult type.

Vedru P. et al. Neurology 41:1382,1991

X-linked adreno-myeloneuropathy associated with 14 novel ALD-gene mutations: no correlation between type of mutation and age of onset.

Wichers M. et al. Hum. Genet. 105:116,1999

Clinical heterogeneity

This is well known in many genetic conditions related to the

- **presence of multigene regulation,**
- **different molecular changes in the principal gene (point mutation, deletion, intron, etc)**
- **epigenetic factors.**
- **The gender influence in the clinical severity may suggest that some endocrine factor could also be involved.**

Clinical variability of phenotype

- Gene-gene interaction
- Gene-environment interaction

Gene-gene interaction

The example of ApoE genotype

Niemann-Pick type C disease: accelerated neurofibrillary tangle formation and amyloid deposition associated with apolipoprotein E epsilon4 homozygosity

M. Simons et al.

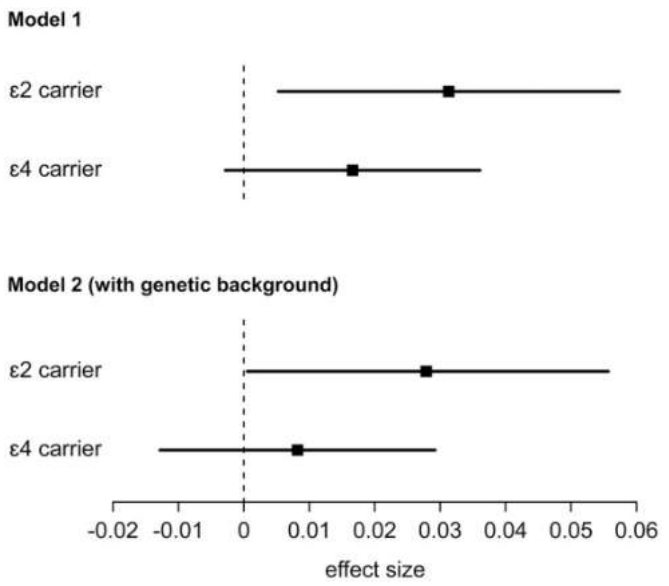
Ann. Neurol. 52: 351-354, 2002

J Cereb Blood Flow Metab. 2016 Jan;36(1):199-203.

APOE ε2 is associated with white matter hyperintensity volume in CADASIL.

Gesierich B, Opherk C, Rosand J, Gonik M, Malik R, Jouvent E, Hervé D, Adib-Samii P, Bevan S, Pianese L, Silvestri S, Dotti MT, De Stefano N, van der Grond J, Boon EM, Pescini F, Rost N, Pantoni L, Oberstein SA, Federico A, Ragno M, Markus HS, Tournier-Lasserve E, Chabriat H, Dichgans M, Duering M, Ewers M.

Apolipoprotein E (APOE) increases the risk for Alzheimer's disease (ε4 allele) and cerebral amyloid angiopathy (ε2 and ε4), but its role in small vessel disease (SVD) is debated. Here we studied the effects of APOE on white matter hyperintensity volume (WMHV) in CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), a nonamyloidogenic angiopathy and inherited early-onset form of pure SVD. Four hundred and eighty-eight subjects were recruited through a multicenter consortium. Compared with APOE ε3/ε3, WMHV was increased in APOE ε2 (P = 0.02) but not APOE ε4. The results remained significant when controlled for genome-wide genetic background variation. Our findings suggest a modifying influence of APOE ε2 on WMHV caused by pure SVD



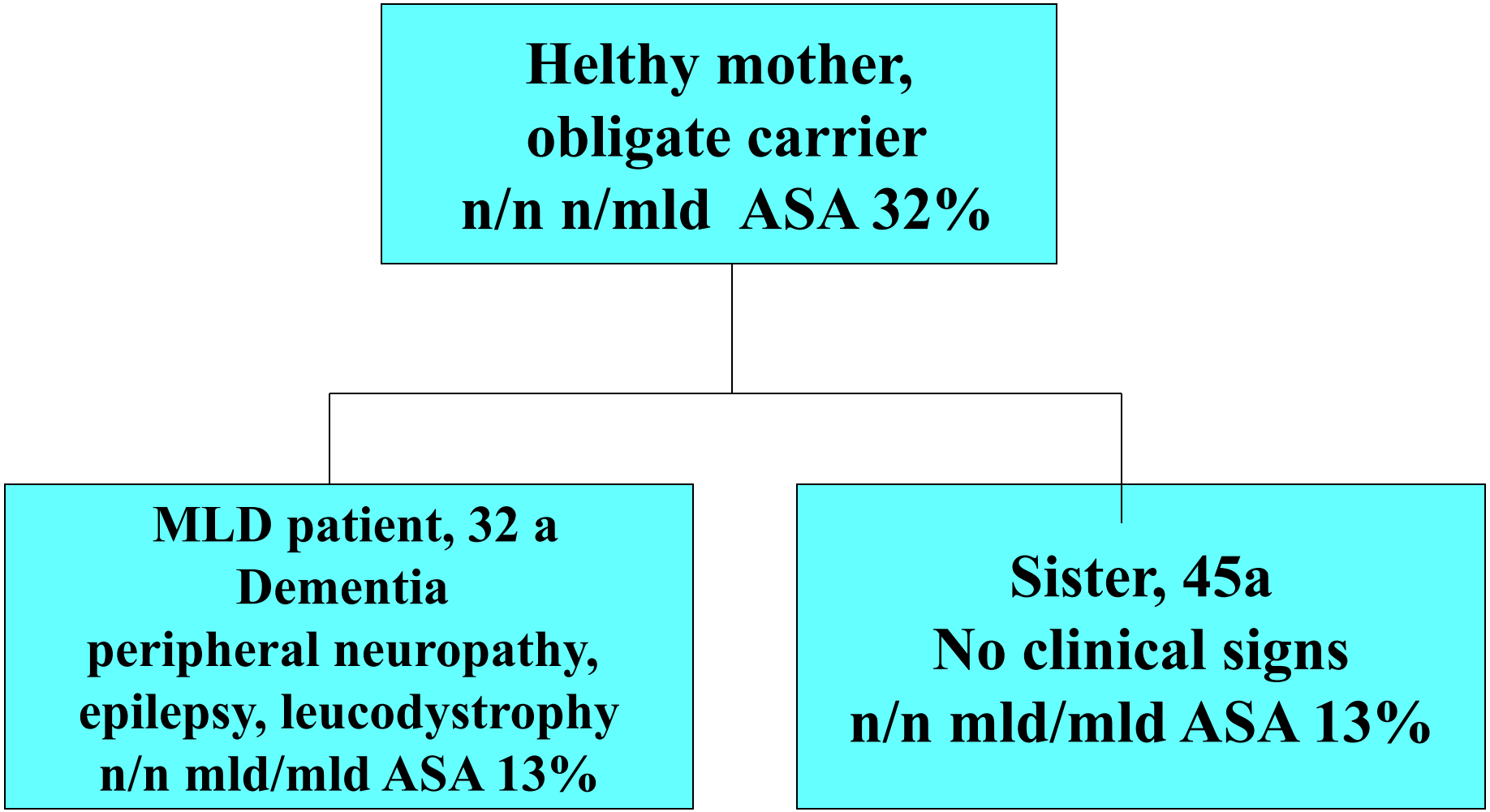
Neurosci Lett. 2001 Nov 2;313(1-2):69-72.

Influence of the prion protein and the apolipoprotein E genotype on the Creutzfeldt-Jakob Disease phenotype.

Van Everbroeck B[1], Croes EA, Pals P, Dermaut B, Jansen G, van Duijn CM, Cruts M, Van Broeckhoven C, Martin JJ, Cras P.

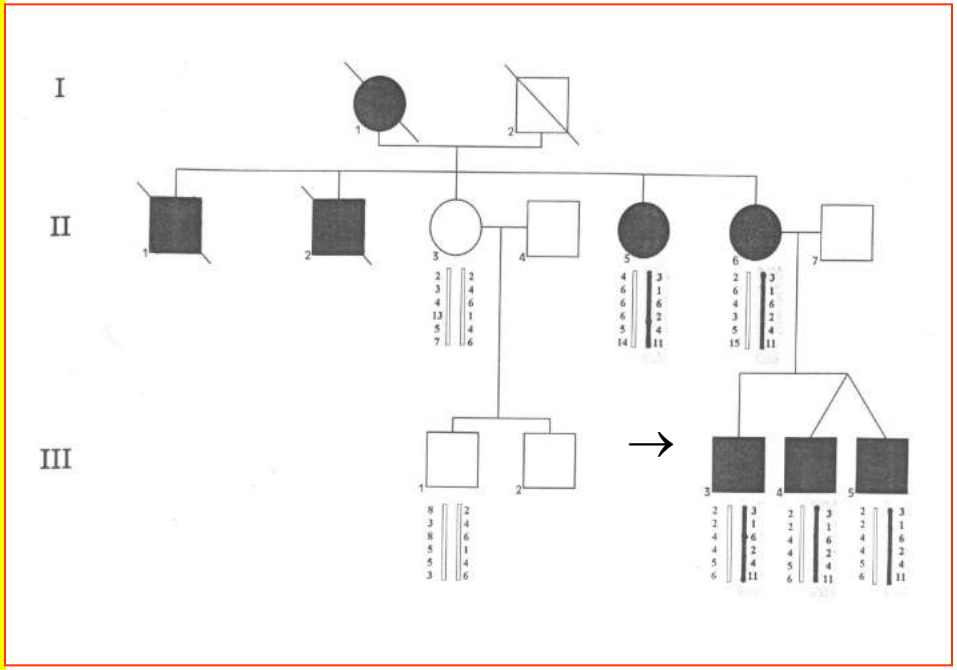
We investigated the risk associated with the codon 129 polymorphism in the prion protein gene (PRNP) and apolipoprotein E gene (APOE) isoforms for development of Creutzfeldt-Jakob disease (CJD) (n=126) and the possible influences on the disease pathology and its most important clinical characteristics. The PRNP M129V (PRNP129) polymorphism was determined using both DNA extracted from formalin fixed and paraffin embedded brain tissue (n=59) and leukocyte extracted DNA (n=67). In the latter group also the PRNP open reading frame and the APOE genotype were analysed and compared to a neurologically unaffected, age and sex matched control group (n=79). We found that methionine homozygosity of the PRNP129 increases the risk for developing CJD. PRNP129 also influenced the prion accumulation patterns in brain. **The APOE 4 allele was an independent risk factor for developing CJD. We further observed a significant dose dependent APOE 4 effect on the number and type of amyloid-beta plaques in the brain of CJD patients.**

Phenotypic variability in a MLD family



CADASIL/ Family Ter…

- III-3: 47 y migraine with aura, TIAs, depression, leukoencephalopathy
- **III-4 : 43 y, mild migraine, leukoencephalopathy, stroke. and dementia. He married. The wife underwent to prenatal diagnosis (affected), decided to continue the pregnancy**
- **III-5: 43 y, mild migraine, mild leukoencephalopathy. Normal QI**
- *II-6: 68y, pseudobulbar palsy, dementia, leukoencephalopathy
- II-5: 75y, mild depression, leukoencephalopathy
- II-1 & 2 died in the adolescence with severe neurological impairment
- I-1; died at 56y, dementia

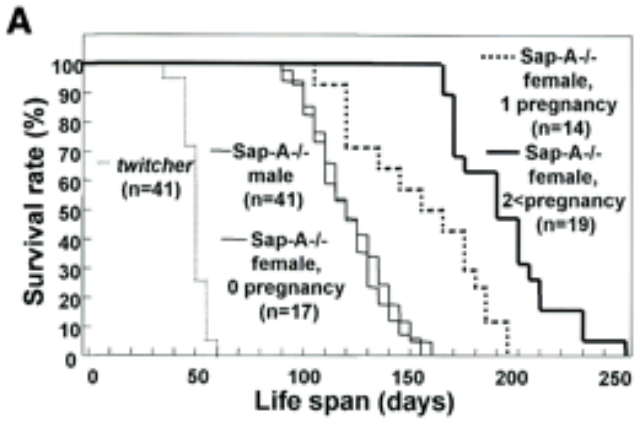


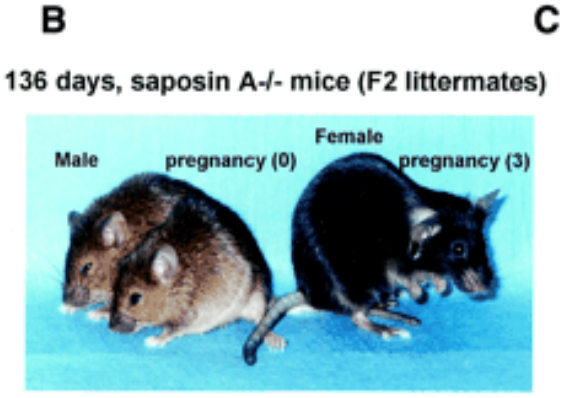
Exon 20 mutation
Arg®1076→Cys©

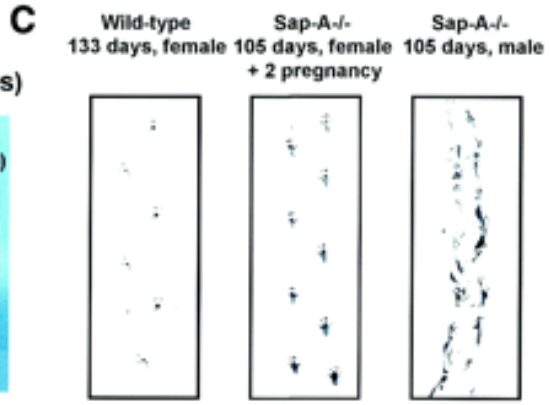
*II-6, Previous diagnosis of ortochromatic LD

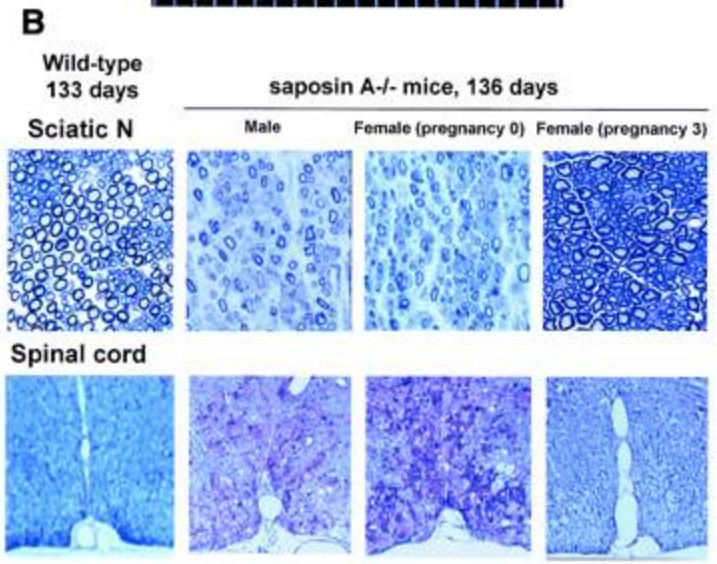
Other endogenous factors

Matsuda J, Vanier MT, Saito Y, Suzuki K, Suzuki K. Dramatic phenotypic improvement during pregnancy in a genetic leukodystrophy: estrogen appears to be a critical factor. Hum Mol Genet. 2001 Nov 1;10(23):2709-15





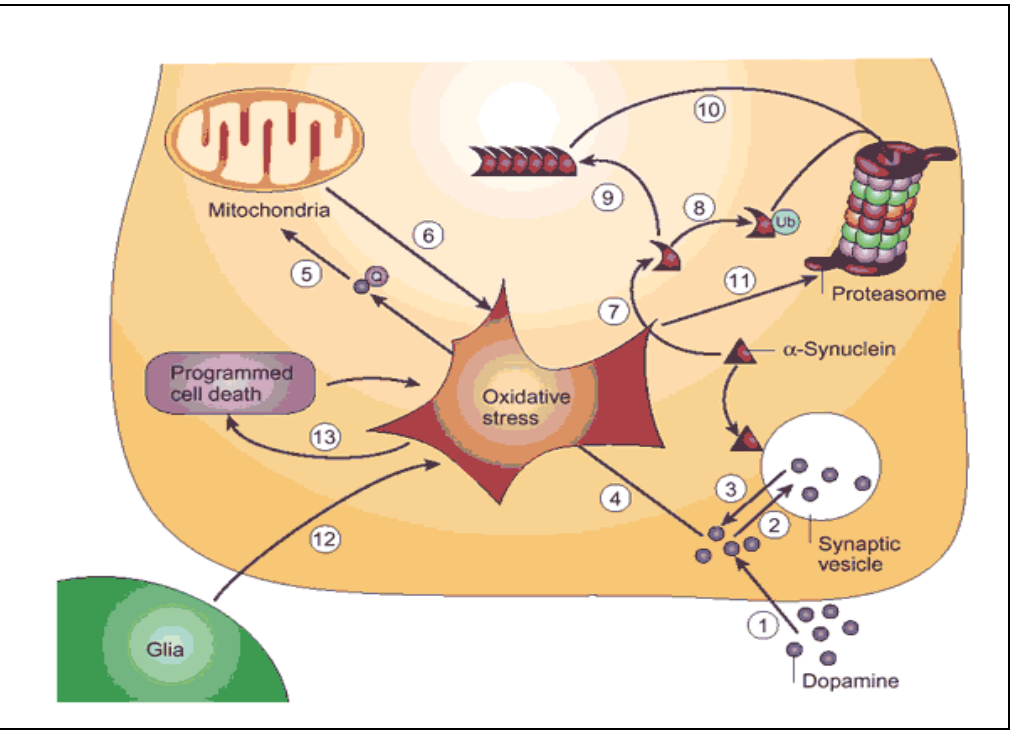




Formichi P, Radi E, Battisti C, Pasqui A, Pompella G, Lazzerini PE, Laghi-Pasini F, Leonini A, Di Stefano A, Federico A.

Psychosine-induced apoptosis and cytokine activation in immune peripheral cells of Krabbe patients.

J Cell Physiol. 2007 Sep;212(3):737-43.


Mitochondria
Programmed cell death
Oxidative stress
Glia
Ub
Proteasome
α-Synuclein
Synaptic vesicle
Dopamine
1
2
3
4
5
6
7
8
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11
12
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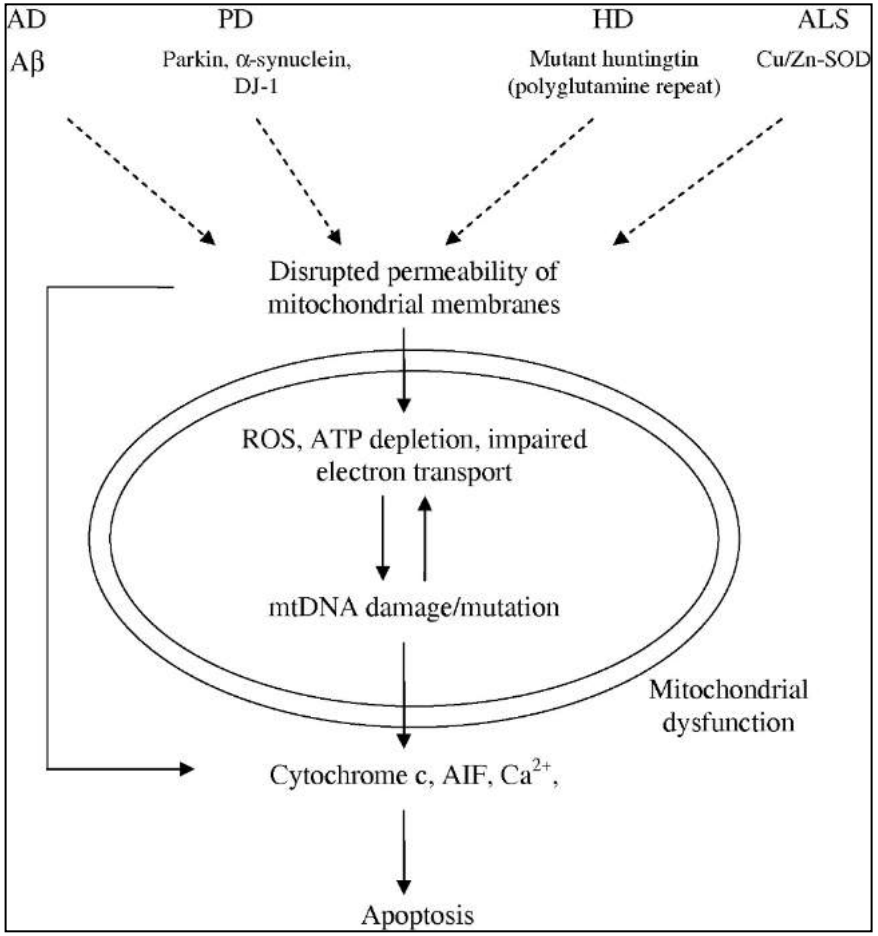

AD
Aβ
PD
Parkin, α-synuclein, DJ-1
HD
Mutant huntingtin (polyglutamine repeat)
ALS
Cu/Zn-SOD
Disrupted permeability of mitochondrial membranes
ROS, ATP depletion, impaired electron transport
mtDNA damage/mutation
Mitochondrial dysfunction
Cytochrome c, AIF, Ca^{2+},
Apoptosis

"I'm fine; I'm just waiting for my disease": the new and growing class of presymptomatic patients.

Kwon JM, **Steiner RD**.

Neurology. 2011 Aug 9;77(6):522-3.

Making diagnosis of Pompe disease at a presymptomatic stage: to treat or not to treat?

Laloui K, Wary C, Carlier RY, Hogrel JY, Caillaud C, Laforêt P.

Neurology. 2011 Aug 9;77(6):594-5.

Exogenous factors modulating phenotypes

- **Toxic factors**
- **Traumatic factors**

Interaction of drugs on genotype

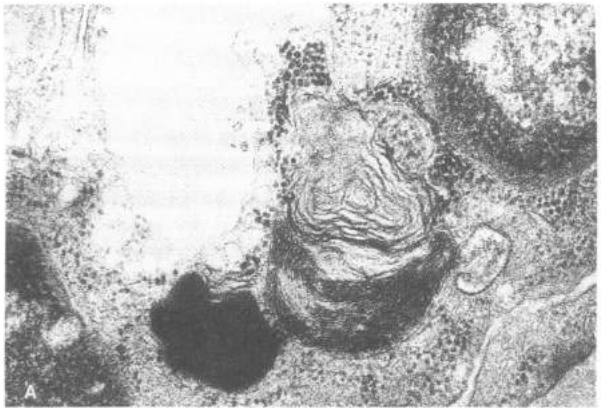
- 15 years old,female,health.Obesity since childhood.
- Severe dietary restriction,and use of anorexiziting drugs as phentermine,fenfluoramine,diethylpropion for 1 year.
- Ataxia with cerebellar atrophy at MR
- Normal biochemistry,muscle biopsy
- mitDNA analysis showed intergenomic 6bp delection,usually not considetred pathogenetic
- Interaction of drugs with mitDNA(??)

