Dysmorphology

A systematic approach of dysmorphological evaluation


BERT, WIE IS JOUW FAVORIETE KUNSTENAAR ?
ZONDER TWIJFEL FRIDA KAHLO ! WAT MIJ ZO AANSPREEKT IS...
DeMorgen
IK WEET HET !!!
DE UNIBROW.
DeMorgen

program

Dysmorphism: an objective evaluation — *Koen Devriendt* — *(9.00-9.45hrs)*

From dysmorphism to a syndrome diagnosis

- pathogenesis & etiology — *Isabelle Maystadt* — *(9.45-10.45 hrs)*
- from phenotype to syndrome recognition * clinical : *Damien Lederer* — *(11.15-12.15 hrs)*
  * 2D and 3D : *Hilde Peeters* — *(14.30-15.00 hrs)*

Variability in expression of syndromes
* ethnicity : *Aimé Lumaka* — *(11.15-11.45 hrs)*
* age : *Griet Van Buggenhout*

Registries of congenital anomalies — *Jenneke Van den Ende* — *(13.20-13.50 hrs)*

ERN – ITHACA — *Alain Verloes* — *(13.50-14.10 hrs)*

Clinical Syndromology — *Marije Meeuwissen & Catheline Vilain*

- the 100 syndromes list
- interactive case discussions with students

Dysmorphology

= the study of congenital malformations,
more specifically
anomalies of morphology or anatomy

dysmorphism : the child with a ‘different’ appearance

Dysmorphism = anomalies

MAJOR ⟷ ***MINOR***

micro- or macrocephaly
club foot
Tetralogy of Fallot
polydactyly
cleft lip

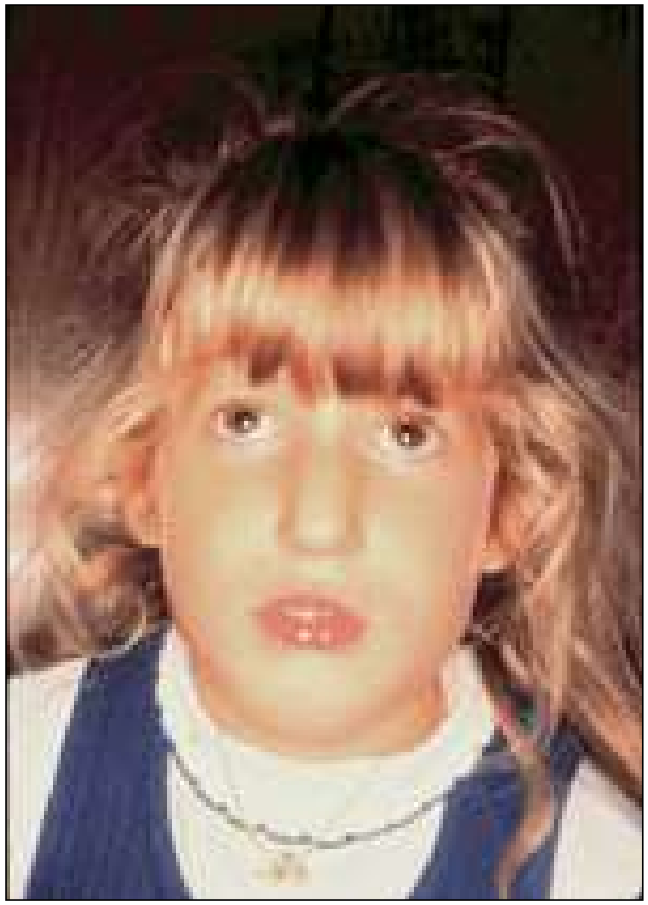
synophris
preauricular pit
syndactyly 2-3
hypertelorism
low set ears

↓ ↓

with **without**

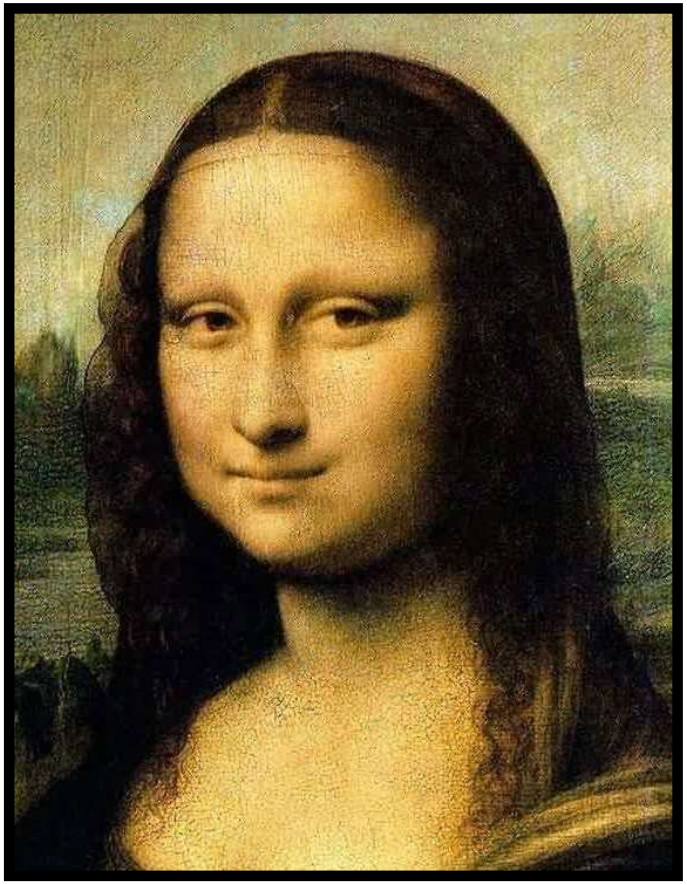
clear functional or esthetic consequences

two children with Tetralogy of Fallot at the pediatric cardiologist



Who will be referred to clinical genetics?

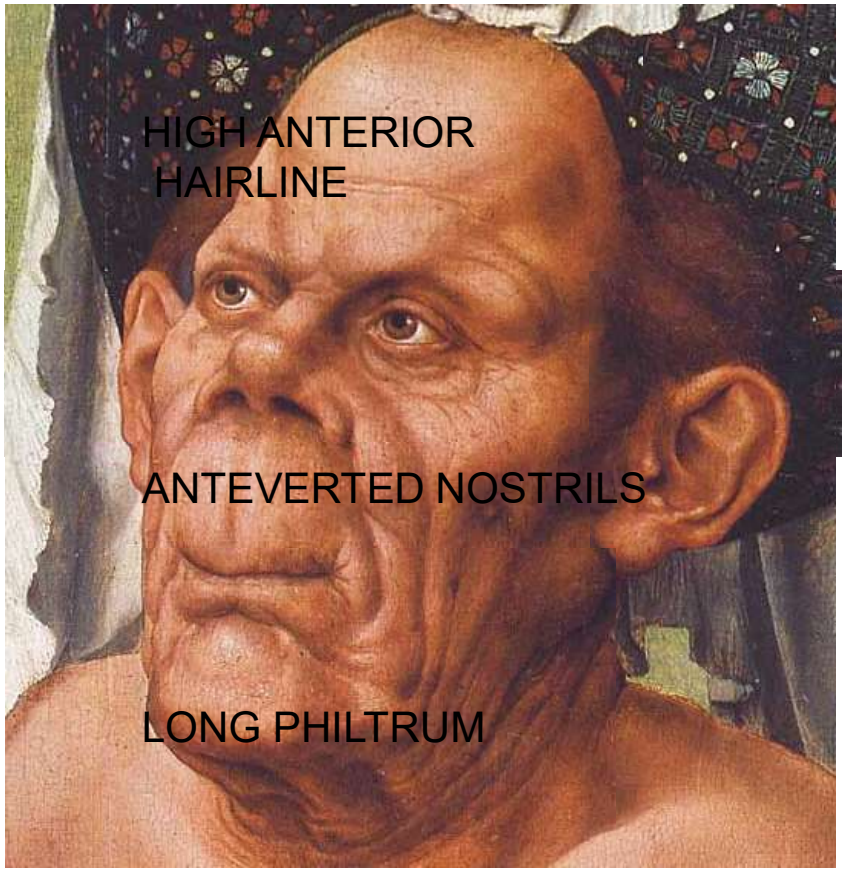
Dysmorphology.
The Leuven school…



Mona Lisa
Da Vinci (1503-1507)

The ugly Duchess
Quinten Matsys (1513)

“dissection”
of dysmorphism



LOW SET EARS
?

dysmorphism : evaluation of minor anomalies

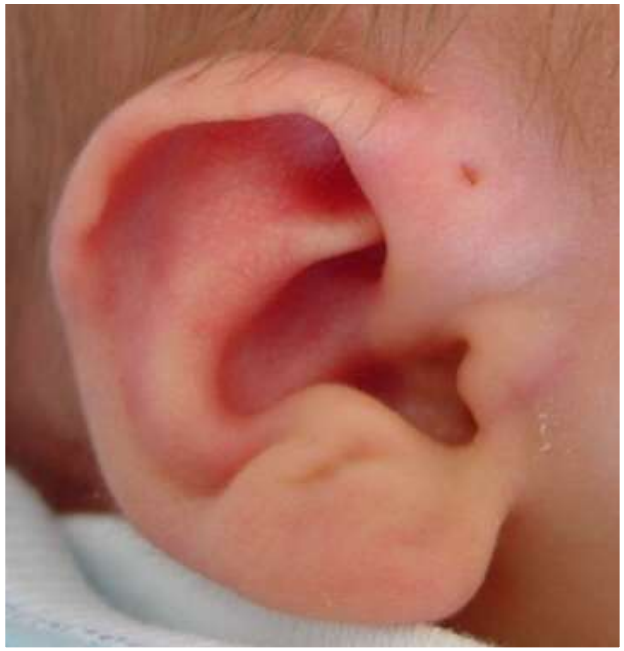
A. Qualitative or *discontinuous features* : YES / NO
e.g. supernumerary nipple, ear pit

B. Quantitative variant or *spectrum variants*

* objective (= measurable) : *e.g. interpupillary distance*
* subjective (= descriptive) : *e.g. anteversion of the nares*

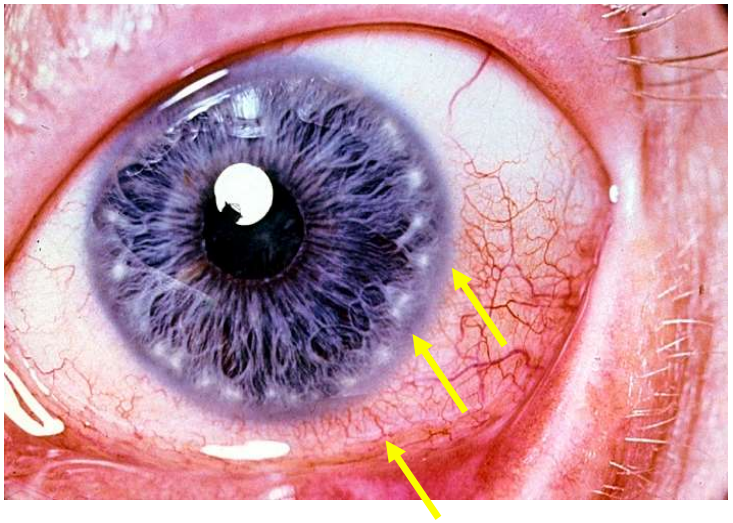
1. DISCONTINUOUS ANOMALY
   present or absent

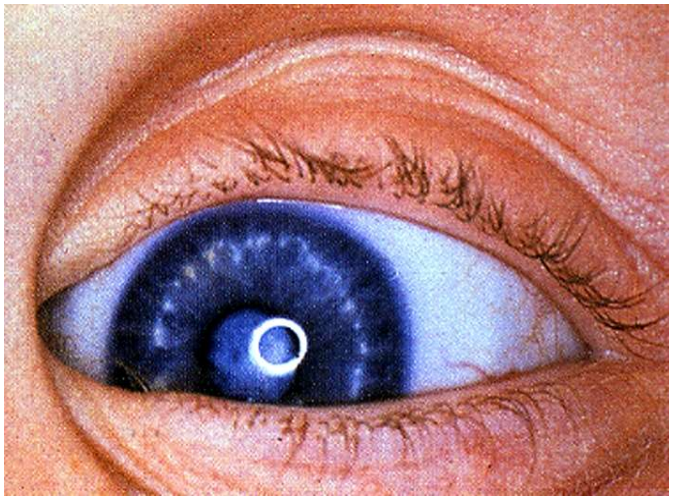
OBJECTIVE

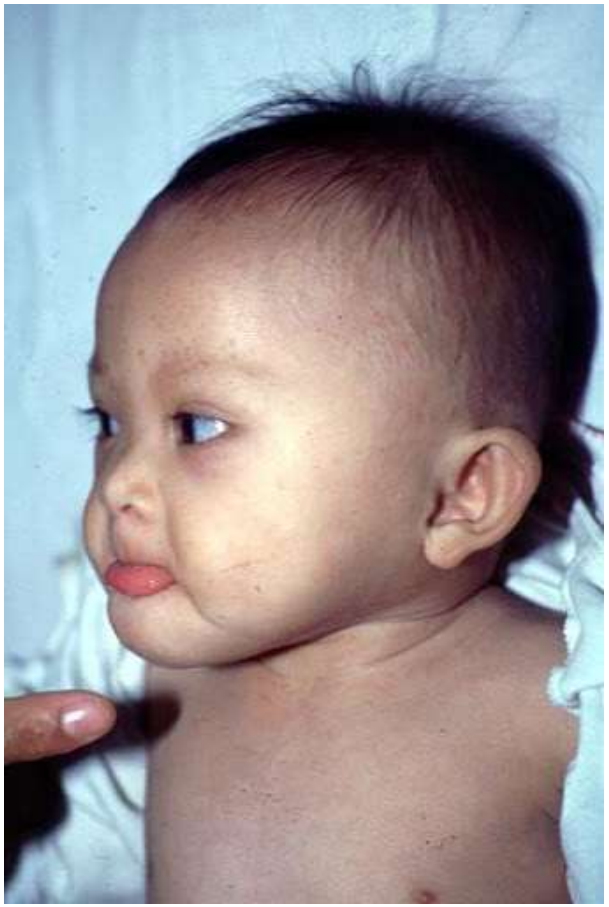


Pre-auricular pit

Brushfield spots







Are these low set ears?

