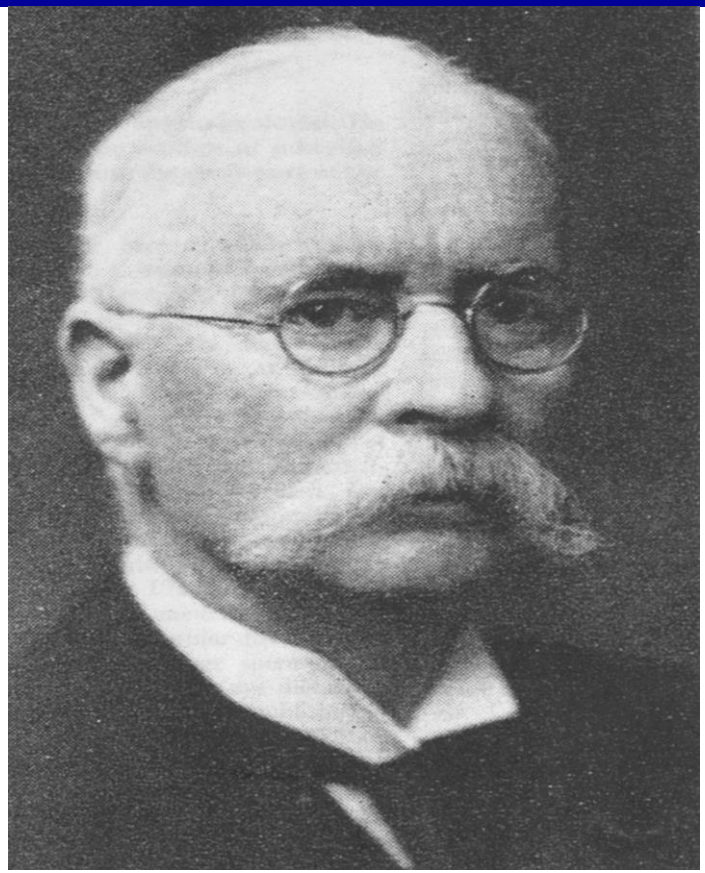
If you can´t look back and

you can´t look forward,

You better look up!!



The Swedish Usher interdiciplinary research group

Swedish database deafblind syndromes

- Started 1988 in cooperation with BTNRH (Kimberling)
- Subcontractor NIH
- 26 years to complete !! ???
- All subjects examined by me
- 2014 460 families with Usher type 1,2 and 3
- Expected total prevalence in Sweden 600
- 200 families with other deafblind syndromes

FileMaker Pro - [ORGINAL 110512 Bara Svenska Usher syndrome data base]

Arkiv Redigera Visa Sätt in Utforma Sökposter Manus Fönster Hjälp

Sök

Layout: Huvudsid

Sökpost: 1

Totalt: 1

Uteslut

Symbol

Sök

The Swedish National Usher Syndrome Database

Name | USH Type | Sex ○F ○M | SWE # | USA #

Place Of Birth
County (PB)
Place Of Residence
County (PR)

Mother's ID.Num
Mother's Name
Mother's PB
County (M)

Diagnostic Age of RP (Y)
Walking Age (M)
DNA available ☐Yes ☐No
Pedigree available ☐Yes ☐No
Other Diseases

Father's ID.Num
Father's Name
Father's PB
County (F)

Family members (including this patient)

Comments

Num. Of Affected Siblings
Num. Of Healthy Siblings

FileMaker Pro - [ORGINAL 110512 Bara Svenska Usher syndrome data base]

Arkiv Redigera Visa Sätt in Utforma Sökposter Manus Fönster Hjälp

Sök

Layout: Audiology

Sökpost: 1

Totalt: 1

Uteslut

Symbol

Sök

Audiology page

ID. Nr.	Name	USH Type	Sex	SWE #	USA #
			○F ○M		

Date	H250	H500	H1k	H2k	H3k	H4k	H6k	H8k	V250	V500	V1k	V2k	V3k	V4k	V6k	V8k

Type of communication: (Oral =1, Sign =2, Both =3)

Diagnostic age of HL (Y)

Type of audiogram:(pure-ton=1, play=2, observation=3)

Speech recognition % (last audiogram)

SR. Result R in %.

SR. Result L in %.

Tympanogram (not done=1, pathological=2, without remark=3)

Tymp. Result R.

Tymp. Result L.

Sök

Layout:

Audiolog

Sökpost:

1

Totalt:
1

Uteslut

Symbol

Sök

ABR (not done=1, pathological=2, without remark=3)

ABR. Result R.

ABR. Result L.

OAE (not done=1, pathological=2, without remark=3)

OAE. Result R.

OAE. Result L.

ECoG. R (not done=1, pathological=2, without remark=3)

ECoG. L (not done=1, pathological=2, without remark=3)

Comments

FileMaker Pro - [ORGINAL 110512 Bara Svenska Usher syndrome data base]

Arkiv Redigera Visa Sätt in Utforma Sökposter Manus Fönster Hjälp

Sök

Layout: Vestibula

Sökpost: 1

Totalt: 1

Uteslut

Symbol

Sök

Vestibular page

Name | USH Type | ○F ○M Sex | SWE # | USA #

Walking age (M) :

ENG done (Yes=1, No=2) :

Age ENG test: | Age ENG test #2:

ENG. Result R. | ENG. Result R.

ENG. Result L. | ENG. Result L.

Calorics done (Yes=1, No=2) :

Age: | Age (test #2):

Result W °/s R: | Result W °/s R

Result C °/s R: | Result C °/s R

Result W °/s L: | Result W °/s L

Result C °/s L: | Result C °/s L

Comments

Age Rotatory test :

Result R.(not done=1, pathological=2, without remark=3):

Result L.(not done=1, pathological=2, without remark=3):

Age Rotatory test #2 :

Result R.(not done=1, pathological=2, without remark=3):

Result L.(not done=1, pathological=2, without remark=3):

FileMaker Pro - [ORGINAL 110512 Bara Svenska Usher syndrome data base]

Arkiv Redigera Visa Sätt in Utforma Sökposter Manus Fönster Hjälp

Sök

Layout: Vision

Sökpost: 1

Totalt: 1

Uteslut

Symbol

Sök

Vision page

ID. Nr.	Name	USH Type	Sex	SWE #	USA #
			○F ○M		

Diagnosis age of RP (y) :

Age ERG test :

ERG.Result R (not done=1, pathological=2, without remark=3, hypofunction=4):

ERG.Result L (not done=1, pathological=2, without remark=3, hypofunction=4):

Age ERG test #2 :

ERG.Result R (not done=1, pathological=2, without remark=3, hypofunction=4):

ERG.Result L (not done=1, pathological=2, without remark=3, hypofunction=4):

Visual field test

Age	Result R	Result L

Visual acuity test

Age	Result R	Result L
	20 /	20 /

Cataract R. (Yes =1, No =2)

Debut of cataract R (Age):

Cataract operated R (Age):

FileMaker Pro - [ORGINAL 110512 Bara Svenska Usher syndrome data base]

Arkiv Redigera Visa Sätt in Utforma Sökposter Manus Fönster Hjälp

Sök

Layout:
Vision

Sökpost:
1

Totalt:
1

Uteslut

Symbol

Sök

Cataract R. (Yes =1, No =2)

Debut of cataract R (Age):

Cataract operated R (Age):

Cataract L. (Yes =1, No= 2)

Debut of cataract L (Age):

Cataract operated L (Age):

Fluorescien angiografi age:

Fluorescien angiografi R. (not done=1, pathological=2, without remark=3):

Fluorescien angiografi R. (not done=1, pathological=2, without remark=3):

Contrast sensitivity age:

Contrast sensitivity R. (not done=1, pathological=2, without remark=3):

Contrast sensitivity L. (not done=1, pathological=2, without remark=3):

Fundoscopic photos done R. (Yes=1, No=2) :

Fundoscopic photos done L. (Yes=1, No=2) :

Pat. is blind (Yes =1, No =2, Unknown =3) :

Comments

FileMaker Pro - [ORGINAL 110512 Bara Svenska Usher syndrome data base]

Arkiv Redigera Visa Sätt in Utforma Sökposter Manus Fönster Hjälp

Sök

Layout: Genetics

Sökpost: 1

Totalt: 1

Uteslut

Symbol

Sök

Genetics page

ID. Nr.	Name	USH Type	Sex	SWE #	USA #	DNA available ☐Yes ☐No
			○F ○M			Pedigree available ☐Yes ☐No

Genetic diagnosis

Patient	Patient's Mother	Patient's Father
Chromosome (p):	Chromosome(m):	Chromosome(f):
Gene (p):	Gene (m):	Gene (f):
Mutation 1(p):	Mutation 1(m):	Mutation 1(f):
Mutation 2(p):	Mutation 2(m):	Mutation 2(f):
Mutation type (p):		

Genetics Conclusions

Research projects from the database

- Epidemiology
- Genetics
- Vision
- Hearing
- Balance
- Co-morbidity
- Cognition
- Psychosocial
- Aging-elederly

Usher type	Number	Conclusive Genetic diagnos	DNA available
Type 1	170	92	120
Type 2	167	120	150
Type 3	27	22	26
Total	364	234 excluded	296 (74 other)

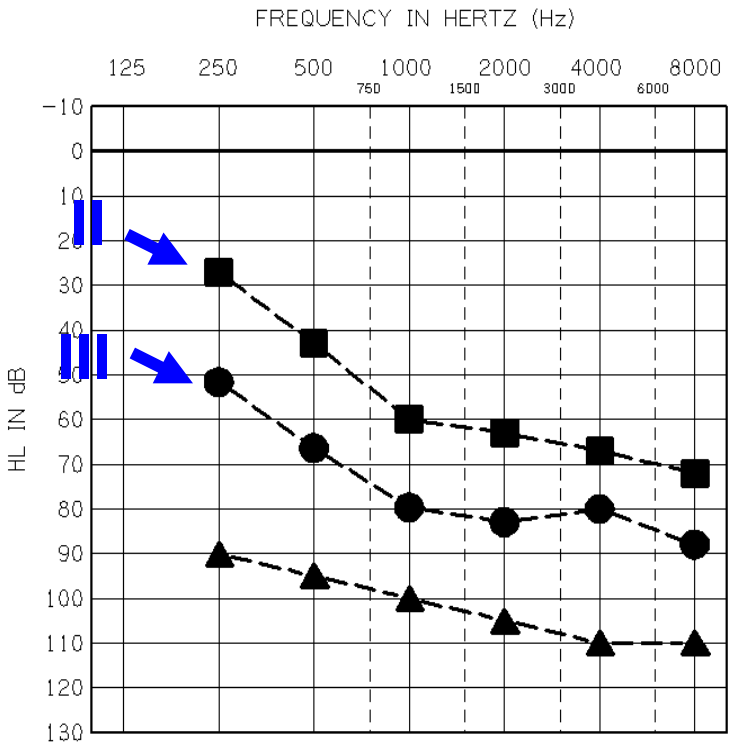
Mean diagnosis age depending on when you were born

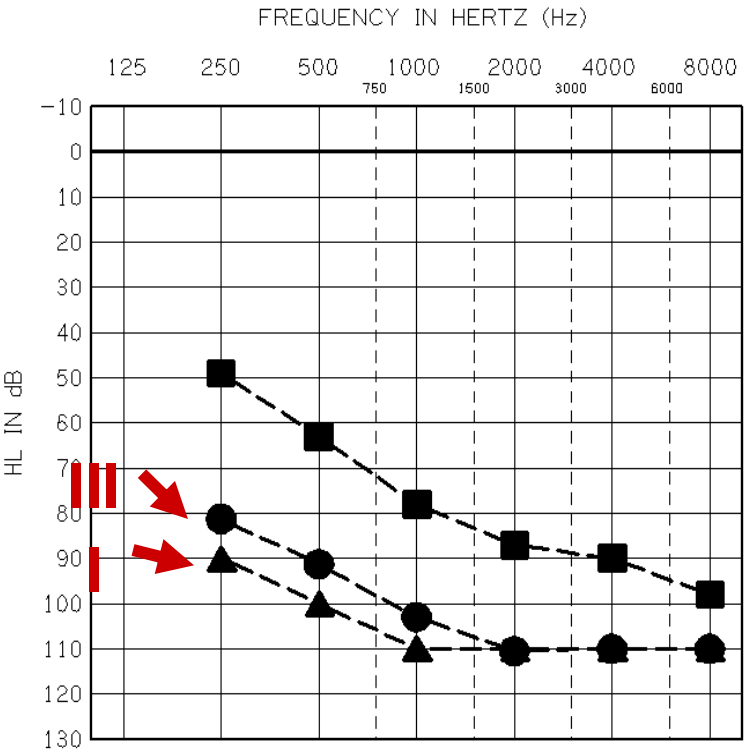
	Usher type I	Usher type II
1910´s		42 y
1920´s	27y	
1930´s	28y	35y
1940´s	24y	29y
1950´s	18y	23y
1960´s	12y	23y
1970´s	9y	19y
1980´s	9y	17y
1990´s	4y	15 y
2000´s	1-4 y	14 y
2010´s	1y	12y

4-9y

40-49y

Comparison of hearing loss between Usher type I, II and III





-■- Usher type II

-●- Usher type III

-▲- Usher type I

-■- Usher type II

-●- Usher type III

-▲- Usher type I

Universitetssjukhuset Örebro
ÖREBRO LÄNS LANDSTING

First study (a long genetic time ago 2000)