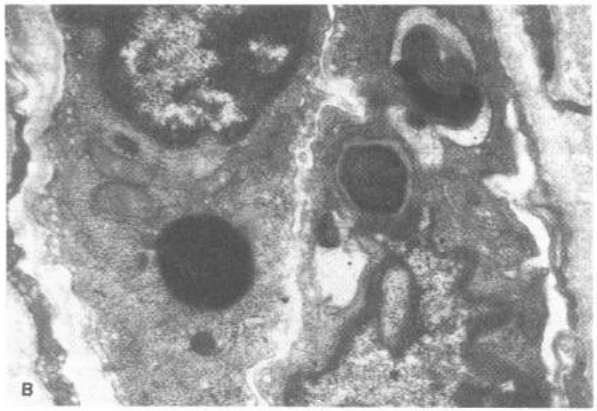
Hereditary optic atrophy (Leber's disease)

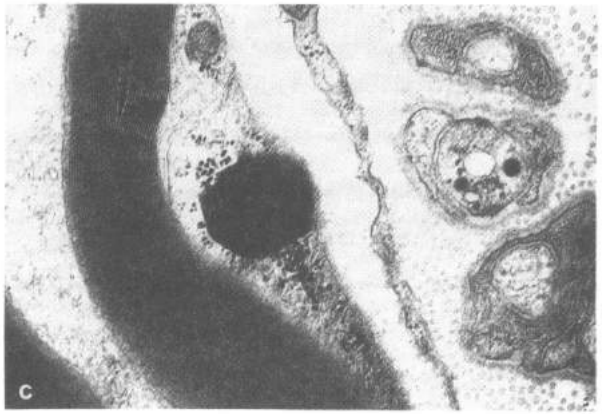
Dotti et al., A case of ethambuthol-induced optic neuropathy harbouring the primary mitocondrial LHON mutation at 11778.

J. Neurol. 245:302,1998

- Onset at 54 y old age after etambutol use as treatment for tubercolosis







Dementia, myoclonus, peripheral neuropathy and lipid-like material in skin biopsy during psychotropic drug treatment

A. Federico et al
Biol. Psychiat. 32: 722-727, 1992

J Neurol Sci. 1992 Jul;110(1-2):215-21.

Imipramine induced lipidosis and dexamethasone effect: morphological and biochemical study in normal and chronic GM2 gangliosidosis fibroblasts.

Palmeri S[1], Mangano L, Battisti C, Malandrini A, Federico A.

A large heterogeneous group of lysosomotropic compounds with a common cationic amphiphilic structure induces in vitro and in vivo lysosomal lipid storage. The biochemical mechanism underlying the lipidosis is still the subject of investigation. The authors report the experimental effect of imipramine and dexamethasone on lysosomal system in cultured skin fibroblasts. Morphological and ultrastructural observations of cells treated with imipramine showed vacuoles with lipidic storage, enlarged lysosomes with electron translucent zones and normal appearance of all the other cytoplasmic organelles. The lysosomal enzyme activities were decreased on biochemical study. On the contrary, an increased enzyme activity was detected in the culture medium. Pretreatment with dexamethasone partially prevented the effect of imipramine. Our results suggest that tricyclic antidepressants may induce lysosomal lipidosis through a dysfunction in the recycling of mannose-6-phosphate receptors and in the trafficking of newly synthesized lysosomal enzymes. Moreover the data presented may provide a clue in understanding some of the side effects observed in patients chronically treated with antidepressant drugs.

Traumatic factors

Very late onset adrenoleukodystrophy: possible precipitation of demyelination by a contusion.

Weller et al. Neurology 42: 367,1992

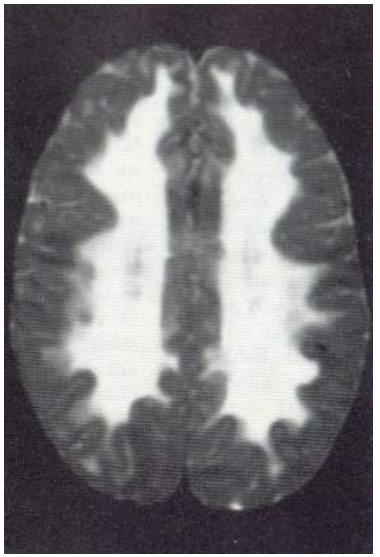
Can head injury influence the site of demyelination in ADL?

Wilkinson I.A. et al., Dev. Med. Child Neurol. 29: 784, 1987

Fright and VWMD

- Vermeulen G, Seidl R, Mercimek-Mahmutoglu S, Rotteveel JJ, Scheper GC, van der Knaap MS. Fright is a provoking factor in vanishing white matter disease. Ann Neurol. 2005 Apr;57(4):560-3.

- Kaczorowska M, Kuczynski D, Jurkiewicz E, Scheper GC, van der Knaap MS, Jozwiak S. Acute fright induces onset of symptoms in vanishing white matter disease-case report. Eur J Paediatr Neurol. 2006 Jul;10(4):192-3



Mutations in eIF2B

Mutation in each of five subunits of translation Initiation Factor eIF2B can cause Leucoencephalopathy with Vanishing White Matter

M. S. van der Knaap et al

Ann. Neurol 51: 264-270, 2002

eIF2B activity decrease

↓

Decrease in protein synthesis in conditions of cellular stress

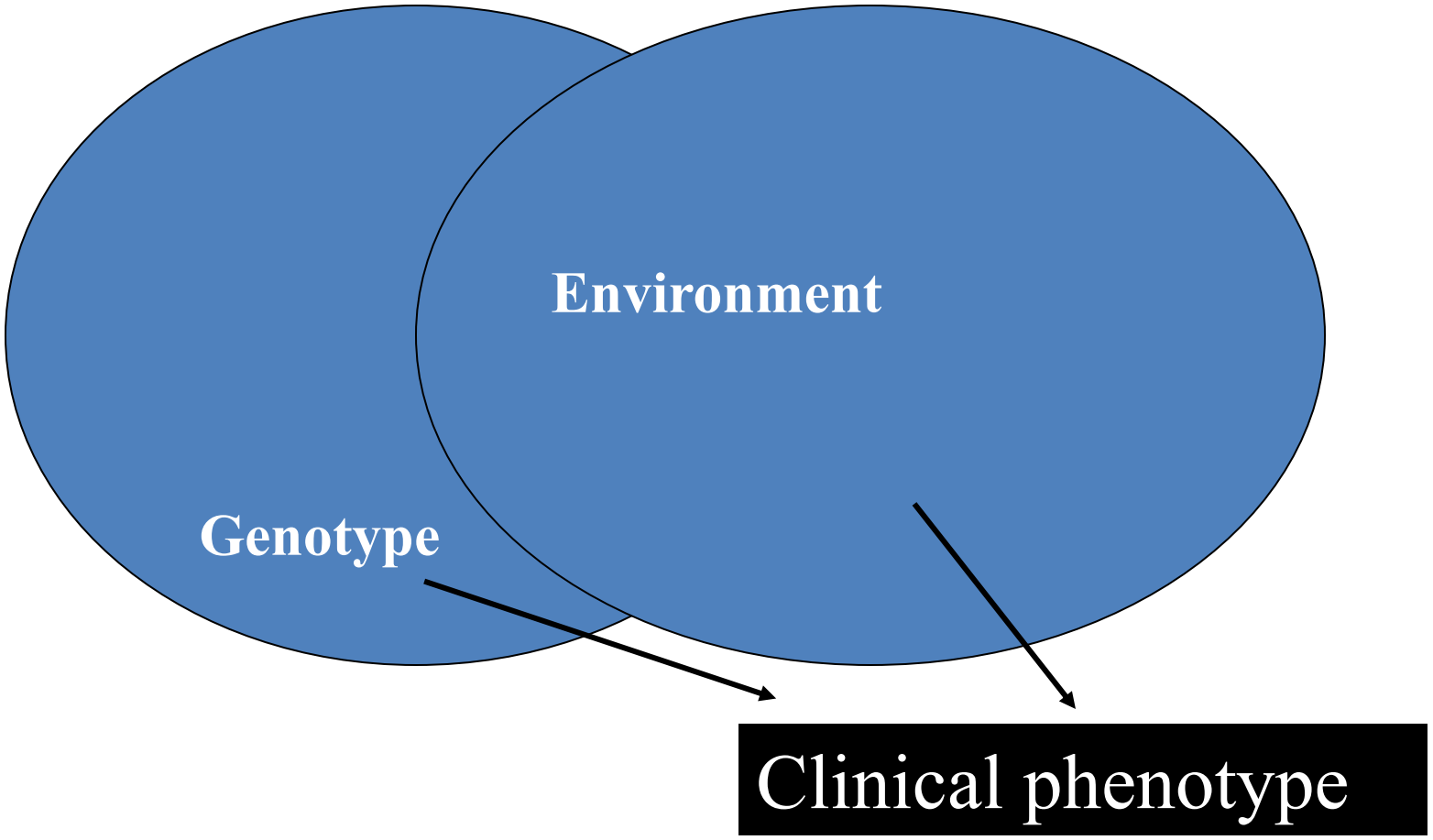
↓

An increase of mutated protein in endoplasmic reticulum activated the

Unfolded Protein Response (UPR),

a compensatory mechanism with inhibition of new protein synthesis and stimulation of signals involved in life and in proapoptotic mechanisms

GENE-ENVIRONMENT INTERACTION



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etc. ,

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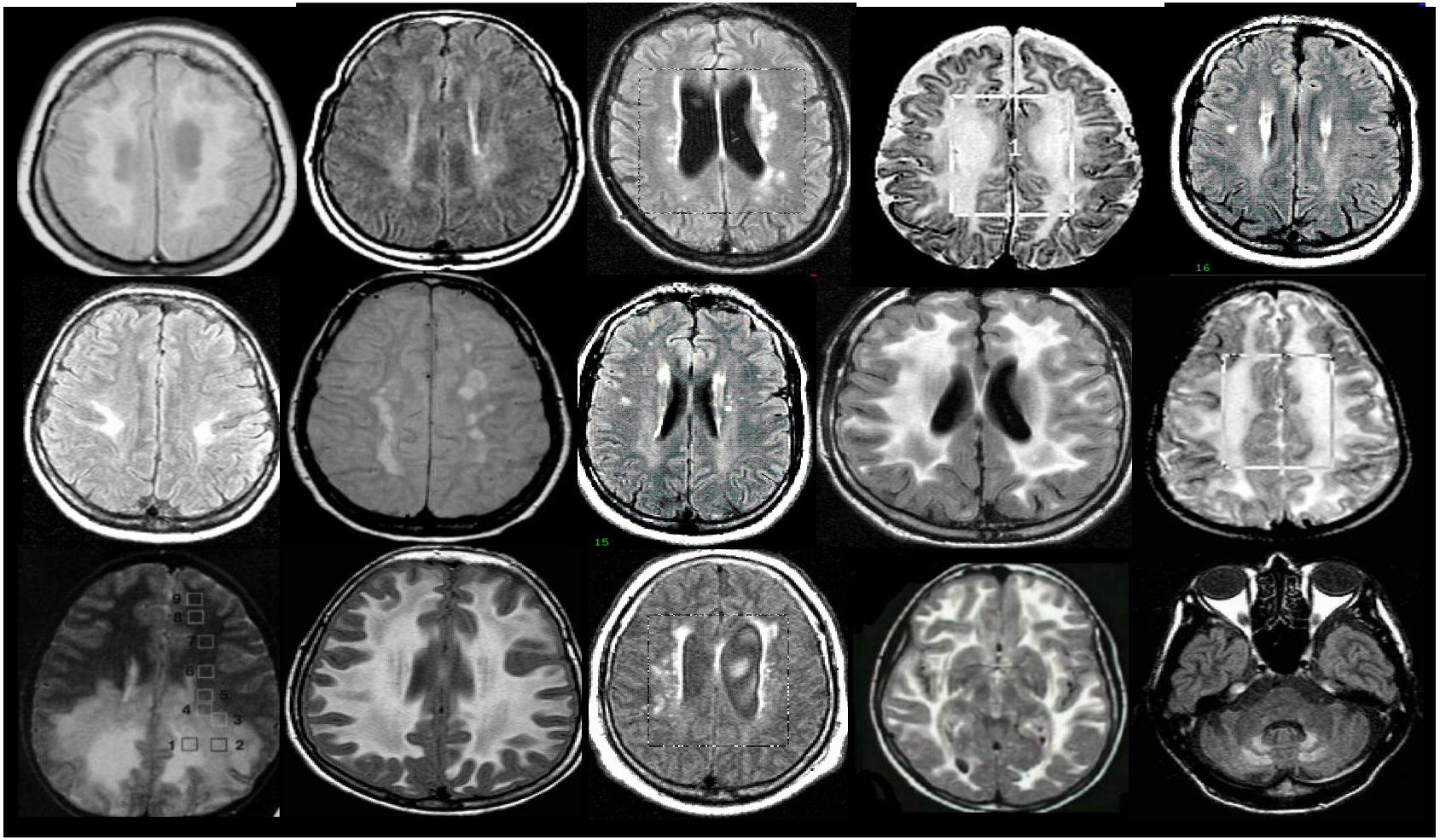
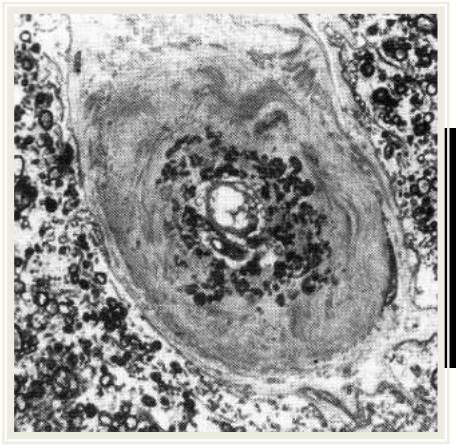
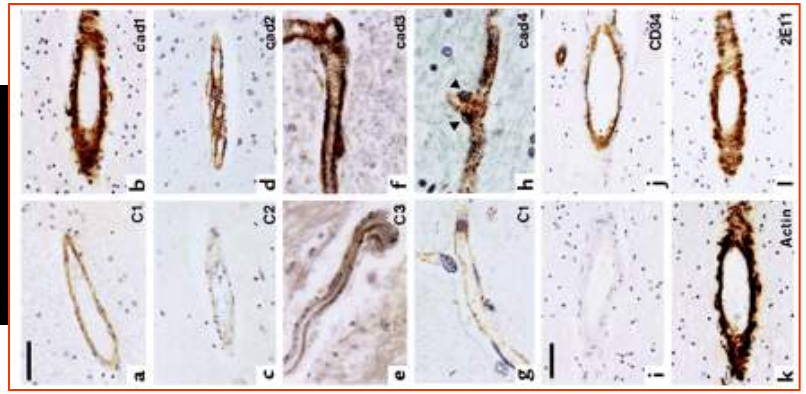
Leukoencephalopathy related to primary **oligodendrocyte** or **astrocyte defect**s





CADASIL



- Evidence of characteristic **granular osmyophilic material (GOM)** within the basal membrane of brain vascular smooth muscle cells;
- These vascular changes were also later reported in nerve, striated muscle and skin.
- Joutel A et al . **Skin biopsy immunostaining with a Notch3 monoclonal antibody for CADASIL diagnosis**. Lancet 2001; 358:2049-51
- Malandrini A, Gaudiano C, Gambelli S, Berti G, Serni G, Bianchi S, Federico A, Dotti MT. Diagnostic value of ultrastructural skin biopsy studies in CADASIL. Neurology. 2007 Apr 24;68(17):1430-2.

Main clinical and biological findings in CADASIL and CARASIL

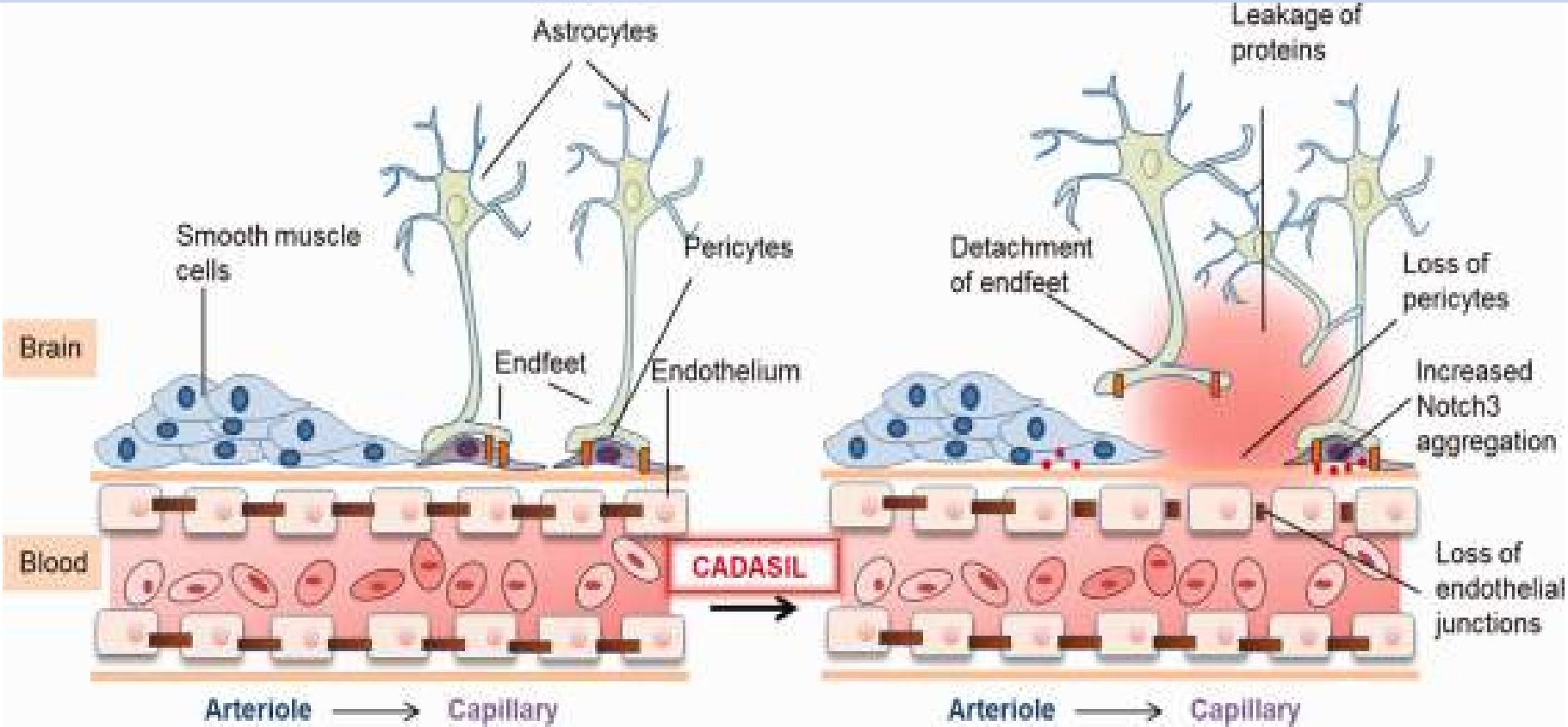
	CADASIL	CARASIL
Onset (years)	40–50	20–30
Clinical features	Migraine, TIA/strokes, psychiatric disorders, cognitive impairment	Cerebrovascular disturbances and strokes (gait and cognitive deficits)
Additional signs	–	Arthropathy, lumbago, spondylosis *deformans*, disc herniation and alopecia in some cases
Inheritance	Autosomal dominant	Autosomal recessive
Cerebral MRI	Involvement of temporal lobe and/or externe capsules	White matter lesions in the periventricular and deep white matter, with sparing of U-fibres.
Gene	*NOTCH3* (chromosome 19q12)	*HTRA1* (chromosome 10q26)
GOMs	+	–

Ann Neurol. 2015 Dec;78(6):887-900.

Pericytes are involved in the pathogenesis of CADASIL.

Ghosh M[1,2,3], Balbi M[1,4], Hellal F[1,3], Dichgans M[1,3], Lindauer U[2,5,3], Plesnila N[1,5,3].

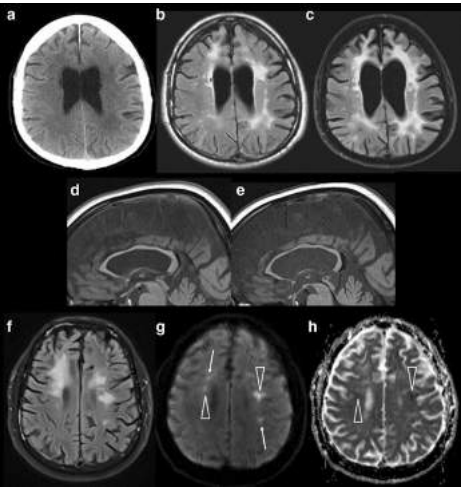
The results show that pericytes are the first cells affected by Notch3 aggregation in CADASIL mice. Pericyte pathology causes opening of the BBB and microvascular dysfunction. Therefore, protecting pericytes may represent a novel therapeutic strategy for vascular dementia.

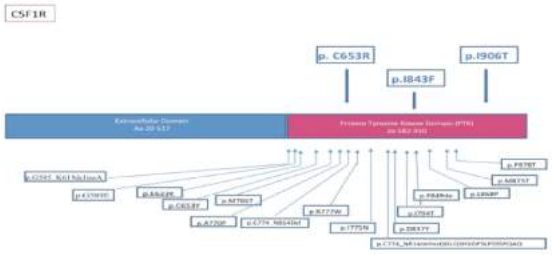


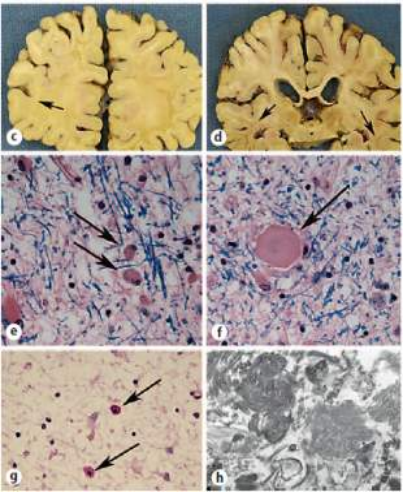
Hereditary diffuse leukoencephalopathy with axonal spheroids: three patients with stroke-like presentation carrying new mutations in the CSF1R gene.

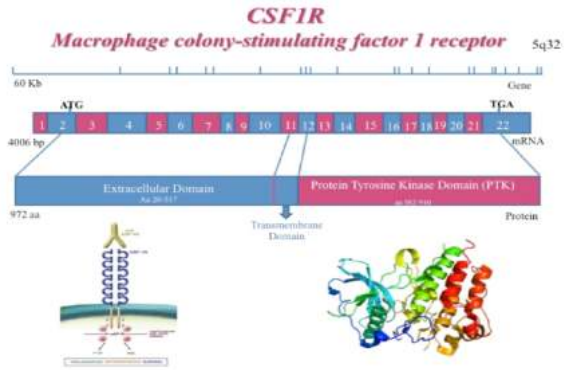
Battisti C, Di Donato I, Bianchi S, Monti L, Formichi P, Rufa A, Taglia I, Cerase A, Dotti MT, Federico A.

