Lysosomal “Storage” Disorders

Karen Fieggen
UCT Human Genetics
Groote Schuur Hospital

Disclosures:

SANOFI GENZYME

Employed full time in public sector

Flights and accommodation to this conference kindly paid for by Sanofi Genzyme

This presentation is intended to facilitate continuing medical education.
The views expressed in this presentation are those of the presenter and do not necessarily reflect the views of Sanofi.
Sanofi does not recommend the use of its products in any manner inconsistent with that described in the local package insert.
Before using any product mentioned herein please refer to the full local prescribing information.

All patient photographs shown are with parental consent for education and are not for reuse

Background

Heterogeneous group of genetic disorders (AR / XL)

> 50 disorders

Prevalence ± 1 in 7000

Lysosomal function largely processing and degrading biomolecules

Most LSD's due to deficient lysosomal enzyme function → substrate accumulation →

cell dysfunction but complex!

Other mechanisms - abnormal protein folding, abnormal transport etc.

Clinical Presentation

Very variable “spectrum”

Typically slowly progressive

Onset anytime from prenatal to late adulthood

Variable expression in part related to residual enzyme activity

Organs most involved - brain, connective tissue, eye and heart

Common clinical presentations

Non immune fetal hydrops

Neurological regression

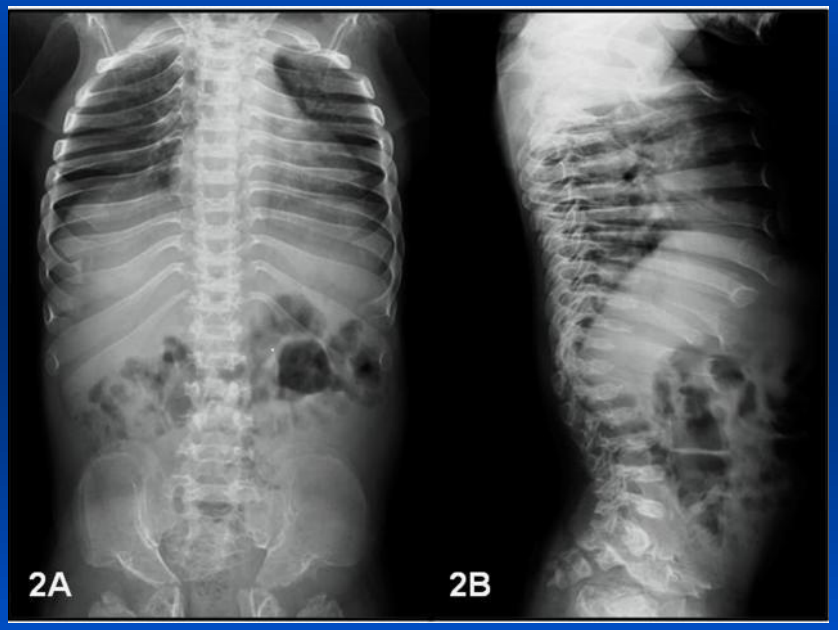
“Storage phenotype” - macrocephaly, coarse facies, visceromegaly, dysotosis multiplex

Cardiomyopathy

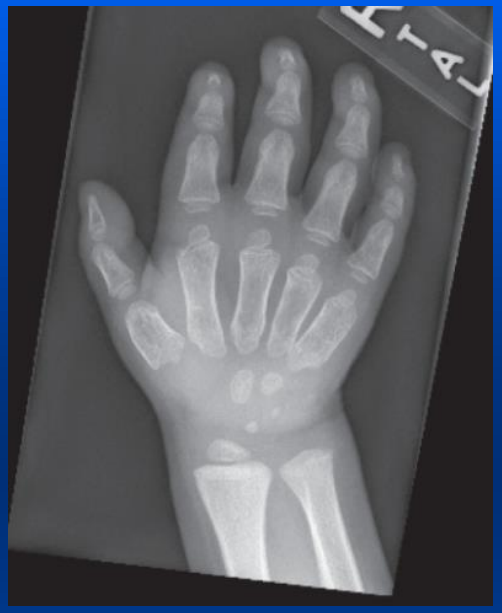
Skeletal or joint symptoms / signs

Dysostosis multiplex

Paddle shaped ribs, and short, thickened clavicles



anterior beaking of the lumbar vertebrae (posterior scalloping



tubular bones - thickened cortices, irregular mtaphyses, underdeveloped epiphyses
phalanges shortened and trapezoidal in shape