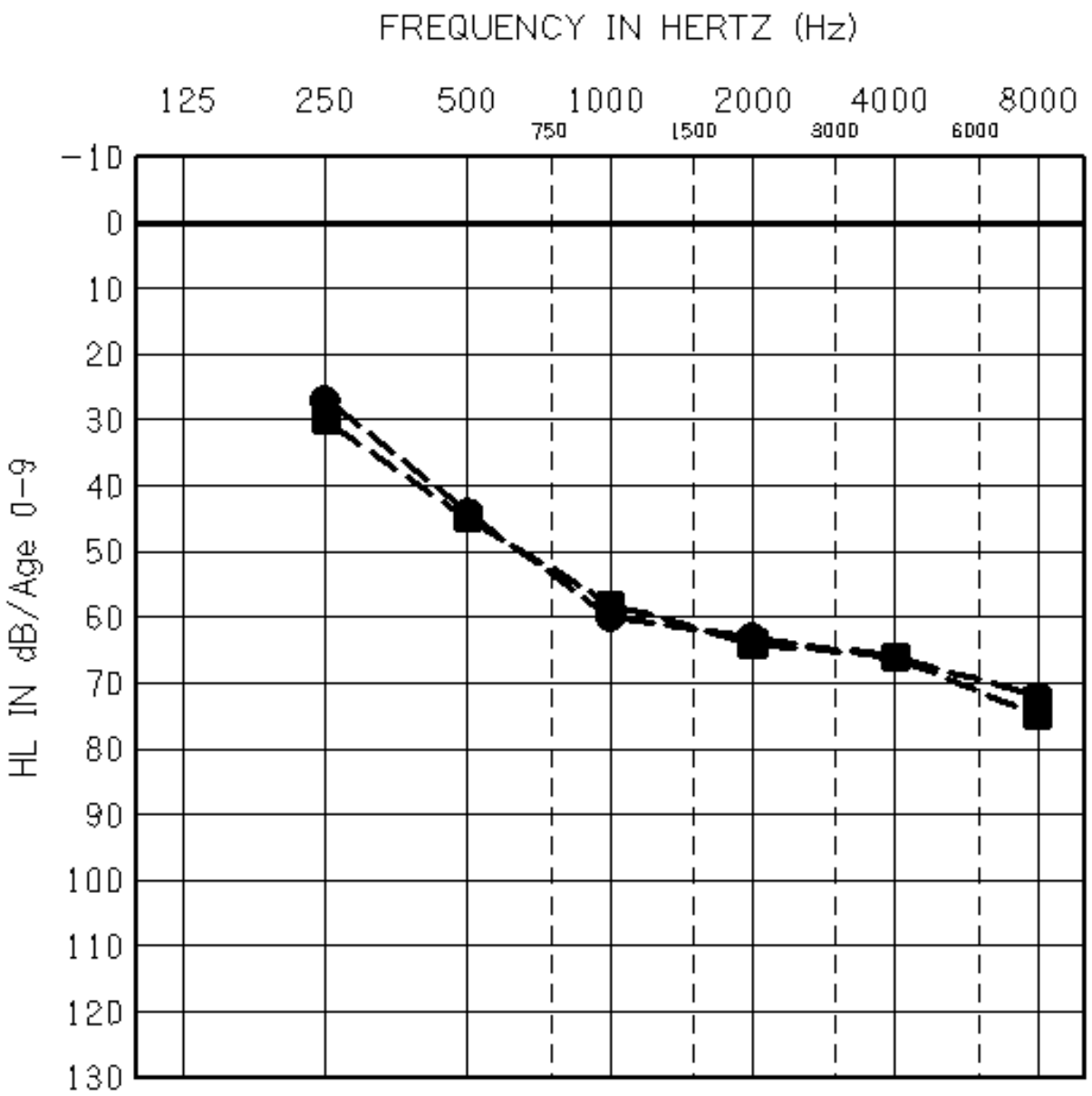
- 109 subjects (54 F, 55 M)
- > 3 audiogram > 5 years

- Usher 2a: 54 (25 F, 29 M)
- Mean age 32 y (4-68)

- Usher non-2a 55 (29 F , 26 M)
- Mean age 31 yr (4-79)