J Neurol. 2014 Apr;261(4):768-72.









Hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS) is an autosomal dominant disorder characterized by white matter neurodegeneration, progressive cognitive decline, and motor symptoms. Histologically, it is characterized by axonal swellings ("spheroids"). To date, over 20 different mutations affecting the tyrosine kinase domain of the protein have been identified in the colony stimulating factor 1 receptor (CSF1R) gene.

We report three unrelated Italian patients affected by HDLS and carrying new CSF1R mutations, thus expanding the mutational spectrum and phenotypic presentation.

CSF1R gene analysis was performed in 15 patients (age range 25–83 years) with undefined leukoencephalopathy and progressive cognitive decline.

In three patients (two males and one female, aged 58, 37, and 48 years, respectively), new heterozygous missense mutations affecting the protein tyrosine kinase domain of the CSF1R gene were detected. In all of these patients, behavioural and cognitive changes were preceded by an ischemic stroke-like episode. A positive family history was present in only one case.

Background 2016

Research

JAMA Neurology | Original Investigation

Analysis of Mutations in *AARS2* in a Series of *CSF1R*-Negative Patients With Adult-Onset Leukoencephalopathy With Axonal Spheroids and Pigmented Glia

David S. Lynch, MRCPI; Wei Jia Zhang, MRCP; Rahul Lakshmanan, FRANZCR; Justin A. Kinsella, PhD; Güneş Altıokka Uzun, MD; Merih Karbay, MD; Zeynep Tüfekçioğlu, MD; Haşmet Hanağası, MD; Georgina Burke, PhD; Nicola Foulds, FRCP; Simon R. Hammans, FRCP; Anupam Bhattacharjee, PhD; Heather Wilson, FRCP; Matthew Adams, FRCR; Mark Walker, FRCPath; James A. R. Nicoll, FRCPath; Jeremy Chataway, FRCP; Nick Fox, FRCP; Indran Davagnanam, FRCR; Rahul Phadke, FRCPath; Henry Houlden, PhD

A group of patients with typical features of ALSP who do not carry *CSF1R* mutations.

This work indicates that mutations in the tRNA synthetase *AARS2* gene cause a **recessive form of ALSP.** The CSF1R and AARS2 proteins have different cellular functions but overlap in a final common pathway of neurodegeneration.

AARS2

Mitochondrial alanyl-tRna synthetase (mtAlaRS)

The mtAlaRS differs from the other mtARSs because in addition to the **aminoacylation domain**, it has a conserved **editing domain** for deacylating tRNAs that have been mischarged with incorrect aminoacids.

Euro et al. 2015

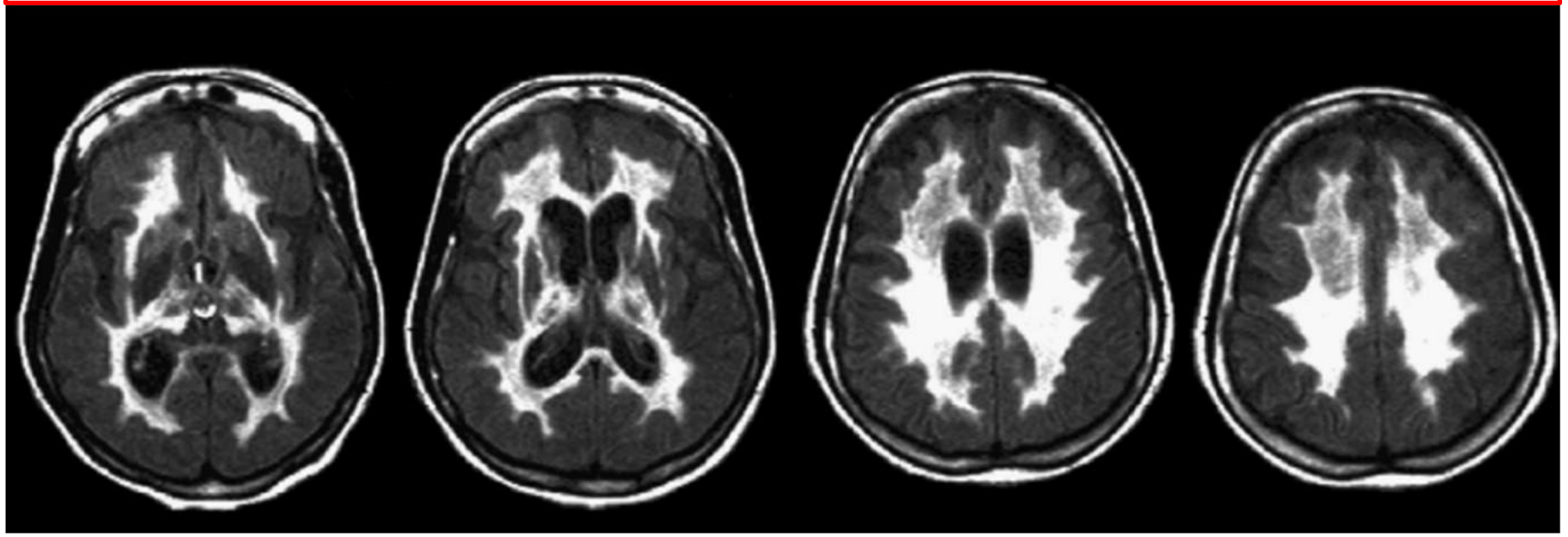
All mutations reduce the aminoacylation activity of the synthetase, the cardiomyopathy homozygous mutations severely compromise aminoacylation. **A partial activity is retained by the mutation combinations (heterozygous mutations) found in the leukodystrophy patients**.

AARS2 (Alanyl-transfer (t)RNA synthetase 2)

Case report:

- Female, died at 36 y
- At age 32, cognitive decline with rapid evolution towards dementia, mood depression, followed by progressive spastic tetraparesis a year later.
- **Secondary amenorrhea**
- At the family history, one sister with amenorrhea, gait impairment and cognitive deterioration since the age of 25 years, diffuse WM abnormalities on brain MRI (she died at 30 y)

Brain MRI: Diffuse leukoencephalopathy with white matter rarefaction. Cortical atrophy. Corspus callosum involvement.



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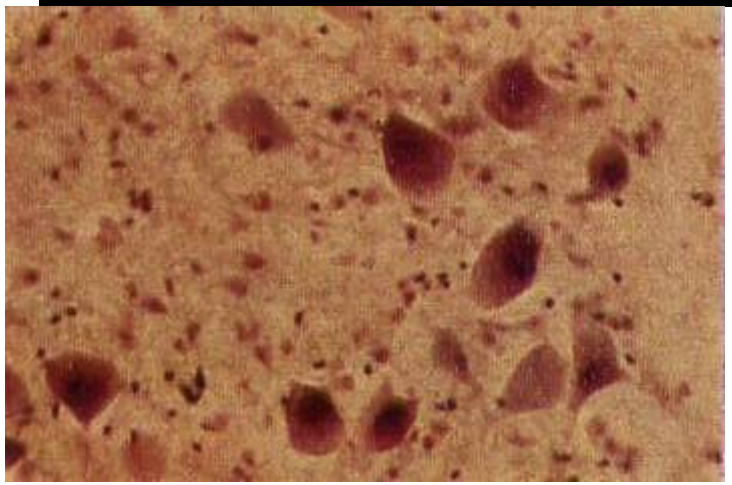
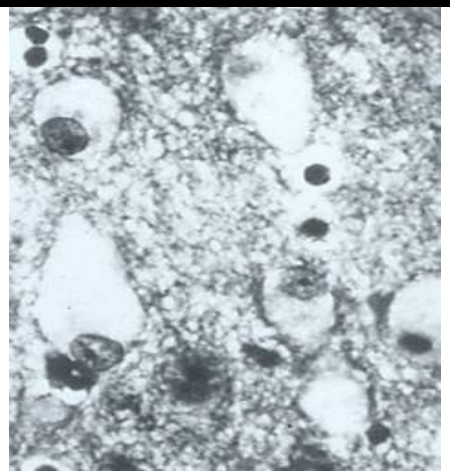
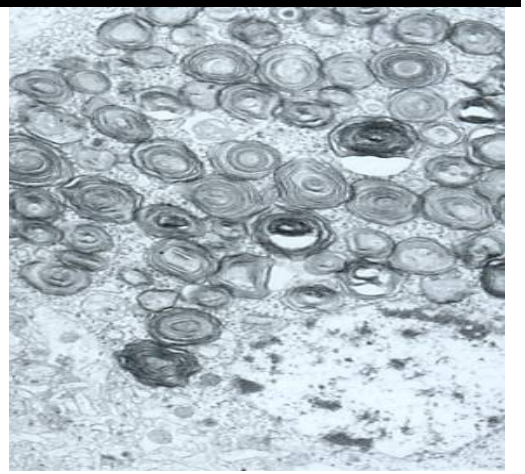
Diseases primarily affecting neurons

- GM1 gangliosidosis
- Gm2 gangliosidosis
- Gaucher disease
- Nieman Pick type C diseases

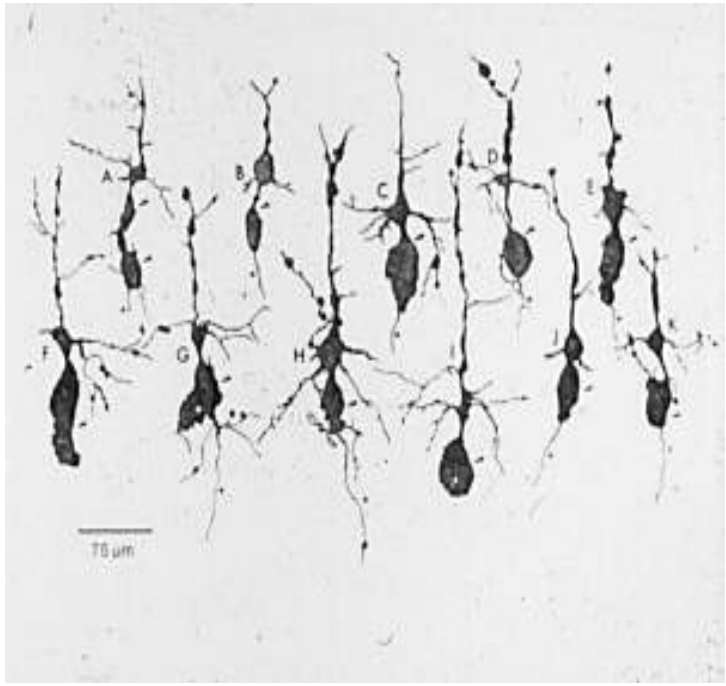
Mechanisms of nerve cell dysfunciton in GM_2 gangliosidoses







- Distention of nerve cells by fine granular material (Schaffer 1905)
- Storage of membrane cytoplasmatic bodies (MCBs) (Terry and Korey 1960)
- Distortion of synaptic structures (neuronal geometry) (Purpura and Suzuki 1976)



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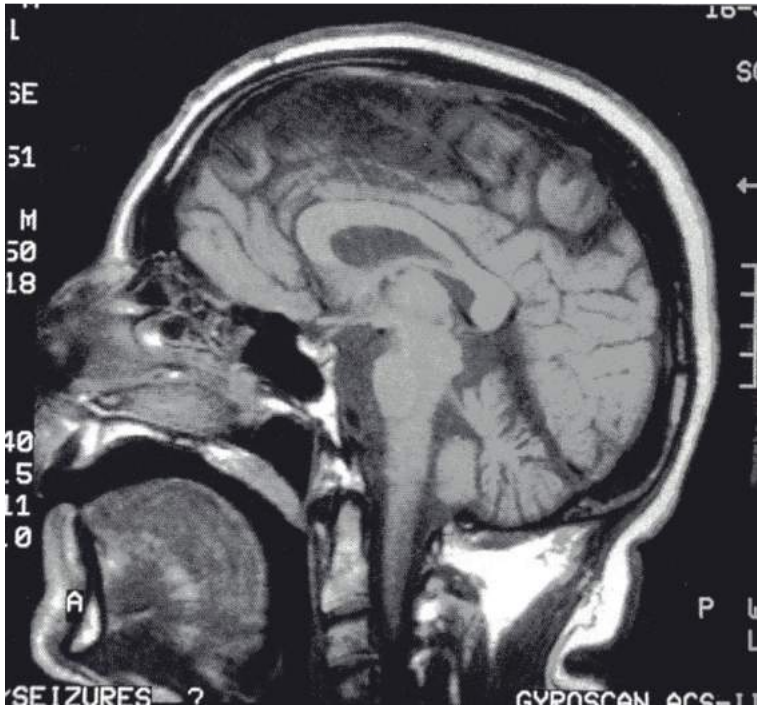
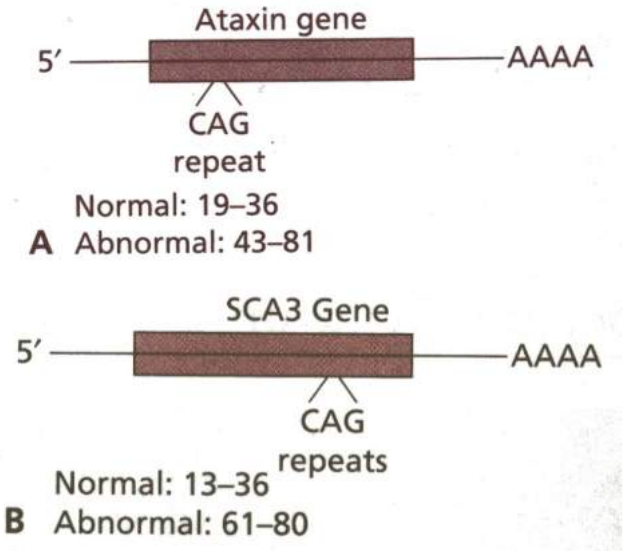
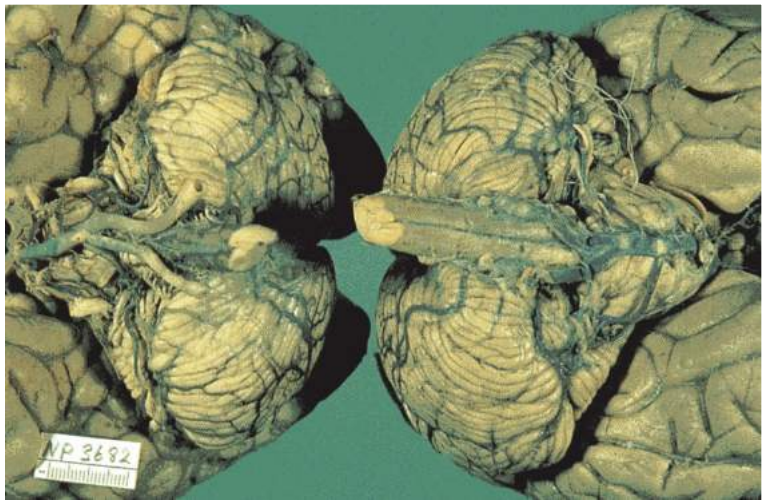
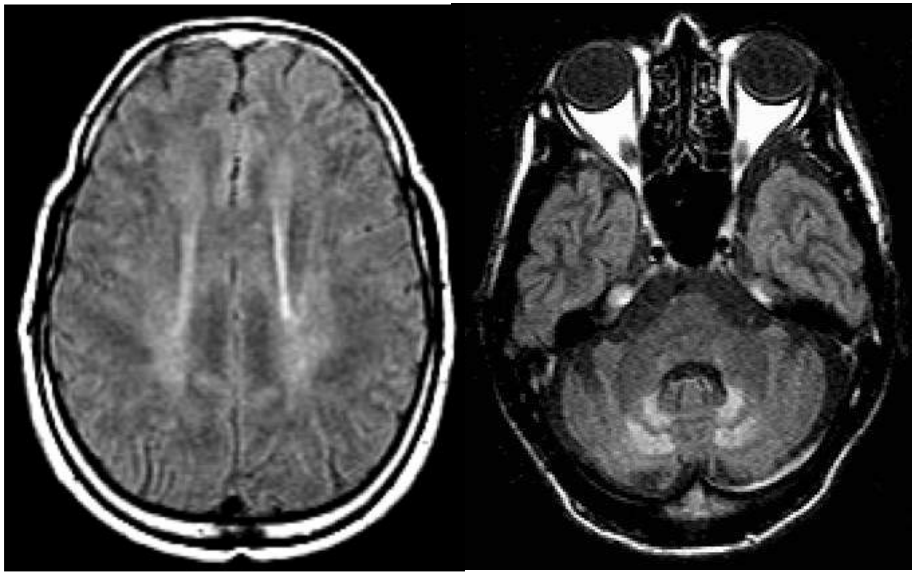
Dominant ataxia







Cerebrotendinous xanthomatosis



J Physiol. 2017 Jun 1;595(11):3607-3620.

The role of dentate nuclei in human oculomotor control: insights from cerebrotendinous xanthomatosis.

Rosini F[1], Pretegiani E[2], Mignarri A[3], Optican LM[2], Serchi V[1], De Stefano N[4], Battaglini M[4], Monti L[5], Dotti MT[3], Federico A[3], Rufa A[1].

KEY POINTS:

A cerebellar dentate nuclei (DN) contribution to volitional oculomotor control has recently been hypothesized but not fully understood. Cerebrotendinous xanthomatosis (CTX) is a rare neurometabolic disease typically characterized by DN damage. In this study, we compared the ocular movement characteristics of two sets of CTX patients, with and without brain MRI evidence of DN involvement, with a set of healthy subjects. **Our results suggest that DN participate in voluntary behaviour, such as the execution of antisaccades, and moreover are involved in controlling the precision of the ocular movement.** The saccadic abnormalities related to DN involvement were independent of global and regional brain atrophy. **Our study confirms the relevant role of DN in voluntary aspects of oculomotion and delineates specific saccadic abnormalities that could be used to detect the involvement of DN in other cerebellar disorders.**

ABSTRACT:

It is well known that the medial cerebellum controls saccadic speed and accuracy. In contrast, the role of the lateral cerebellum (cerebellar hemispheres and dentate nuclei, DN) is less well understood. Cerebrotendinous xanthomatosis (CTX) is a lipid storage disorder due to mutations in CYP27A1, typically characterized by DN damage. CTX thus provides a unique opportunity to study DN in human oculomotor control. We analysed horizontal and vertical visually guided saccades and horizontal antisaccades of 19 CTX patients. Results were related to the presence/absence of DN involvement and compared with those of healthy subjects. To evaluate the contribution of other areas, abnormal saccadic parameters were compared with global and regional brain volumes. CTX patients executed normally accurate saccades with normal main sequence relationships, indicating that the brainstem and medial cerebellar structures were functionally spared. Patients with CTX executed more frequent multistep saccades and directional errors during the antisaccade task than controls. CTX patients with DN damage showed less precise saccades with longer latencies, and more frequent directional errors, usually not followed by corrections, than either controls or patients without DN involvement. These saccadic abnormalities related to DN involvement but were independent of global and regional brain atrophy. We hypothesize that two different cerebellar networks contribute to the metrics of a movement: the medial cerebellar structures determine accuracy, whereas the lateral cerebellar structures control precision. The lateral cerebellum (hemispheres and DN) also participates in modulating goal directed gaze behaviour, by prioritizing volitional over reflexive movements.

J Neurol. 2017 May;264(5):862-874.

The spectrum of magnetic resonance findings in cerebrotendinous xanthomatosis: redefinition and evidence of new markers of disease progression.

Mignarri A[1], Dotti MT[2], Federico A[1], De Stefano N[1], Battaglini M[1], Grazzini I[3], Galluzzi P[3], Monti L[3].