Diagnosis

Screen for metabolites
- False + and false -
- Urine / blood

Diagnose with specific enzyme assay
- Lymphocytes
- Fibroblasts
- Amniocytes

Confirm / family management with molecular genetic analysis
- *Some genotype phenotype correlations but limited*
- *Increasingly important*

Management principles

Index of suspicion!

Surveillance and supportive management

Genetic counseling

Specific therapy

- Decrease substrate
- Reduce degradation
- Replace enzyme
- Replace “factory”
- Gene therapy

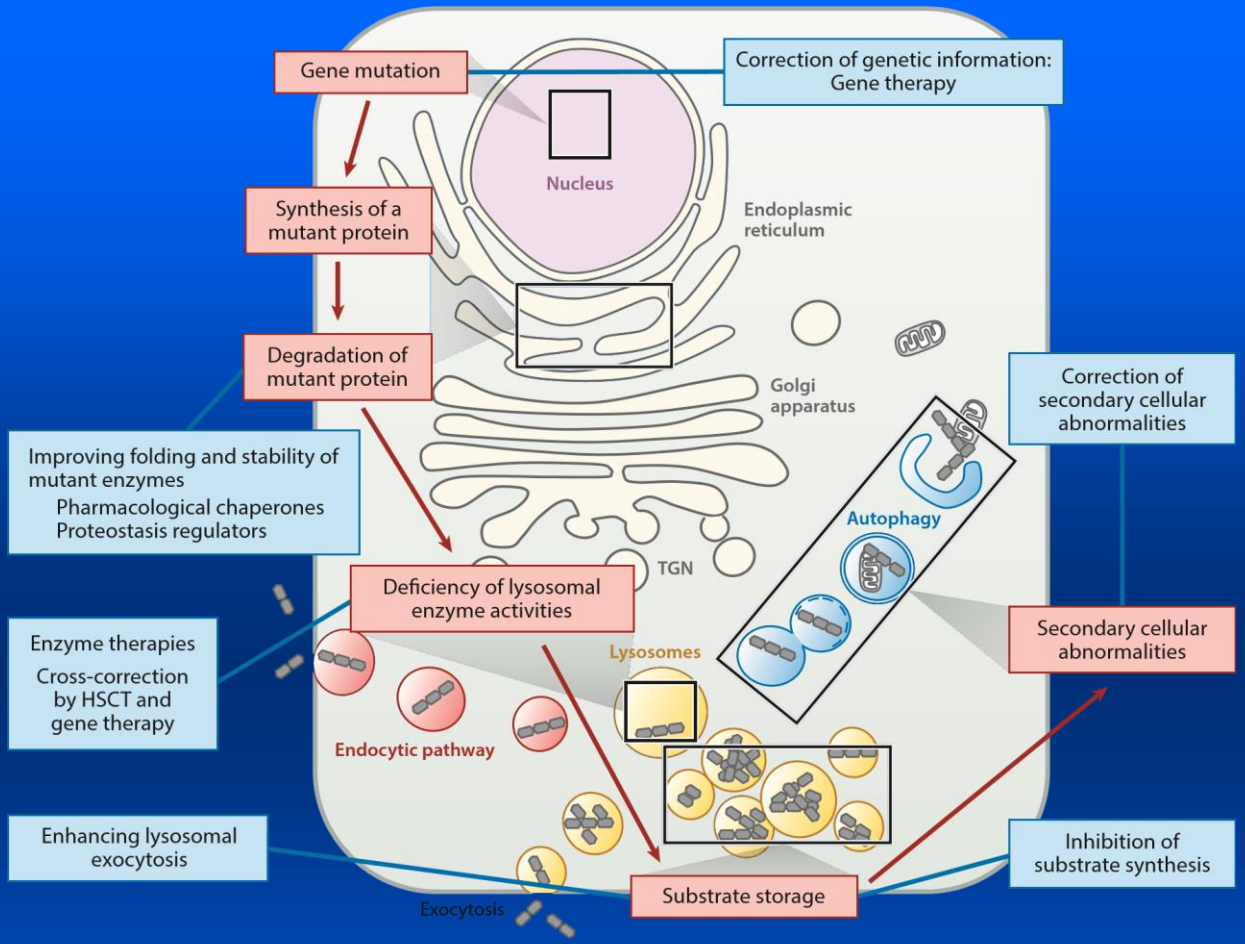


Figure 1

The pathogenetic cascade of lysosomal storage diseases and the therapeutic approaches to treating these disorders.

Lysosomal Storage Diseases: From Pathophysiology to Therapy
Giancarlo Parenti, Generoso Andria2 and Andrea Ballabio
Annu. Rev. Med. 2015. 66:471–86

Some LSD's responsive to ERT

Mucopolysaccharidoses

Characterised by abnormal metabolism of glycosamnioglycans *(urinary screening test)*

Autosomal recessive except MPS II X-linked

Type I - IX (no V or VIII….)

Subtypes

Variable clinical expression in single gene (MPS I)
Variable cause with same phenotype (MPS III and IV)

MPS I

Hurler /Hurler-Scheie/ Scheie syndrome

Prenatal

Hydrops fetalis

Severe

1- 2 yrs of age (though retrospectively ? before 1)

hernias, gradual coarsening of features with hypotonia.

gibbus / kyphosis, organomegaly, macroglossia

hearing dysfunction, cloudy corneas (retina/ glaucoma)

progressive skeletal changes , cardiac involvement,

(valves and CMO), airway obstruction , and intellectual disability, hydrocephalus, CTS..

Attenuated

Onset mid childhood with focus on bone and joint symptoms

Neurological function normal to mild ID