Elements of morphology: Standard terminology for the head and face (p 6-28)
Judith E. Allanson, Christopher Cunniff, H. Eugene Hoyme, Julie McGaughran, Max Muenke, Giovanni Neri
Published Online: Jan 5 2009 10:20AM
DOI: 10.1002/ajmg.a.32612

Abstract | References | Full Text: HTML, PDF (Size: 1595K)
Save Article

Elements of morphology: Standard terminology for the periorbital region (p 29-39)
Bryan D. Hall, John M. Graham Jr., Suzanne B. Cassidy, John M. Opitz
Published Online: Jan 5 2009 10:17AM
DOI: 10.1002/ajmg.a.32597

Abstract | References | Full Text: HTML, PDF (Size: 450K)
Save Article

Elements of morphology: Standard terminology for the ear (p 40-60)
Alasdair Hunter, Jaime L. Frias, Gabriele Gillessen-Kaesbach, Helen Hughes, Kenneth Lyons Jones, Louise Wilson
Published Online: Jan 16 2009 4:26PM
DOI: 10.1002/ajmg.a.32599

Abstract | References | Full Text: HTML, PDF (Size: 1250K)
Save Article

Elements of morphology: Standard terminology for the nose and philtrum (p 61-76)
Raoul C.M. Hennekam, Valerie Cormier-Daire, Judith G. Hall, Károly Méhes, Michael Patton, Roger E. Stevenson
Published Online: Jan 16 2009 4:26PM
DOI: 10.1002/ajmg.a.32600

Elements of morphology: Standard terminology for the lips, mouth, and oral region (p 77-92)
John C. Carey, M. Michael Cohen Jr., Cynthia J.R. Curry, Koenraad Devriendt, Lewis B. Holmes, Alain Verloes
Published Online: Jan 5 2009 10:18AM
DOI: 10.1002/ajmg.a.32602

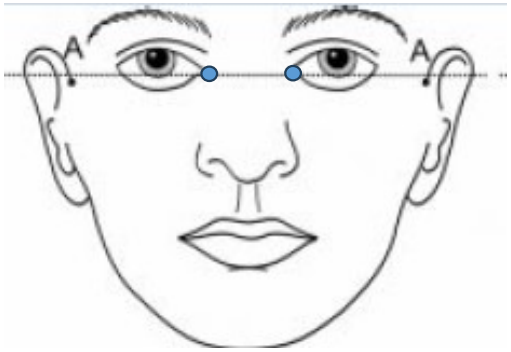
Abstract | References | Full Text: HTML, PDF (Size: 744K)
Save Article

Elements of morphology: Standard terminology for the hands and feet (p 93-127)
Leslie G. Biesecker, Jon M. Aase, Carol Clericuzio, Fiorella Gurrieri, I. Karen Temple, Helga Toriello
Published Online: Jan 5 2009 10:24AM
DOI: 10.1002/ajmg.a.32596

Am J Med Genet
January 2009

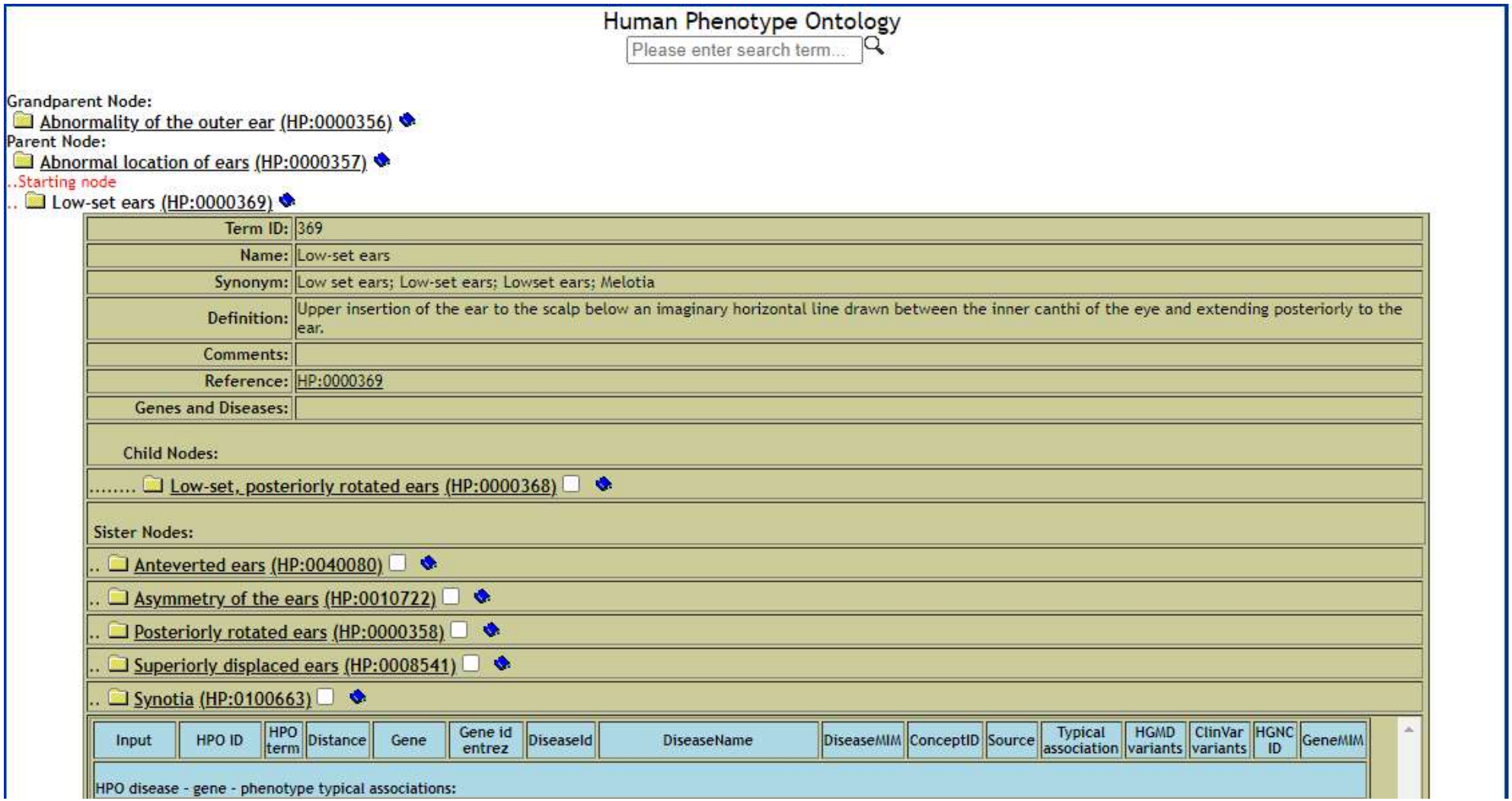
Low set ears

Upper insertion of the ear to the scalp
below an imaginary horizontal passing through the inner canthi
and extend that line posteriorly to the ear



- Independent of size of the ear helix
- Independent of the position of the outer canthi
  (upslant – downslant)

Standard terminology : HUMAN PHENOTYPE ONTOLOGY



Human Phenotype Ontology

Please enter search term...

Grandparent Node:
Abnormality of the outer ear (HP:0000356)
Parent Node:
Abnormal location of ears (HP:0000357)
..Starting node
.. Low-set ears (HP:0000369)

Term ID:	369
Name:	Low-set ears
Synonym:	Low set ears; Low-set ears; Lowset ears; Melotia
Definition:	Upper insertion of the ear to the scalp below an imaginary horizontal line drawn between the inner canthi of the eye and extending posteriorly to the ear.
Comments:	
Reference:	HP:0000369
Genes and Diseases:	

Child Nodes:

..... Low-set, posteriorly rotated ears (HP:0000368)

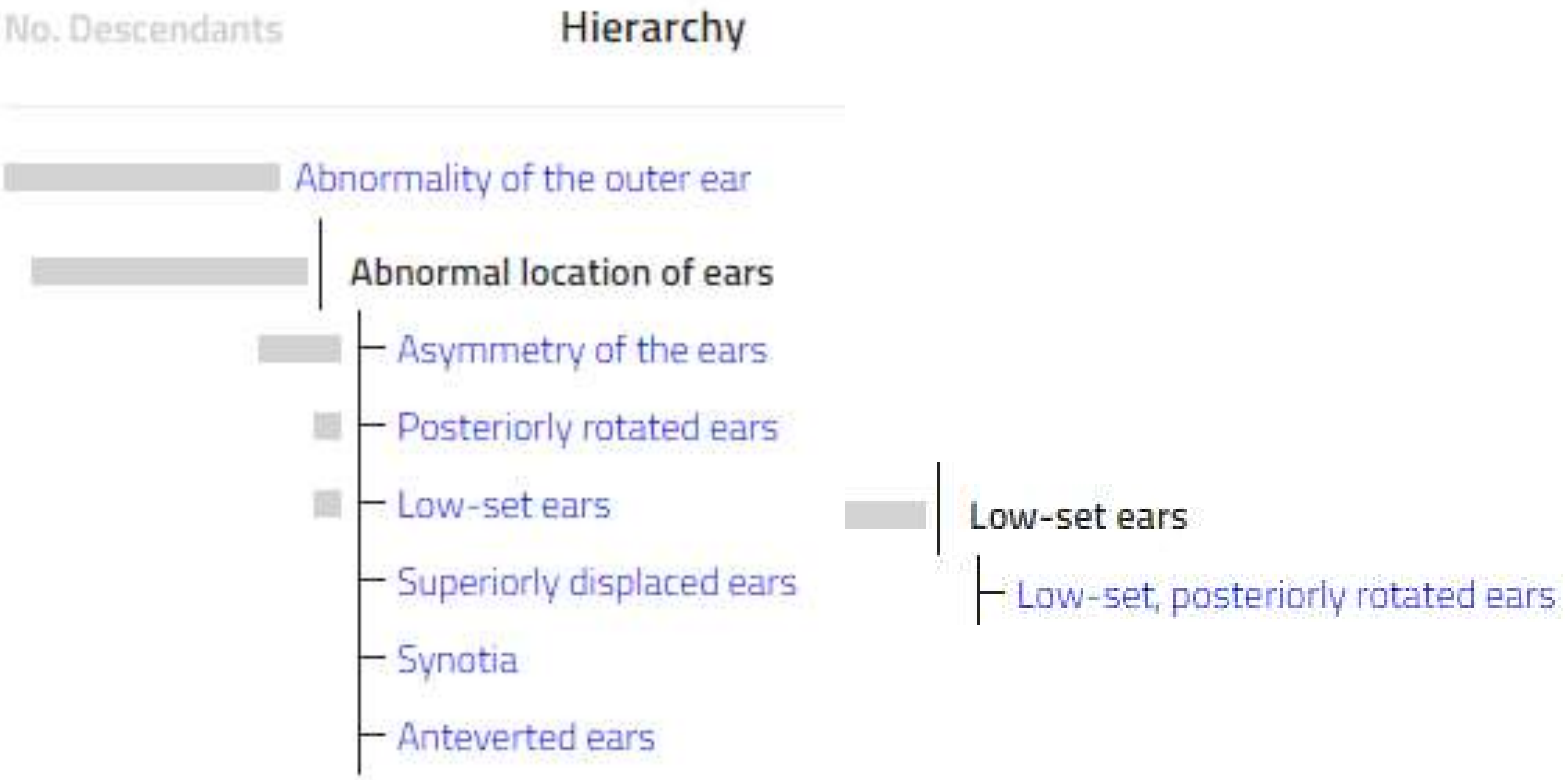
Sister Nodes:

.. Anteverted ears (HP:0040080)
.. Asymmetry of the ears (HP:0010722)
.. Posteriorly rotated ears (HP:0000358)
.. Superiorly displaced ears (HP:0008541)
.. Synotia (HP:0100663)

Input	HPO ID	HPO term	Distance	Gene	Gene id entrez	DiseaseId	DiseaseName	DiseaseMIM	ConceptID	Source	Typical association	HGMD variants	ClinVar variants	HGNC ID	GeneMIM

HPO disease - gene - phenotype typical associations:

ONTOLOGY


No. Descendants
Hierarchy
Abnormality of the outer ear
Abnormal location of ears
Asymmetry of the ears
Posteriorly rotated ears
Low-set ears
Superiorly displaced ears
Synotia
Anteverted ears
Low-set ears
Low-set, posteriorly rotated ears

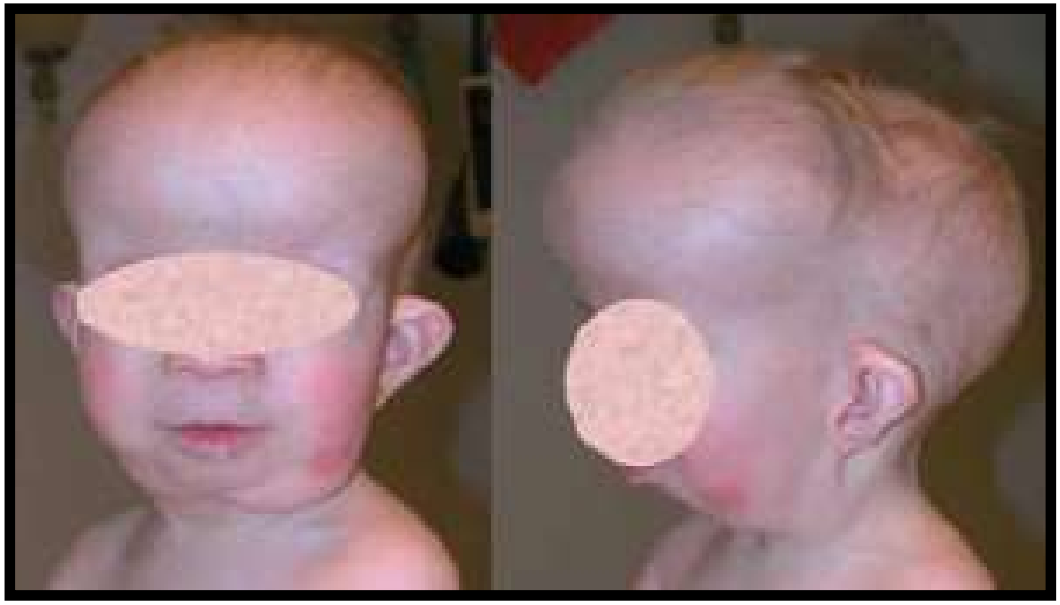
How do you call this feature ?

Forehead, Prominent

Definition: Forward prominence of the entire forehead, due to protrusion of the frontal bone (Fig. 35). *subjective*

Comments: This is not the same as ***Frontal bossing*** (see below).