Cerebrotendinous xanthomatosis (CTX) is a metabolic disease characterized by systemic signs and neurological impairment, which can be prevented if chenodeoxycholic acid (CDCA) treatment is started early. Despite brain MRI represents an essential diagnostic tool, the spectrum of findings is worth to be reappraised, and follow-up data are needed. We performed clinical evaluation and brain MRI in 38 CTX patients. Sixteen of them who were untreated at baseline examination underwent clinical and MRI follow-up after long-term treatment with CDCA. Brain MRI abnormalities included cortical and cerebellar atrophy, and T2W/FLAIR hyperintensity involving subcortical, periventricular, and cerebellar white matter, the brainstem and the dentate nuclei. Regarding the dentate nuclei, we also observed T1W/FLAIR hypointensity consistent with cerebellar vacuolation and T1W/FLAIR/SW hypointense alterations compatibly with calcification in a subgroup of patients. Long-term follow-up showed that clinical and neuroradiological stability or progression were almost invariably associated. In patients with cerebellar vacuolation at baseline, a worsening over time was observed, while subjects lacking vacuoles were clinically and neuroradiologically stable at follow-up. The brains of CTX patients very often show both supratentorial and infratentorial abnormalities at MRI, the latter being related to clinical disability and including a wide spectrum of dentate nuclei alterations. The presence of cerebellar vacuolation may be regarded as a useful biomarker of disease progression and unsatisfactory response to therapy. On the other hand, the absence of dentate nuclei signal alteration should be considered an indicator of better prognosis

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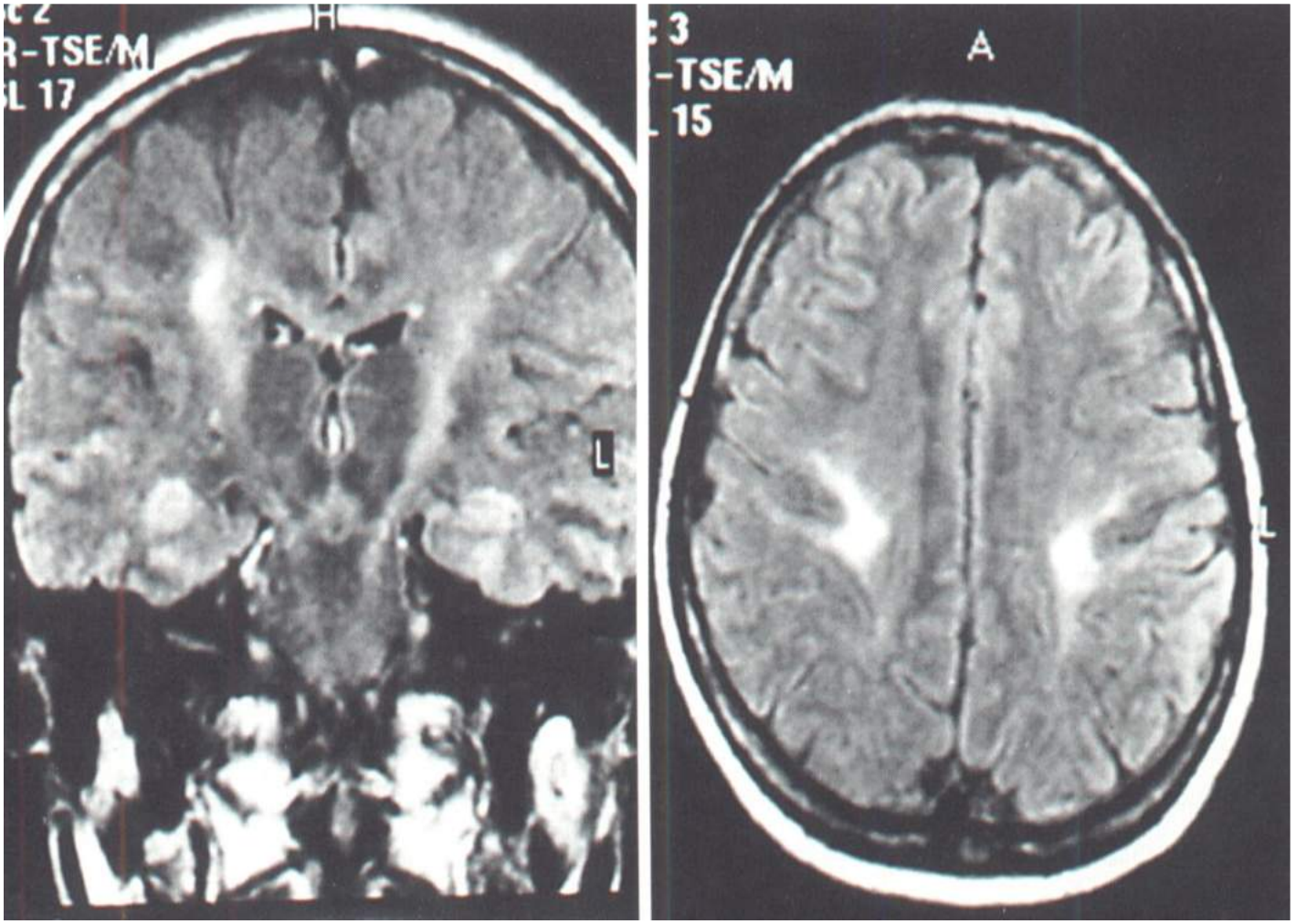
Adult Krabbe's disease

De Stefano et al. J.Neurol.247: 226-228, 2001



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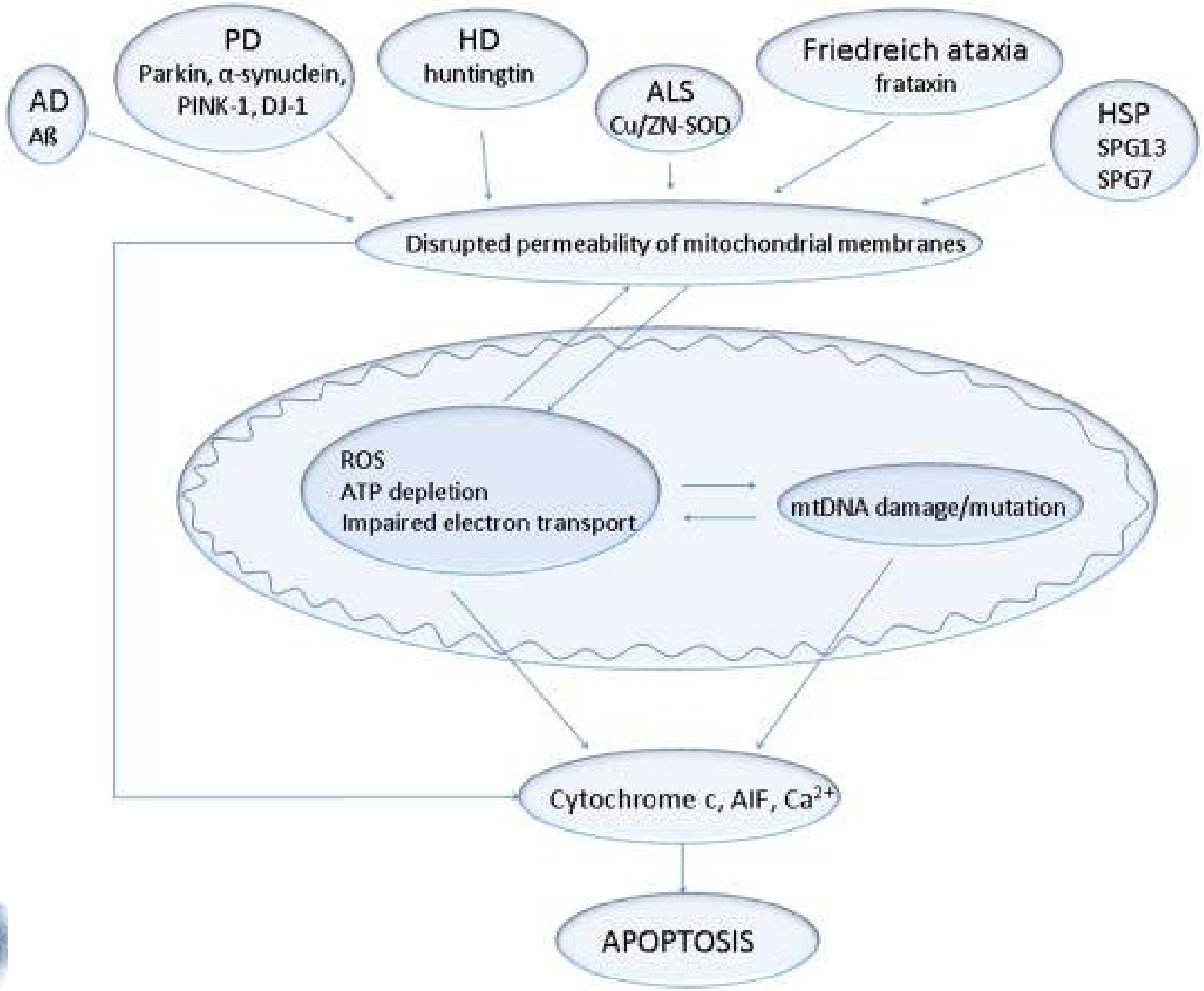


Federico et al, Journal of the Neurological Sciences, 2012.
Volume 322, Issues 1–2, 15 November 2012, Pages 254–262

Amboni M, Pellecchia MT, Cozzolino A, Picillo M, Vitale C, Barone P, Varrone A, Garavaglia B, Gambelli S, Federico A.

Cerebellar and pyramidal dysfunctions, palpebral ptosis and weakness as presenting symptoms of PARK-2.

Mov Disord. 2009 Jan 30;24(2):303-5.

Parkin and mitochondria

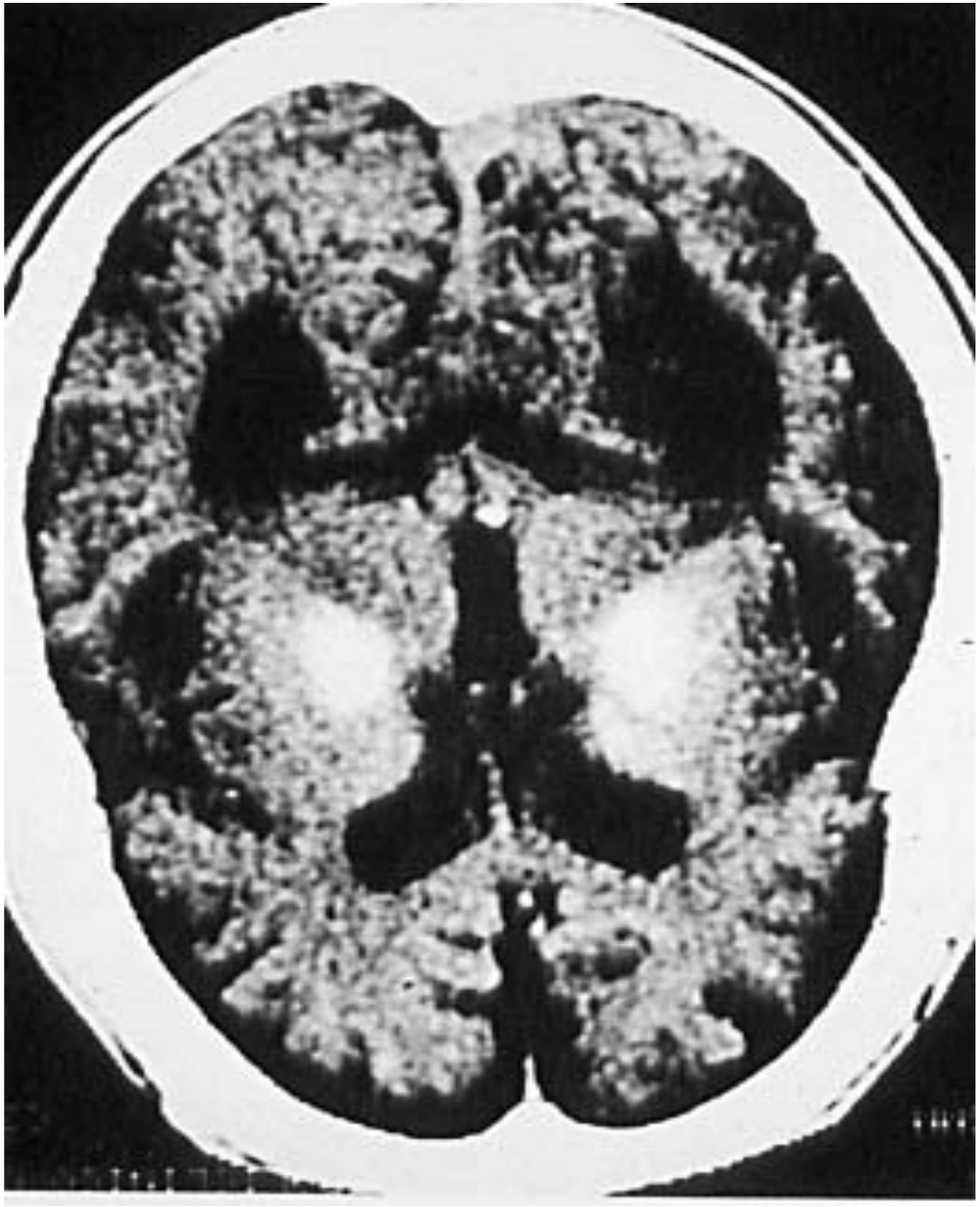
- Darios F, Corti O, Lucking CB, Hampe C, Muriel MP, Abbas N, Gu WJ, Hirsch EC, Rooney T, Ruberg M, Brice A.
  Parkin prevents mitochondrial swelling and cytochrome c release in mitochondria-dependent cell death. *Hum Mol Genet* 2003;2(5):517-26

- Kuroda Y, Mitsui T, Kunishige M, Matsumoto T.
  Parkin affects mitochondrial function and apoptosis in neuronal and myogenic cells. *Biochem Biophys Res Commun* 2006;348(3):787-793

- Palacini JJ, Sagi D, Goldberg MS, Krauss S, Motz C, Wacker M, Klose J, Shen J.
  Mitochondrial dysfunction and oxidative damage in parkin-deficient mice. *J Biol Chem* 2004;279(18):18614-22

- Greene JC, Whitworth AJ, Kuo I, Andrews LA, Feany MB, Pallanck LJ. Mitochondrial pathology and apoptotic muscle degeneration in Drosophila parkin mutants. *Proc Nati Acad Sci* U.S.A 2003;100(7):4078-83

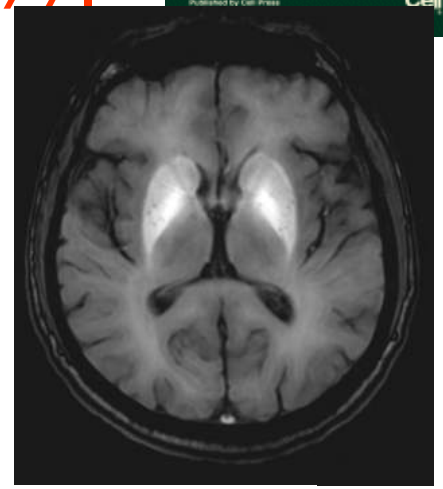
- Stichel CC, Zhu XR, Bader V, Linnartz B, Schmidt S, Lübbert H.
  Mono- and double-mutant mouse models of Parkinson's disease display severe mitochondrial damage. *Hum Mol Genet*. 2007 Oct 15;16(20):3377-93.

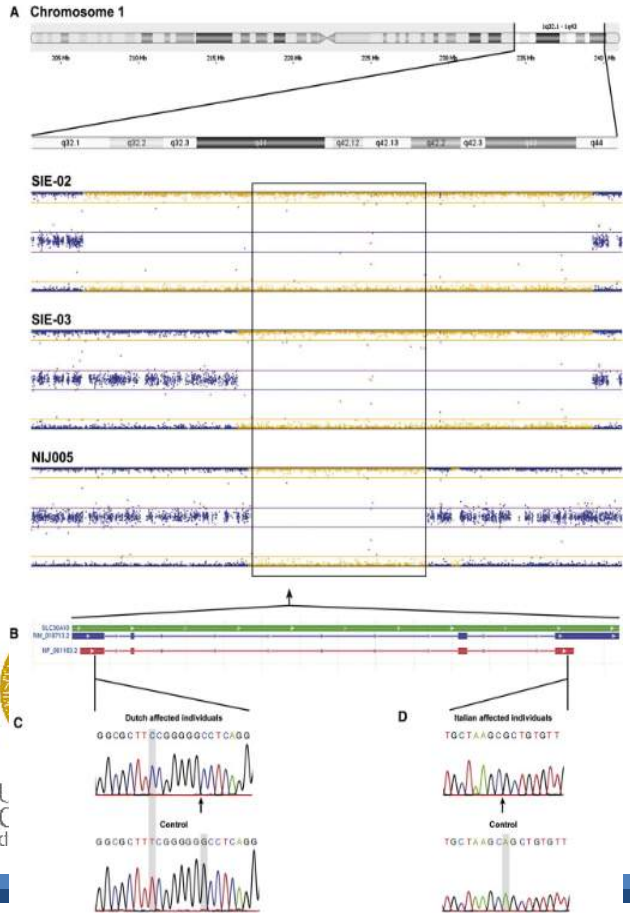


Mutations in SLC30A10 cause parkinsonism and dystonia with hypermanganesemia, polycythemia, and chronic liver disease.

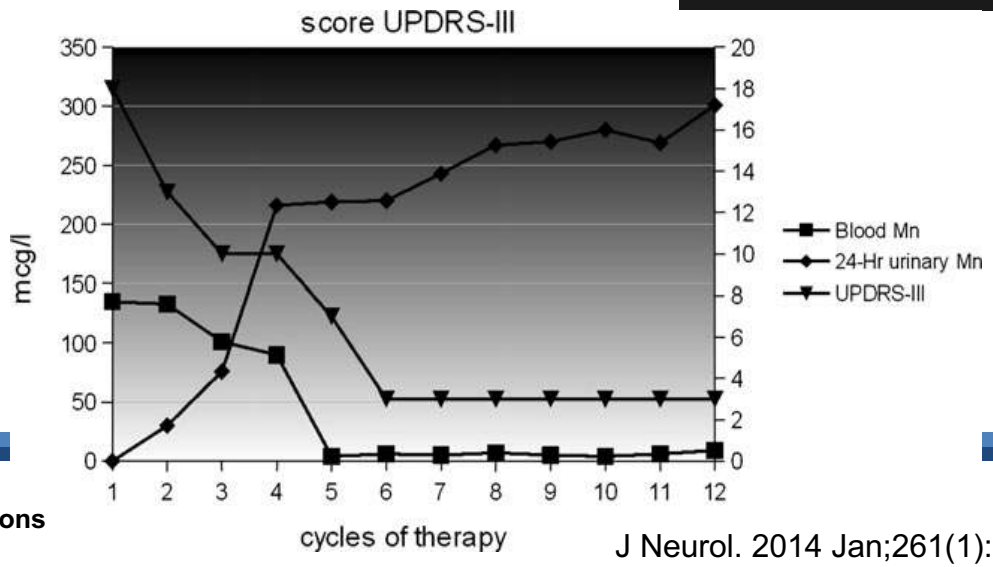
Quadri M, Federico A, et al.

Am J Hum Genet. 2012 Mar 9;90(3):467-77.



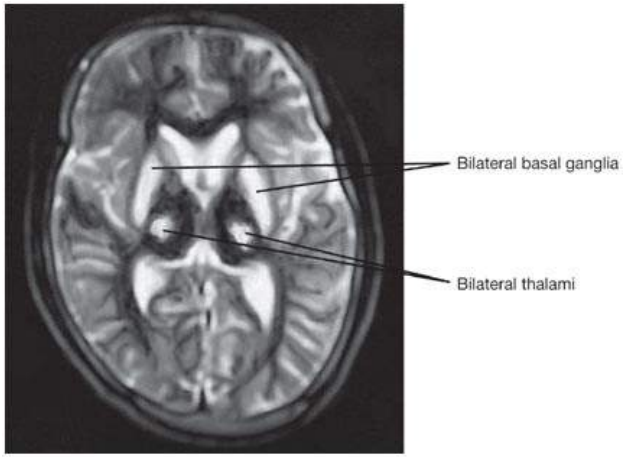


Homozygosity mapping and detection of *SLC30A10* mutations

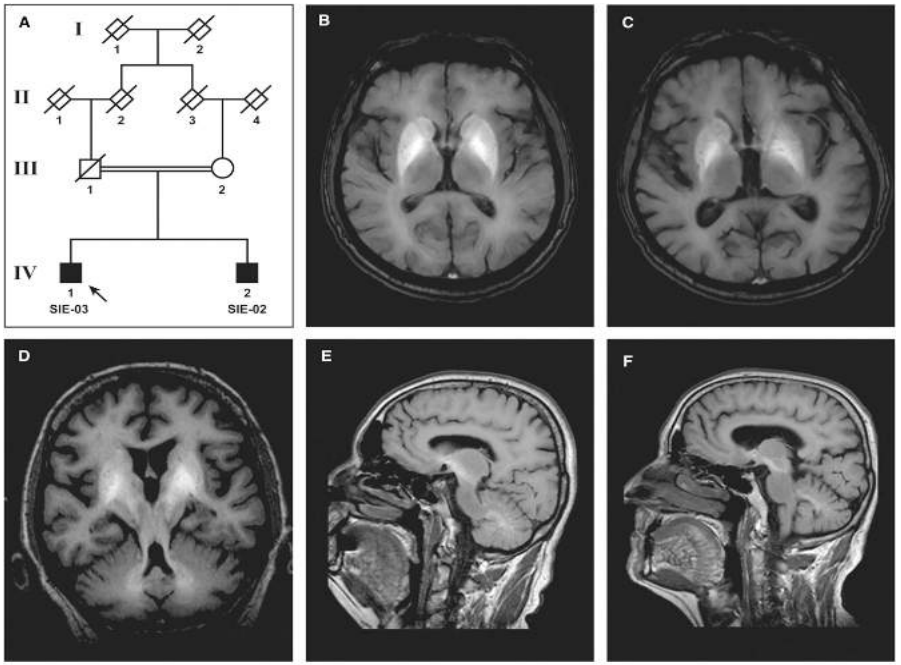


J Neurol. 2014 Jan;261(1):227-8.

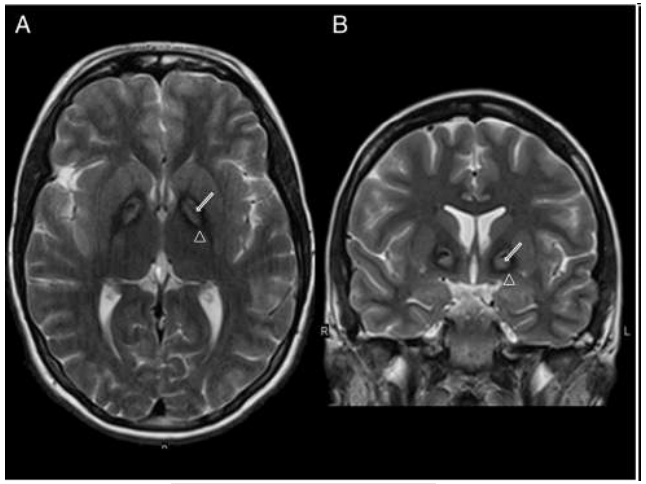
Mineral accumulation in basal nuclei



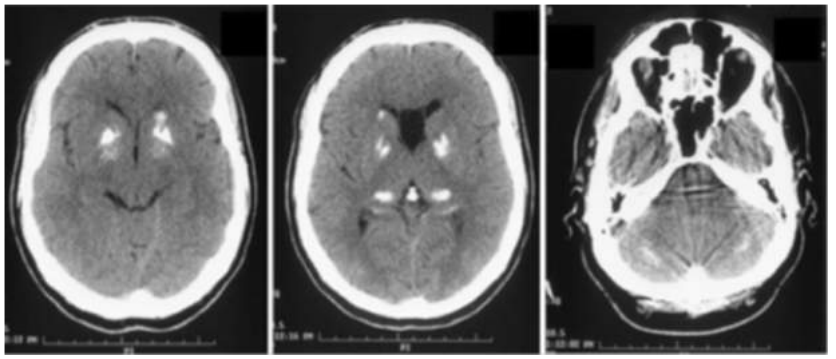
Cooper (Wilson's disease)



Manganese (dystonia/parkinsonism)



iron (NBIAs)



Calcium (Fahr Disease)

Genetics of Fahr's disease: new insights

Gene symbol	Chromosomal locus	Protein name
SLC20A2	8p11.21	Sodium-dependent phosphate transporter 2
PDGFRB	5q32	Platelet-derived growth factor receptor beta
PDGFB	22q13	Platelet-derived growth factor beta

In 2012 has been identified the first diseases-related gene , IBGC3, named SLC20A2, codifying for the Sodium-dependent phosphate transporter 2 (Nat Genet 2012). (PiT2)

PiT2 is expressed in almost all tissues and has a fundamental role in the inorganic phosphorus homeostasis .

Gene *SLC20A2* mutations are in more than 40% of the familial forms of brain calcifications.

J Cell Physiol. 2018 Mar;233(3):2324-2331.

Primary familial brain calcification with a novel SLC20A2 mutation: Analysis of PiT-2 expression and localization.

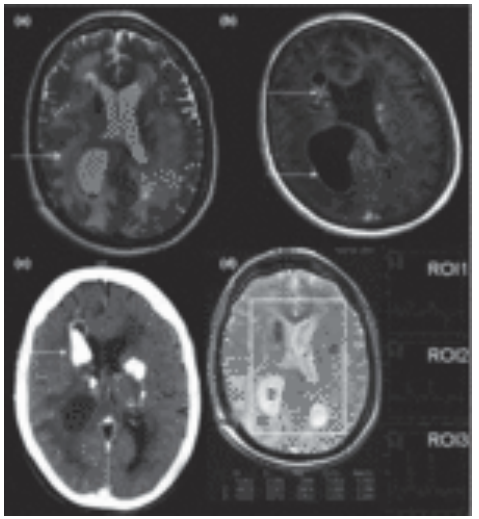
Taglia I[1], Formichi P[1], Battisti C[1], Peppoloni G[1], Barghigiani M[2], Tessa A[2], Federico A[1].