Cardiac valvular disease and hearing loss common


MedPix™
:: Source: usuhs pathology ::
- 2001-07-16 10:07:

Management

Supportive

Airway
Heart
Mobility
Hearing
Vision
Anaesthetics

TEAM BEST!!

Treatment

ERT

Blood Brain Barrier a problem

Improvement in growth, airway, joints , facial coarseness, mobility, liver size and quality of life

Role in attenuated form is well established
Severe form + HSCT

Early diagnosis important but prediction of severity not always clear

If family history phenotype easier but with newborn screening may be harder

Not generally recommended in severe MPS 1 with established developmental delay…..
but many co- morbidities and may still improve quality of life

HCST

reduces facial coarseness, and hepatosplenomegaly, improves hearing, and maintains normal heart function

skeletal manifestations and corneal clouding progress

“optimise’ condition with period of ERT before HSCT and may have some benefit later from ERT with certain symptoms that evolve post transplant

before significant developmental delay appears to slow the course of cognitive decline

“Gold standard” in severe (I-H) patients less than 2.5yrs

MPS II
Hunter syndrome

Severe

- Very similar to MPS I
- Slightly later onset
- Early joint stiffening
- Clear corneas usually

Attenuated

- Typically no or minimal neurological dysfunction
- May have significant systemic effects
- Joints / bone presentation

Supportive

As for MPS I

Specific

ERT

Largely used in attenuated form

- Does not cross BBB
- Improvement in effort tolerance and FVC/ visceromegaly
- ? Improved airway, joints , facial coarseness, mobility, QOL
- Individualise in more severe patients (early diagnosis ??)