Method II

Age 0-9

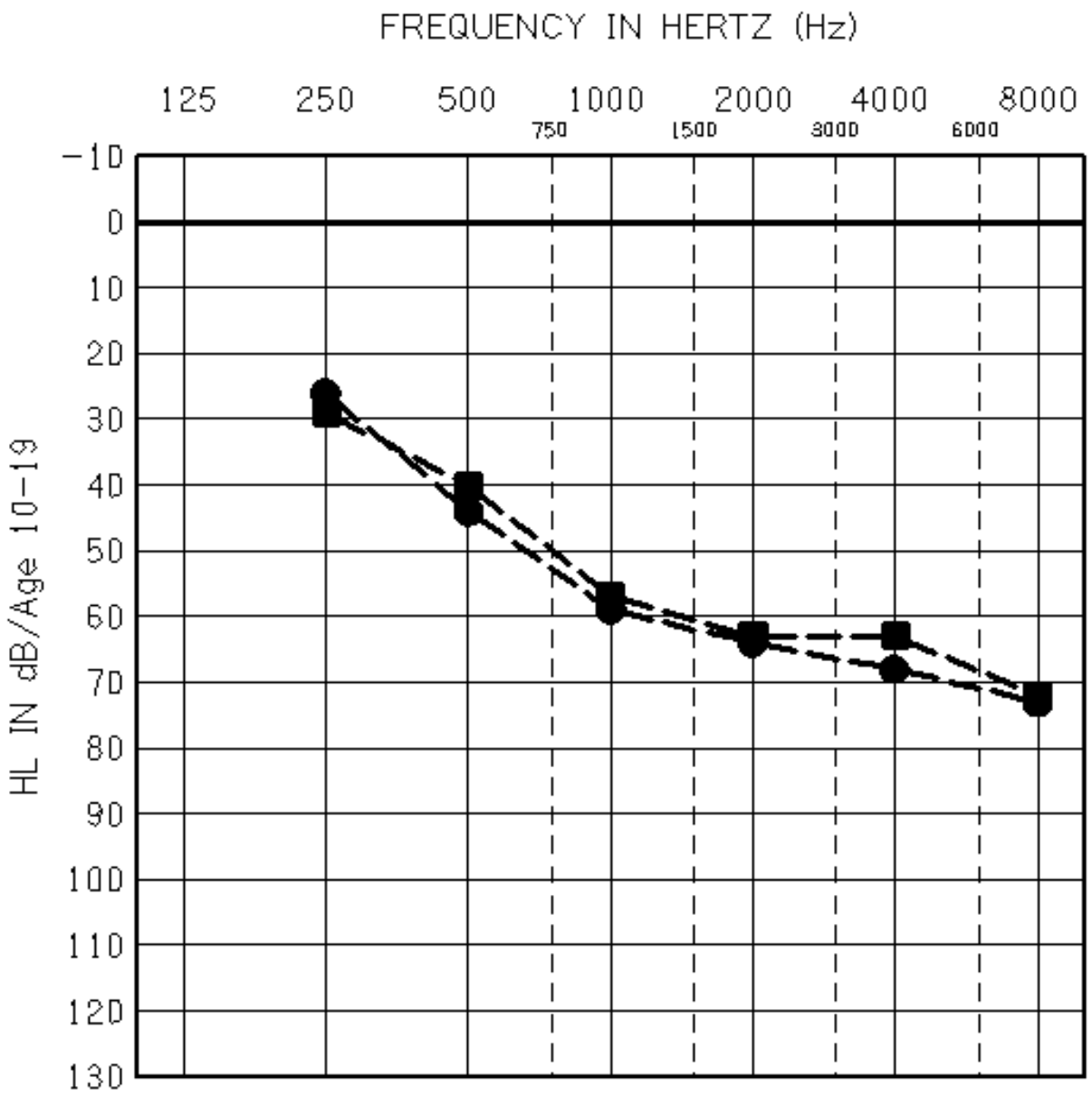


Usher IIa --●--

and non- IIa --■--

Method II

Age 10-19

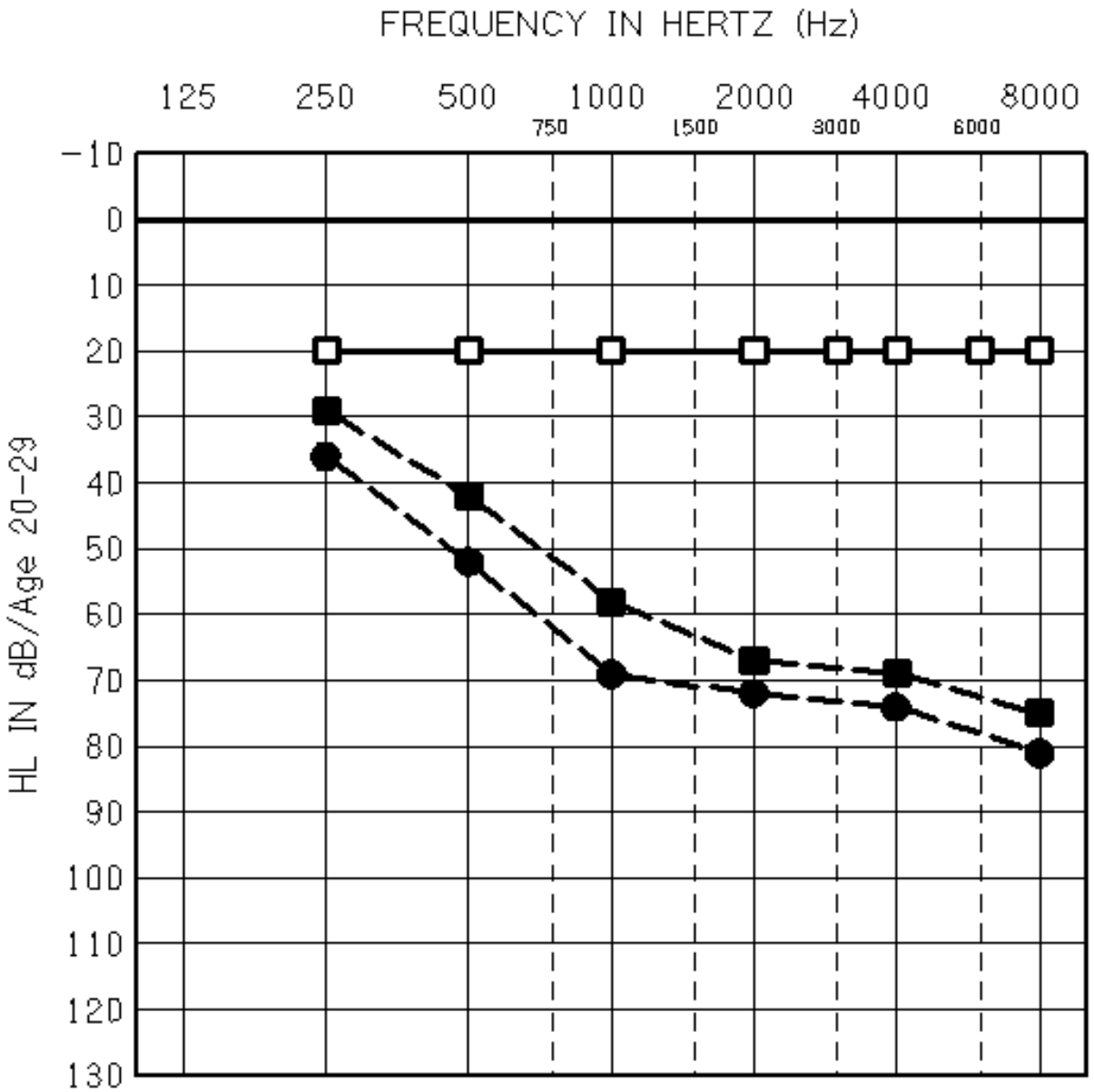


Usher IIa --●--

non- IIa --■--

Method II

Age 20-29



Usher IIa --●--

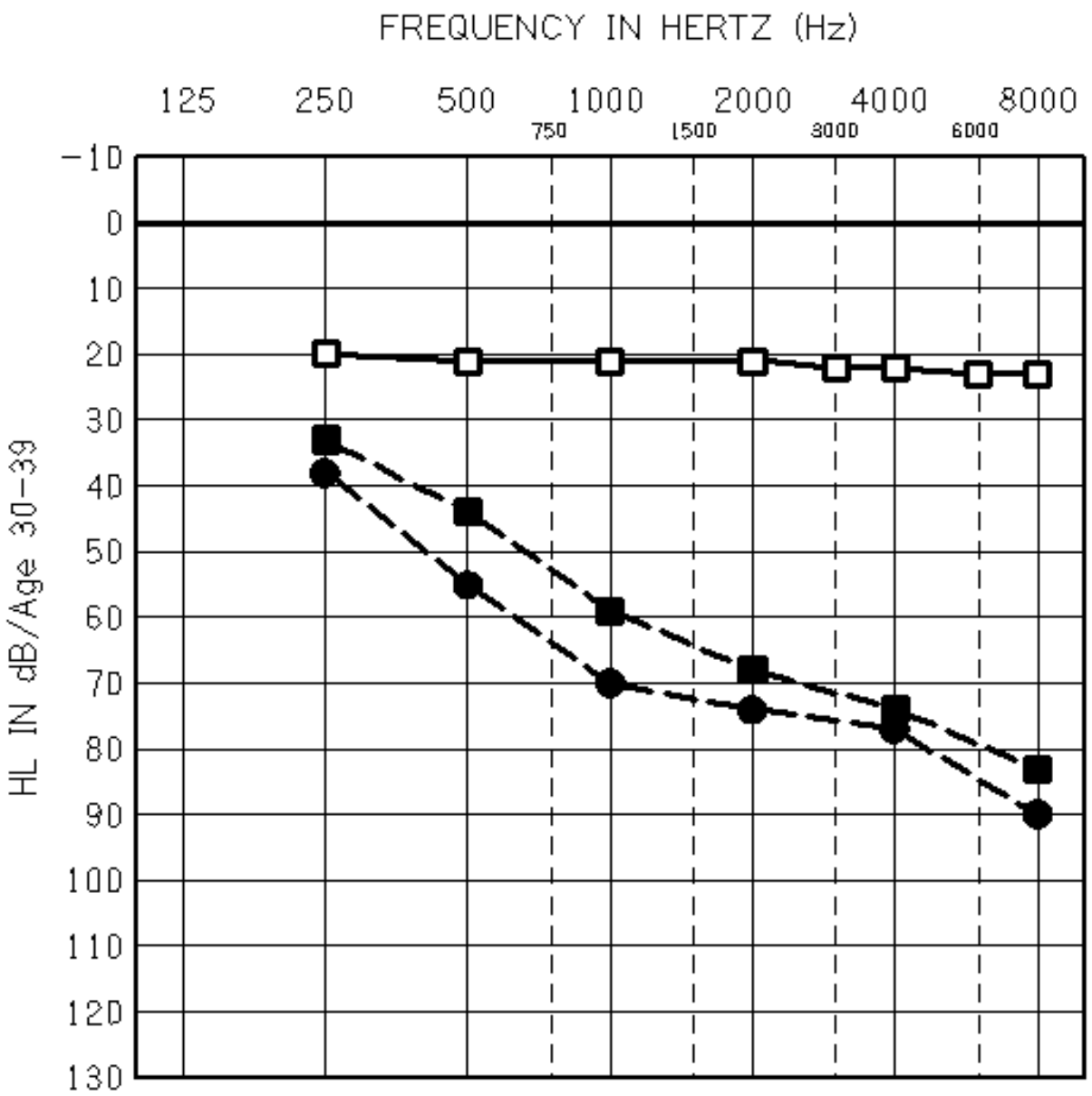
and non- IIa --■--

ISO 7029

(control) --□--

Method II

Age 30-39



Usher IIa --●--

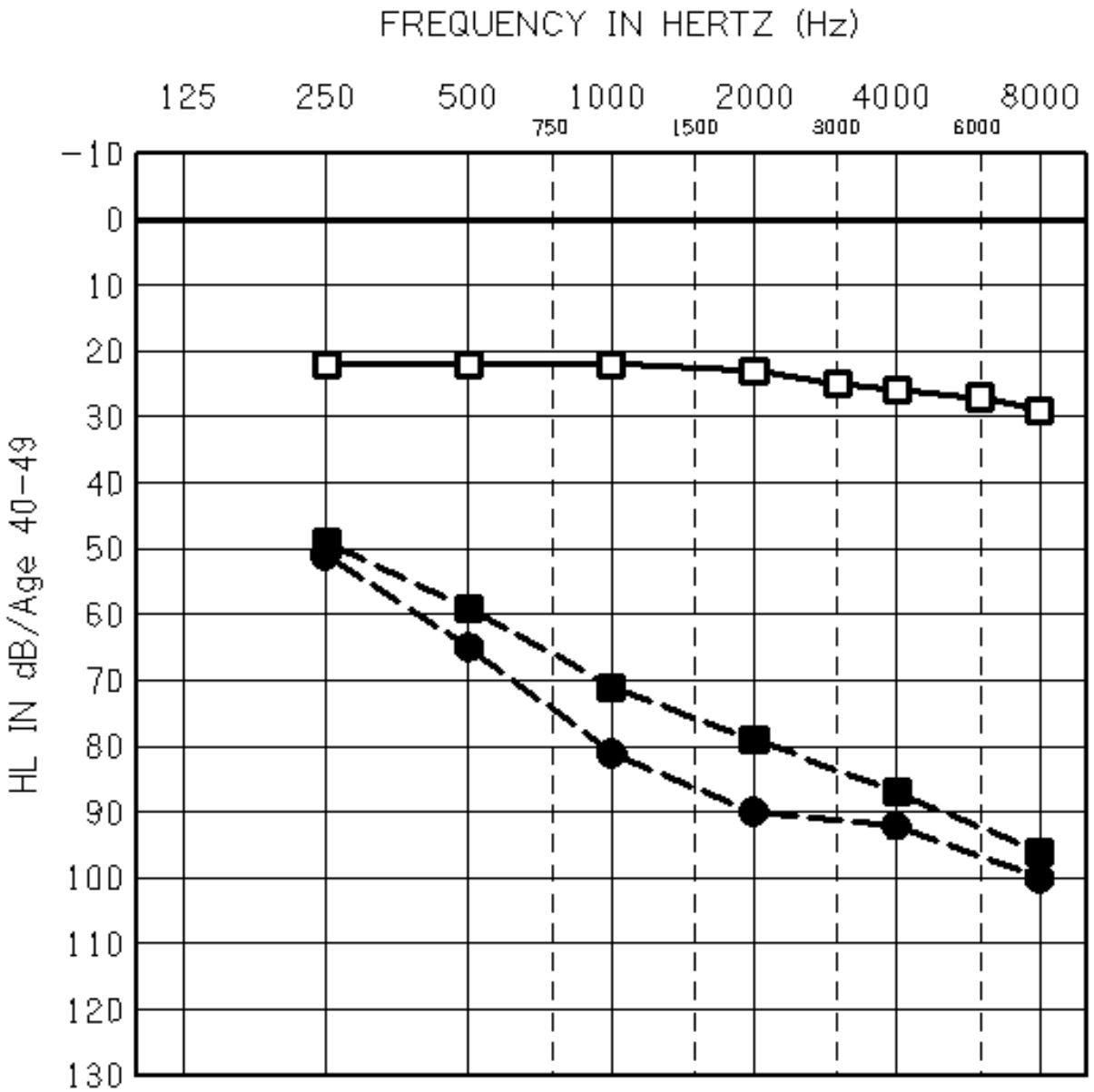
and non- IIa --■--

ISO 7029

(control) --□--

Method II

Age 40-49



Usher IIa --●--

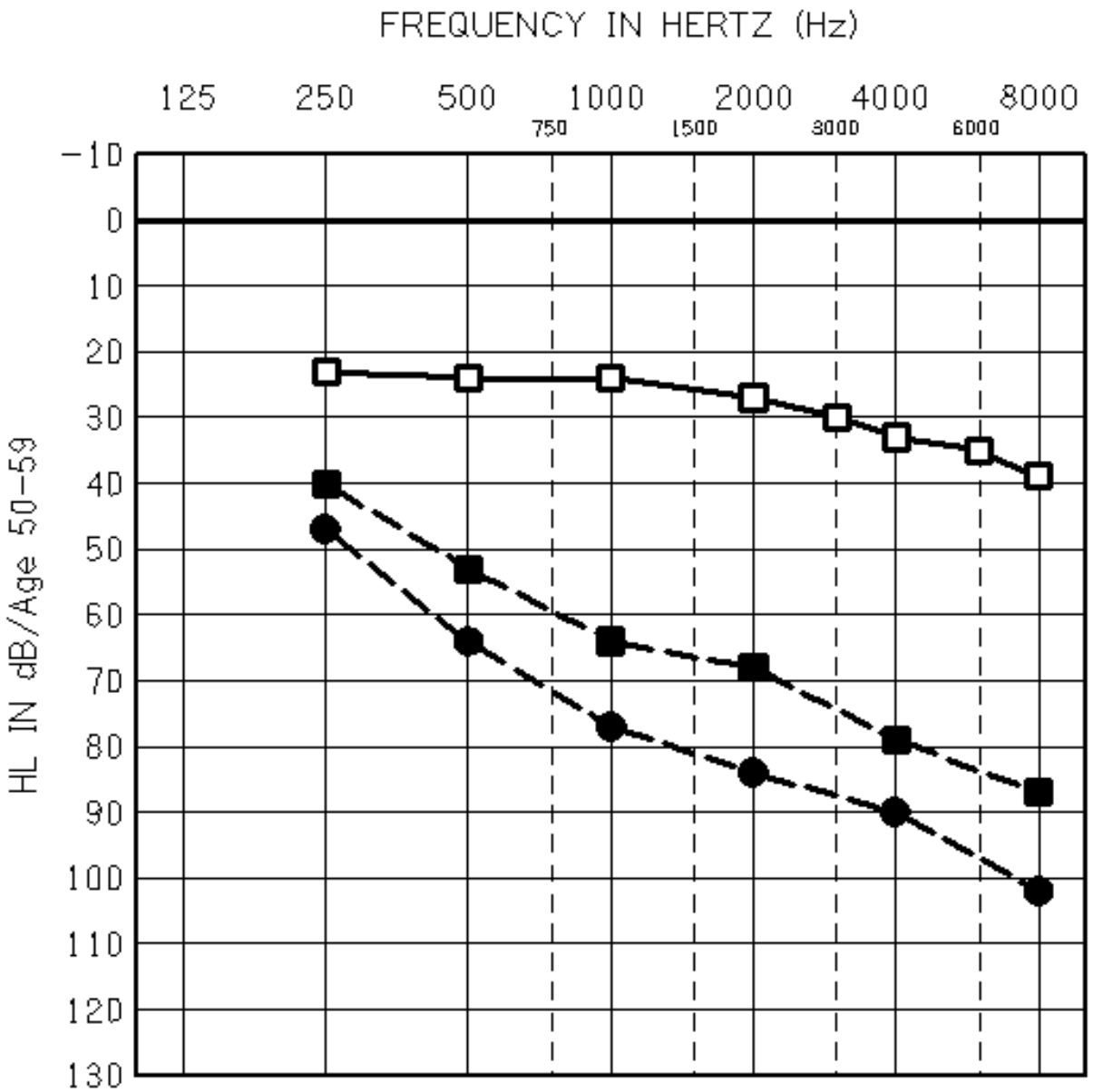
and non- IIa --■--

ISO 7029

(control) --□-- .