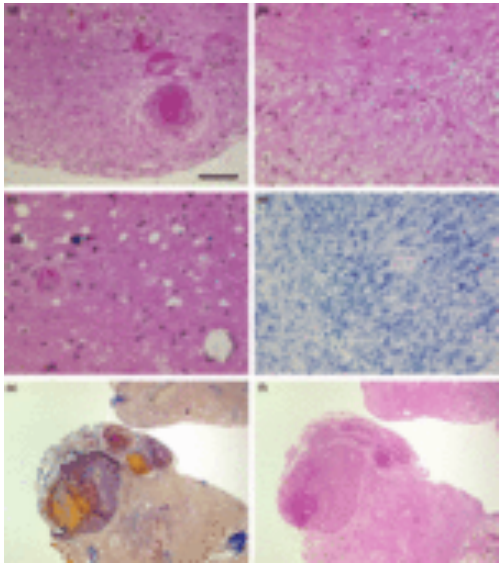
Primary familial brain calcification (PFBC) is an autosomal dominant rare disorder characterized by bilateral and symmetric brain calcifications, and neuropsychiatric manifestations. Four genes have been linked to PFBC: SLC20A2, PDGFRB, PDGFB, and XPR1. In this study, we report molecular and clinical data of a PFBC patient carrying a novel SLC20A2 mutation and we investigate the impact of the mutation on PiT-2 expression and function. Sanger sequencing of SLC20A2, PDGFRB, PDGFB, XPR1 led to the identification of a novel duplication of twelve nucleotides (c.1876_1887dup/ p.Trp626_Thr629dup) in SLC20A2 gene. SLC20A2 encodes for a cell membrane transporter (PiT-2) involved in maintenance of inorganic phosphate homeostasis.

We performed an analysis of expression and functionality of PiT-2 protein in patient primary cultured fibroblasts. In patient fibroblasts, the mutation does not affect PiT-2 expression but alter sub-cellular localization. The Pi-uptake assay revealed a less Pi depletion in patient than in control fibroblasts, suggesting that SLC20A2 duplication may impair Pi internalization. This is the first study reporting sub-cellular expression analysis of mutant PiT-2 in primary cultured fibroblasts from a PFBC patient, showing that p.Trp626_Thr629dup in SLC20A2 alters PiT-2 sub-cellular localization and reduces Pi-uptake, leading to onset of PFBC in our patient.

Leucoencephalopathy with intracranial calcifications

- Cognitive decline, epileptic seizures and progressive neurological symptoms and signs.
- Diffuse abnormal signal increase in the white matter (T2-weighted sequences), extensive calcifications in the basal ganglia, cerebellar grey nuclei and central white matter, as well as large parenchymal cysts with mass effect.
- Ectatic small vessels, sometimes arranged in an angioma-like pattern, vascular and parenchymal calcifications and pronounced gliosis with so-called Rosenthal fibres.





2016
LCC CAUSATIVE GENE: *SNORD118*

Encodes the box C/D small nucleolar RNA (snoRNA) U8. Box C/D snoRNAs are evolutionarily conserved RNAs involved in ribosomal biogenesis and function

Nat Genet. 2016 Oct;48(10):1185-92. doi: 10.1038/ng.3661. Epub 2016 Aug 29.

Mutations in SNORD118 cause the cerebral microangiopathy leukoencephalopathy with calcifications and cysts.

Jenkinson EM[1], Rodero MP[2], Kasher PR[1], Uggenti C[2], Oojageer A[1], Goosey LC[1], Rose Y[2], Kershaw CJ[3], Urquhart JE[1], Williams SG[1], Bhaskar SS[1], O'Sullivan J[1], Baerlocher GM[4,5], Haubitz M[4,5], Aubert G[6,7], Barañano KW[8,9], Barnicoat AJ[10], Battini R[11], Berger A[12,13], Blair EM[14], Brunstrom-Hernandez JE[15,16], Buckard JA[17], Cassiman DM[18], Caumes R[19], Cordelli DM[20], De Waele LM[21,22], Fay AJ[16], Ferreira P[23], Fletcher NA[24], Fryer AE[25], Goel H[26,27], Hemingway CA[28], Henneke M[29], Hughes I[30], Jefferson RJ[31], Kumar R[32], Lagae L[22], Landrieu PG[33], Lourenço CM[34], Malpas TJ[35], Mehta SG[36], Metz I[37], Naidu S[38], Õunap K[39,40], Panzer A[41], Prabhakar P[28], Quaghebeur G[42], Schiffmann R[43], Sherr EH[44], Sinnathuray KR[45], Soh C[46], Stewart HS[14], Stone J[47], Van Esch H[48], Van Mol CE[49], Vanderver A[50,51], Wakeling EL[52], Whitney A[53], Pavitt GD[3], Griffiths-Jones S[3], Rice GI[1], Revy P[54,55], van der Knaap MS[56,57], Livingston JH[58], O'Keefe RT[3], Crow YJ[1,2,55].

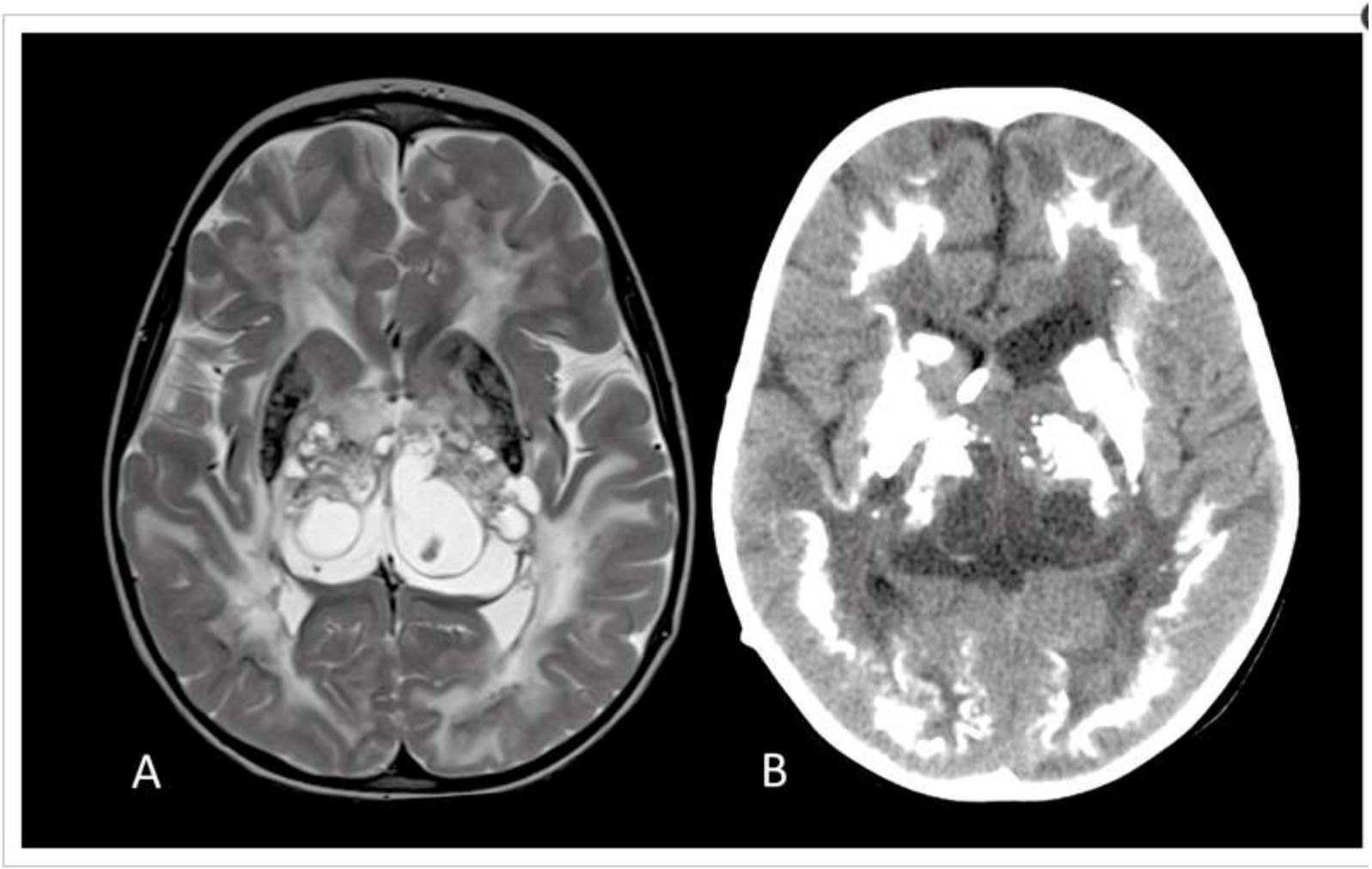
⊕ **Author information**

Abstract

Although ribosomes are ubiquitous and essential for life, recent data indicate that monogenic causes of ribosomal dysfunction can confer a remarkable degree of specificity in terms of human disease phenotype. Box C/D small nucleolar RNAs (snoRNAs) are evolutionarily conserved non-protein-coding RNAs involved in ribosome biogenesis. Here we show that biallelic mutations in the gene SNORD118, encoding the box C/D snoRNA U8, cause the cerebral microangiopathy leukoencephalopathy with calcifications and cysts (LCC), presenting at any age from early childhood to late adulthood. These mutations affect U8 expression, processing and protein binding and thus implicate U8 as essential in cerebral vascular homeostasis.

Autosomal Recessive disease

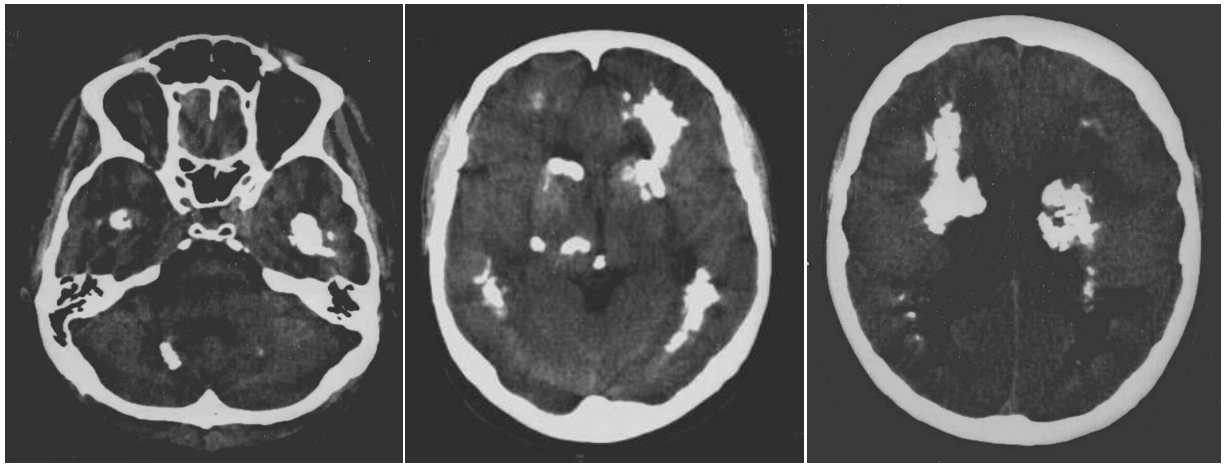
Typical LCC brain MRI and CT scan



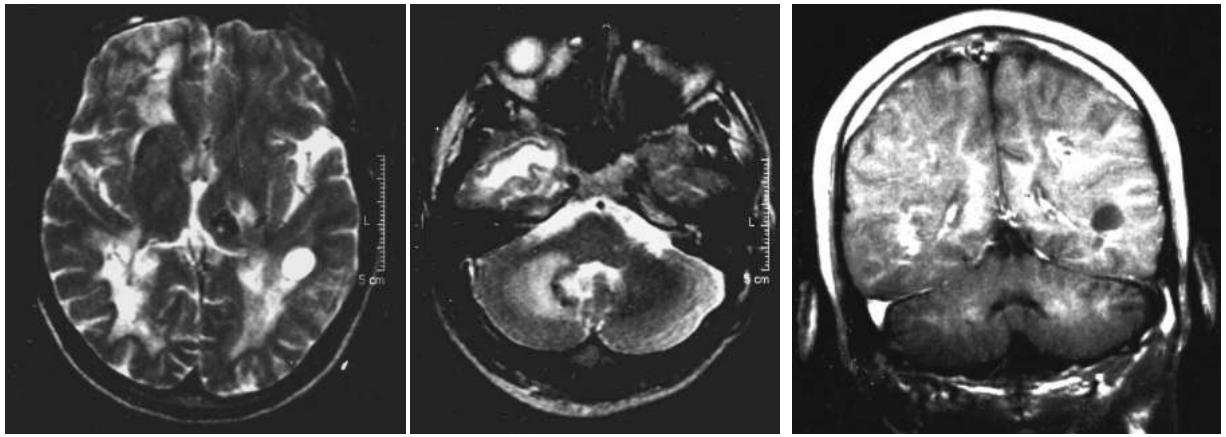
Jenkinson et al 2016

LCC case report:

The patient, a 19 years old man has a clinical history of early onset seizures and slowly progressive neurological impairment with mild mental retardation.

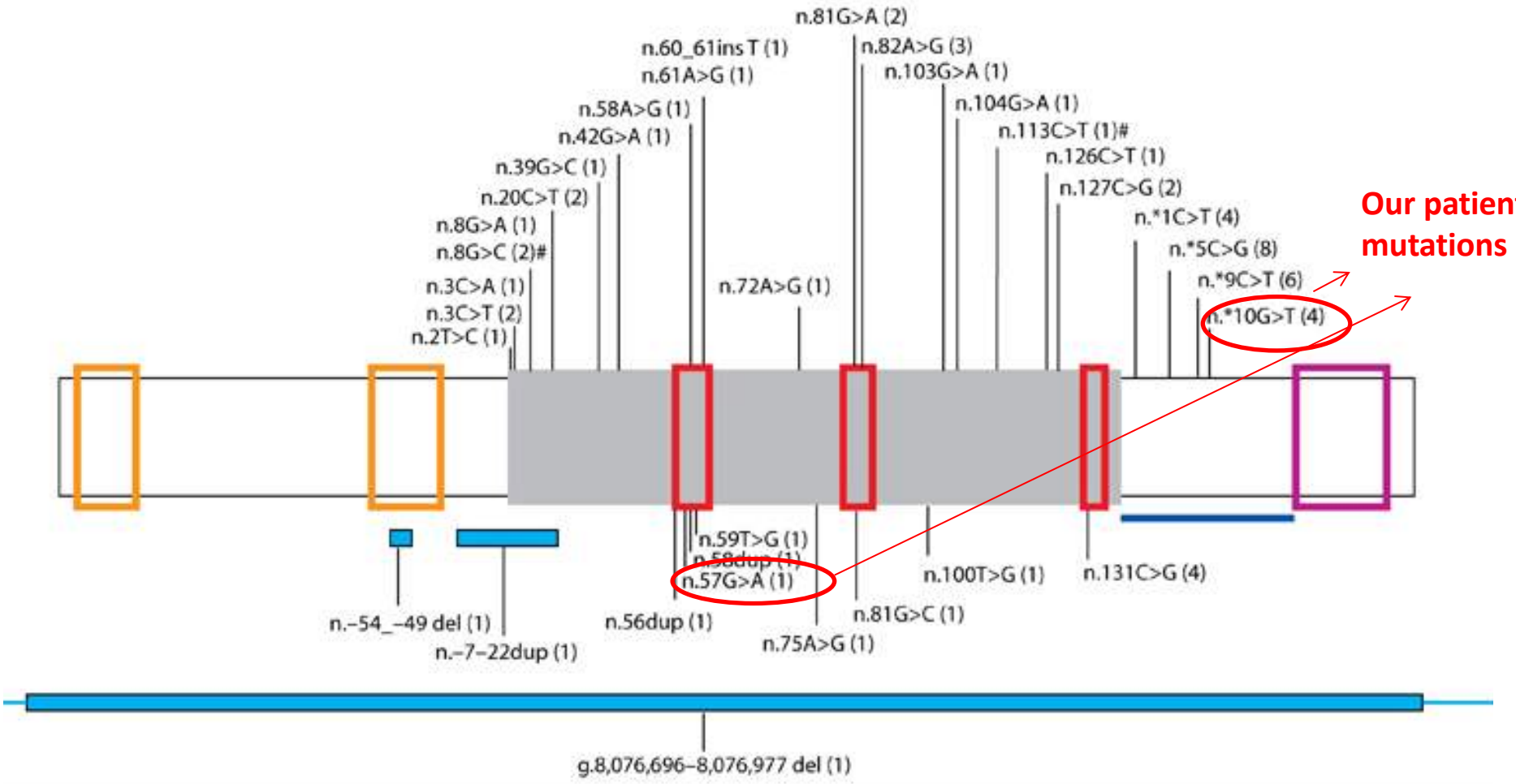


CT SCAN



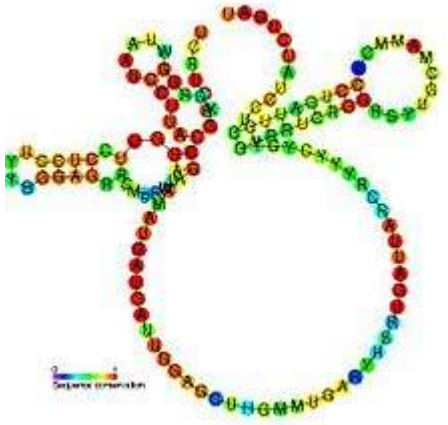
MRI

SNORD118 mutations



Jenkinson et al 2016

SNORD118



The ribosome consists of ribosomal RNA (rRNA) and ribosomal proteins (RPs). SNORD118 encodes the box C/D small nucleolar RNA (snoRNA) U8. Box C/D snoRNAs are evolutionarily conserved RNAs involved in **ribosomal biogenesis and function**.

Jenkinson et al. 2016

Variant in the promoter region (n.-54_-49del) of U8 affects expression of the snoRNA.

Alterations in the C box (n.57G>A; n.58A>G; n.61A>G; n.60_61insT) disturb the association of U8 with the snoRNA-binding protein 15.5K.

Variants in the 3' end (n.*5C>G) of the gene confer aberrant processing of the precursor U8 snoRNA.

These variants act as loss of function mutations

- Male, 59 years old, Married , One adopted child

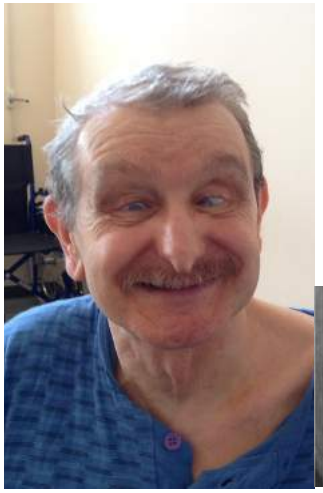
Patient's family history Father and mother died for cerebral ischaemia, Older brother (64 y) affected by glaucoma, One cousin affected by glaucoma and cataract, Grandfather affected by bilateral blindness

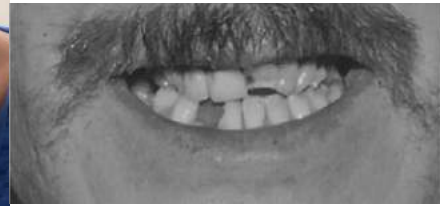
Patient's medical history

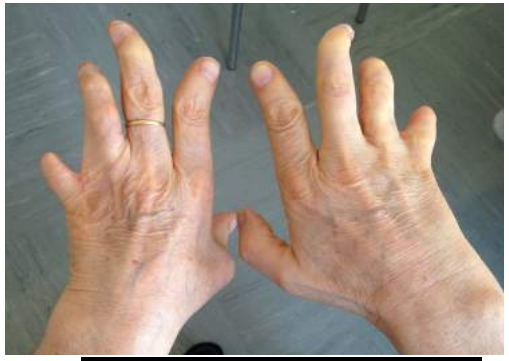
- Born with bilateral **syndactyly of the 3rd, 4th and 5th finger** surgically corrected at 1 year
- **Decreased visual acuity** from infancy
- **Microdontia and teeth loss** (partial denture at 39y)
- Bilateral **glaucoma** surgically treated at 38y
- Bilateral **cataract** surgically treated at 42y
- **Bilateral blindness at 43y, Bipolar disorder and Azoospermia**

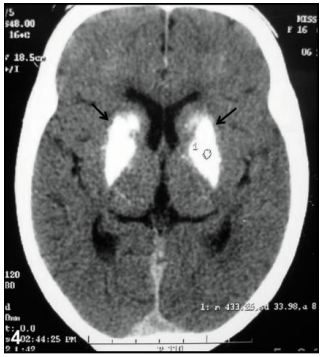
• Neurological symptoms Progressive **gait disturbance** started 4-5 years before, Concomitant **urinary and bowel incontinence ,** Unsteadiness, **Frequent falls**, Previous hospitalizations and suspect of Hydrocephalus and evidence at CT scan of cerebral calcifications

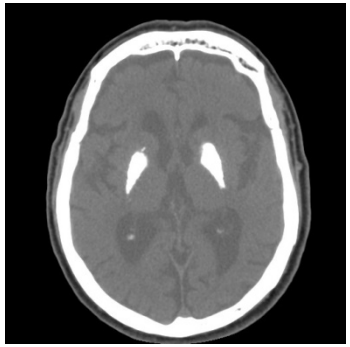
Oculodentodigital dysplasia with massive brain calcification and a new mutation of GJA1 gene.
Tumminelli G, Di Donato I, Guida V, Rufa A, De Luca A, Federico A.
J Alzheimers Dis. 2015;49(1):27-30

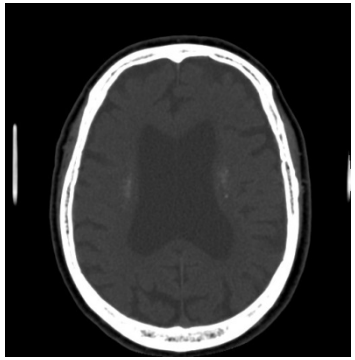


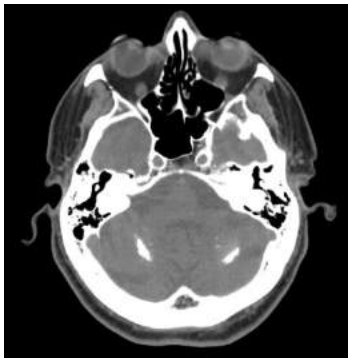












Calcifications in basal nuclei, in cerebellar nuclei and periventricularly with hydrocephalus

- Laboratory and strumental investigations
  - Normal Calcium and Phosphorus Metabolism
  - Abnormal motor and somatosensorial evoked potentials
  - Audiogram showed mild bilateral hypoacusia
- Genetic testing