"enzyme replacement therapy with idursulfase is effective in relation to functional capacity (distance walked in six minutes and forced vital capacity), liver and spleen volumes and urine glycosaminoglycan excretion in people with mucopolysaccharidosis type II compared with placebo"

Cochrane Database Syst Rev. 2016 Feb Enzyme replacement therapy with idursulfase for mucopolysaccharidosis type II (Hunter syndrome).

da Silva EM1, Strufaldi MW, Andriolo RB, Silva LA.

HCST

- Little data
- Uncertain benefit - may stabilise ? No CNS effect

MPS IV

Morquio syndrome Type A /B

"Skeletal "

Usually normal growth in 1st year

Fall off in growth with disproportion and deformity

Short trunk "dwarfism"

No CNS dysfunction (unless secondary)

Joints lax NB Odontoid hypoplasia and unstable CCJ

Minimal coarsening and systemic features

corneal opacity – slit lamp

hernias, cardiac valve abnormalities, hepatomegaly

Treatment

Supportive – *stabilise neck!*

ERT for IV A – improved walk / QOL ? Effect on bones

MPS VI
Maroteaux Lamy syndrome

Severe

From 1st year of life to adulthood
Skeletal manifestations often first
Facial coarsening follows
Joints, airway and heart all involved
Frequent ear and chest infections
Corneal clouding, glaucoma.. Retina
Hydrocephalus , CTS and myelopathy

Attenuated / Mild

Often very slowly progressive over many decades

Management

Supportive

Often need tracheostomy for UAO in severe type

Specific

ERT

Considered first line therapy

Does not cross BBB

Improvement in improved walking endurance and stair climbing

? ?Improved airway, joints , visceromegaly, heart (LV)

HCST

Improves facial dysmorphism and heart

Uncertain benefit on bones - may improve joint mobility

Glycogen storage disorder Type II
Pompe Disease

Infantile

CLASSIC:— 1st month or 2 floppy, feeding, respiratory and cardiac failure / LVOTO

ATYPICAL – later 1st year or 2… less cardiac more weakness

Late onset

Muscle weakness NB proximal and respiratory

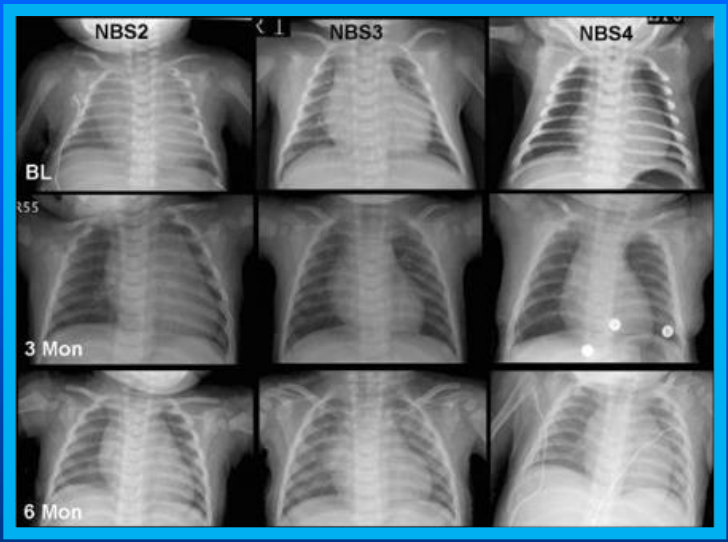
(CK can be normal)

Treatment

Enzyme diagnosis urgently..

Supportive – careful cardiac!!