Replaces: Forehead, bulging



Frontal Bossing

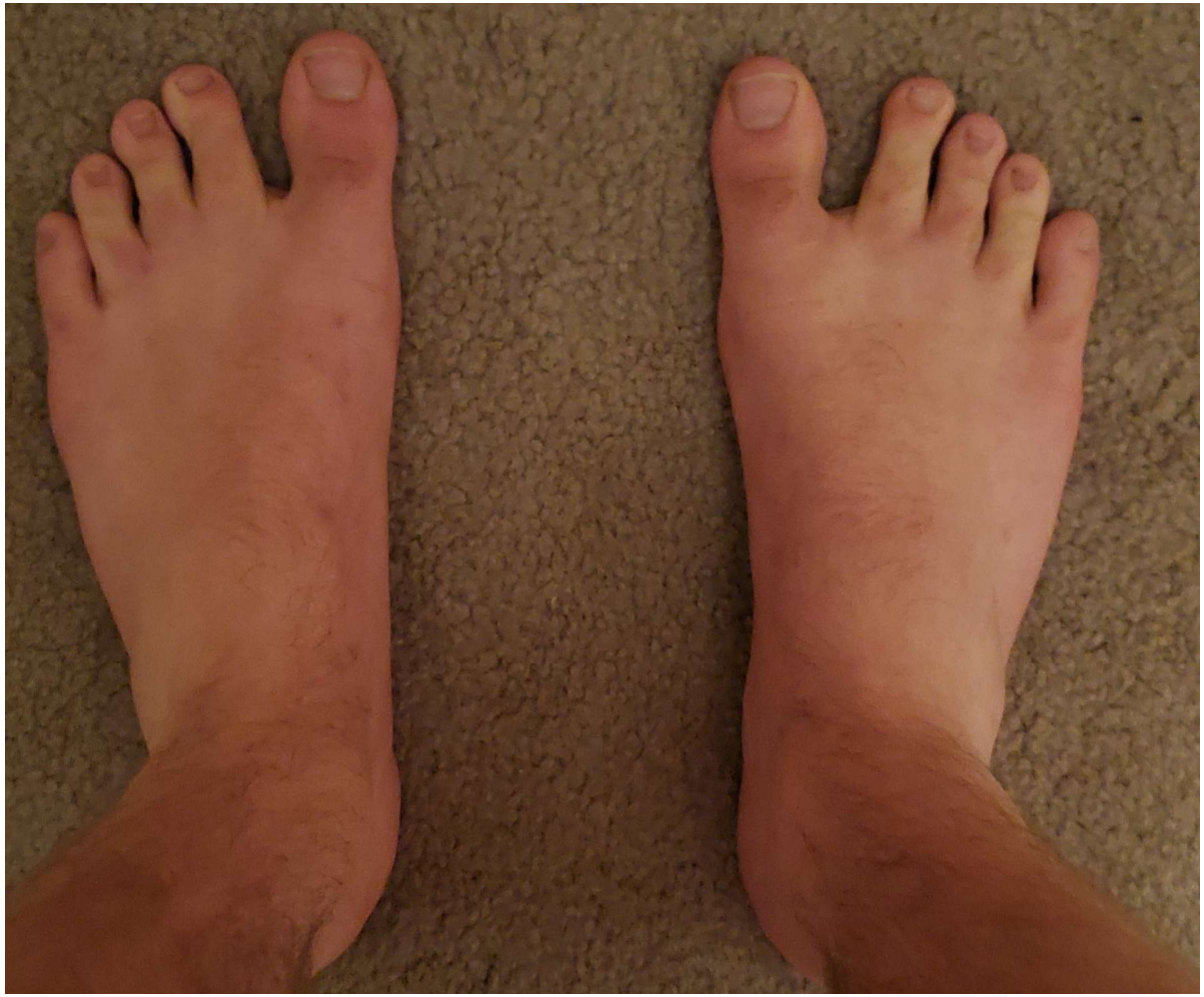
Definition: Bilateral bulging of the lateral frontal bone prominences with relative sparing of the midline (Fig. 38). *subjective*

Comments: This is not the same as ***Prominent forehead*** (see above)

Replaces: Forehead, bulging

Anomaly or common variant ?

1. Prevalence in the reference population



How do you describe this ?

Sandal Gap

Definition: A widely spaced gap between the first toe (the great toe) and the second toe (Fig. 61). *subjective*

Comment: The term is a subjective one but should be used when the gap between the toes is as wide as the second toe is broad.

Is this an anomaly ?

By definition :

prevalence in reference population

< or = 4% => anomaly

more than 4% => common variant

<u>Remarks</u> :

- no scientifc reason for a cut-off value of 4%
- recently a cut-off value of 2,5% has been suggested (Hennekam et al. AJMG 2013)

Reference prevalence figures ?

American Journal of Medical Genetics Part A 140A:2091–2109 (2006)

Normal Values for Morphological Abnormalities in School Children

Johannes H.M. Merks,[1]* Heval M. Özgen,[2] Theresia L.M. Cluitmans,[3]
Jaqueline M. van der Burg-van Rijn,[4] Jan Maarten Cobben,[2]
Flora E. van Leeuwen,[5] and Raoul C.M. Hennekam[2,6]

<u>remark</u> : prevalence figures may differ according to

- ethnicity
- age => newborns –> use other references

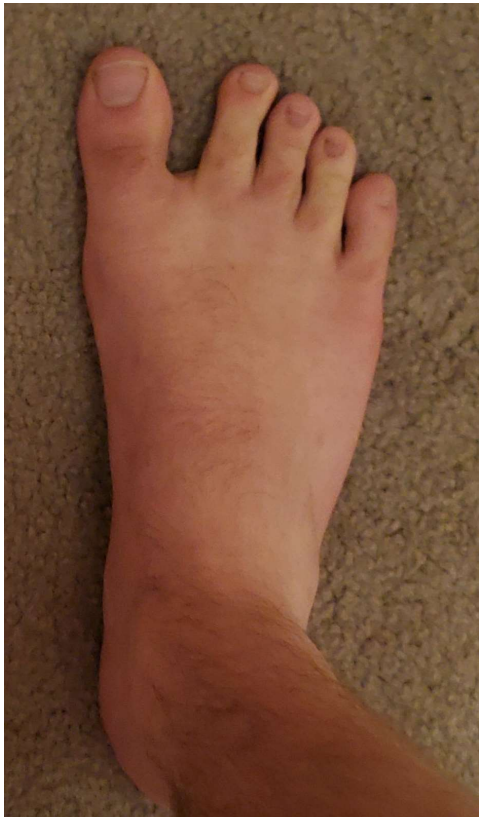
Prevalence may depend **on the age**

TABLE III. Comparison of Prevalence (%) of Specific Phenotypic Abnormalities in Earlier Studies in Newborn Infants and the Present Study in School Children

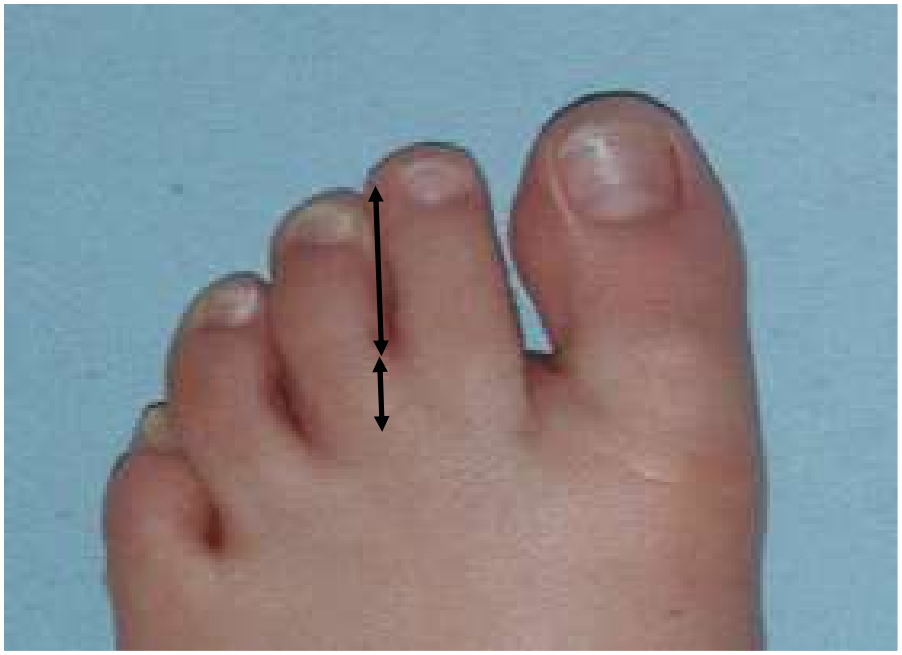
	Our study (n = 923)	Marden et al. [1964] (n = 4,412)	Leppig et al. [1987] (n = 4,305)	Méhes [1983] (n = 4,589)
Epicanthus (bilateral)	3.5	0.6	1.4	0.7
Upward slant of palpebral fissures	3.9	<0.1	—	3.01
Unfolded helix	2.5	3.52	<4	—
Darwinian tubercle	4.6	11	<4	—
Ear posteriorly rotated	1.4	0.25	—	0.11
(Pre)auricular sinus (bilateral)	0	0.1	0.1	0.1
(Pre)auricular tags	0.3	0.2	0.1	0.6
Flat nasal bridge	2.5	7.3	<4	—
Prominent nasal bridge*	11.5	—	<4	—
Extra nipples	2.8	—	<4	0.22
Dimple over sacrum	—	0.02	0.09	1.2
Single transverse crease (bilateral)	2.3	2.2	0.7	2.8
Bridged palmar crease	2.7	1.04	<4	—
Single crease fifth finger	—	0.02	0	0.1
Clinodactyly fifth finger	3.6	0.99	—	0.42
Syndactyly toes 2–3	0.3	0.2	0.2	0.2
Sandal gap	26.3	—	<4	0.36
Café-au-lait spots*	16.8	<0.1	—	—

Only items reported in at least three studies are listed, together with two examples of items (*) showing clear age dependency.

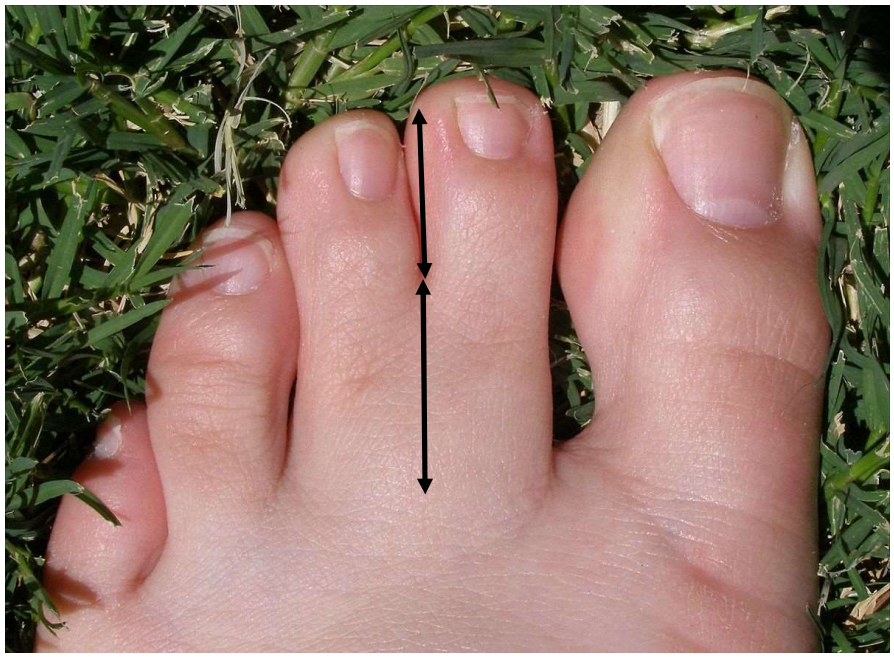
Common variant or rare anomaly ?



Prevalence 26,3 %



NORMAL



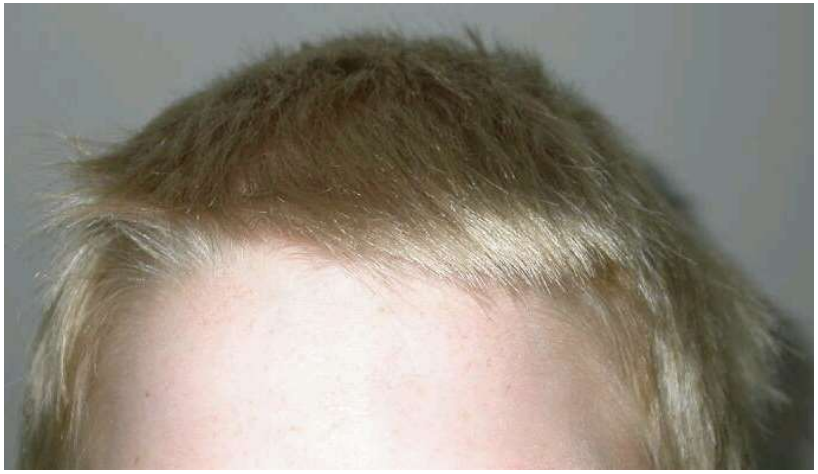
prevalence : 0,4%

Cutaneous syndactyly

Definition: A soft tissue continuity in the A/P axis between adjacent foot digits that involves **at least half** of the P/D length of one of the two involved digits.

Objective

Common variant or rare anomaly ?