Analysis of the GJA1 gene revealed a heterozygote missense mutation

NM_000165.3; c.124G>C; p.Glu42Gln

Diagnosis **Oculodentodigital Dysplasia**

Oculodentodigital Dysplasia

- Definitive delineation by Meyer-Schwickerath in 1957 who introduced the term "Dysplasia oculo-dento-digitalis"
- In 1963, Gorlin et al. reviewed the known cases and defined the core features of the syndrome

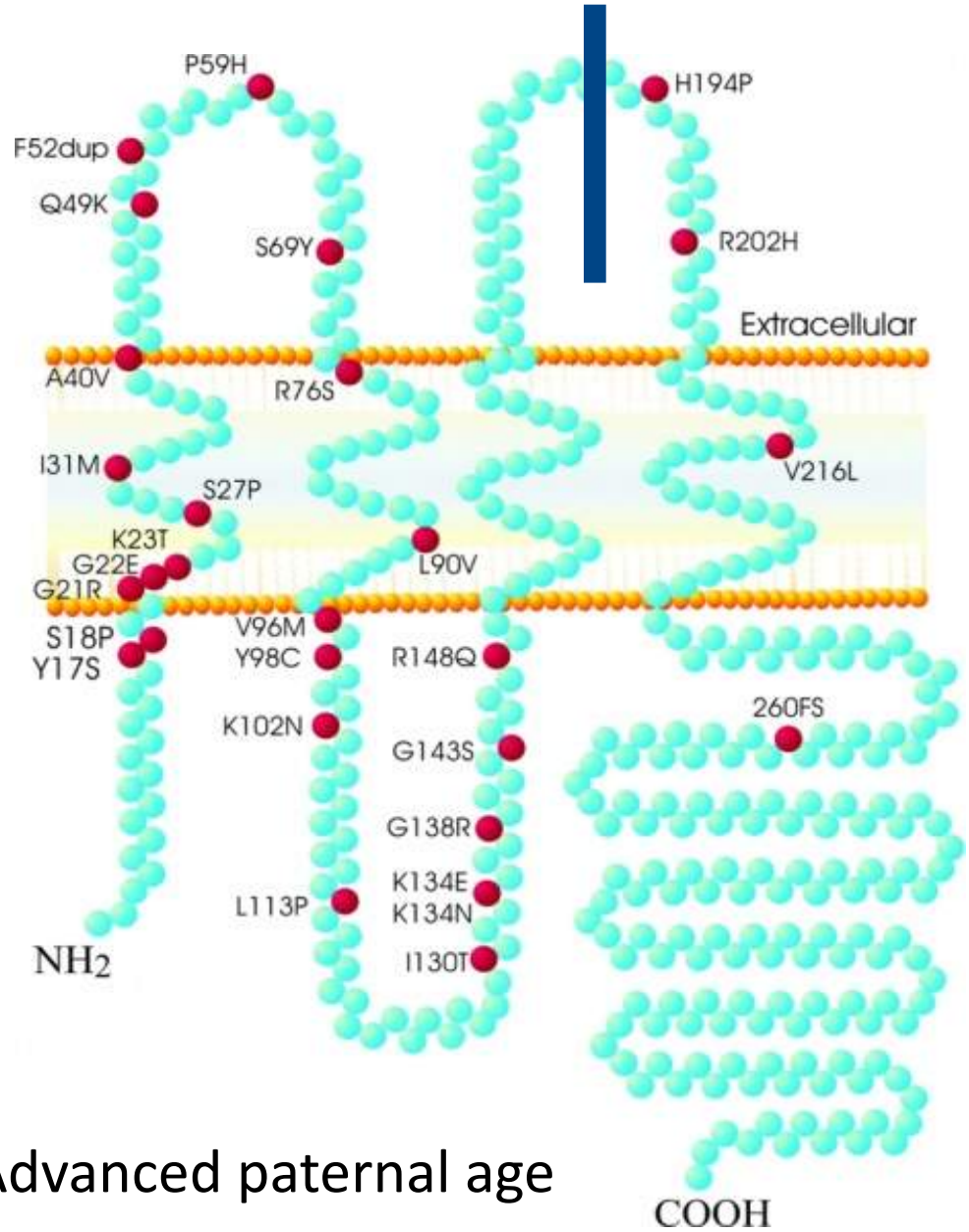
- To date 250 cases have been described (mostly caucasians)
- Prevalence < 1/1,000,000
- In the affected families males and females are found in equal numbers while in sporadic forms females seem to be more susceptible
- Mainly autosomal dominant, high penetrance, inter- and intrafamilial phenotype variability

Oculodentodigital Dysplasia

Etiology

Mutations in the GJA1 gene (6q21-23.2) coding for Connexine 43

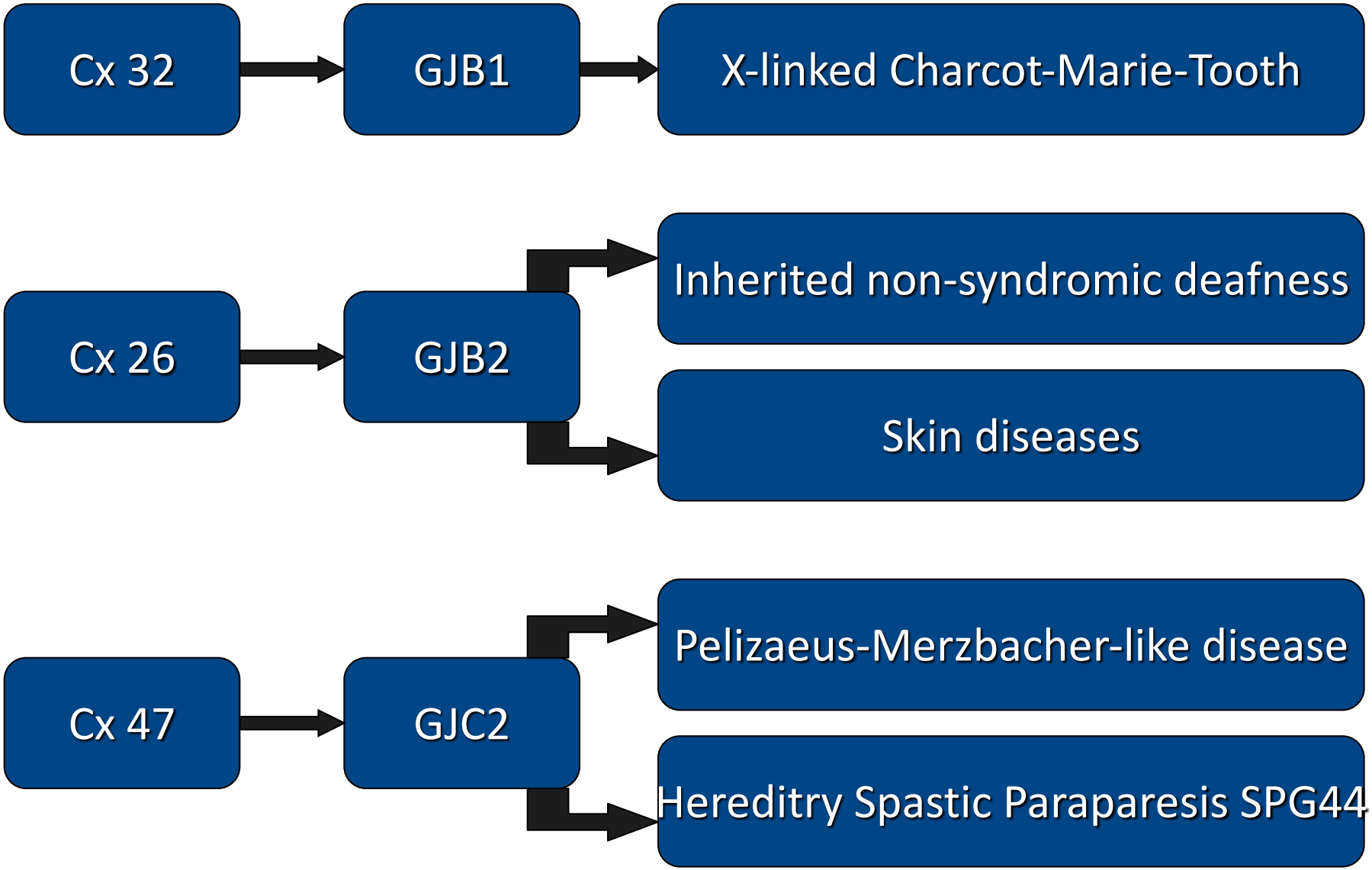
- 85% → dominant missense
- 15% → codon duplications, codon deletions, frameshift mutations, recessive nonsense mutations



High rate of the novo mutations → Advanced paternal age

Oculodentodigital Dysplasia

- **"Connexinopathies"**



Gap junction alfa 12 protein gene and connexin 47

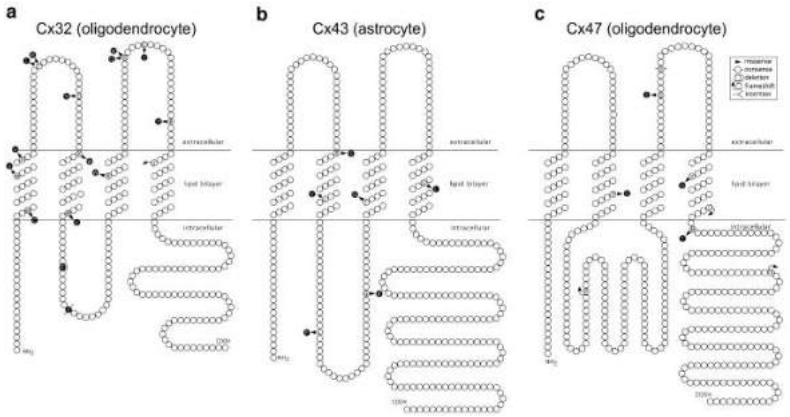
- In some families with a PMD-like phenotype (spastic paraparesis type 2) has been showed a mutation of the gap junction alfa 12, codifying for connexin 47.
- In such patients the oligodendrocytes survival semms to be normal, while the formation of compact myelin is abnormal, followed by a rapid axonal degeneration.

Connexin 43 and glial cells

- **Deletion of astrocyte connexins 43 and 30 leads to a dysmyelinating phenotype and hippocampal CA1 vacuolation.**

  Lutz SE, Zhao Y, Gulinello M, Lee SC, Raine CS, Brosnan CF.

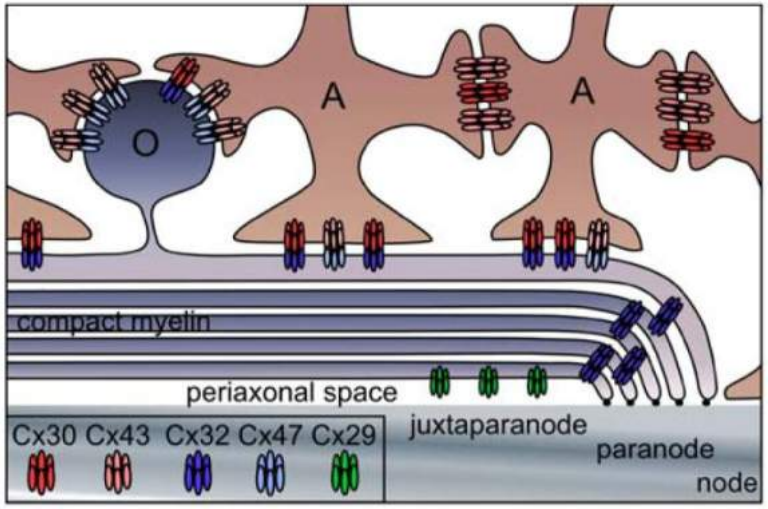
  J Neurosci. 2009 Jun 17;29(24):7743-52



- **Connexin43 is involved in the effect of endothelin-1 on astrocyte proliferation and glucose uptake.**

  Herrero-González S, Valle-Casuso JC, Sánchez-Alvarez R, Giaume C, Medina JM, Tabernero A.

  Glia. 2009 Jan 15;57(2):222-33



Selective vulnerability to a metabolic factor of different CNS cells

- **The regulation of enzyme synthesis and cell turnover can vary in different types of cells: neurons with long axons and large synaptic terminals can differ in metabolic capacity from short interneurons.**
- **The saturation of residual enzyme activity is reached more quickly in some cells than in others.**
- **In agreement with the hypothesis of critical metabolic flow, a certain turnover of intermediate metabolites in a given metabolic pathway is necessary to maintain normal function; turnover can vary from one functional system to another.**
- **Residual capacity to degrade certain substrates may be selectively affected in more vulnerable systems**

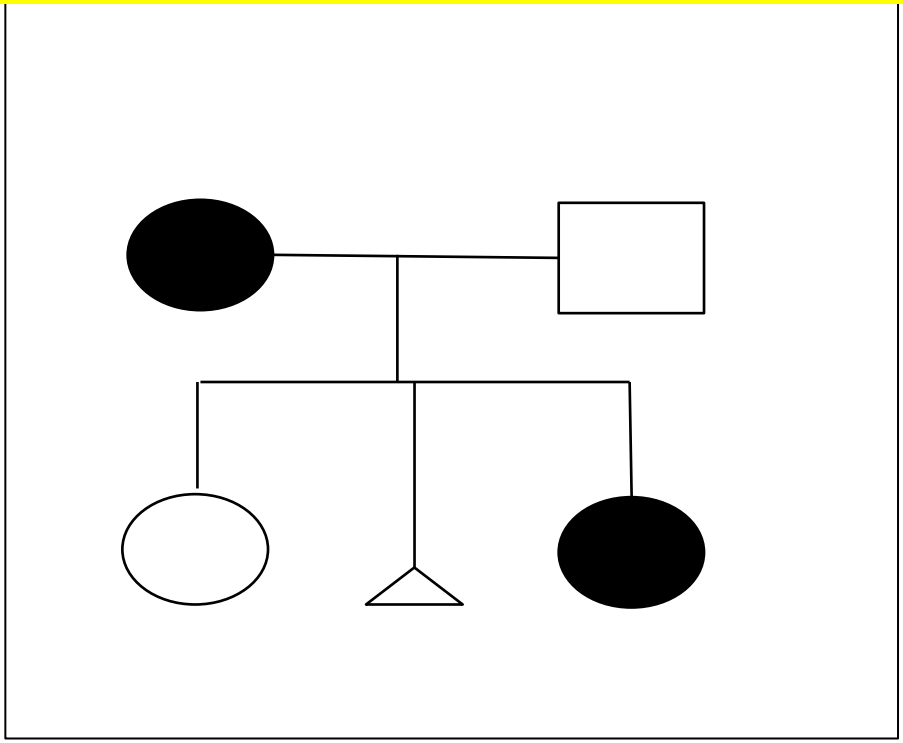
The opening of the possibility of pathogenetic treatments

Therapeutic approach to rare neurologic diseases started by

- A) decreasing levels of toxic metabolites by diet
- B) removal toxic substrates by transfusions, plasmapheresis, peritoneal dyalisis and drugs
- C) substitution of deficient metabolites (Leucocyte and plasma infusions; organs transplantations; fibroblasts transplantations; bone marrow transplantation);
- D) direct supply of deficient metabolite
- E) enzymatic induction by coenzymes
- F) enzyme therapy.
- G) More recently gene therapy is a reality for many conditions.

The application of the new molecular genetic analysis (NGS,GWG, etc)

- A family with a progressive spastic-ataxic syndrome, associated with WM changes at MR.
- The second pregnancy, a male, resulted in aborption.



CASE REPORT

Pt1 29 years (daugther)

Onset ⟹ age 10 ⟹ Slowly progressive spastic paraparesis – mild ataxia
Cyclothymia from adolescence
Optic neuritis at 28 years
Treatment with high-dose intravenous steroids with mild clinical response

Neurological examination ⟹ Spastic-ataxic syndrome. Sporadic bladder incontinence.
SPRS: 24/52

Screening for leukoencephalopathies (Lupus anti-coagulant, lysosomal enzymes, fatty acids): negative

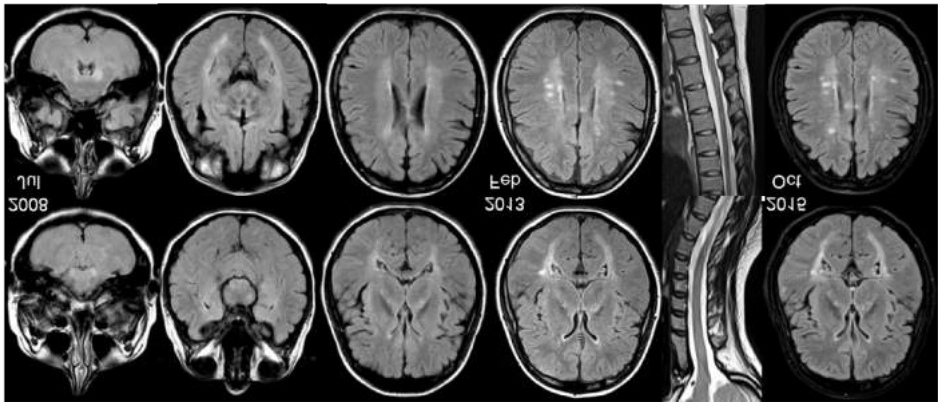
CSF examination: presence of oligoclonal bands. Increased IgG synthesis and IgG index

Anti-Acquaporine4 antibodies assay: negative

Visual Evoked Potenzials: increased latency of P100

Electromiography: sensory-motor mainly axonal polineuropathy

Neuropsycological examination : Mild cognitive impairment. MMSE: 23/30



Diffuse and confluent hyperintensity on T2-weighted and FLAIR images in deep and periventricular WM of both cortical hemispheres, and multiple focal lesions which increased in number during the 7-year follow-up .
Patchy and confluent hyperintensities of the spinal cord WM without gadolinium-contrast enhancement.

CASE REPORT

Pt2 53 years (mother)

Onset ⟹ juvenile ⟹ Slowly progressive spastic paraparesis .

Neurological examination: spastic-ataxic syndrome. SPRS: 29/52

CSF examination: absence of oligoclonal bands. IgG synthesis was increased

Anti-Acquaporine4 antibodies assay: negative

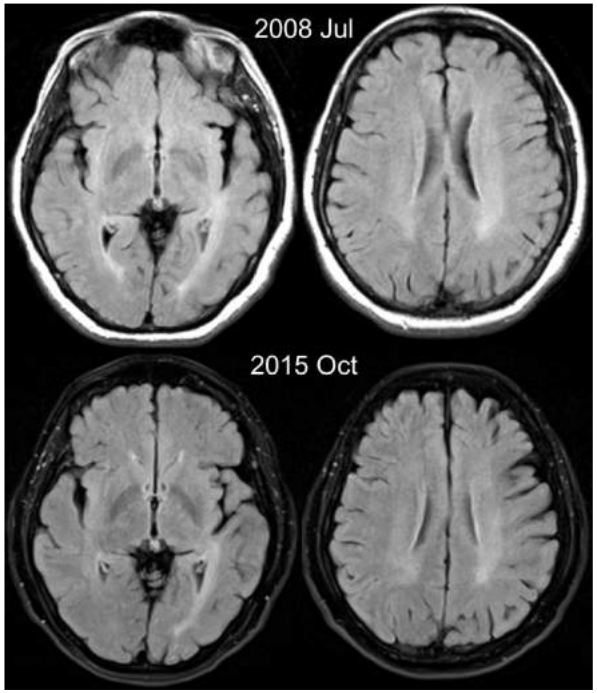
Visual Evoked Potentials: increased latency of P100

Electromiography: sensory-motor mainly axonal polineuropathy

Neuropsycological examination : Mild cognitive impairment

Screening for leukoencephalopathies (Lupus anti-coagulant, lysosomal enzymes, fatty acids): negative

Neuropsycological examination: cognitive impairment. MMSE: 20/30



Deep and periventricular WM showed diffuse confluent high signal intensity on T2-weighted and FLAIR images without abnormal gadolinium-enhancement

Question: Diagnostic suspicion?

a) Hereditary Spastic Paraparesis (one of the HSP forms?, dominant inheritance)

b) Familial Multiple sclerosis

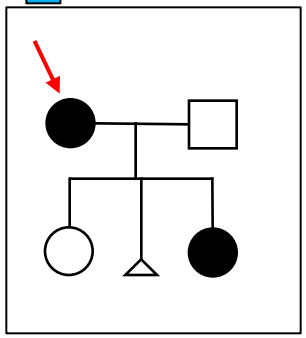
c) Spheroid leucoencephalopathy (dominant)

d) Paelizaeus Merzbacker disease (X-linked)

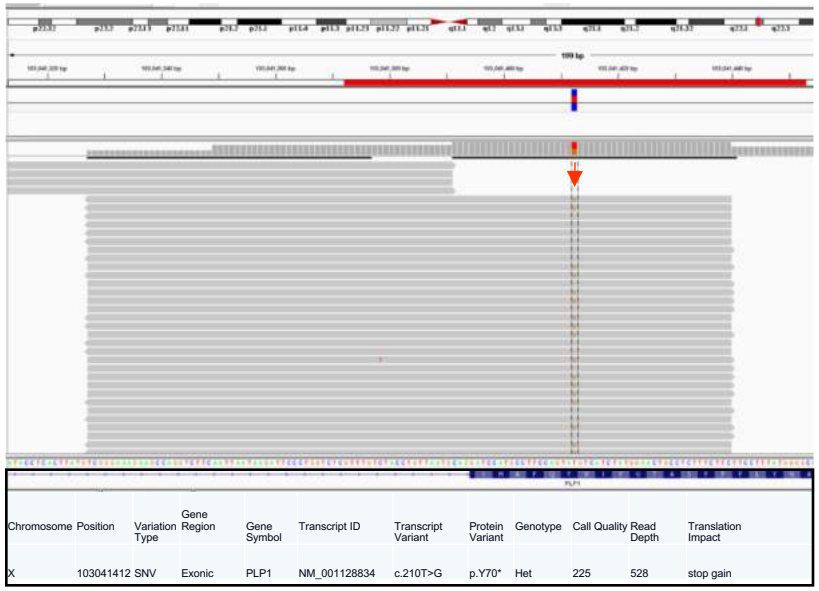
Answer: d)

Analysis of 72 HSP genes
Using targeted
Next Generation Sequencing (NGS)

AFG3L2, ALDH18A1, AMPD2, AP4B1, AP4E1, AP4M1, AP4S1, AP5Z1, ARL6IP1, ARSI, ATL1, B4GALNT1, BICD2, BSCL2, C12ORF65, C19ORF12, CCT5, CPT1C, CYP2U1, CYP7B1, DDHD1, DDHD2, ENTPD1, ERLIN1, ERLIN2, EXOSC, FA2H, FLRT1, GAD1, GBA2, GJC2, HSPD1, KIAA0196, KIF1A, KIF1C, KIF5A, L1CAM, LYST, MAG, MARS, MARS2, MTPAP, NIPA1, NT5C2, OPA1, OPA3, PANK2, PGAP1, PLA2G6, PLP1, PNPLA6, RAB3GAP2, REEP1, REEP2, RTN2, SACS, SLC16A2, SPG11, SLC33A1, SPG20, SPG21, SPG7, TECPR2, TFG, TRPV4, USP8, VPS37, AVRK1, WDR48, ZFR, ZFYVE26, ZFYVE27