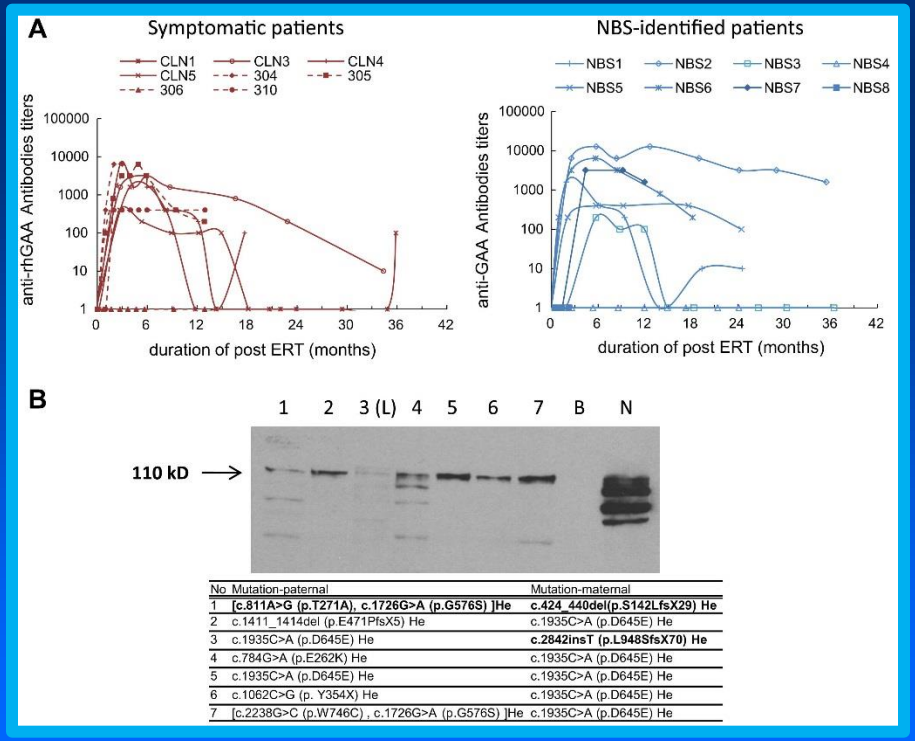
ERT



Pompe Disease in Infants: Improving the Prognosis by Newborn Screening and Early Treatment

Yin-Hsiu Chien, Ni-Chung Lee, Beth L. Thurberg, Shu-Chuan Chiang, Xiaokui KateZhang, Joan Keutzer, Ai-Chu Huang, Mei-Hwan Wu, Pei-Hsin Huang, Fuu-JenTsai, Yuan-Tsong Chen, Wuh-Liang Hwu

Pediatrics Dec 2009, 124 (6) e1116-e1125;



No	Mutation-paternal	Mutation-maternal
1	**[c.811A>G (p.T271A), c.1726G>A (p.G576S)]He**	**c.424_440del(p.S142LfsX29) He**
2	c.1411_1414del (p.E471PfsX5) He	c.1935C>A (p.D645E) He
3	c.1935C>A (p.D645E) He	**c.2842insT (p.L948SfsX70) He**
4	c.784G>A (p.E262K) He	c.1935C>A (p.D645E) He
5	c.1935C>A (p.D645E) He	c.1935C>A (p.D645E) He
6	c.1062C>G (p. Y354X) He	c.1935C>A (p.D645E) He
7	[c.2238G>C (p.W746C) , c.1726G>A (p.G576S)]He	c.1935C>A (p.D645E) He

Pompe Disease: Early Diagnosis and Early Treatment Make a Difference

Chien, Yin-Hsiu et al.

Pediatrics & Neonatology , Volume 54 , Issue 4 , 219 - 227

Gaucher Disease

Type 1

Bone disease (osteopenia, focal lytic / sclerotic lesions/osteonecrosis), Hepatosplenomegaly, anaemia and thrombocytopenia

Lung disease *NO* primary central nervous system disease

Type 2 and 3

+ CNS disease

Cardiovascular

Calcification of the mitral and aortic valves, mild splenomegaly, corneal opacities, and supranuclear ophthalmoplegia (homozygous D409H allele)