Method II

Age 50-59



Usher IIa --●--

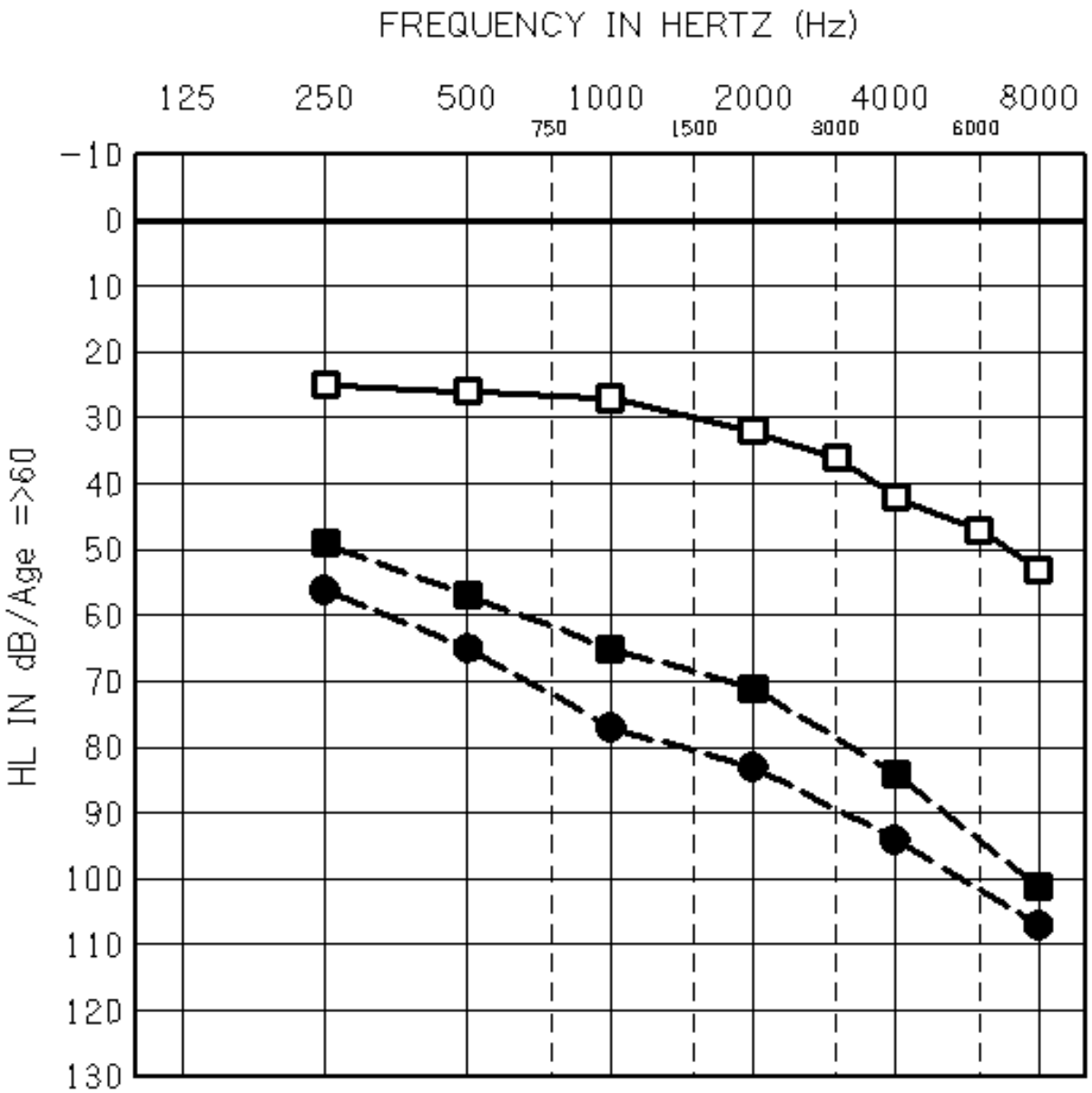
and non- IIa --■--

ISO 7029

(control) --□--

Method II

Age ≥ 60



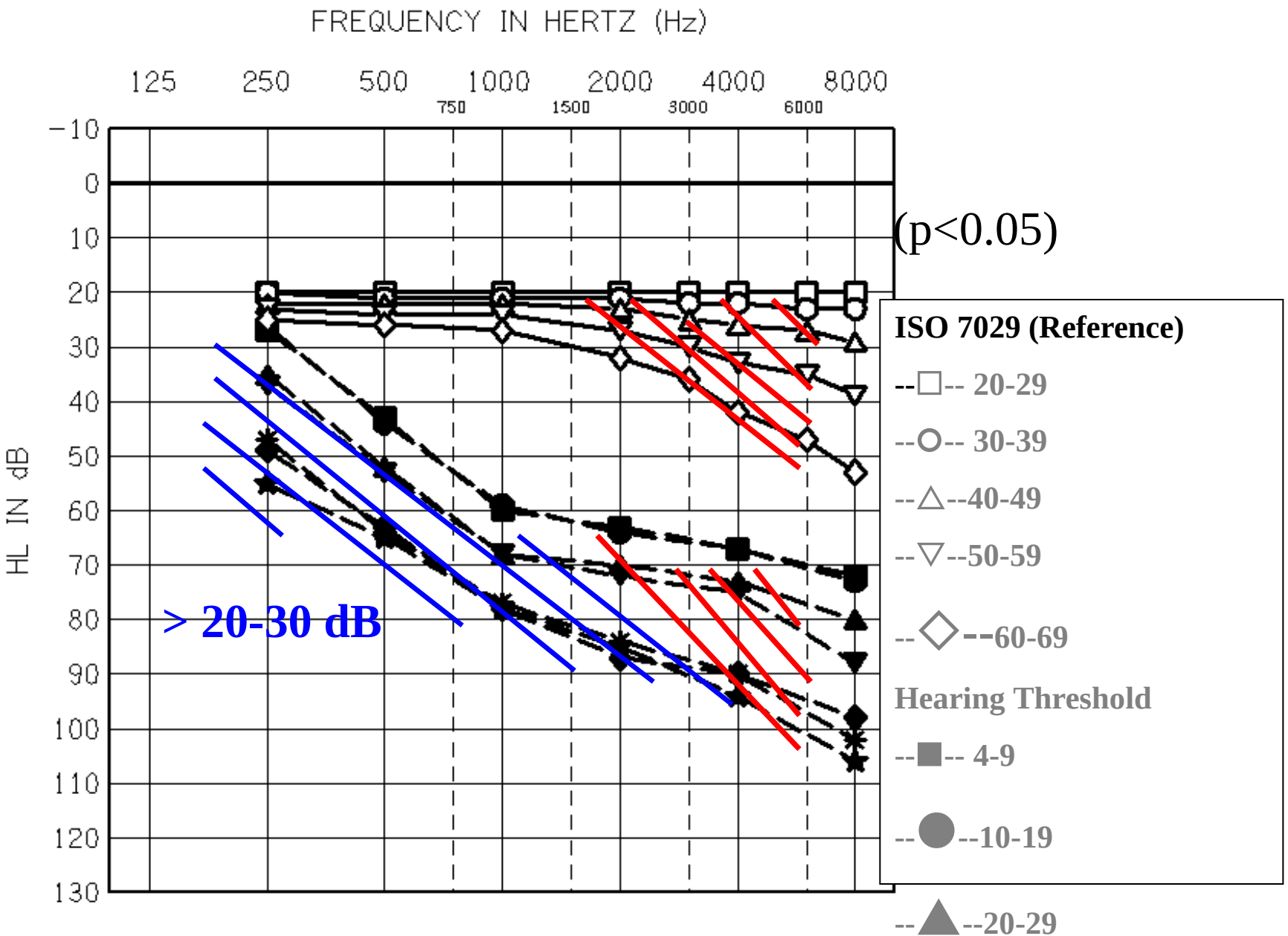
Usher IIa --●--

and non- IIa --■--

ISO 7029

(control) --□--

402 audiogram / 80 subjects Usher typ IIa



Conclusions

I) Significant hearing loss progression was found in few affected individuals

II) Usher IIa appears to progress at an earlier age than non-IIA . This defines a unique auditory phenotype for Usher IIA.

III) Usher IIa mean auditory thresholds are more pronounced than Usher non-IIA in a number of frequencies throughout life.

IV) Low frequency hearing loss progression observed in both groups is greater than seen in presbyacusis.

V) Individual hearing loss progression was noted in both groups.

VI) The rate of progression in both groups was nonlinear and largest in the 40's (5th decade)

VII) Hearing loss progression was both bilateral and unilateral, suggesting modifying factors which may be genetic or environmental.

Is this true today ???

Questions

- How much do environment influence the degree of hearing loss?
- Is there here a gene specific phenotype ?
- Will some mutations give a more pronounced HL ?
- Is a more detailed prognosis possible to make ?
- A cliff hanger !!!

To be continued by Dr Pennings (next talk)

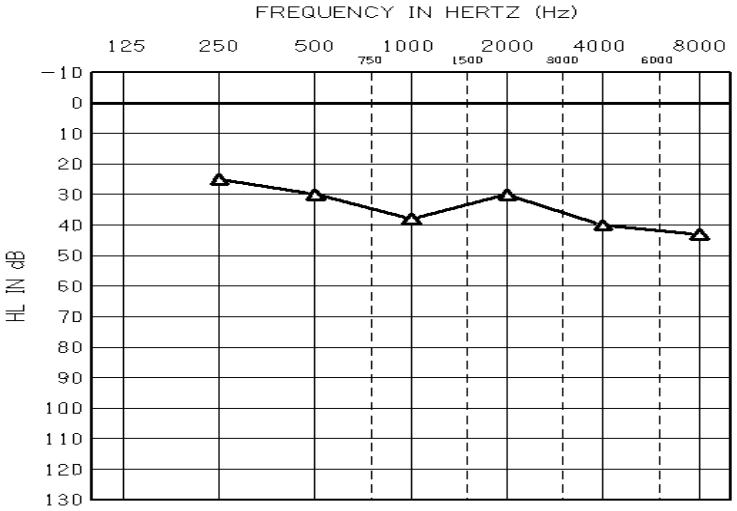
What about siblings with the same mutations and similar environmental background?

- Int J Audiol 2013 Dec;52(12):832-7. doi: 10.3109/14992027.2013.839885. Epub 2013 Oct 28.
- Expressivity of hearing loss in cases with Usher syndrome type IIA. Sadeghi A, Cohn ES, Kimberling WJ, Halvarsson G and Möller C

Table 1. Distribution of study subjects by gender, age, country and mutation.

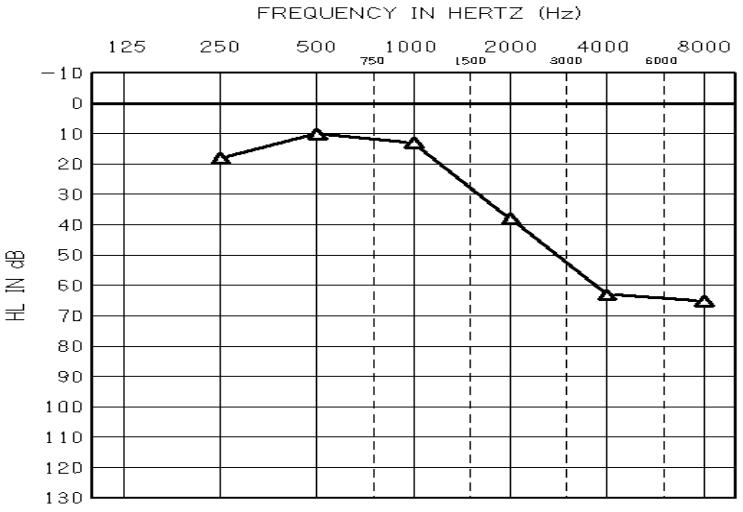
Family	Sex	Age	Ancestry (Country)	First Pathological Mutation	Second Pathological Mutation
133	M	75	Swedish (Sweden)	1036A→C	R1295X
133	M	74	Swedish (Sweden)	1036A→C	R1295X
133	M	68	Swedish (Sweden)	1036A→C	R1295X
133	F	68	Swedish (Sweden)	1036A→C	R1295X
137	M	35	Swedish (Sweden)	2299delG	Not found
137	M	41	Swedish (Sweden)	2299delG	Not found
145	M	35	Swedish (Sweden)	2299delG	Not found
145	F	36	Swedish (Sweden)	2299delG	Not found
145	F	43	Swedish (Sweden)	2299delG	Not found
186	F	56	Swedish (Sweden)	1036A→C	1036A→C
186	F	26	Swedish (Sweden)	1036A→C	1036A→C
186	F	47	Swedish (Sweden)	1036A→C	1036A→C
239	F	53	European (USA)	2299delG	Not found
242	M	15	European (Australia)	2299delG	2299delG
242	F	12	European (Australia)	2299delG	2299delG
252	F	69	European (USA)	2299delG	Not found
254	M	37	European (USA)	2299delG	Not found
260	M	43	European (USA)	2299delG	Not found

M = male; F = female.