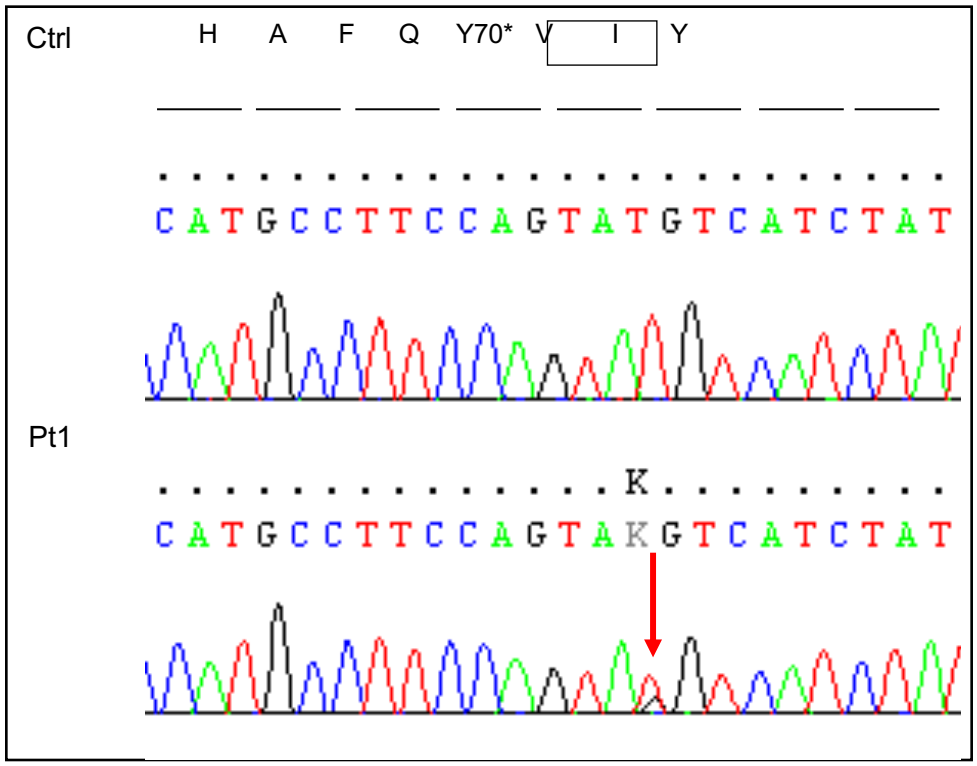
PLP1
c.210T>C/p.Y70*



Chromosome	Position	Variation Type	Gene Region	Gene Symbol	Transcript ID	Transcript Variant	Protein Variant	Genotype	Call Quality	Read Depth	Translation Impact
X	103041412	SNV	Exonic	PLP1	NM_001128834	c.210T>G	p.Y70*	Het	225	528	stop gain

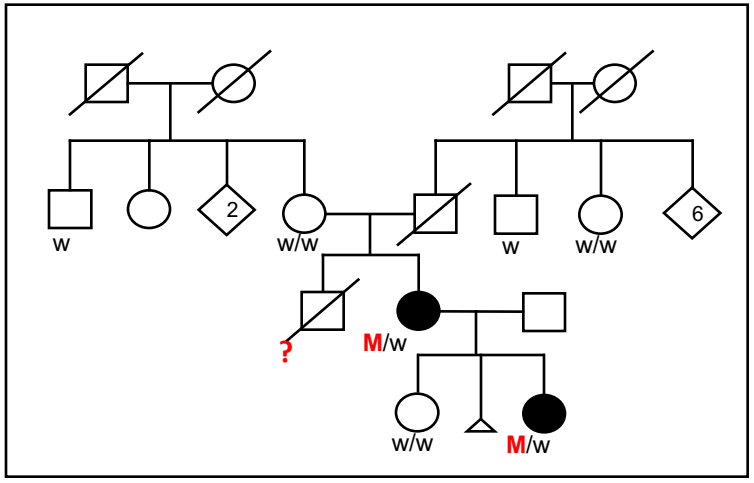
***De novo* occurence of**
c.210T>C/p.Y70*
or
Germline mosaicism?

RESULTS



Sanger sequencing analysis detected the heterozygous c.210T>C/p.Y70* in the daughter (Pt1)

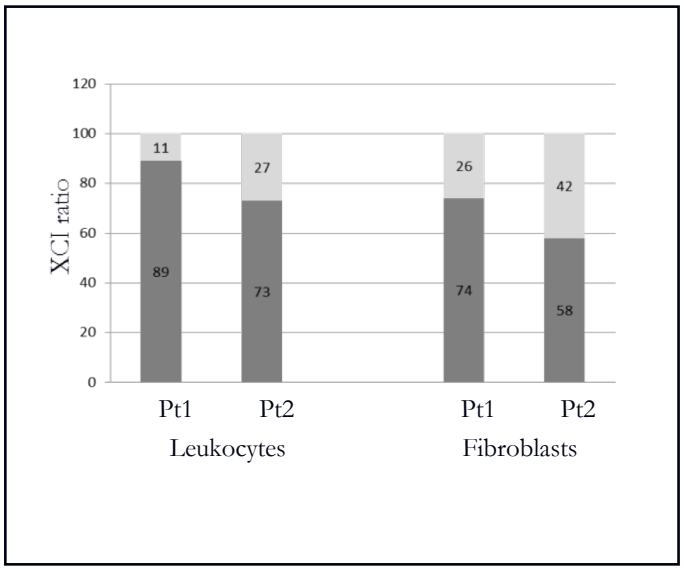
Segregation analysis



***De novo* occurence of c.210T>C/p.Y70*
or
Germline mosaicism?**

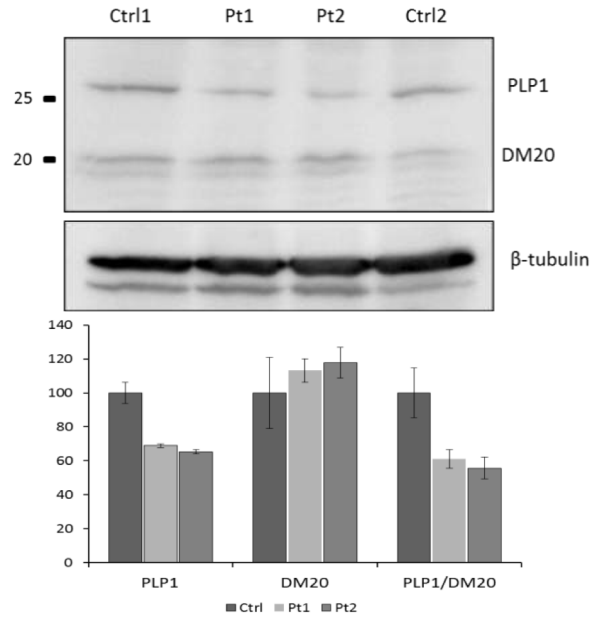
RESULTS

X inactivation pattern (XCI)



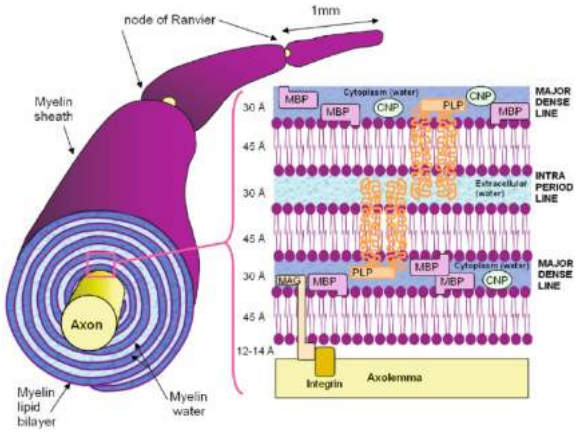
- In Pt1 we observed an extremely (89:11) and a moderately (74:26) skewed XCI in leukocytes and fibroblasts
- In the mother (Pt2) moderately skewed XCI pattern (73:27) was seen in leukocytes

PLP1 carrier females may develop late-onset neurological manifestations because of secondary skewing of XCI (Inoue; Neurogenetics 2005)



Significant reduction of PLP1 protein expression (about 40% of normal values)

In addition to the *PLP1* gene abnormality, a second event of skewed X chromosome inactivation is needed for the disorder to manifest in a female.



PMP in females

SPG2 mimicking multiple sclerosis in a family identified using next generation sequencing.
Rubegni A, **Battisti C**, Tessa A, Cerase A, Doccini S, Malandrini A, Santorelli FM, **Federico A**.
J Neurol Sci. 2017 Apr 15;375:198-202

Unusual presentation of Pelizaeus-Merzbacher disease: female patient with deletion of the proteolipid protein 1 gene.
Brender T[1], Wallerstein D[1], Sum J[1], Wallerstein R[1]. Case Rep Genet. 2015;2015:453105

Callosal disconnection syndrome in symptomatic female carrier of Pelizaeus-Merzbacher disease.
Kim Y[1], Asano Y[2], Koide R[3], Kimura H[2], Saitsu H[4], Matsumoto N[4], Bandoh M[2] J. Neurol. Sci. 2015 Nov 15;358(1-2):461-2.

Classic Pelizaeus-Merzbacher disease in a girl with an unbalanced chromosomal translocation and functional duplication of PLP1.
Yiu EM, Farrell SA, Soman T Mov Disord. 2009 Oct 30;24(14):

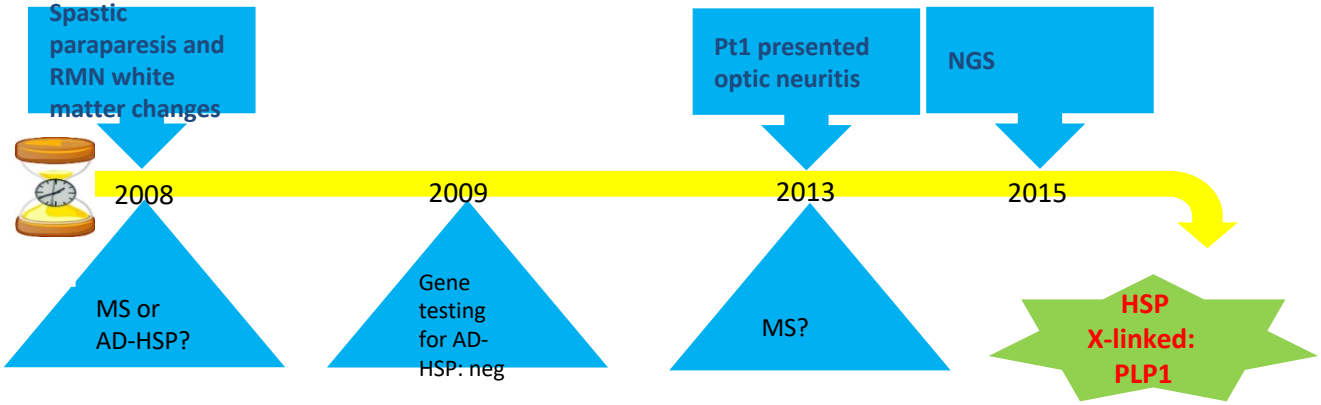
Primary progressive multiple sclerosis as a phenotype of a PLP1 gene mutation.
Warshawsky I[1], Rudick RA, Staugaitis SM, Natowicz MR. Ann Neurol. 2005 Sep;58(3):470-3.

This case goes against dogma that mothers of severely affected sons are asymptomatic as adults and expands the differential diagnosis of primary progressive multiple sclerosis to include proteolipid protein 1 gene mutations

CONCLUSIONS

- **SPG2 and other single gene disorders share clinical and radiologic features with PPMS and definition of the molecular defect require a more comprehensive NGS-based approach.**
- **Females can be affected, albeit rarely, with PMD so it needs to be considered in patients both males and females with progressing spasticity.**

- ***PLP1* should be tested in women with spastic paraparesis, cognitive decline, and WM changes**

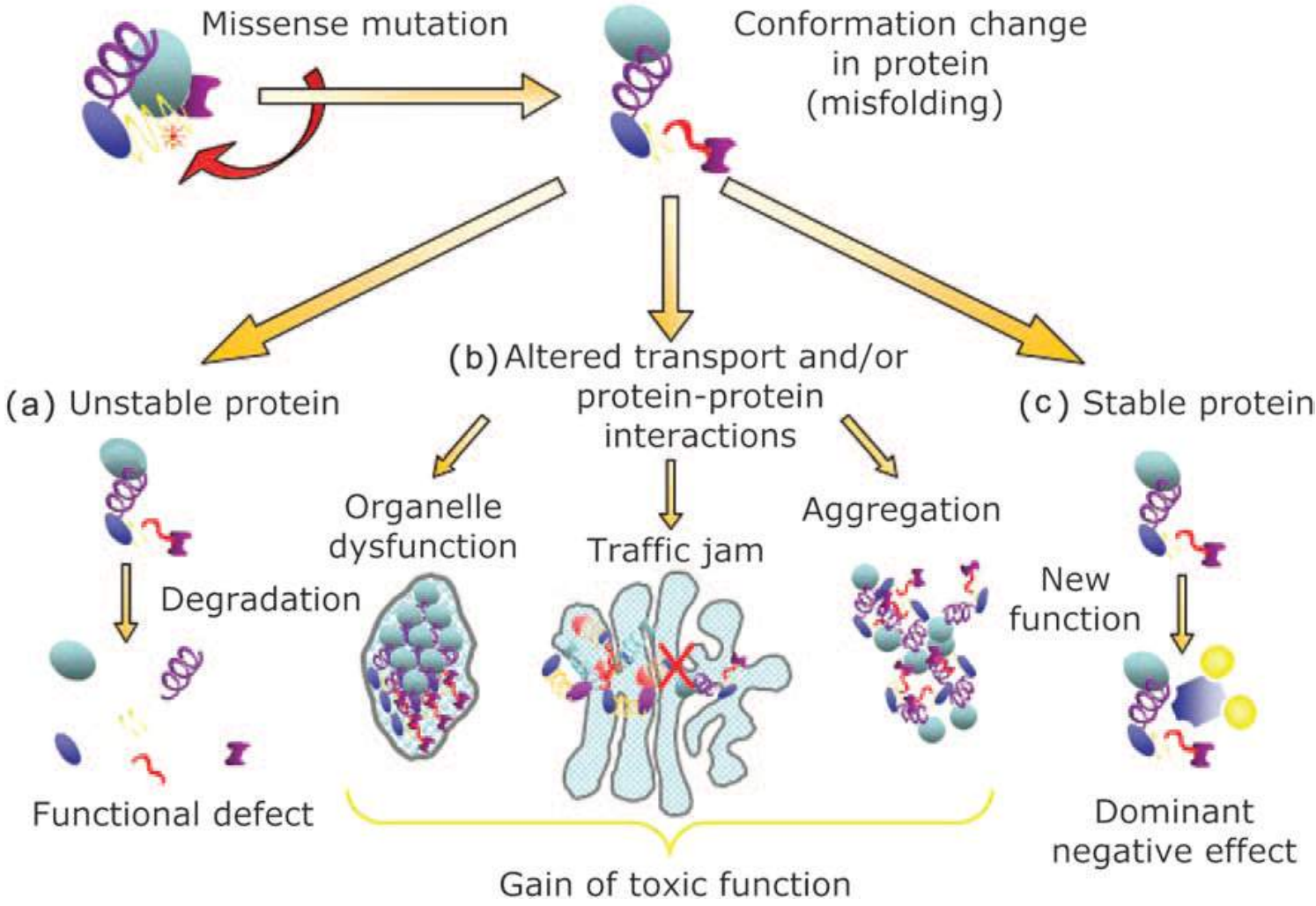


What we learned about the lesson by the late onset rare neurometabolic deseases as a model for understanding the functions of the nervous system?

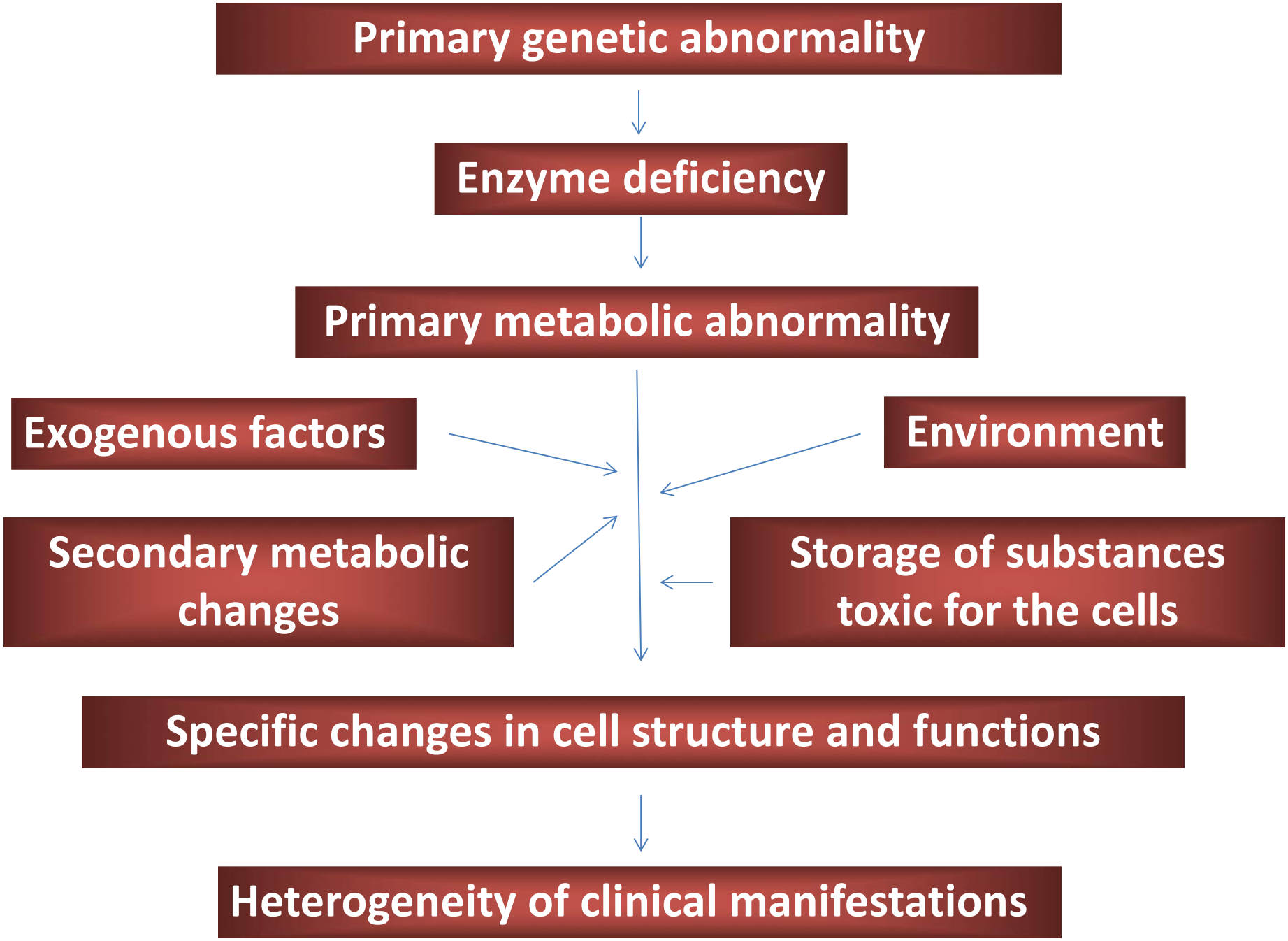
1. **Their extreme clinical heterogeneity, characterized by a different vulnerability of neuroaxonal system to a molecular defect**
2. **The possibility of an infantile onset, with a severe and rapidly evolving clinical features, due to the interaction of the primary metabolic disturbance in the biochemical mechanisms of brain maturation and development**
3. **The presence of late onset cases, with a slow evolution suggesting a neuro-axonal abyotrophic process**
4. **Their molecular heterogeneity**
5. **The possibility of the presence of minor clinical signs in heterozytotes, who may also be at risk for some more common pathology.**

Gene mutations

- Mutations resulting in some residual enzyme activity include missense mutations that do not completely abolish folding, processing and activity of the protein.
- Mutations affecting splicing but located outside the consensus site and producing variable amount of normally and abnormally spliced transcripts result in some residual enzyme activity as do some mutations affecting regulatory regions of the gene (TATA box and others and polyadenulation sites)
- Null alleles may be due to splice-site mutations or deletion.
- Missense mutations originate enzymes frequently fold incorrectly and retained in the endoplasmic reticulum and subsequently degradated.



In Mendelian disorders, a missense mutation results in a conformational change in the protein. Misfolding of a protein can lead to several different scenarios. (a) The protein may be unstable and hence be degraded, resulting in a functional defect; (b) the misfolded protein may be processed differently or may interact with other proteins, leading to organelle dysfunction, traffic jamming' or aggregation. All these mechanisms may result in a toxic gain in function; (c) the conformational change may result in a stable protein with a deleterious effect. This is known as a dominant-negative effect


Primary genetic abnormality
Enzyme deficiency
Primary metabolic abnormality
Exogenous factors
Environment
Secondary metabolic changes
Storage of substances toxic for the cells
Specific changes in cell structure and functions
Heterogeneity of clinical manifestations

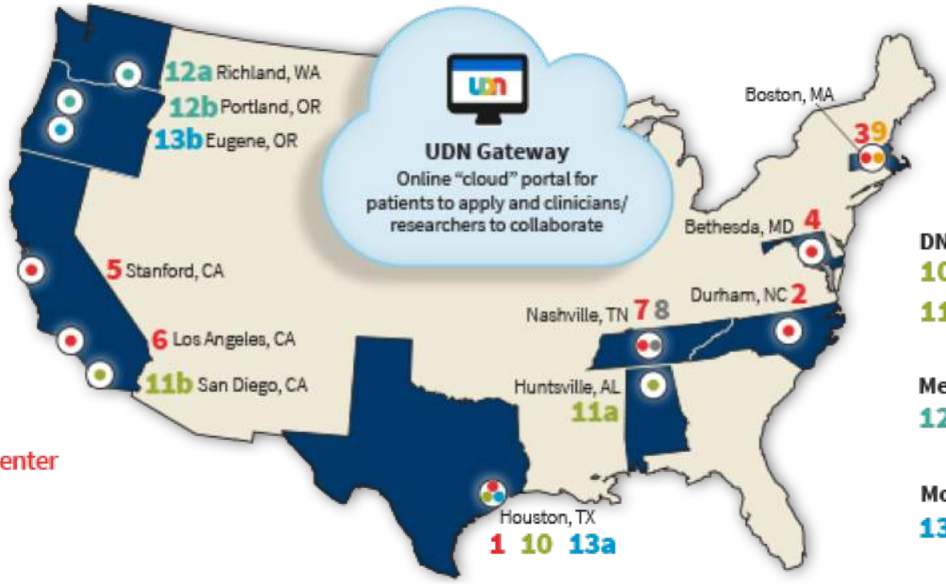
But, numerous neurologic patients remain still undiagnosed!.....