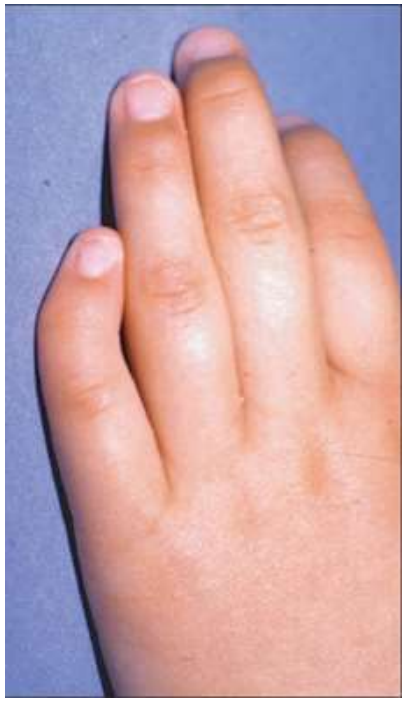
Hair, Frontal Upsweep

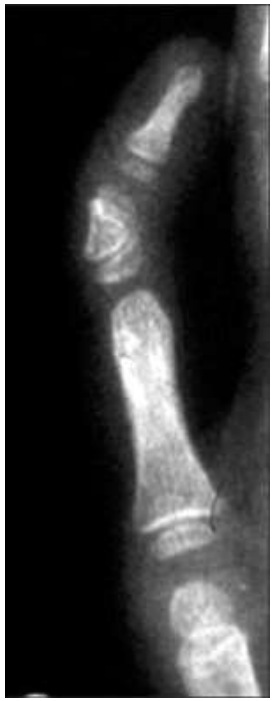
Definition: Upward and/or sideward growth of anterior hair subjective

Replaces: Cowlick, which may be considered pejorative

prevalence : 15,8%

Common variant or rare anomaly ?

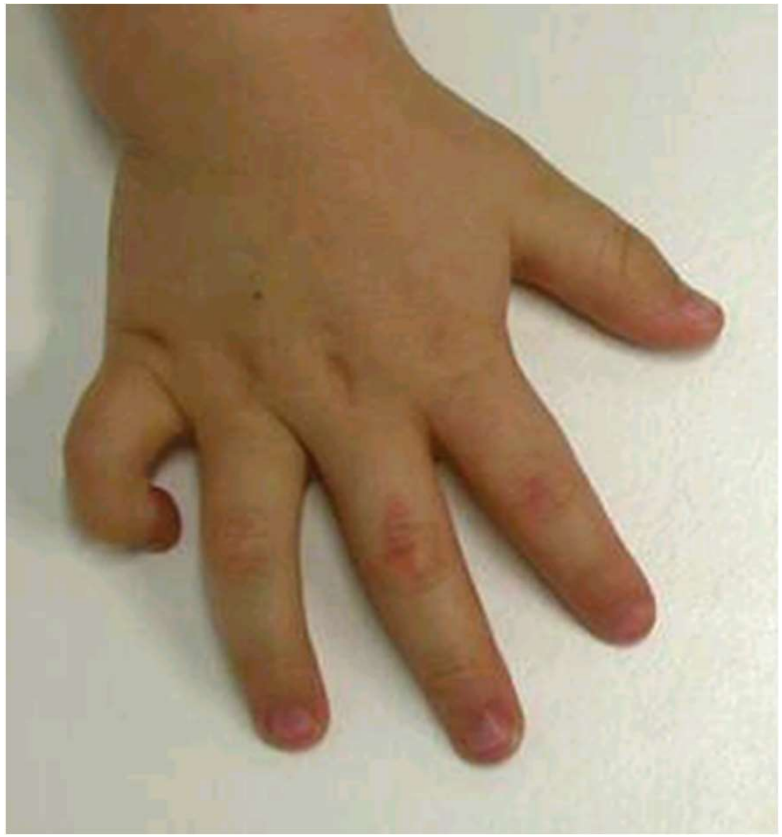


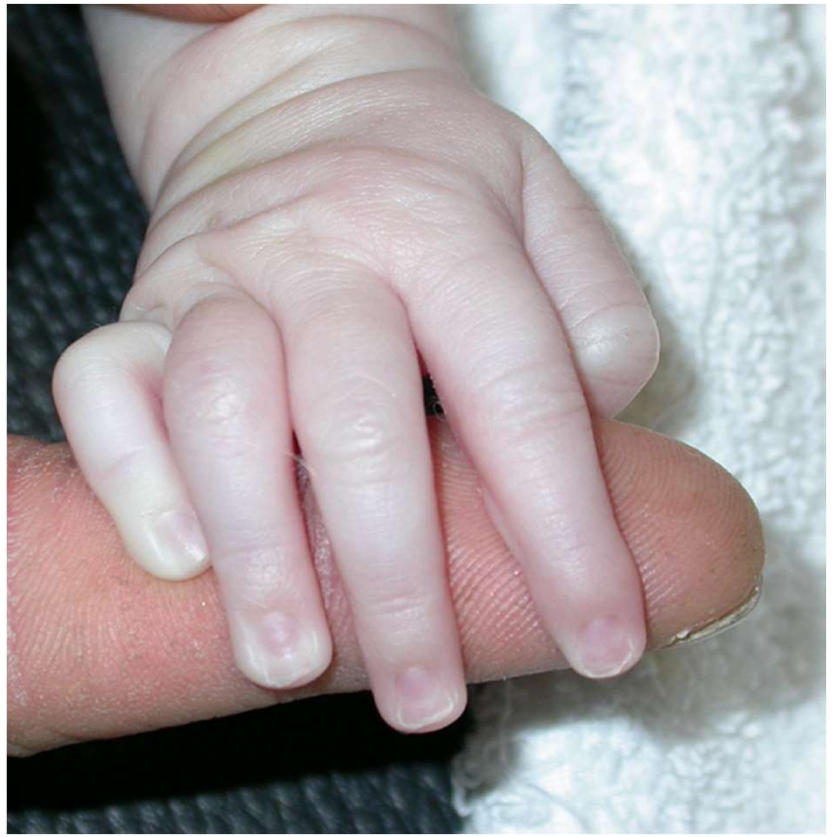


Clinodactyly

Definition: A digit that is laterally curved in the plane of the palm
subjective
Comment: The curvature in this term is restricted to the phalanges and does not refer to deviation at the MCPJ/MTPJ
Typically involves an abnormally shaped middle phalanx, but this is not obligate.

prevalence :
3,6%





Camptodactyly

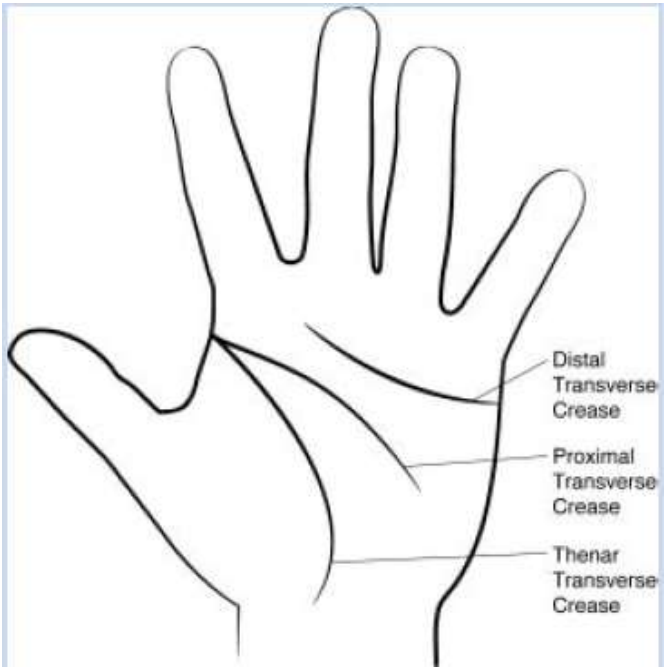
Definition: The distal and/or proximal interphalangeal joints of the finger(s) cannot be extended to 180 by either active or passive extension

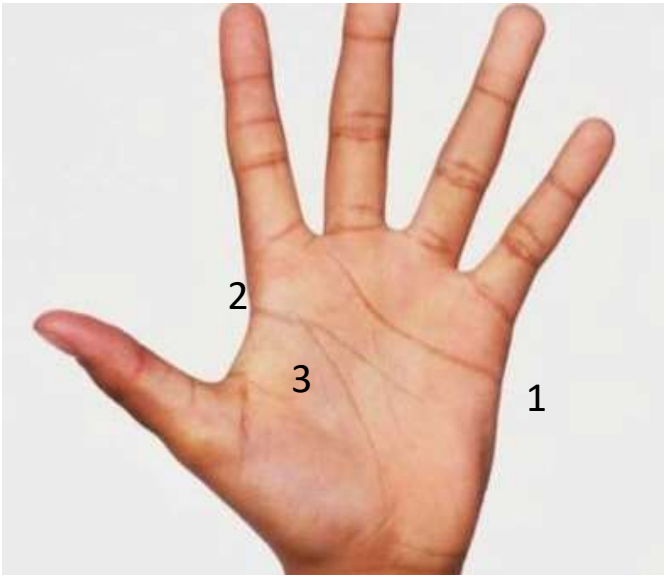
three major palmar creases

1. Distal transverse crease
from the radial side of the hand
proximal to the base of the index finger or the second interdigital space
and extends toward the ulnar side of the palm.

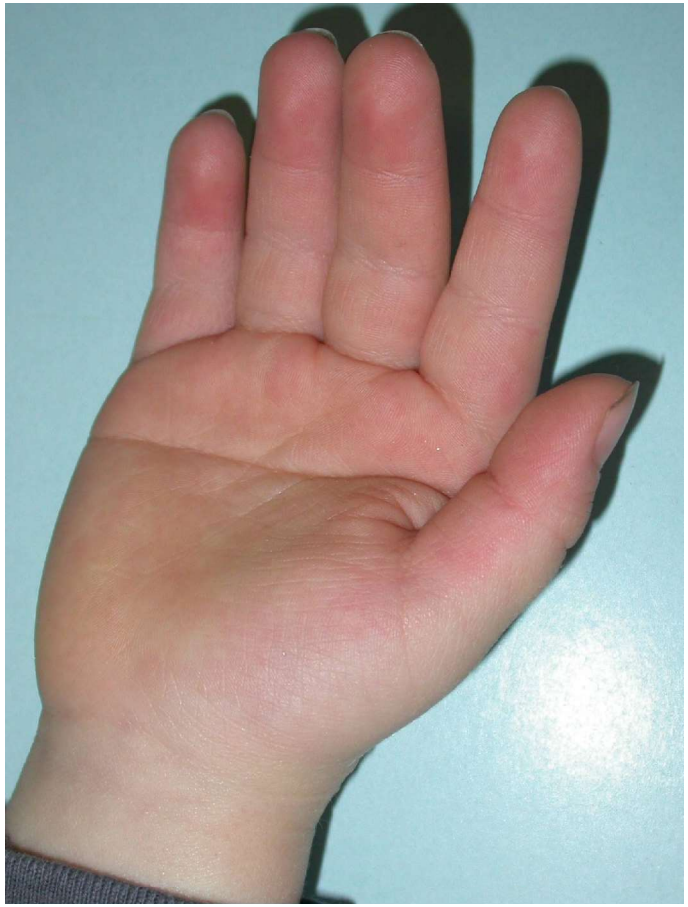
2. Proximal transverse crease
begins on the radial (anterior) side of the palm in the first interdigital space
and extends across the palm towards,
but does not typically reach, the ulnar side of the palm.

3. Thenar transverse crease
One end is typically coincident with the radial part of the proximal transverse crease
and extends proximally toward the wrist.





Common variant or rare anomaly ?



Palmar Crease, Single Transverse

Definition: The distal and proximal transverse palmar creases are merged into a single transverse palmar crease objective

prevalence :
- unilateral 2,3%
- bilateral 1%

Common variant or rare anomaly ?

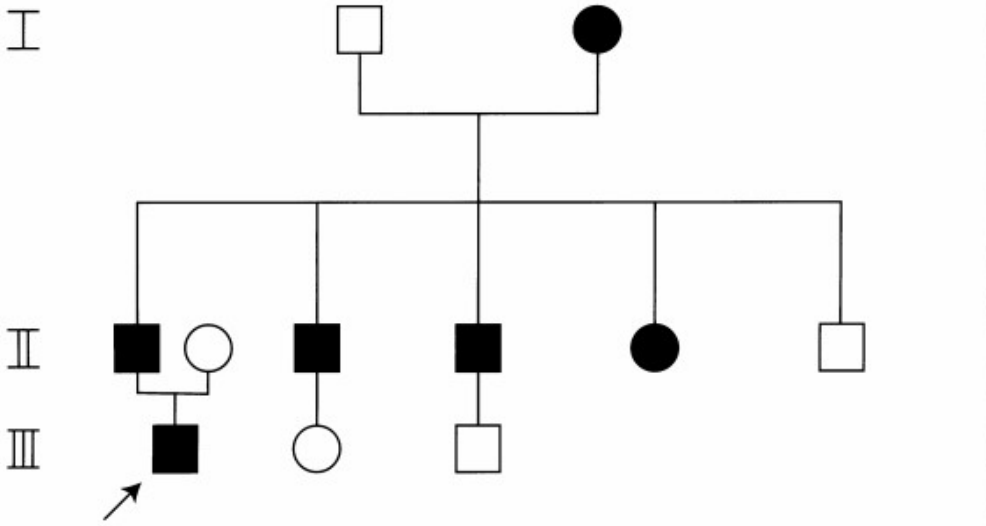
1. **Prevalence** in the reference population
2. Familial occurrence

Familial Clinodactyly of the Fifth Finger

Alexander K.C. Leung, MBBS, FRCPC, FRCP (UK & Ireland), FRCPCH; and C. Pion Kao, MD, FRCPC
Calgary, Alberta, Canada

We describe a caucasian family of which whom five members in three generations had clinodactyly of the fifth fingers. This report confirms that clinodactyly of the fifth finger can be transmitted as an autosomal dominant trait. (*J Natl Med Assoc.* 2003;95:1198–1200.)