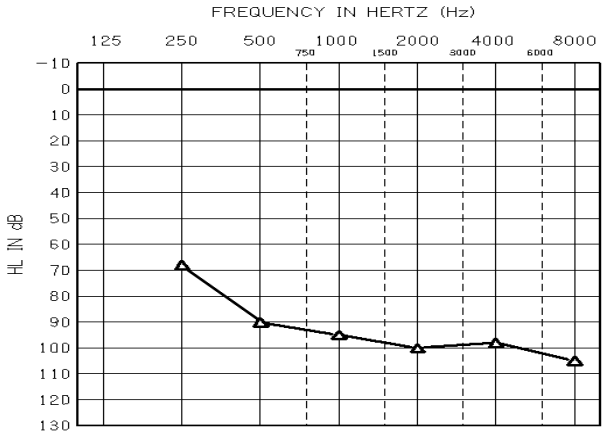
#239-♀Mutation: 2299delG

Age: 27



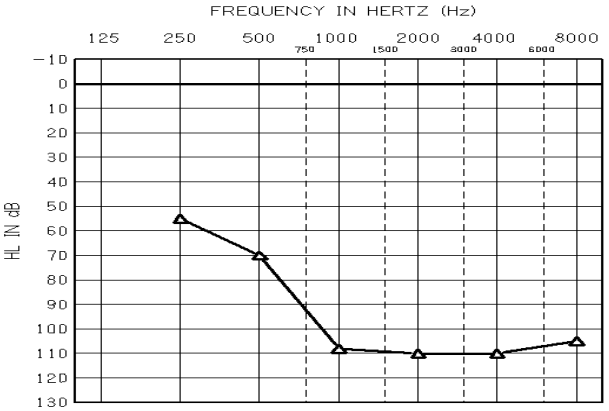
#252-♀Mutation: 2299delG

Age: 32



#254-♂Mutation: 2299delG

Age: 27



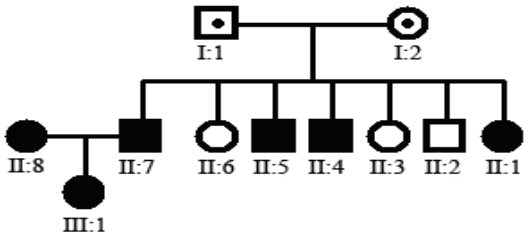
#260-♂

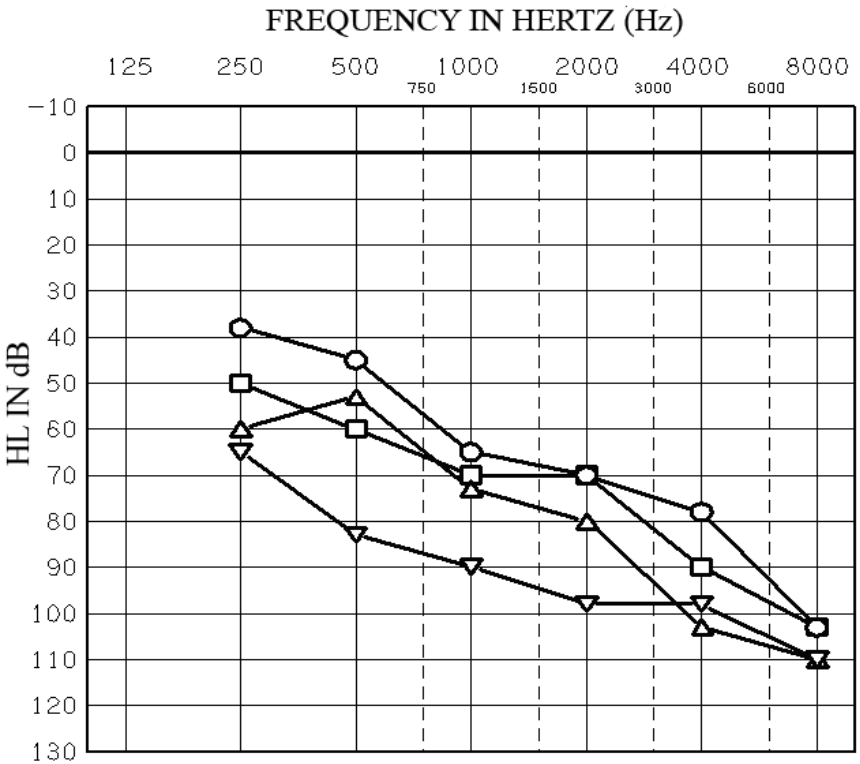
Mutation: 2299delG Age: 26

Universitetssjukhuset Örebro
ÖREBRO LÄNS LANDSTING

Fam. #133

Mutation : 1036 A>C



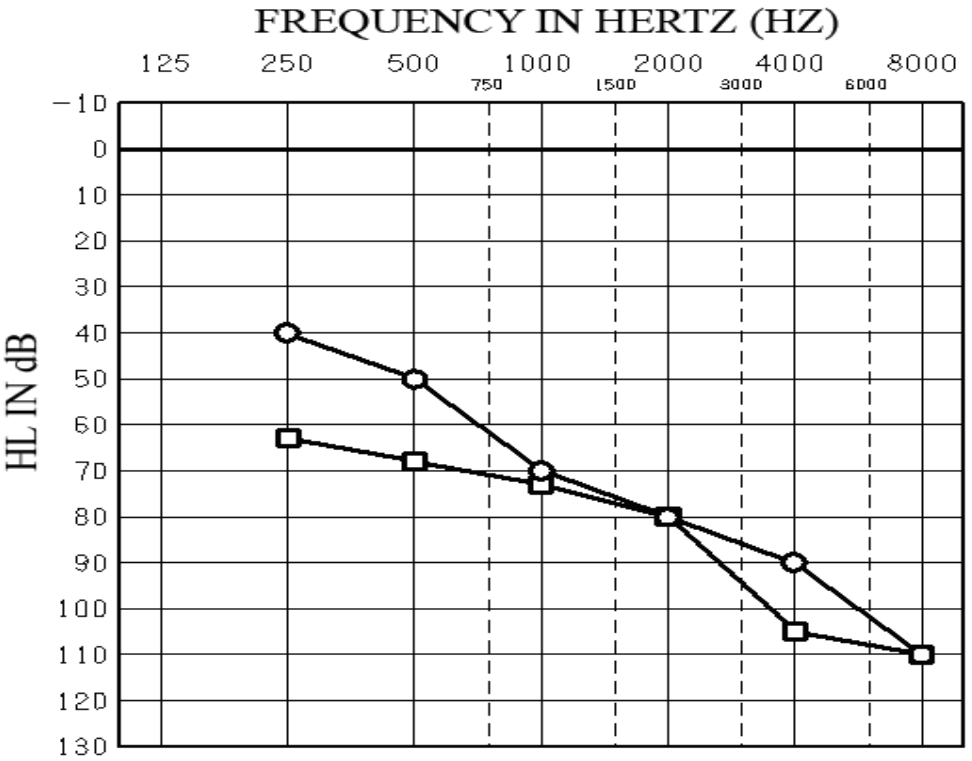


II:1 ---▽--- 68y

II:4 ---○--- 64y

II:5 ---△--- 68y

II:7 ---□--- 63y

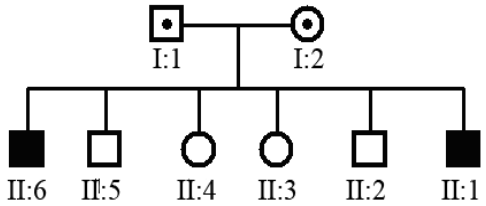


II:4 ---○--- 74y

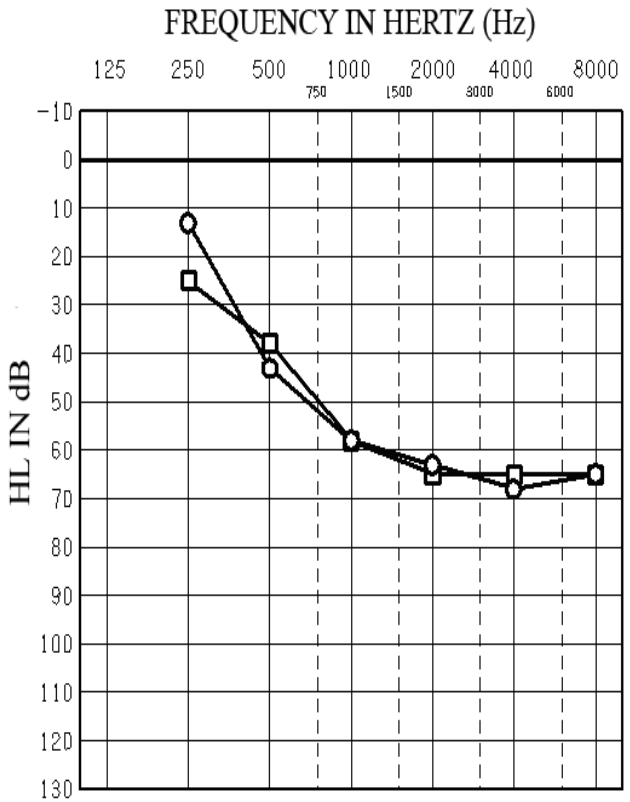
II:7 ---□--- 75y

Universitetssjukhuset Örebro
ÖREBRO LÄNS LANDSTING

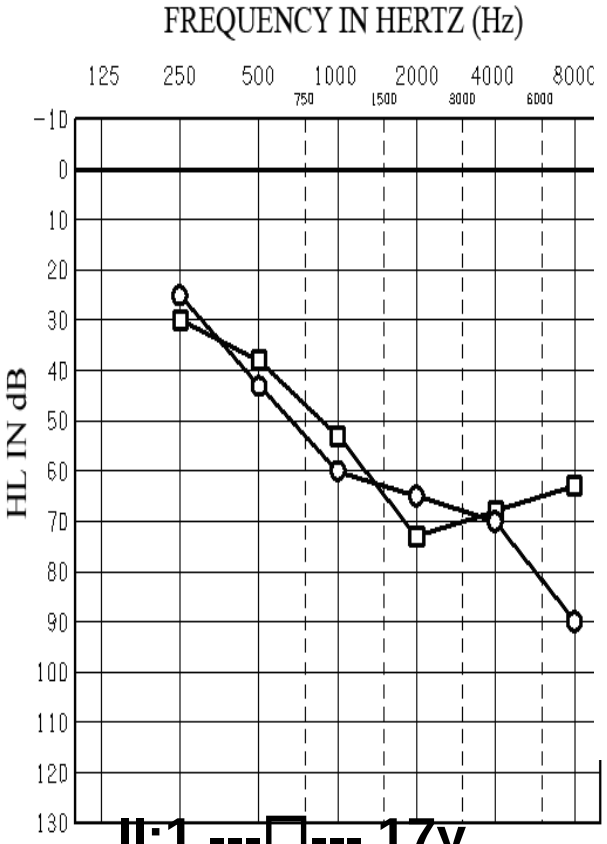
Fam. #137



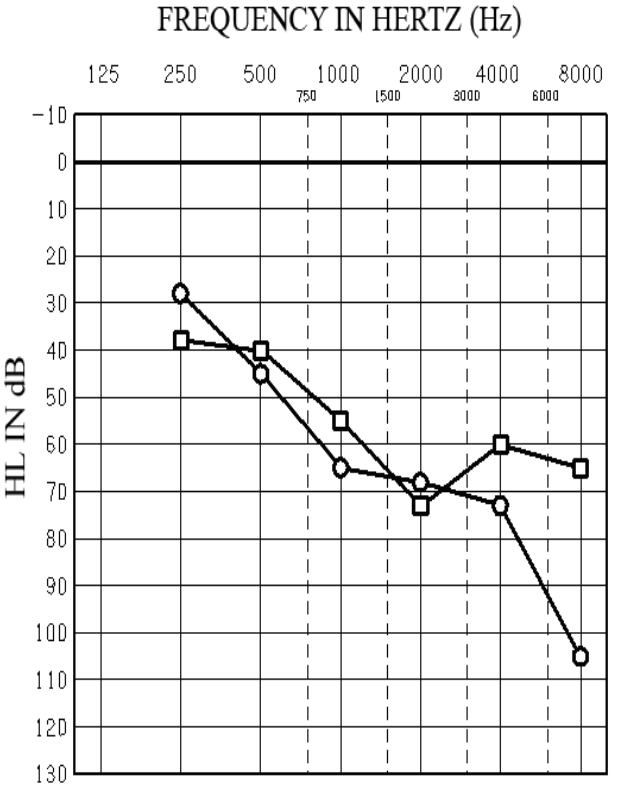
Mutation :2299delG



II:1 ---□--- 6y
II:6 ---○--- 6y

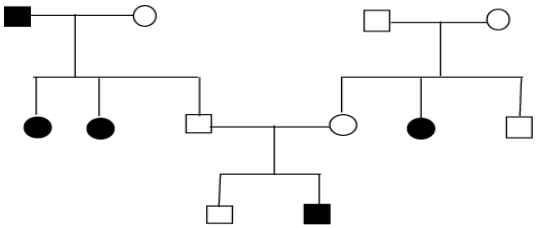


II:1 ---□--- 17y
II:6 ---○--- 17y



II:1 ---□--- 35y
II:6 ---○--- 35y

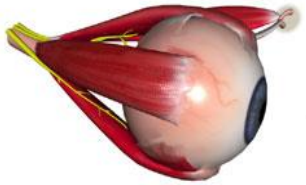
Auditory conclusions

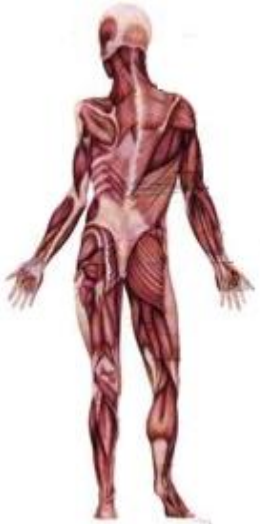


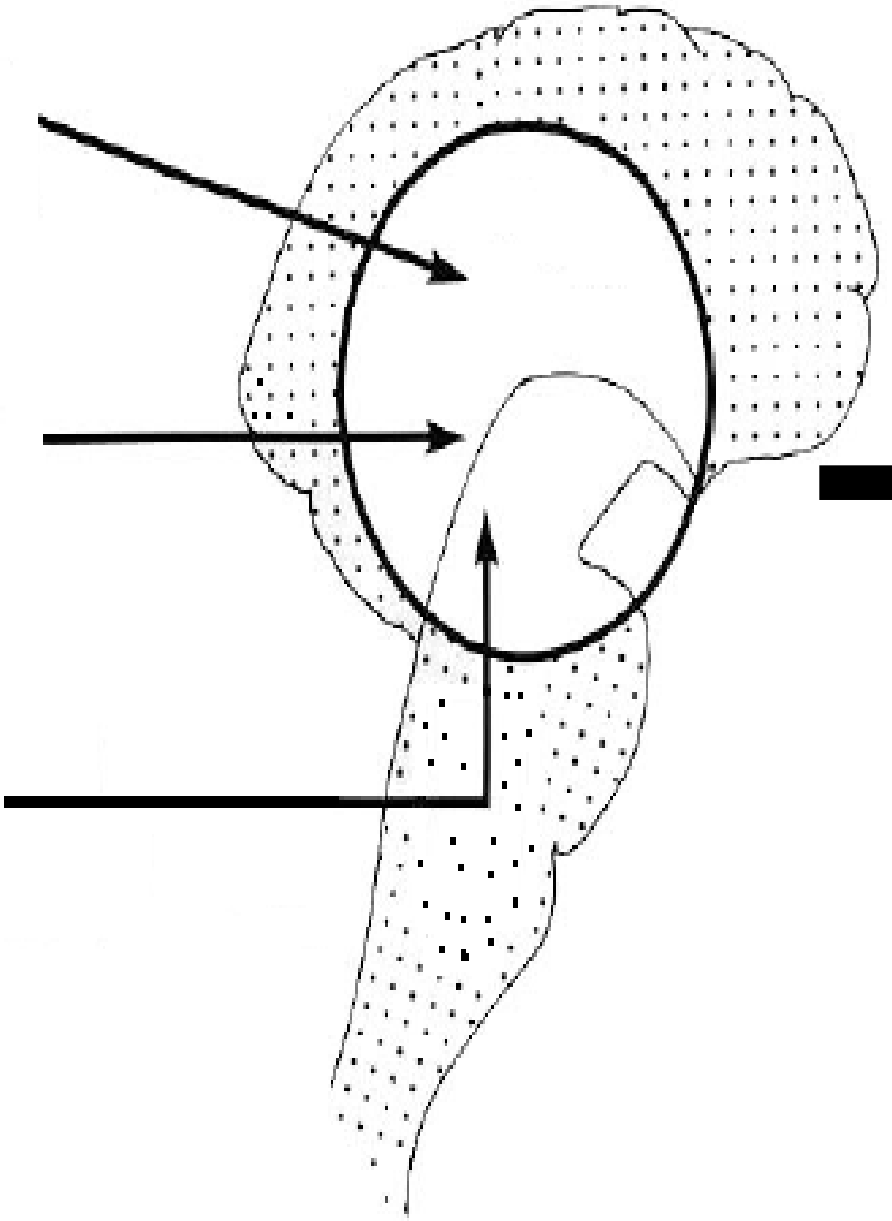
The majority have the same rate of progression within The family