Perinatal lethal

Non immune hydrops

Treatment

Enzyme diagnosis

Supportive

Specific therapy

ERT
Effects on bone disease, visceral involvement and QOL

Limited effect on CNS manifestations but may stabilize

Substrate reduction

Chaperone Rx

BMT …largely replaced by ERT

3 months Rx

18 months Rx

4 years Rx

Photographs courtesy of Sanofi Genzyme

Fabry Disease

X-linked but males and females affected

Females ? milder / reduced penetrance

Enzyme diagnosis in males / molecular diagnosis in females

Childhood

Acroparasthesias and Abdominal pain

Hypohidrosis

Boys ~7 Girls ~9

Adulthood

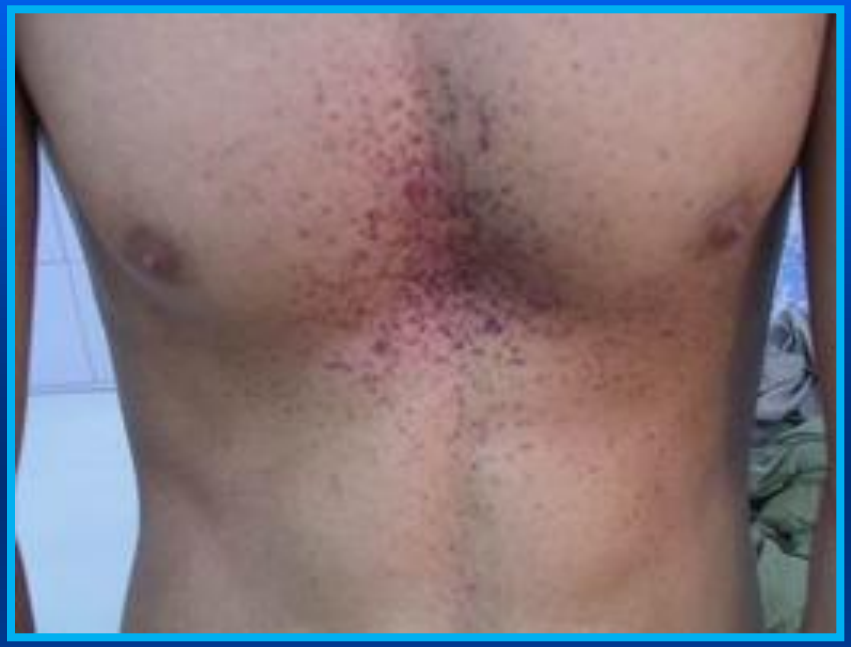
Renal disease

proteinuria -> end stage renal disease

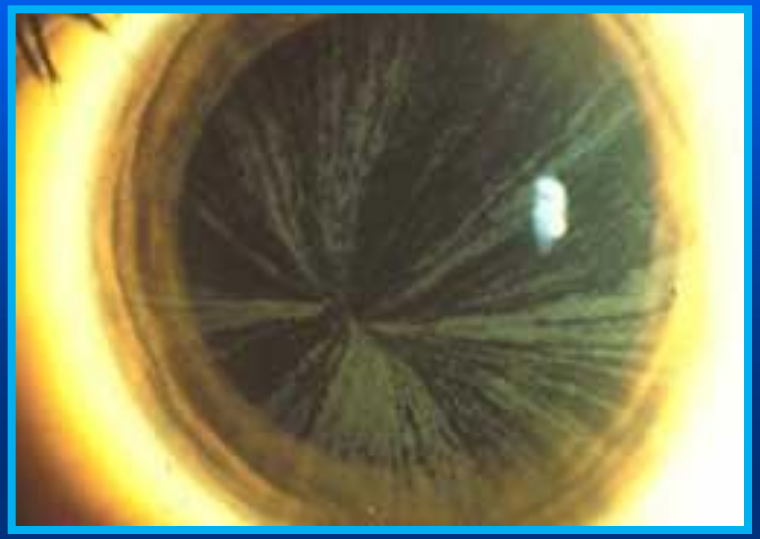
Cardiovascular disease

CMO, valvar disease, rhythm disturbance

Stroke



Angiokeratomas



Cornea verticillata

Treatment

Supportive

Pain, renal, cardiac

ERT
Improves symptoms, cardiac function
"Uncertain" long term effect on renal and cerebrovascular disease?
Significantly better outcome for treated registry patients than historical 'controls'