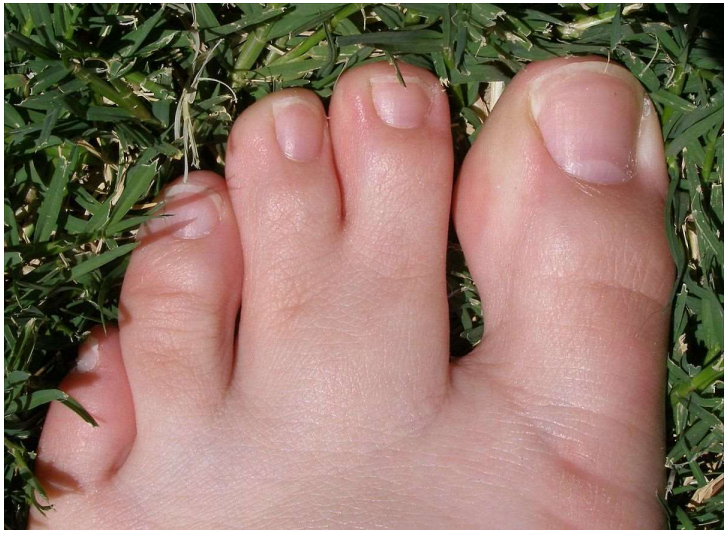
Figure 1. Pedigree of Affected Kinship

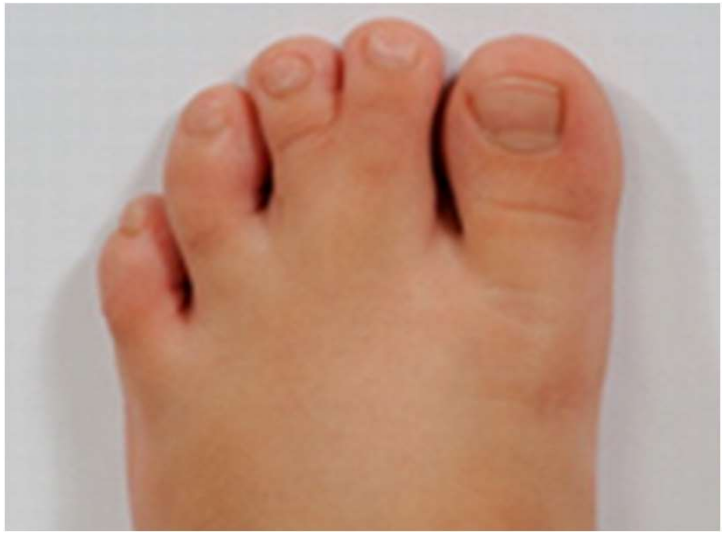


Arrow indicates proband. Black symbol means affected patient with bilateral clinodactyly of the fifth finger.

Common variant or rare anomaly ?

1. Prevalence in the reference population
2. Familial occurrence
3. Special subtypes



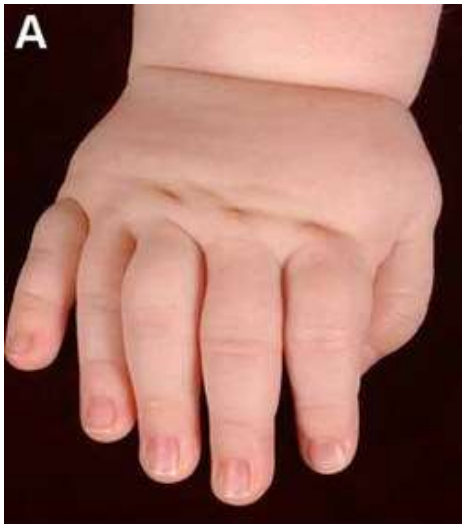


“V”-shaped 2-3 syndactyly

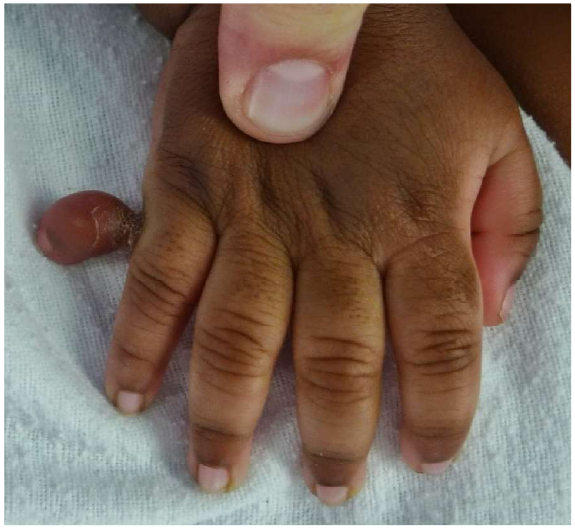
As seen in Smith-Lemli-Opitz

Common variant or rare anomaly ?

1. Prevalence in the reference population
2. Familial occurrence
3. Special subtypes



POSTAXIAL POLYDACTYLY



TYPE A
a fully formed digit

more often indicative of a syndrome

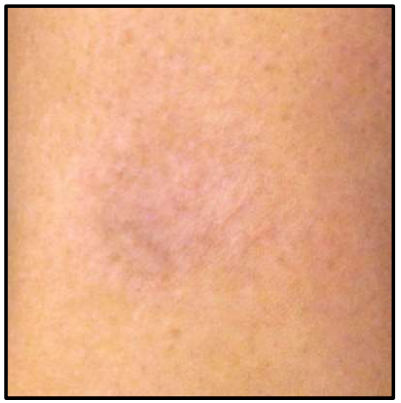
Type B (digitus minimus)
a pedunculated, non-articulating, non-functional appendage).

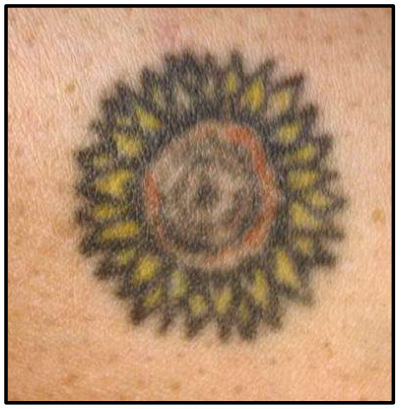
Isolated in 95% of affected newborns !
Often familial
Common in Africa (1,8% vs 0,12% in Caucasians)

Common variant or rare anomaly ?

1. Prevalence in the reference population
2. Familial occurrence
3. Special subtypes
4. **Acquired anomalies**





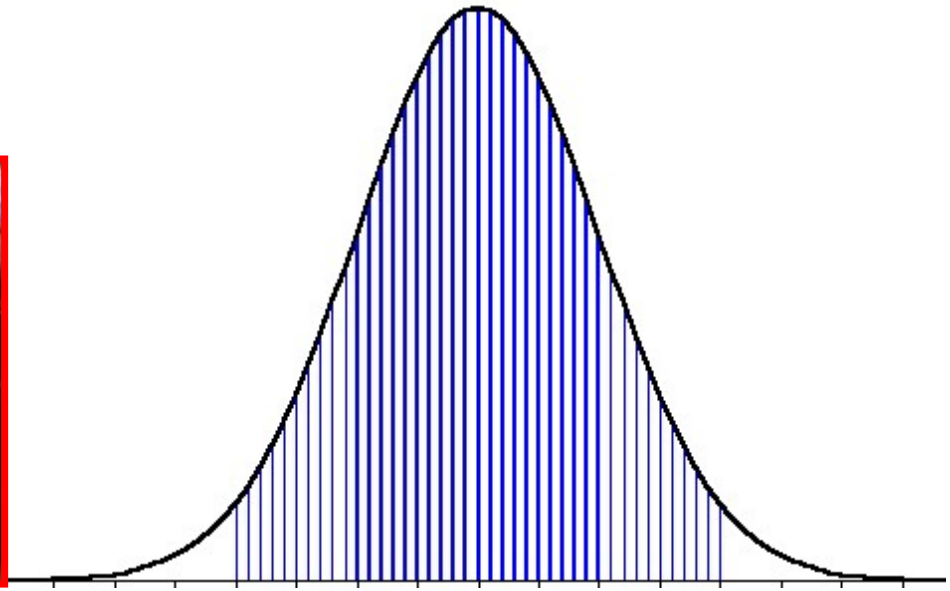



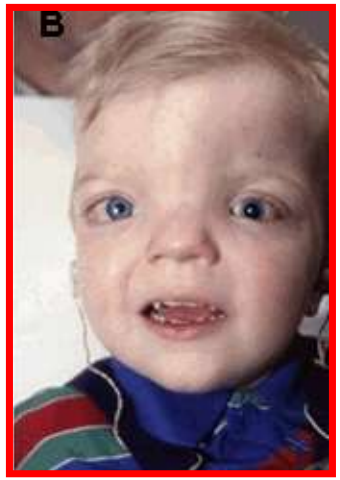
2. CONTINUOUS features

objective & measurable

normal

Distance between the eyes





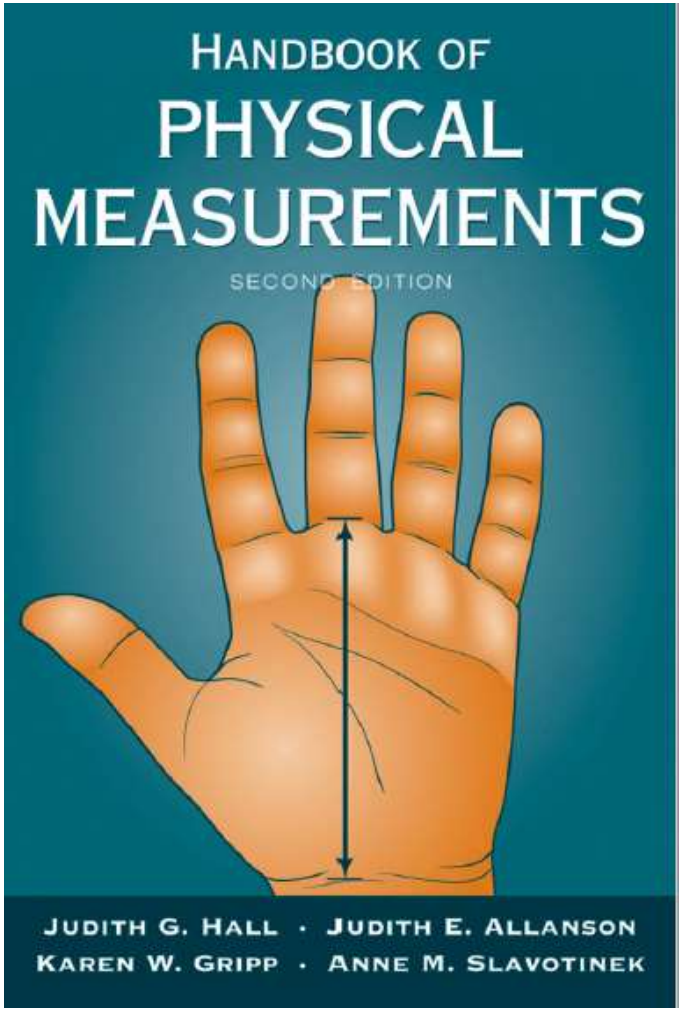
hypotelorism

abnormal = mean +/- 2SD

hypertelorism

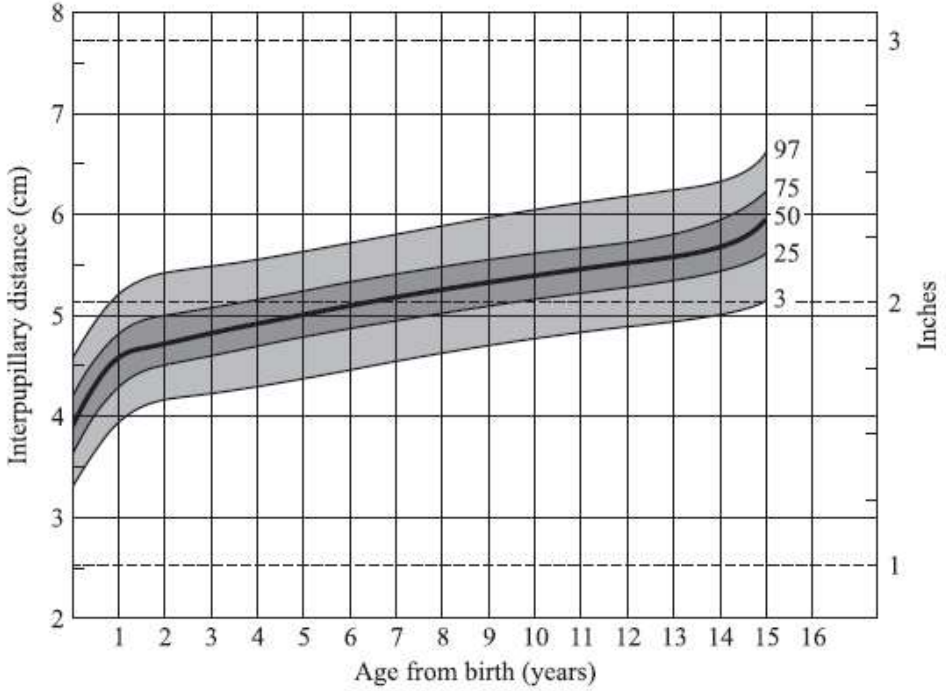
Anomaly or common variant ?

Normal values = reference charts



distance between the pupillae

Figure 7.41 Interpupillary distance, birth to 16 years. From Feingold and Bossert (1974), by permission.

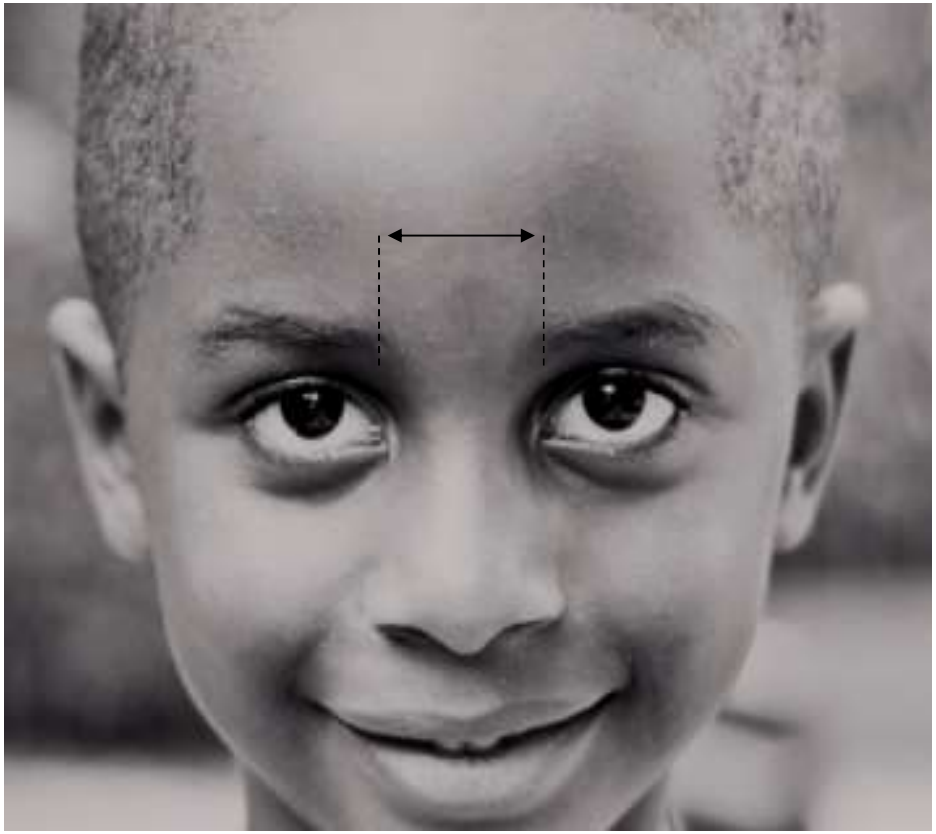


NOT ADEQUATE FOR AFRICANS !