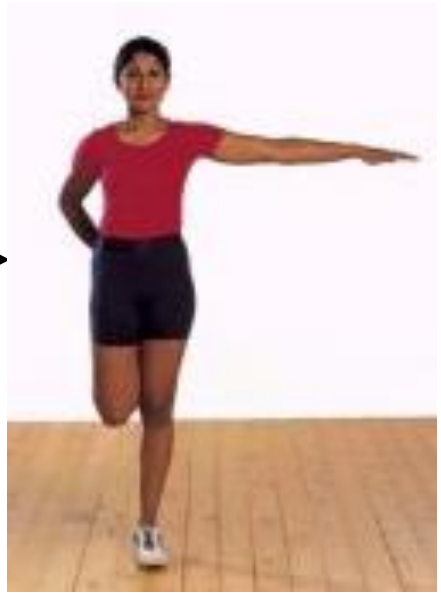
Input

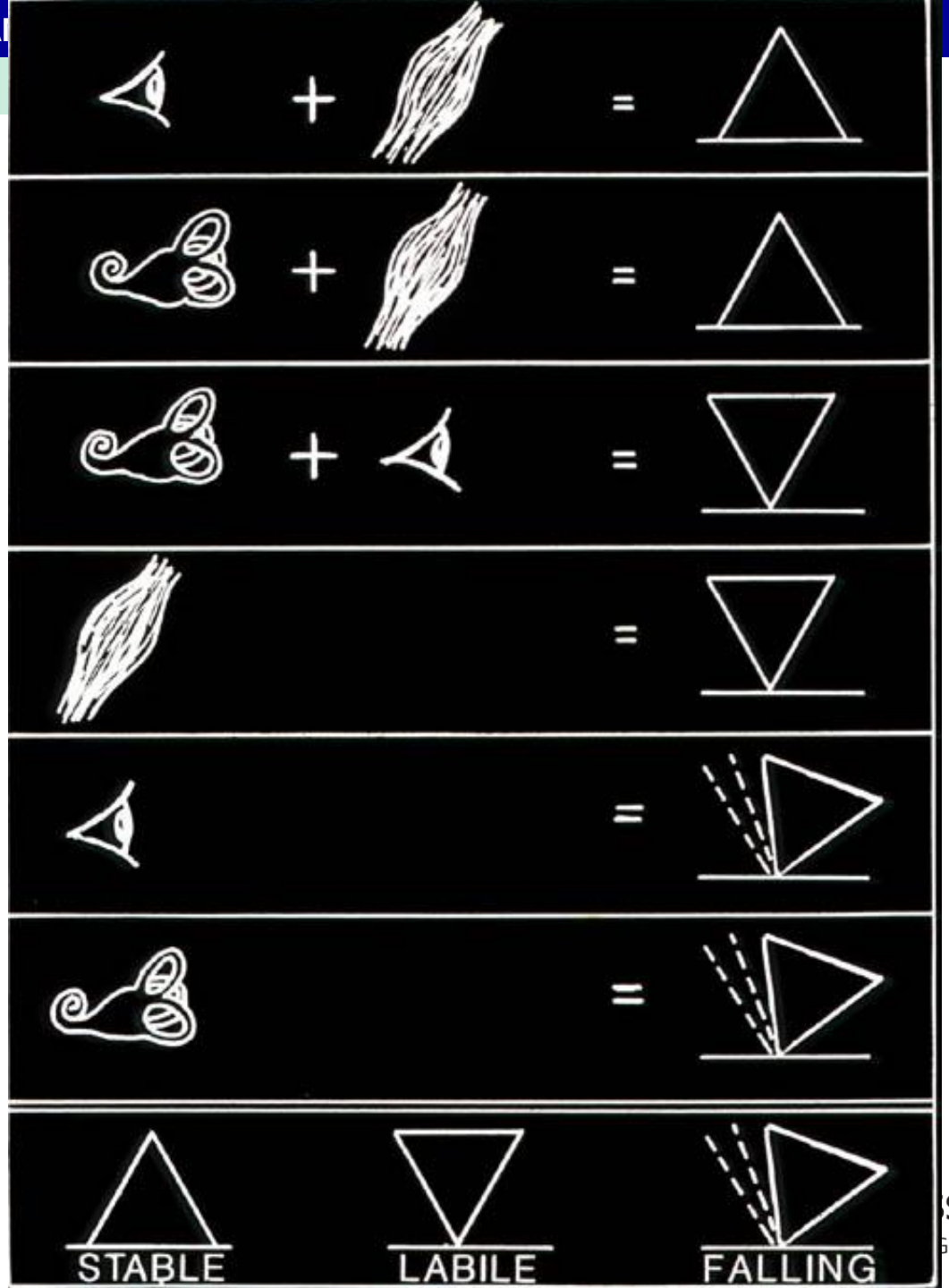
output



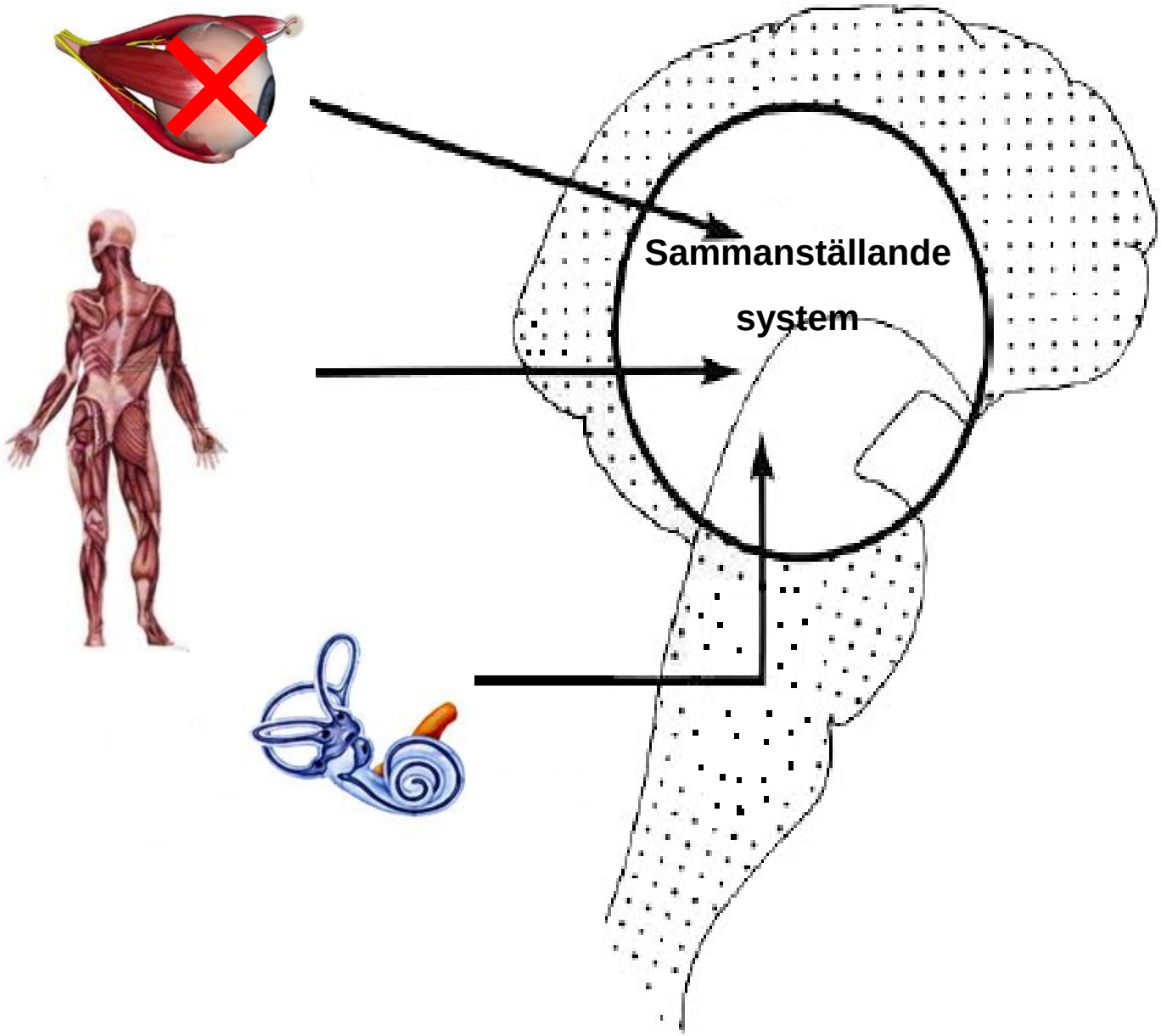




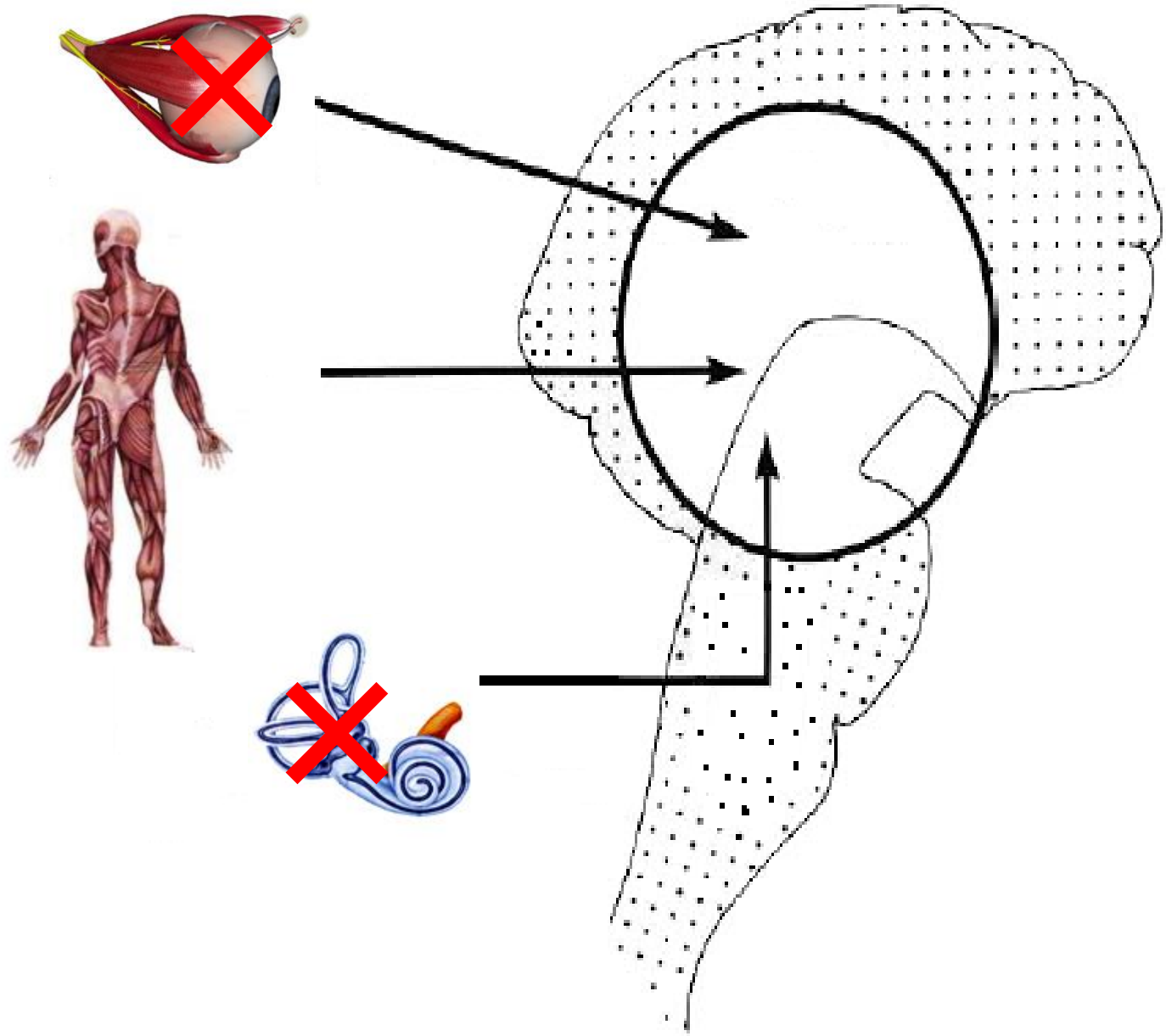



STABLE
LABILE
FALLING

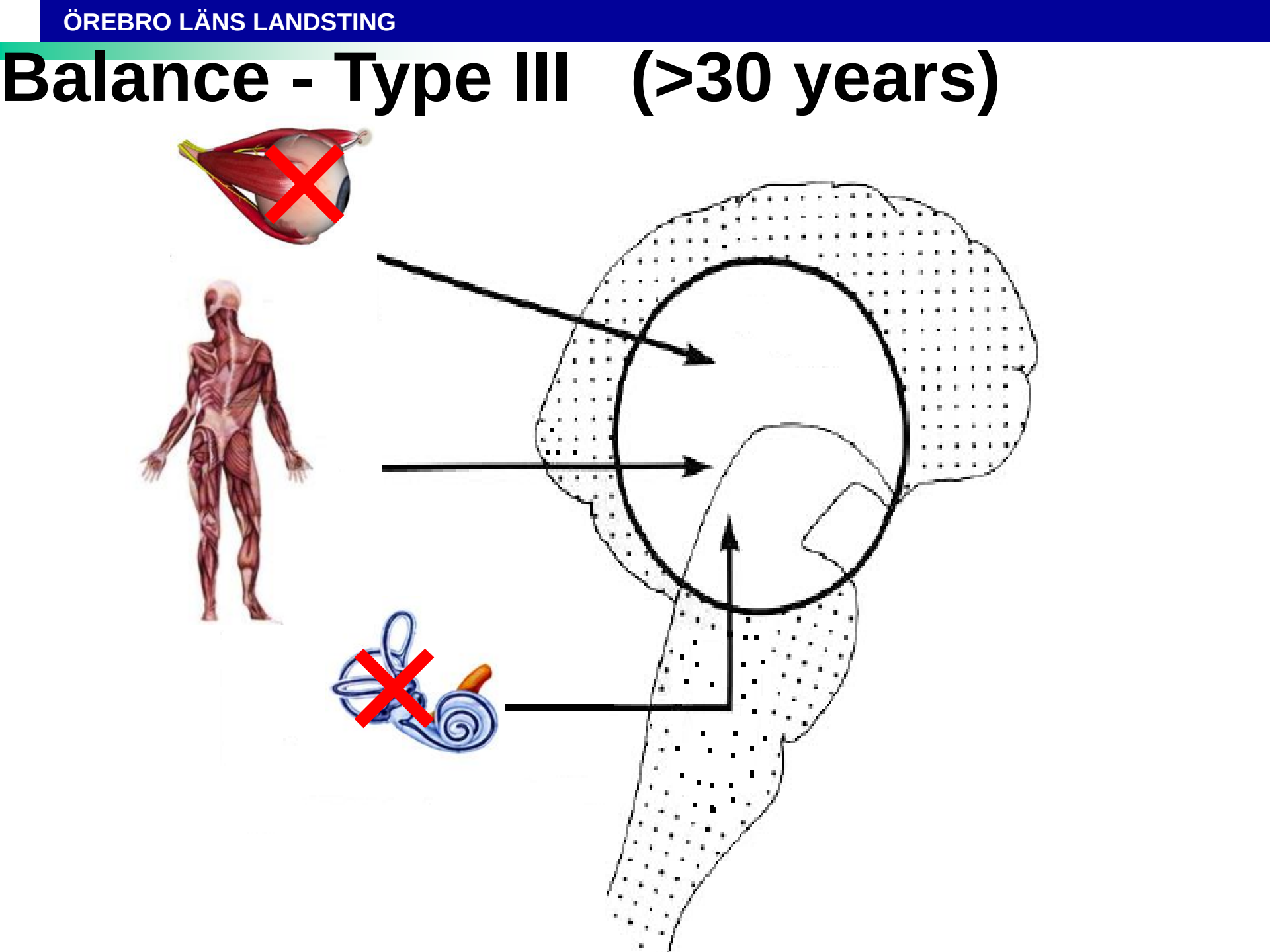
Balance - type II



Balance - Type I



Balance - Type III (>30 years)



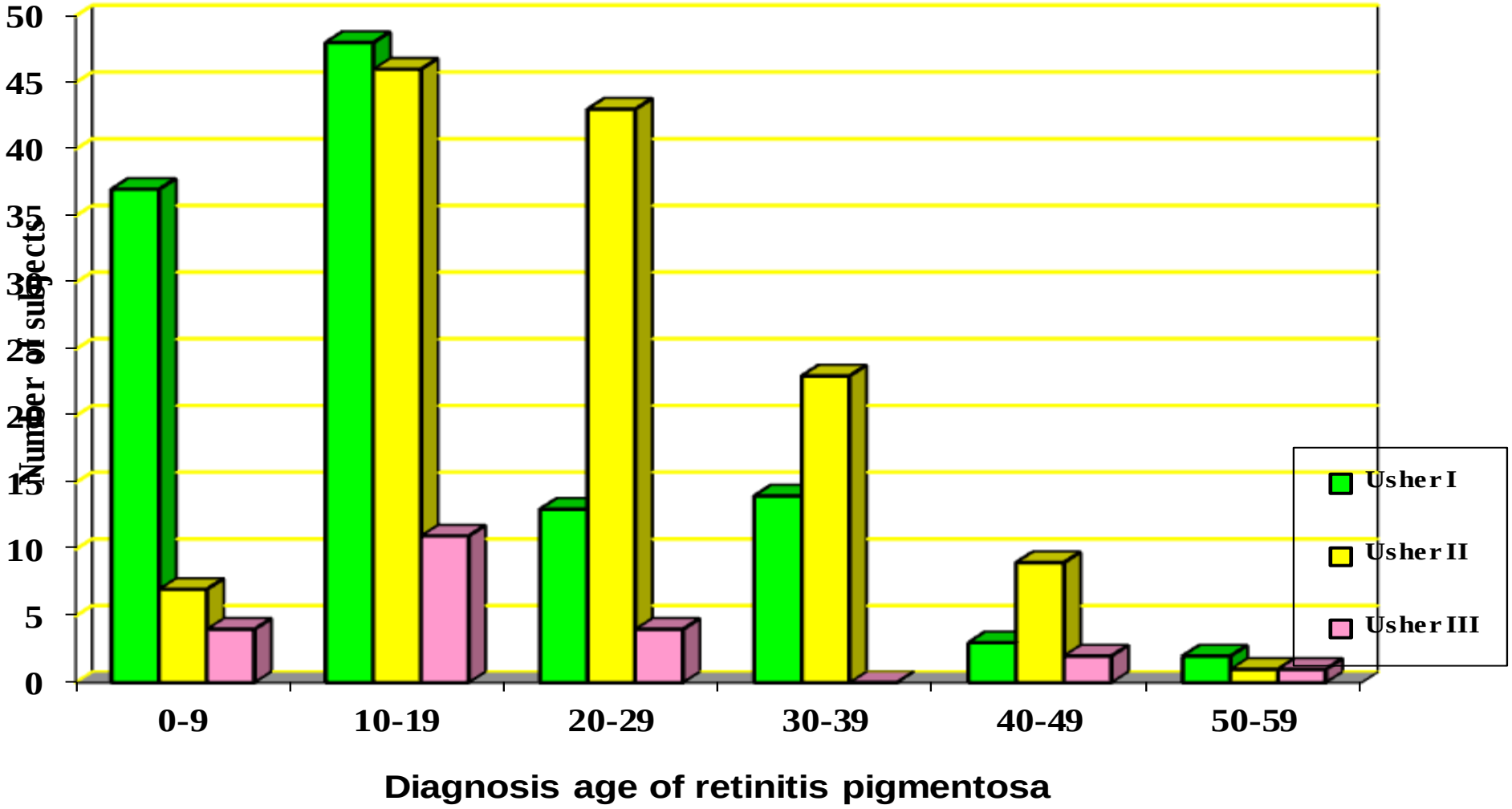
Childhood motor milestones