The Undiagnosed Diseases Network (UDN)

- The UDN is a research study funded by the National Institutes of Health Common Fund. The UDN is made up of clinical and research centers across the United States working to improve diagnosis and care of patients with undiagnosed diseases.
- https://rarediseases.info.nih.gov/guides/pages/24/tips-for-the-undiagnosed

Seven clinical sites

1. Baylor College of Medicine and Texas Children's Hospital
2. Duke Medicine with Columbia University Medical Center
3. Harvard Teaching Hospitals (BCH, BWH, MGH)
4. National Institutes of Health
5. Stanford Medicine
6. UCLA School of Medicine
7. Vanderbilt University Medical Center



Six additional research sites

Central Biorepository
8 Vanderbilt University Medical Center

Coordinating Center
9 Harvard Medical School

DNA Sequencing Core Facilities
10 Baylor College of Medicine
11 a HudsonAlpha Institute for Biotechnology *with*
b Illumina

Metabolomics Core Facility
12 a Pacific Northwest National Laboratories *with*
b Oregon Health & Science University

Model Organisms Screening Center
13 a Baylor College of Medicine *with*
b University of Oregon

Major European Grant for New Research Program: Solve-RD

January 19, 2018

We are excited to report on a new large-scale research Program called Solve-RD! The Solve-RD research program is a project funded by the EU's Horizon 2020 that will directly involve the European Reference Networks (ERNs) in order to diagnose currently undiagnosed rare disease patients using the latest in genetic technologies (i.e. 'multi-omics' methods).

A €15 million grant was awarded to the consortium, led my Prof Olaf Riess from the University of Tübingen, Prof Han Brunner from the Radboud University Nijmegen Medical Centre and Prof Anthony Brookes from the University of Leicester, to fund this innovative and ambitious project. An additional 18 other partner organisations (including Orphanet and EURORDIS) will also be involved.

Currently, Solve-RD includes a core group of four ERNs: the ERNs for rare neurological diseases (ERN-RND), neuromuscular diseases (ERN-EURO-NMD), congenital malformations and intellectual disability (ERN-ITHACA) and genetic tumor risk syndromes (ERN-GENTURIS). These ERNs will be the first to share and analyse their patient data, followed by others at a later date. This collaborative project aims to increase our knowledge on rare diseases (and their causes) and will have a significant impact on the diagnosis and treatment of rare disease patients across Europe.

EAN Rare Neurological Diseases Task Force

National Neurological Member Societies

Albania, Armenia, Austria, Azerbaijan, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, FYRO Macedonia, Finland, France, Georgia, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Latvia, Lithuania, Luxembourg, Moldova, Montenegro, Norway, Poland, Portugal, Romania, Russian Federation, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, The Netherlands, Turkey, Ukraine, United Kingdom, Uzbekistan

Associate Member Societies

Algeria, Egypt, Jordan, Lebanon, Libyan Arab Jamahiriya, Morocco, Palestinian Territory, Occupied, Syrian Arab Republic, Tunisia

EAN Rare Neurological Diseases Task Force

Responsibility for the Task Force rests with the EAN Scientific Committee and particularly with Scientific Committee Chair, Antonio Federico and Scientific Committe Member, Antonio Toscano.

Task Force can be reached via email at scientific@eaneurology.org.

The aims of the RNDs Task Force, in regard to the overarching European Council Recommendation, can be defined as follows:

- **To advise and assist the European Commission Public Health Directorate in promoting prevention of RNDs.**
- **To enhance diagnosis and treatment of RNDs through trans-European co-ordination.**
- **To provide a forum for discussion and exchange of experience on all issues related to RNDs.**

The specific objectives are:

- **To widen access to high quality information on causes, screening, diagnosis, , treatment, counselling and general care for RNDs.**
- **To promote availability of high quality epidemiological data across Europe regarding incidence, prevalence, survival and any differences within and between countries.**
- **To promote the creation of networks of centres of excellence in relation to diagnosis, treatment and outcome measures**
- **To promote the development of a classification and coding system for RNDs to supplement the International Classification of Diseases, in liaison with the World Health Organisation (WHO).**
- **To promote effective surveillance, early warning and cluster response in relation to changing risk factors for RNDs.**
- **To promote new therapeutic trials for RNDs.**
- **To facilitate development of different models of cross-border health care and health care funding, including consideration of quality control issues.**
- **To promote the exchange of ideas and information regarding quality of life issues, and regarding patient preference and choice.**
- **To develop and disseminate best practice consensus by presenting and comparing national health information.**

EAN Rare Neurological Diseases Task Force

- ALBERT C LUDOLPH (ALS and frontotemporal dementia)
- VINCENZO SILANI (ALS and frontotemporal dementia)
- WALTER STRUHAL (Autonomic nervous system disorders)
- MAX J HILZ (Autonomic nervous system disorders)
- PIETRO CORTELLI (Autonomic nervous system disorders)
- JAUME CAMPISTOL (Child neurology)
- NADIA BAHI-BUISSON (Child neurology)
- PIERANGELO VEGGIOTTI (Child neurology)
- ROCCO LIGUORI (Clinical neurophysiology)
- SANDRO SORBI (Dementia and cognitive disorders)
- PETER BERLIT (General neurology)
- WOLFGANG HEIDE (Higher cortical functions)
- JOHAN SELLNER (Infectious diseases)
- MARINA DE KONING TIJSSEN (Movement disorders)
- TIMOTHY LYNCH (Movement disorders)
- LUTZ HARMS (Neurocritical care)
- DANIEL KONDZIELLA (Neurocritical care)
- JESÚS DE PEDRO CUESTA (Neuroepidemiology)
- MAURA PUGLIATTI (Neuroepidemiology)
- DAVIDE PAREYSON (Neurogenetics)
- JEAN-MARC BURGUNDER (Neurogenetics)
- KAROLINA DZIEZYC (Neurogenetics)
- SVETLANA KOPISHINSKAYA (Neurogenetics)
- ALTIN KUWO (Neurogenetics)
- ETTORE SALSANO (Neurogenetics)
- FEDERICA AGOSTA (Neuroimaging)
- JAN VERSCHUUREN (Neuroimmunology)
- RICCARDO SOFFIETTI (Neuro-oncology)
- MICHAEL WELLER (Neuro-oncology)
- KATHY OLIVER (Neuro-oncology)
- MICHAEL STRUPP (Neuro-ophthalmology and -otology)
- DAFIN MURESANU (Neurorehabilitation)
- MAURIZIO LEONE (Neurotoxicology)
- RADU TANASESCU (Neurotoxicology)
- SVETLANA KOPINSHINKSAYA (Pain)
- DAVID OLIVER (Palliative care)
- GEERT MAYER (Sleep-wake disorders)
- ANNA CZLONKOWSKA (Stroke)
- NICHOLAS GUTOWSKI (Translational neurology)

Rare Neurologic Diseases Working Group

The aims of the Working Group are:

- **To reduce the rare neurological diseases list through specification of the main symptoms, diagnostic criteria and through production of guidelines for diagnosis.**
- **To review facilities for diagnosis of RND in Europe (to produce a list of available facilities and their addresses), indicating the main centers interested in different disorders where genetic, biochemical and other laboratory tests are possible.**
- **To analyze the attitude of European neurologists to RND and to identify the state of the art of this issue in the different European countries.**
- **To stimulate number of registries for RND, data bank and bio banks. (These are the main aims of the EU, within the research projects in the Biomed Program.)**
- **To create European Networks for RND for diagnosis and research.**
- **To facilitate teaching courses around Europe.**
- **To act as information service on RND within the EAN, that will be able, with the help of different experts present in the Working Group, to answer questions from patients, families and doctors (online). New data, new findings, research funds, treatment methods shall be presented to the general public. There will be also space for discussion on rare diseases.**


www.eaneurology.org/amsterdam2017
AMSTERDAM, THE NETHERLANDS, JUNE 24 - 27, 2017
3RD CONGRESS OF THE EUROPEAN ACADEMY OF NEUROLOGY
european academy of neurology
ean

EAN Guideline Production Group – 1st Science workshop on guideline production

April 1, 2017

Further aim:
New EAN Panel
Guidelines and good clinical practice"

15-16 May 2017 Milan

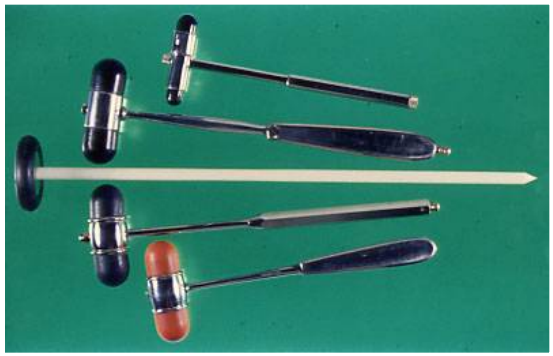
The study of rare diseases: butterfly collecting or an entrèe to understanding common conditions?

K. Talbot

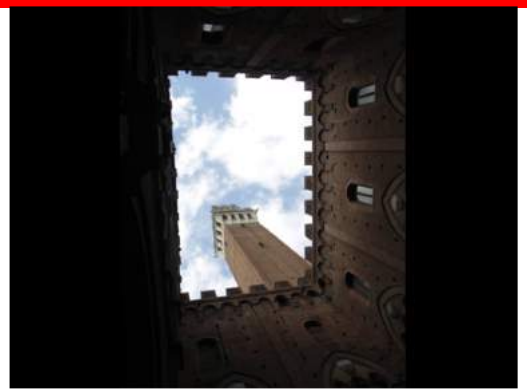
Pract. Neurol. 7: 210-211, 2007

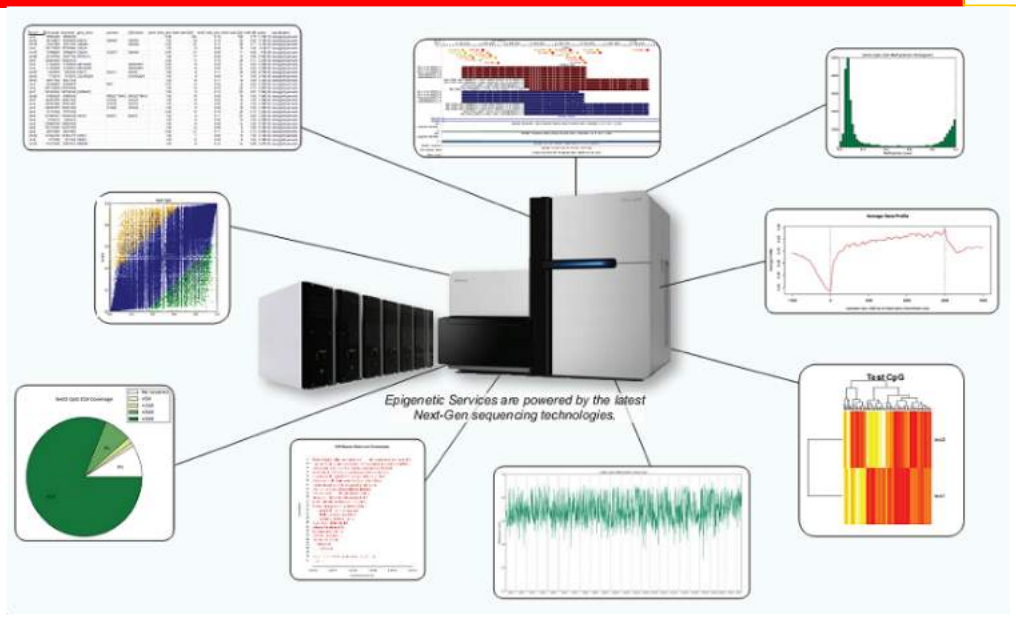
"Nature is nowhere accustommed more openly to display her secret mysteres than in cases where she shows traces after working apart from the beathen path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discoveries of the usual law of nature by careful investigation of causes of rarer forms of diseases. For it has been found, in almost all things, that what they contain of useful or applicable is hardly preceived under we are deprived of them or they become deranged in some way".

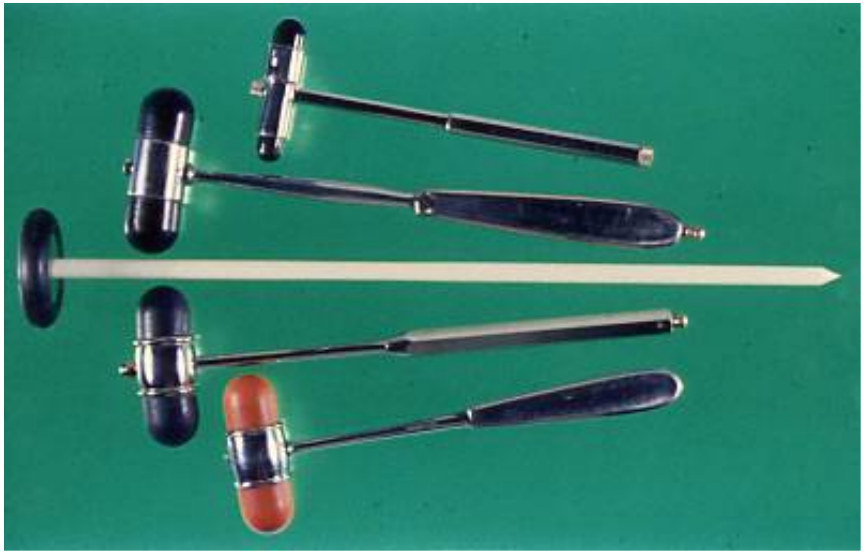
William Harvey, 1647



Unit Clinical Neurology and Neurometabolic Diseases
Director: A Federico federico@unisi.it







Government of Western Australia
Department of Health

What an Undiagnosed Diseases Program would do for WA

Rare diseases and the diagnostic odyssey

Rare diseases (RD) are a health priority. They are estimated to affect up to 6–8% of the population which in WA is up to 190,000 people, including more than 60,000 children. Many RD have their onset in childhood, continue for life, and are disabling and burdensome to individuals, families and the healthcare system.

An accurate diagnosis is the bedrock of best practice medical care. For RD achieving a diagnosis is particularly challenging. There are 5,000–8,000 known RD and most are complex with multisystem dysfunction.

Many patients experience a diagnostic odyssey. In a European study, 25% of individuals waited 5-30 years for a diagnosis and in 40% of instances the initial diagnosis was wrong (2). A recent WA lead study showed similar findings (3).

What is an undiagnosed disease?

An undiagnosed disease is a long-standing medical condition for which the health system has been unable to provide a diagnosis.

An Undiagnosed Disease Program for Western Australia

GENETIC SERVICES OF WESTERN AUSTRALIA

The health system could say...

- We have more comprehensively addressed the needs of individuals and families living with undiagnosed diseases.
- We can further partner with patients in the development of new management approaches.
- We can benefit from health savings.
- We can be lead partners in global health networks.
- We can further support clinical training and clinical translational research.

Families could say...

- We have closure.
- We are less isolated.
- We better understand what the future might (or might not) hold.
- We have avenues for better treatment, disorder specific medicines or best practice medical care.
- We have improved engagement with the health system.
- We can make financial savings.
- We have improved emotional well being.

Those not receiving a definitive diagnosis could say...

- We have closure for our family.
- The avenues to pursue a diagnosis have been further and more cohesively explored.
- We are less isolated, through connection with the community of undiagnosed individuals e.g. through UDP-related resources and relevant organisations such as Syndromes Without A Name (SWAN) and the Genetic and Rare Diseases Network WA (GaRDN).
- We have improved medical care by integration with relevant services and/ or specialists.
- We can give insight into better management and contribute to the development of new therapies.
- We have improved engagement with the health system.

Undiagnosed Diseases Network

The Undiagnosed Diseases Program and Network

The Undiagnosed Diseases Program was established within the USA National Institutes of Health (NIH) in 2008. It has become a global network of clinical genetics centres, using multidisciplinary teams, to provide diagnoses for patients with severe undiagnosed diseases.

Many UDN patients have previously visited multiple specialists, have had many hospital admissions and a myriad of investigations.

Diagnosis for those who had none

As a consequence of having no diagnosis, patients, and their families experience anxiety, uncertainty and sometimes inappropriate management of their condition.

In these most diagnostically intractable cases 25% have received a definitive diagnosis. This figure is higher when in children.

Health System Savings

For adult patients, direct costs accrued within the health system prior to assessment by the UDN was estimated to be a minimum of US$ 36,000 (AU$ 49,000) per patient.

With an early, accurate diagnosis much of this cost would have been averted. Future savings will also accrue along with an individuals life span

Preliminary assessments by the UDN suggest that the cost per patient diagnosed is less than a single admission in a tertiary hospital.

Paediatric costings are begin finalised and are anticipated to reveal similar high pre-existing costs and savings opportunities.

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Molecular Genetics and Metabolism 116 (2015) 223–225

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Commentary

Undiagnosed Diseases Network International (UDNI): White paper for global actions to meet patient needs

Domenica Taruscio[a,*], Stephen C. Groft[b], Helene Cederroth[c], Béla Melegh[d], Paul Lasko[e], Kenjiro Kosaki[f], Gareth Baynam[g,h,i,j,k,l], Alexa McCray[m], William A. Gahl[n]

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[h] Office of Population Health, Public Health Division, WA Department of Health, Australia
[i] Telethon Kids Institute, Perth, Australia
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See comment in PubMed Commons belowMedicine (Baltimore). 2017 Dec;96(50):e8970. doi: 10.1097/MD.0000000000008970.

Are parents of children with Cockayne syndrome manifesting features of the disorder?: Case reports.

Abstract

RATIONALE:

Postnatal growth failure and progressive neurologic dysfunction and increasing multiorgan involvement are the main clinical features of Cockayne syndrome (CS). CS is a rare autosomal recessive disorder of the group of DNA repair diseases. Usually, genetic carriers, such as parents of patients, are not at risk for developing the disease.

PATIENT CONCERNS:

A series of 14 family subjects (6 children with age range from 6 months to 4 years with CS) and 9 parents (aged from 23 to 34 years) from consanguineous families is reported.

DIAGNOSES:

Ultraviolet irradiation studies were performed on these children and were indicative of CS.

INTERVENTIONS:

Cells of skin fibroblast from these children with the disease showed a symmetrical accumulation of chromosomal aberrations and the nuclear lamina aberrations. Our results showed a significant and simultaneous increase of percent of blebbs and invaginations of the nuclear lamina in all cases CS. The pronounced changes in 12.6 times at atypical form (girl); in 8.5 times at severe form (boy) and in 5.6 times at light form (boy). Percentage of metaphases with chromosomal aberration is significantly higher in CS cells: in 4 times at atypical form, in 3 times at hard form, and in 2 times at light form. The parents of these families (consanguineous families) were intellectually variable between normal/borderline intelligence, though most manifested a constellation of skeletal and extraskeletal abnormalities and notably, the characteristic cachectic facial appearance. The parents were considered as manifesting the mild type of CS, because they showed no abnormalities of DNA repair.

OUTCOMES:

Clinical manifestations in heterozygote carriers of an autosomal recessive disorders is a rare phenomenon as carriers are usually healthy.

LESSONS:

The interesting finding of the families studied is that there appeared to be a multitude of carriers manifesting with normal to borderline intelligence but with a wide spectrum of skeletal and extraskeletal abnormalities.

J Natl Cancer Inst. 2005 Jun 1;97(11):813-22.

Cancer risks and mortality in heterozygous ATM mutation carriers.

Thompson D[1], Duedal S, Kirner J, McGuffog L, Last J, Reiman A, Byrd P, Taylor M, Easton DF.

Abstract

BACKGROUND:

Homozygous or compound heterozygous mutations in the ATM gene are the principal cause of ataxia telangiectasia (A-T). Several studies have suggested that heterozygous carriers of ATM mutations are at increased risk of breast cancer and perhaps of other cancers, but the precise risk is uncertain.

METHODS:

Cancer incidence and mortality information for 1160 relatives of 169 UK A-T patients (including 247 obligate carriers) was obtained through the National Health Service Central Registry. Relative risks (RRs) of cancer in carriers, allowing for genotype uncertainty, were estimated with a maximum-likelihood approach that used the EM algorithm. Maximum-likelihood estimates of cancer risks associated with three groups of mutations were calculated using the pedigree analysis program MENDEL. All statistical tests were two-sided.

RESULTS:

The overall relative risk of breast cancer in carriers was 2.23 (95% confidence interval [CI] = 1.16 to 4.28) compared with the general population but was 4.94 (95% CI = 1.90 to 12.9) in those younger than age 50 years. The relative risk for all cancers other than breast cancer was 2.05 (95% CI = 1.09 to 3.84) in female carriers and 1.23 (95% CI = 0.76 to 2.00) in male carriers. Breast cancer was the only site for which a clear risk increase was seen, although there was some evidence of excess risks of colorectal cancer (RR = 2.54, 95% CI = 1.06 to 6.09) and stomach cancer (RR = 3.39, 95% CI = 0.86 to 13.4). Carriers of mutations predicted to encode a full-length ATM protein had cancer risks similar to those of people carrying truncating mutations.

CONCLUSION:

These results confirm a moderate risk of breast cancer in A-T heterozygotes and give some evidence of an excess risk of other cancers but provide no support for large mutation-specific differences in risk.

Gene. 2018 Jan 30;641:259-264. doi: 10.1016/j.gene.2017.10.064. Epub 2017 Oct 25.

Female Fabry disease patients and X-chromosome inactivation.

Juchniewicz P[1], Kloska A[1], Tylki-Szymańska A[2], Jakóbkiewicz-Banecka J[1], Węgrzyn G[3], Moskot M[4], Gabig-Cimińska M[4], Piotrowska E[5].

Abstract

Fabry disease is an X-linked inherited lysosomal storage disorder caused by mutations in the gene encoding α-galactosidase A (GLA). Once it was thought to affect only hemizygous males. Over the last fifteen years, research has shown that most females carrying mutated allele also develop symptoms, demonstrating a wide range of disease severity, from a virtually asymptomatic to more classical profile, with cardiac, renal, and cerebrovascular manifestations. This variable expression in females is thought to be influenced by the process of X-chromosome inactivation (XCI). The aim of this study was to assess severity of the clinical phenotype, to analyze XCI patterns, and to estimate their effect on disease manifestation in twelve female Fabry disease patients from five unrelated Polish families. Our analyses revealed that patients presented with the broad range of disease expression - from mild to severe, and their clinical involvement did not correlate with XCI profiles. Female carriers of the mutation in the GLA gene with the random XCI may present with the wide range of disease signs and symptoms. Thus, XCI is not a main factor in the phenotype variability of Fabry disease manifestation in heterozygous females.

Amiodarone and neurologic disorders

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