Normal interpupillary distance

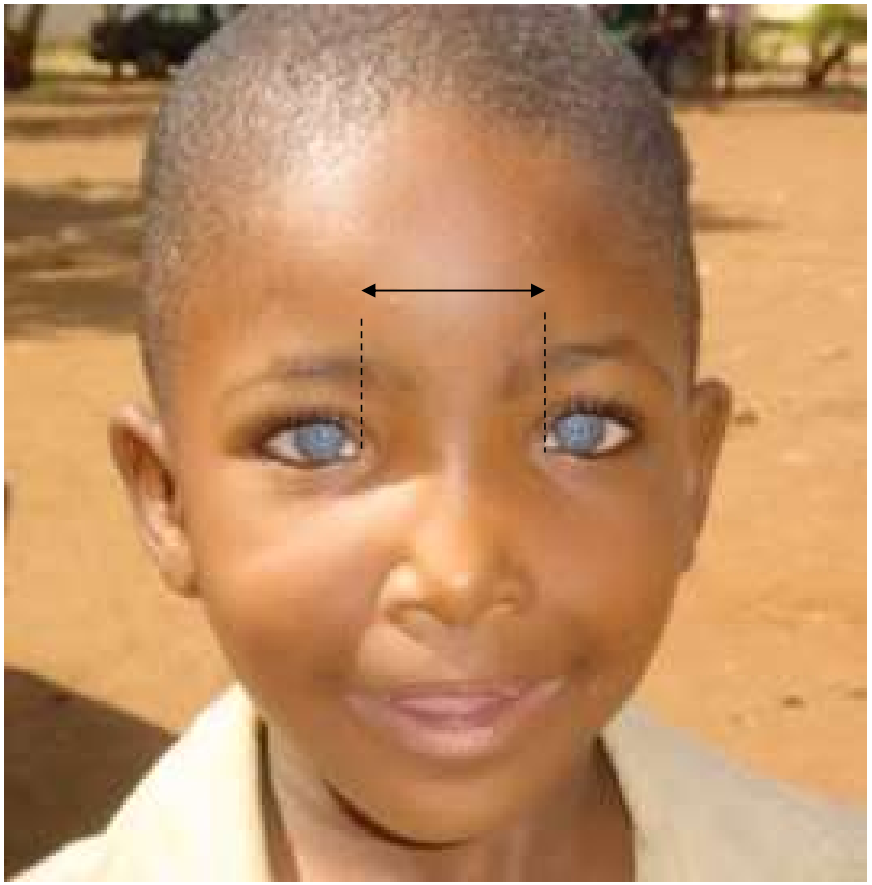
But eyes are not ‘normal’ ?

Distance between inner canthi (ICD)



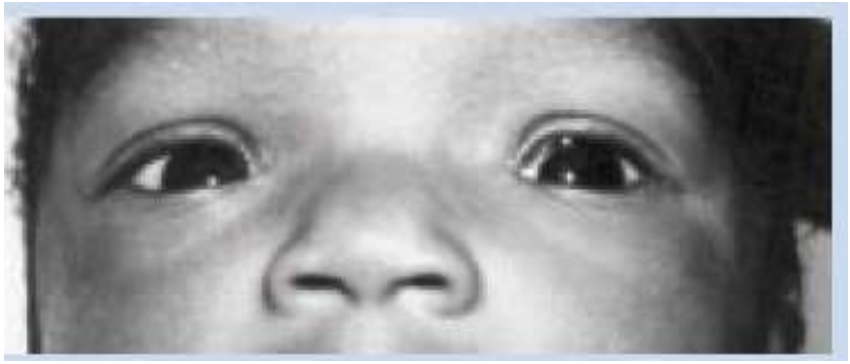
Distance between external canthi (OCD)

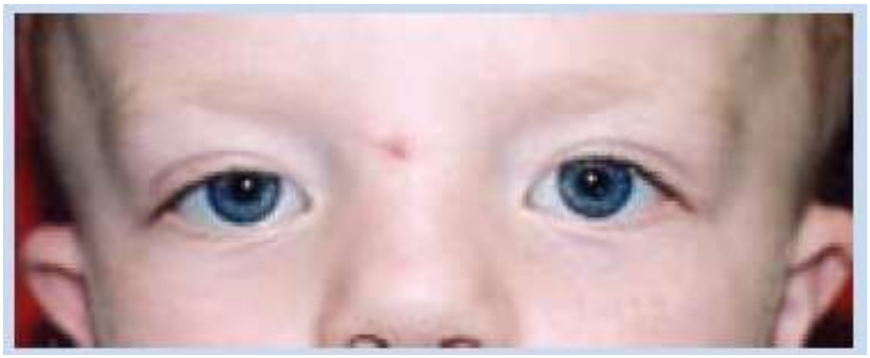
Normal interpupillary distance, but ….



Increased ICD
= lateral placement of inner canthi

= dystopia canthorum

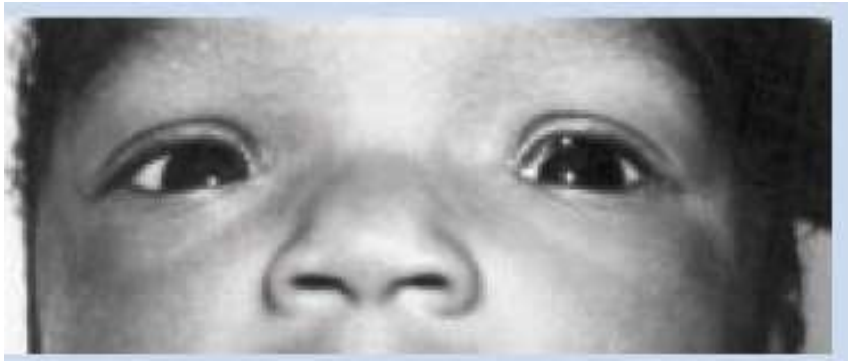




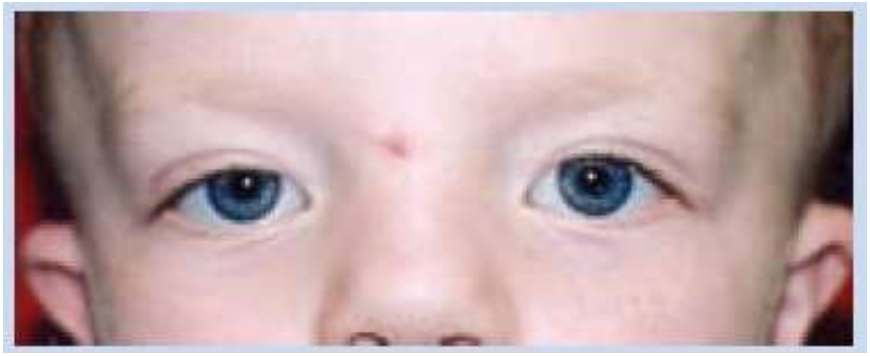
Hypertelorism?

Telecanthus

Telecanthus
and hypertelorism?



Telecanthus
and hypertelorism?

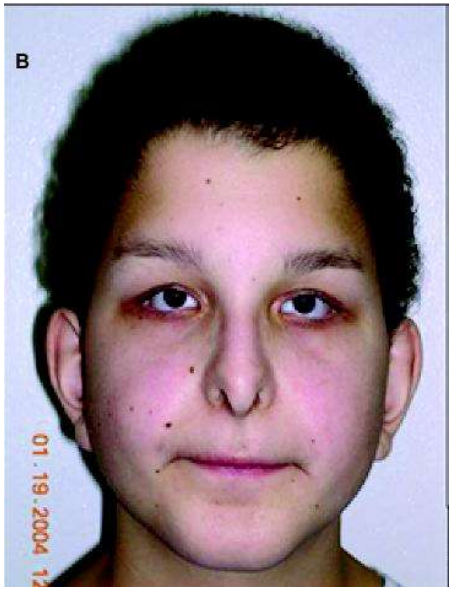


Hypertelorism?

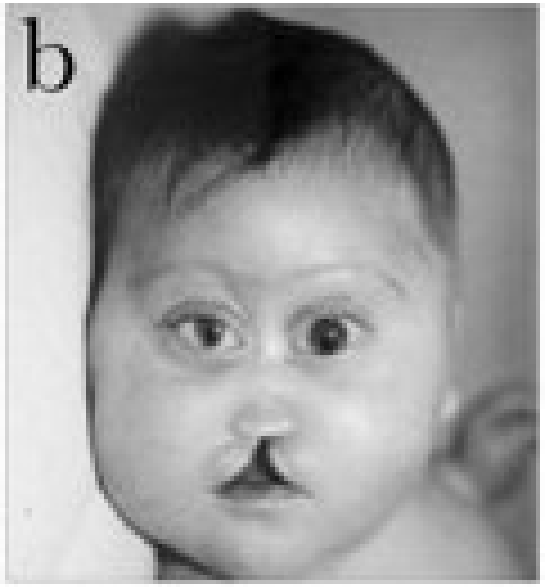
Telecanthus

PITFALLS

Which of these children has true hypotelorism ?



A



B

C

Pitfalls
CONTEXT IS IMPORTANT !

Large ears ?

Absolute value : no
Relative to microcephalic head circumference : yes

Head circumference in adults
Correction for height (>16j)

Archives of Disease in Childhood 1992; **67**: 1286–1287

Centiles for adult head circumference

K M D Bushby, T Cole, J N S Matthews, J A Goodship

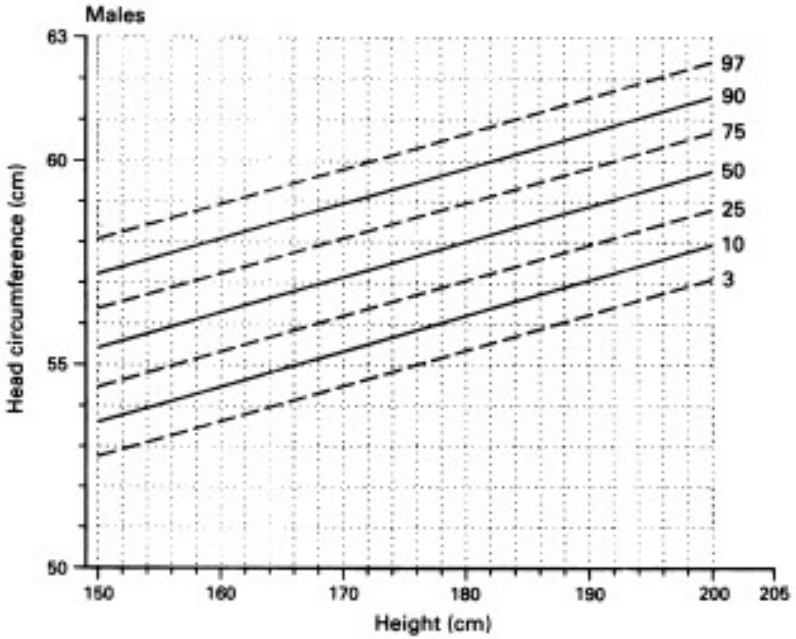


Figure 3 Centile chart for head circumference against height constructed from our data for use in adult males. For comparison, on the Tanner charts the 97th centile for head circumference for a boy of 16 years is 57·7 cm and the 50th centile 55 cm.

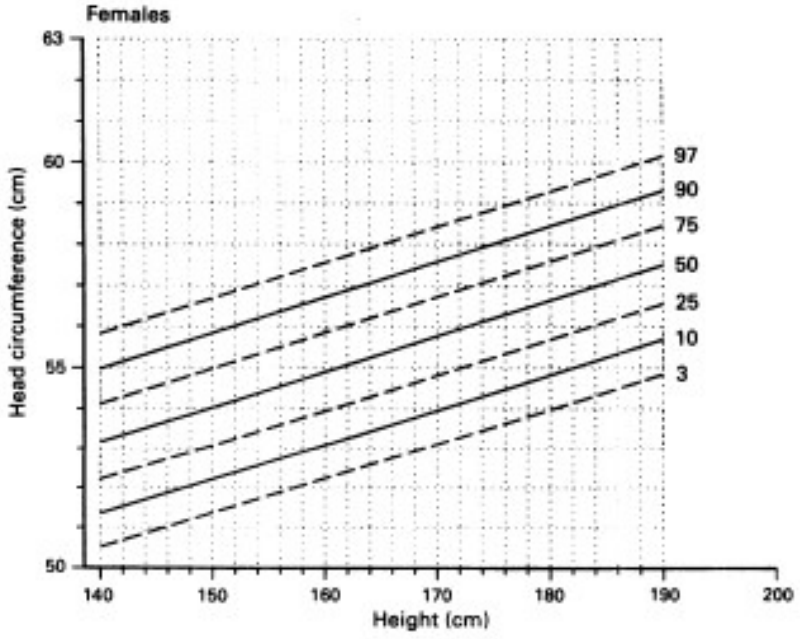


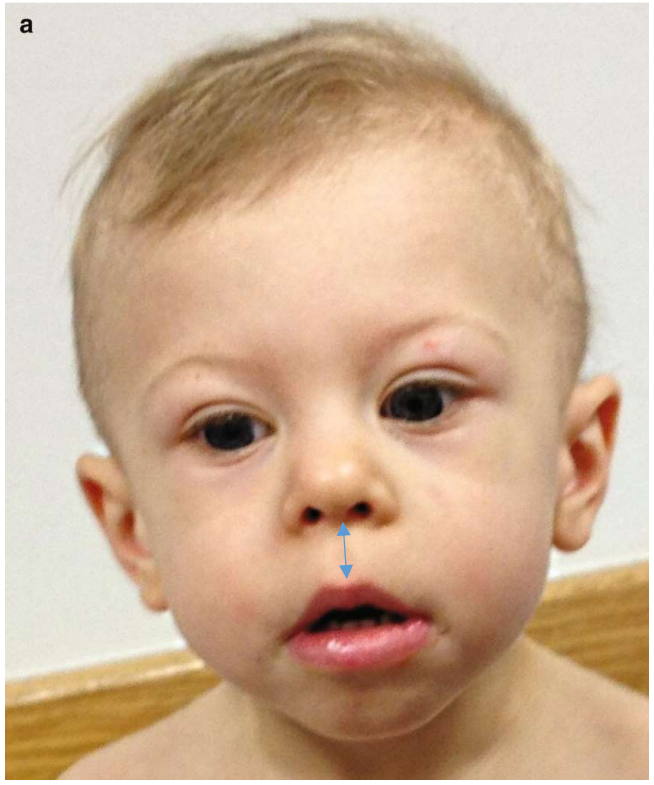
Figure 4 Centile chart for head circumference against height constructed from our data for use in adult females. For comparison, on the Tanner charts the 97th centile for a girl of 16 years is 56·4 cm and the 50th centile 54·2 cm.