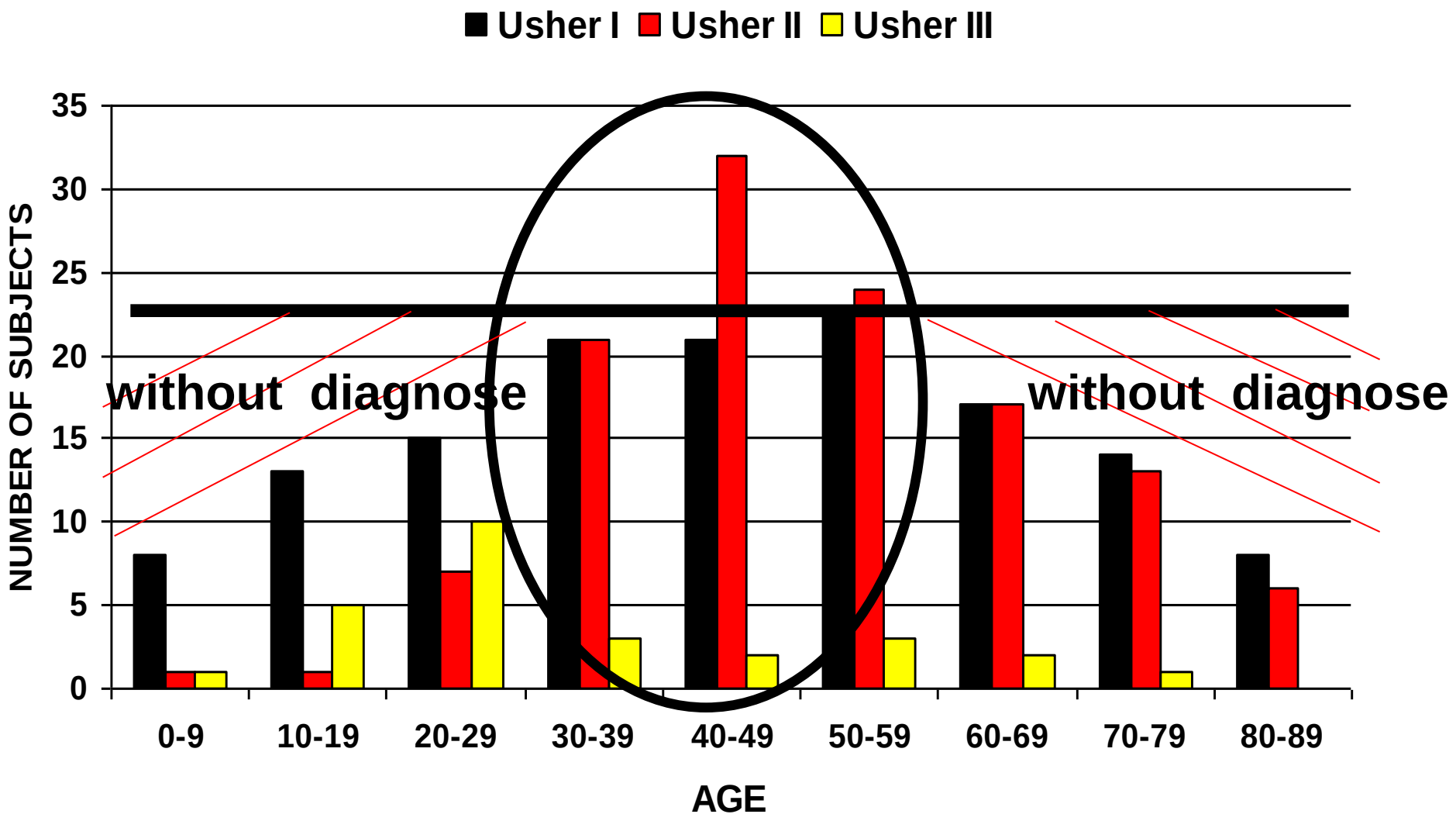
6 weeks	hold the head of the plane of the body
12 weeks	the head above the plane of the body
16 weeks	good head control
6 months	unsupported sitting
10 months	standing up with support
12 months	walking

Conclusions balance

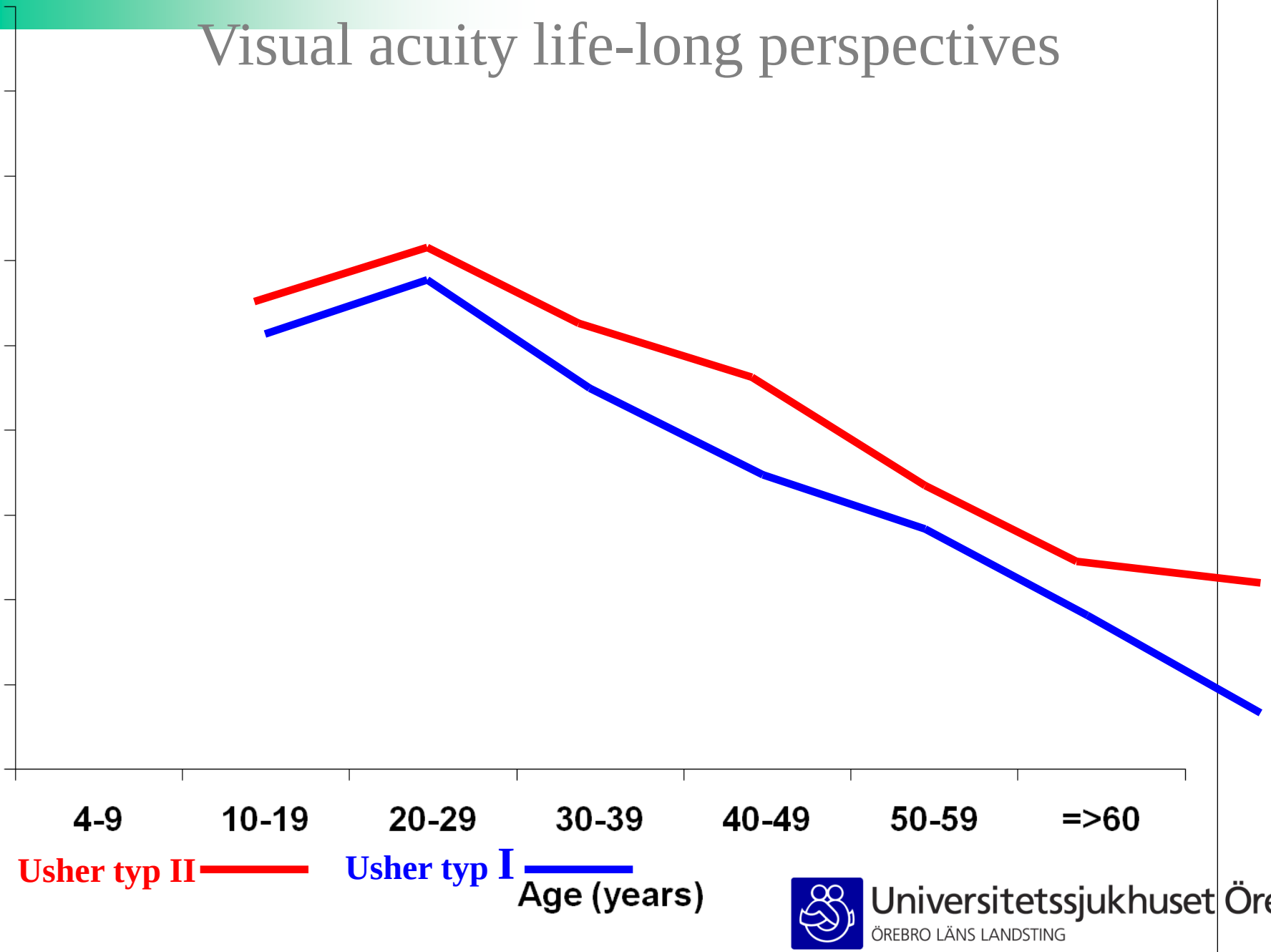
- Walking age < 18 months at least one vestibular organ have function
- Usher type II and III