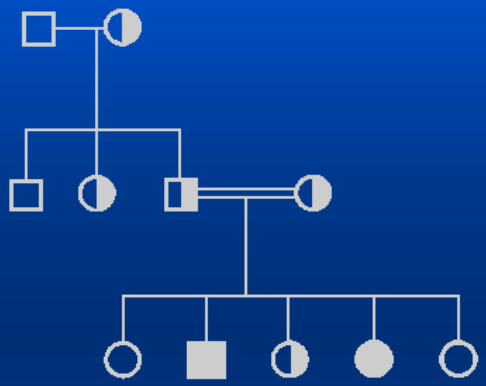
"Trials comparing enzyme replacement therapy to placebo show significant improvement with enzyme replacement therapy in regard to microvascular endothelial deposits of globotriaosylceramide and in pain-related quality of life"

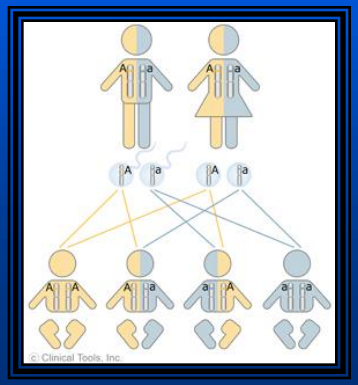
Cochrane Database Syst Rev. 2016 Jul 25;7:.
Enzyme replacement therapy for Anderson-Fabry disease.
El Dib R, Gomaa H, Carvalho RP, Camargo SE, Bazan R, Barretti P, Barreto FC

? timing of treatment important
? subtype of disease important

Genetic counselling

Autosomal recessive

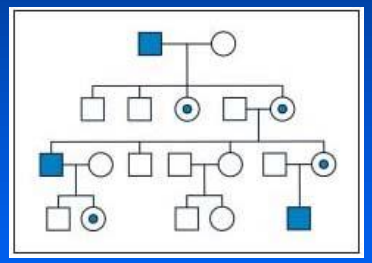


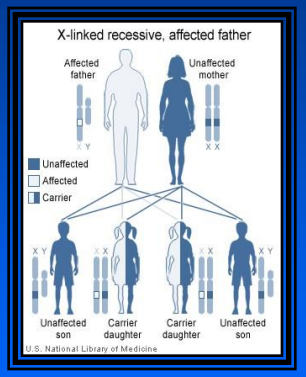


Parents unaffected
Often no family history!
25% risk for siblings

e.g. Gaucher disease

X linked - recessive

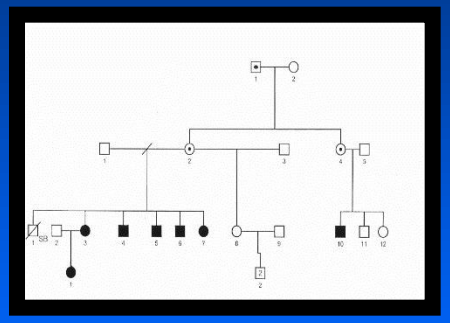




e.g MPS II

Males affected
Female carriers

X linked – “semi” dominant



Males and females affected
Females milder
All daughters of affected man “carriers”

e.g Fabry disease

So to the future…

Therapy options

(none curative yet)

- ERT
- HSCT
- Substrate reduction
- Chaperone therapy

New approaches – Intrathecal / Intrarticular ERT
Better understanding of cell biology and pathophysiology

Gene therapy not quite there but trials in MPS III + other LSD's

Prenatal / preimplantation genetic diagnosis
Must know what you are looking for – DNA on affected child

Early therapy is likely to be key…

Recognition and reliable diagnosis
Newborn screening
Genotype phenotype correlations

Still many unanswered questions

More data needed
RCT not that easy once medication registered
Registry participation important

Thank you.