Pitfalls

1. Context is important – relative versus absolute values
2. Neutral expression of the face

Philtum

- Length
- smoothness



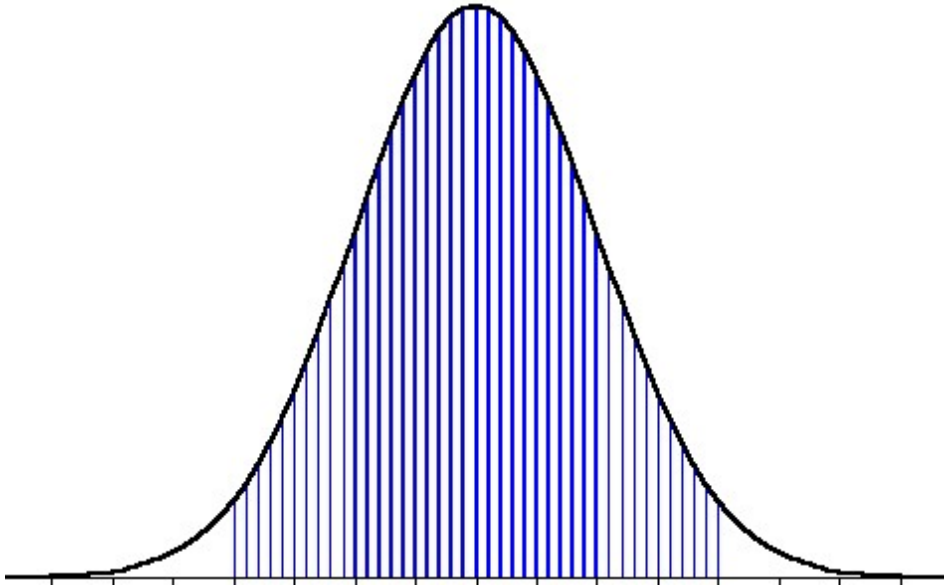
2. CONTINUOUS features

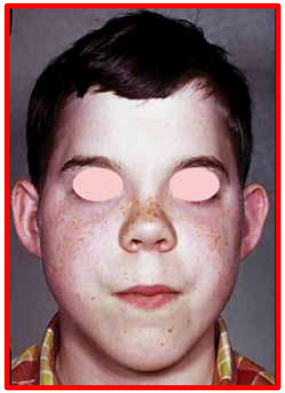
subjective

= not (easily) measurable

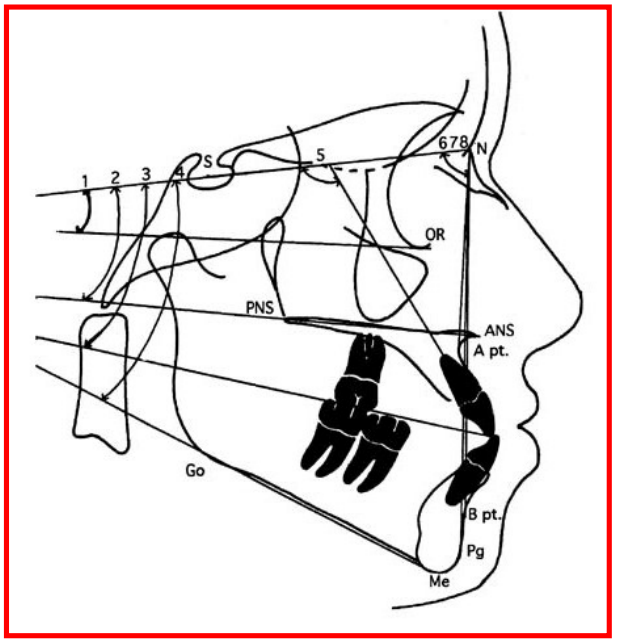
normal

Midfacial hypoplasia





Prominent midfacies


1
2
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S
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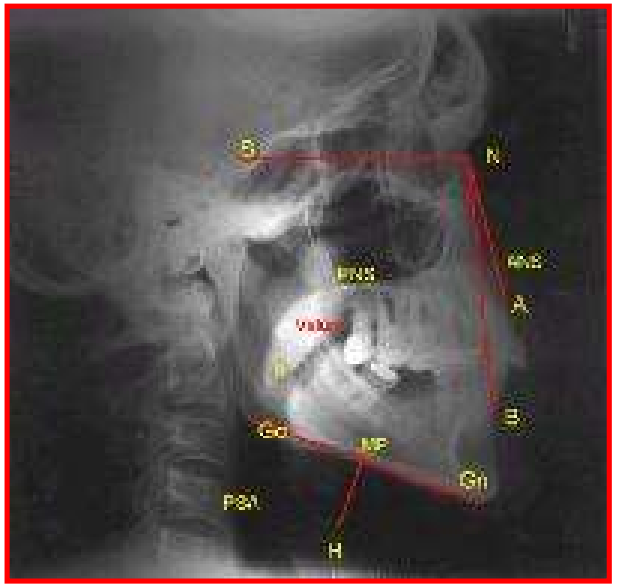
8
N
OR
PNS
ANS
A pt.
Go
B pt.
Pg
Me


S
N
PNS
ANS
A
Go
MP
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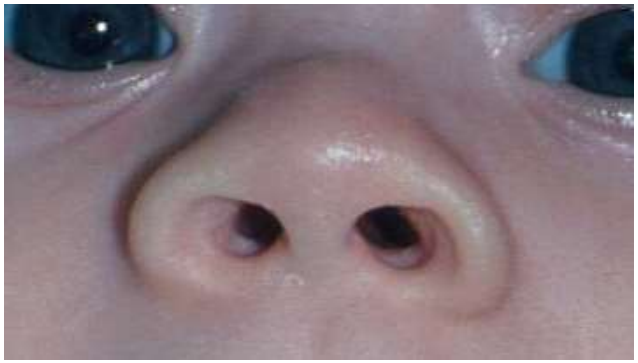
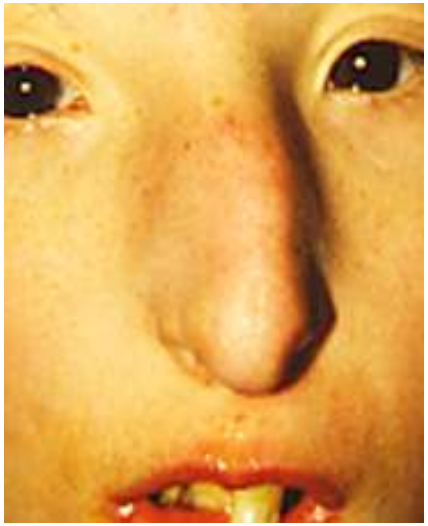
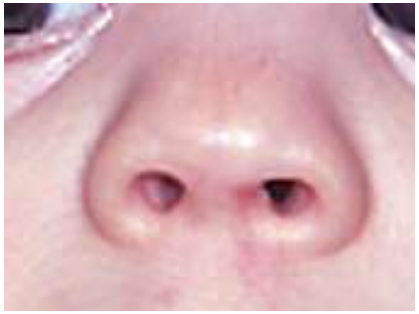
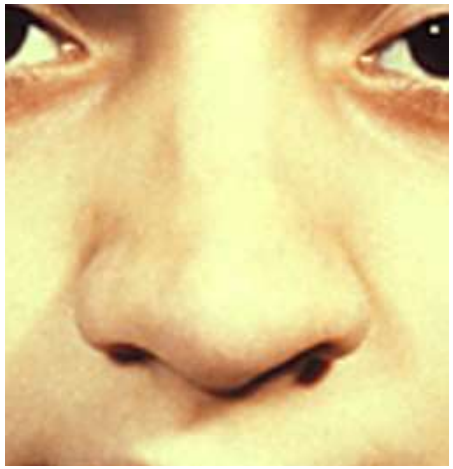
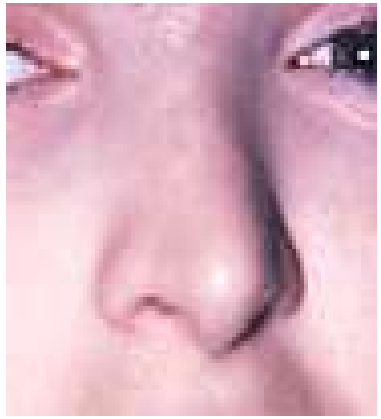
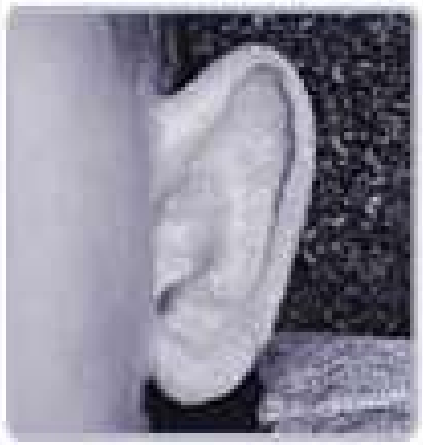
H

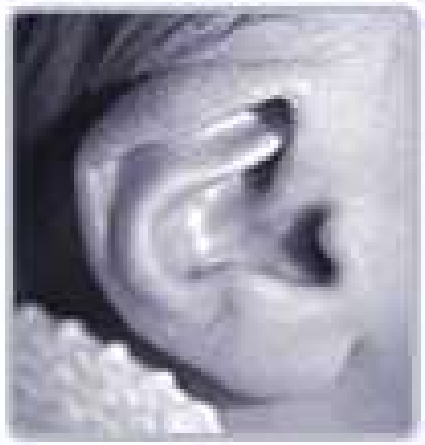






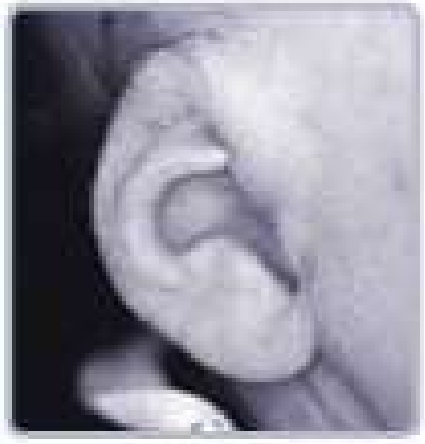
Bat ear

Lop ear

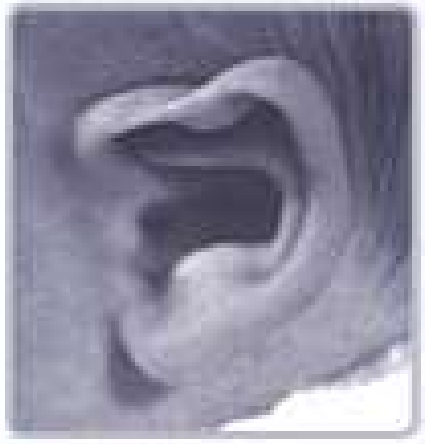


Cup deformity

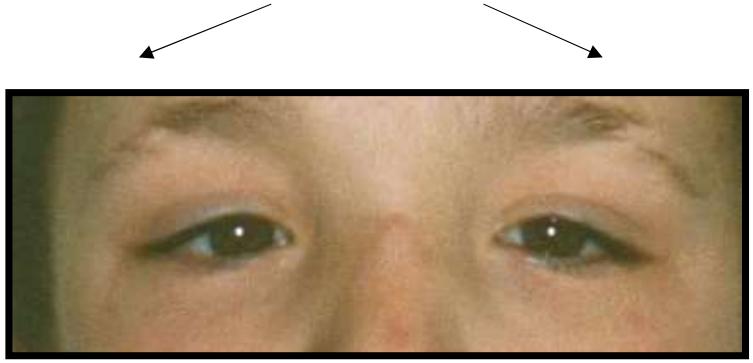
Stahl's bar



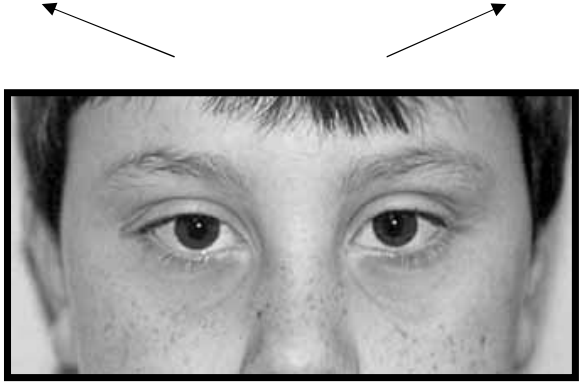
Cryptotia



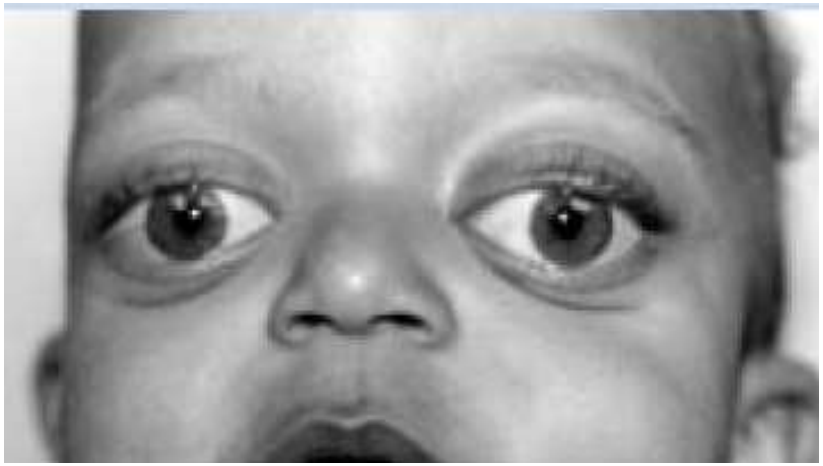
Rim kink



Downslant position of the eyes

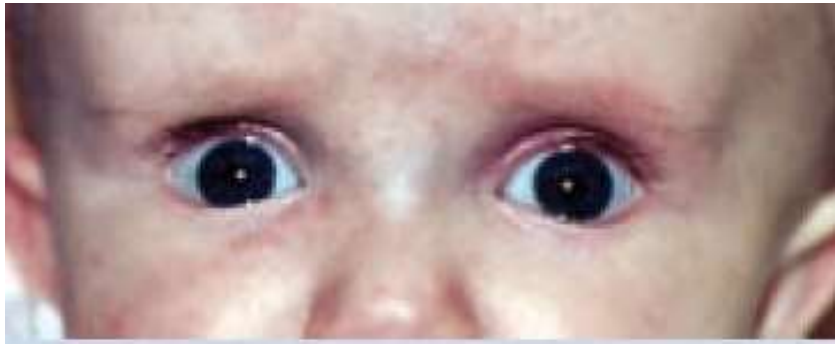


upslant position of the eyes



Proptosis

An eye that is protruding anterior to the plane of the face to a greater extent than is typical
Subjective
Synonym = prominent eyes