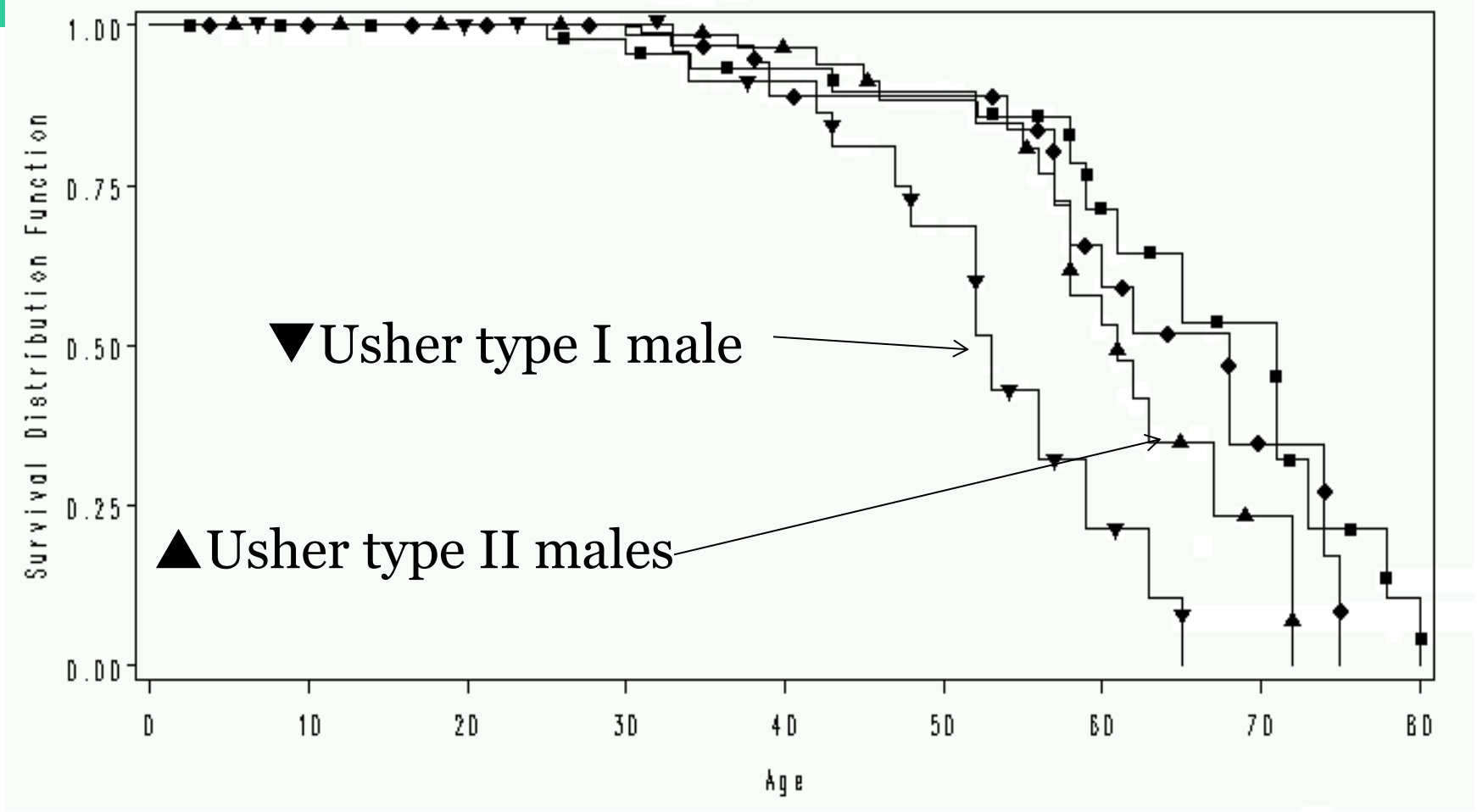
- > 18 months
  - Bilateral vest. areflexia, CNS
  - The vast majority have Usher type I
  - New problems with CI
  - Always assess vestibular function before CI


50
45
40
35
30
25
20
15
10
5
0
Number of subjects
0-9
10-19
20-29
30-39
40-49
50-59
Usher I
Usher II
Usher III
Diagnosis age of retinitis pigmentosa


Usher I
Usher II
Usher III
NUMBER OF SUBJECTS
35
30
25
20
15
10
5
0
without diagnose
without diagnose
0-9
10-19
20-29
30-39
40-49
50-59
60-69
70-79
80-89
AGE

Visual acuity life-long perspectives





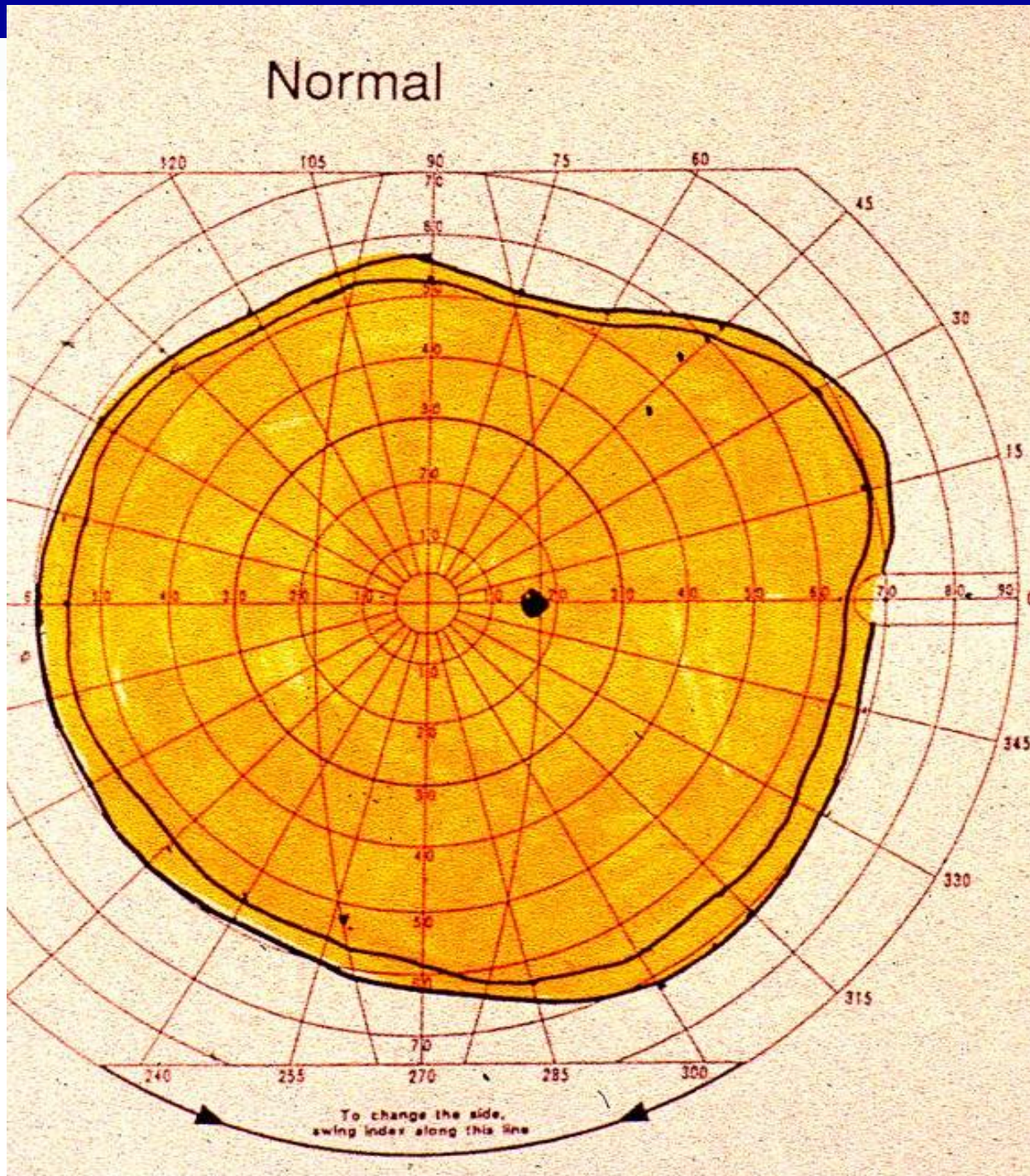
visual acuity of 20/200 (legally blindness) at different ages.

■Usher type I female, ◆Usher type II female,

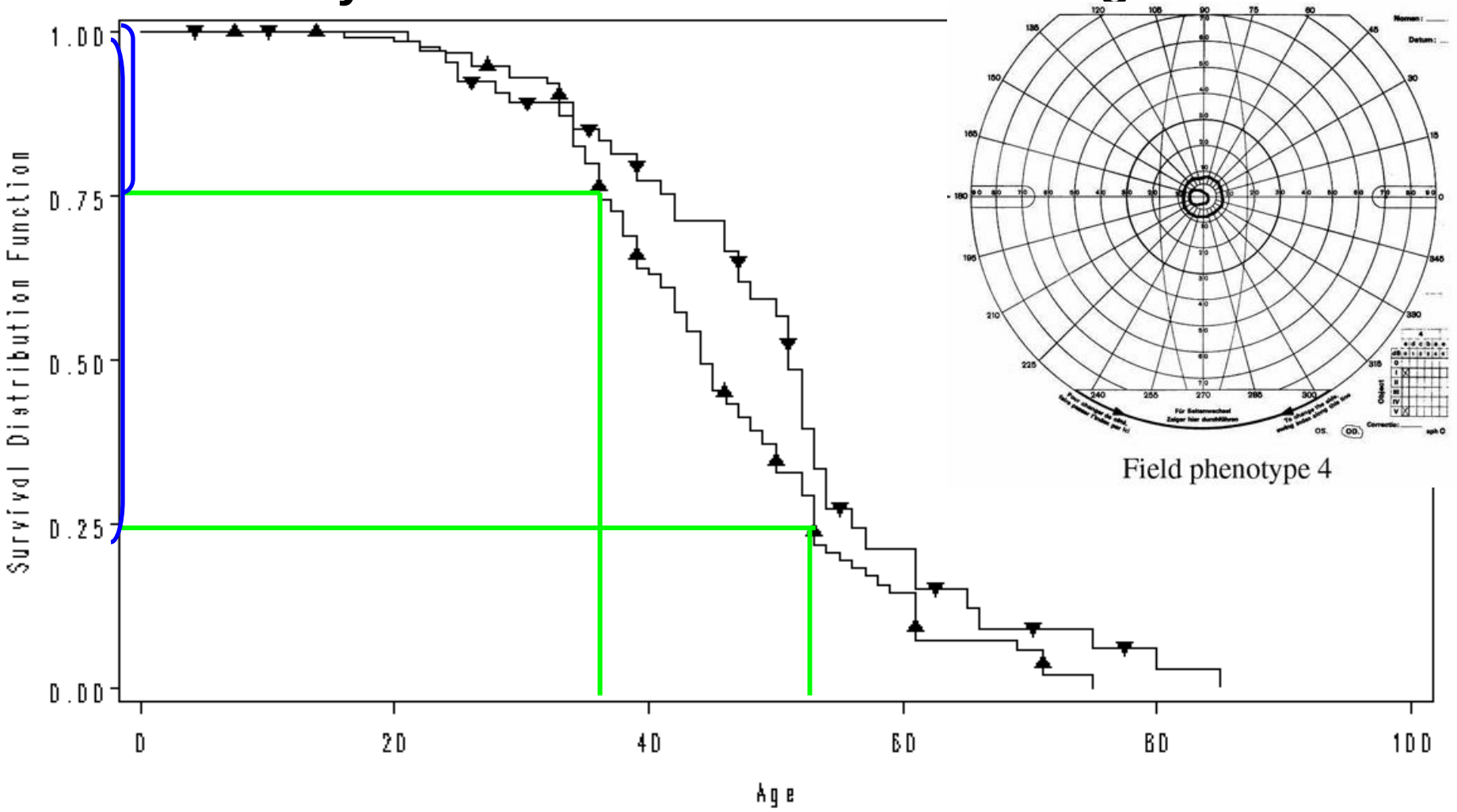
Field phenotype 1

Suggested by

Grover et al.,



Survival analysis- visual field end result 5 deg



Field phenotype 4

Usher type I

Usher type II

($p<0.05$)

Visual Conclusions

At 50 years of age 75% a remaining central visual field 5-10 degrees

RP seems to be more severe in USH1

Cataract more than 80% at 40 y

Geno-phenotype difference 1B and 1D ?

Diagnosis is made to late, problems from early childhood

New large study together with Ed Stone

Despair

I went to the doctor and he told me that I would go deaf and blind. He does not know why, not when, but it might be in the near future. Then the doctor abruptly left the room.

No, not my hearing, not my vision!!!!

It is not fair! How could God do this to me?

Why wasn´t I told until I was grown up?

Somebody help me !!!!

Is it important to explore geno-phenotype differneces?

Yes!!

Diagnosis

Prognosis

Rehabilitation

Treatment

Common language

Respect

Patient

Clincican

Scienticst