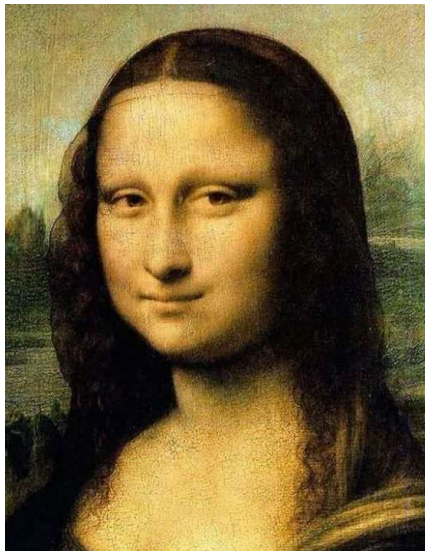
Eye, Deeply Set

An eye that is more deeply recessed into the plane of the face than is typical
Subjective
Synonym = sunken eyes

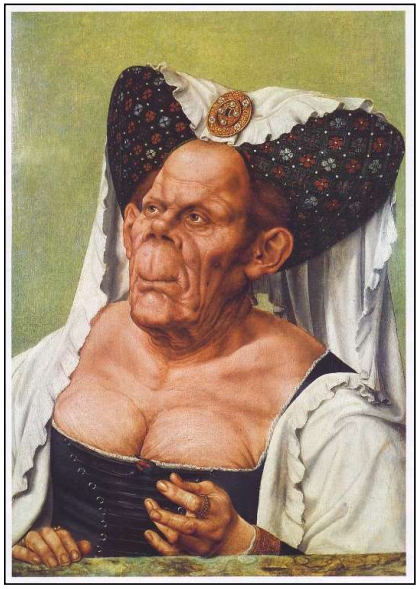
Deep plantar grooves

What is the value of minor anomalies?

1. Dysmorphism = multiple minor anomalies

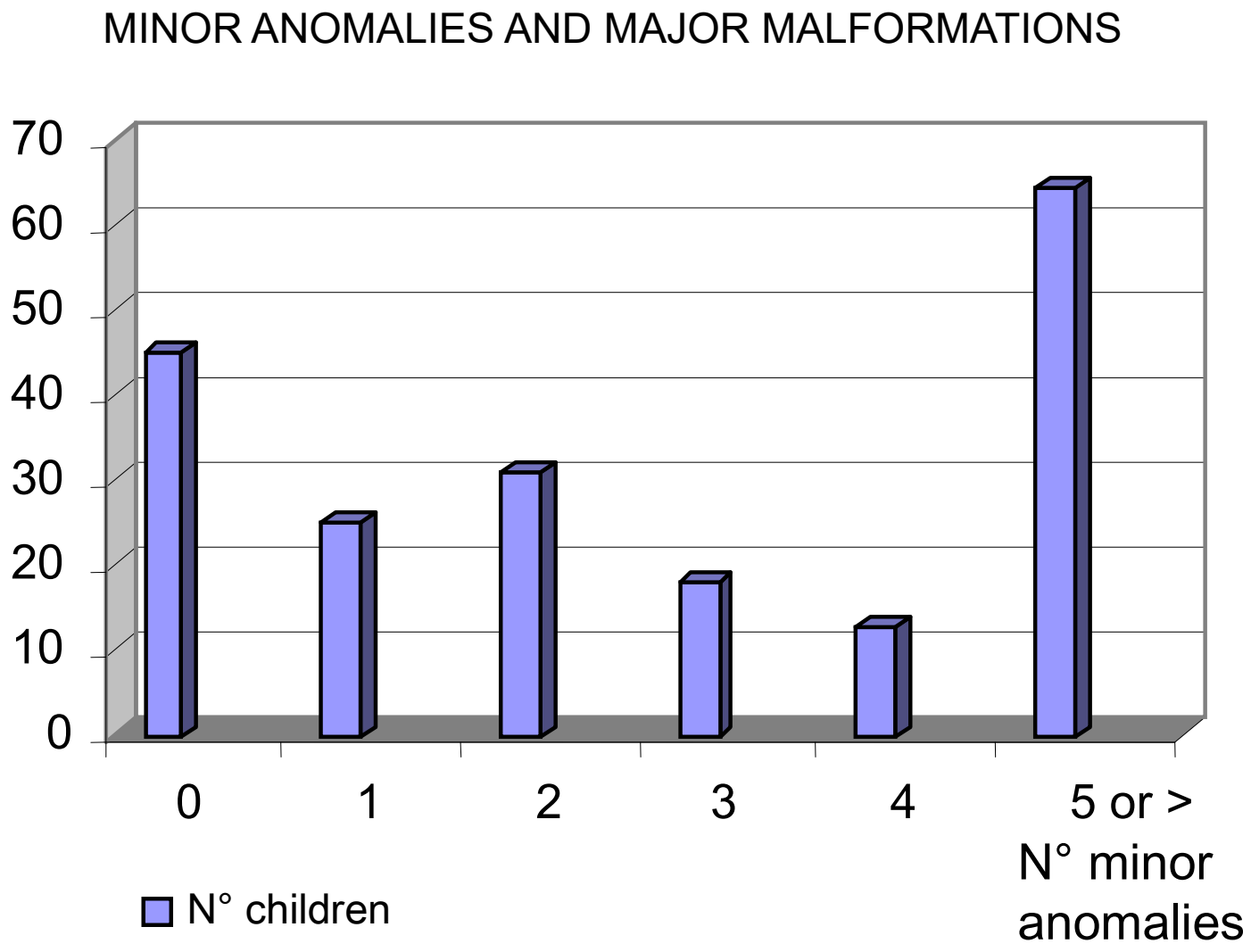


eumorph



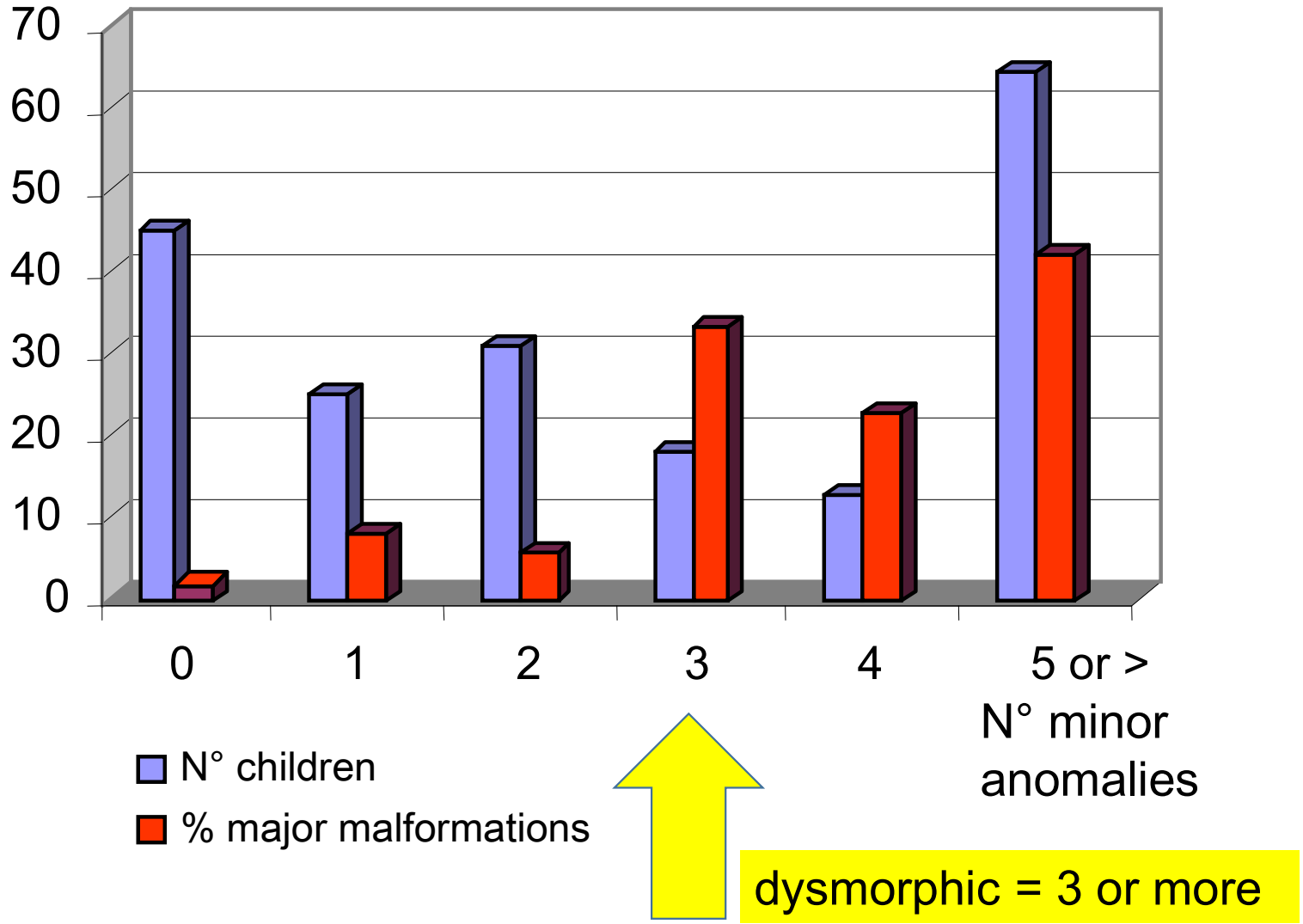
dysmorph

2. Number of minor anomalies correlates with risk of a major anomaly

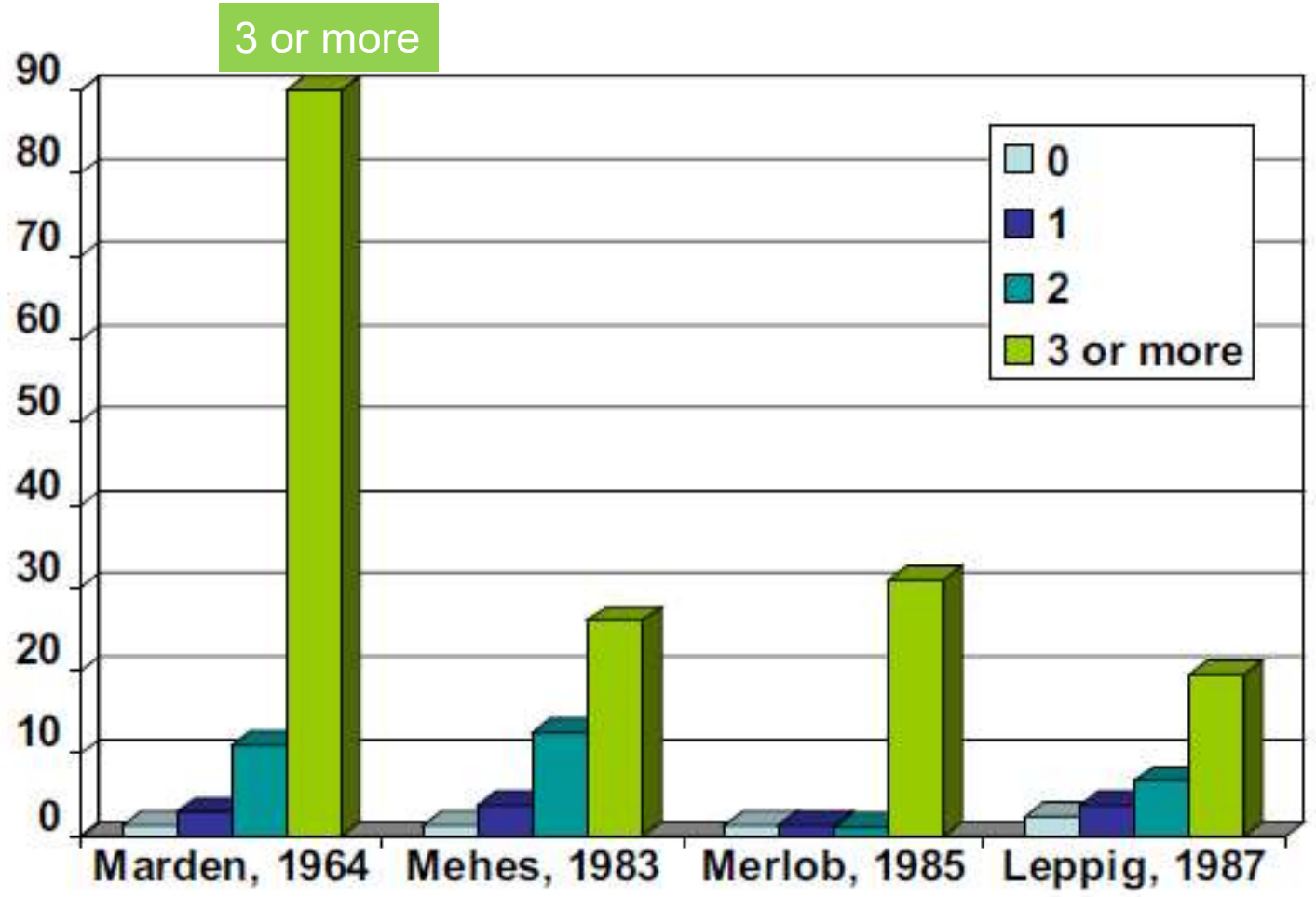


K. Devriendt & M. Holvoet in school for children with ID

MINOR ANOMALIES AND MAJOR MALFORMATIONS : abnormal development

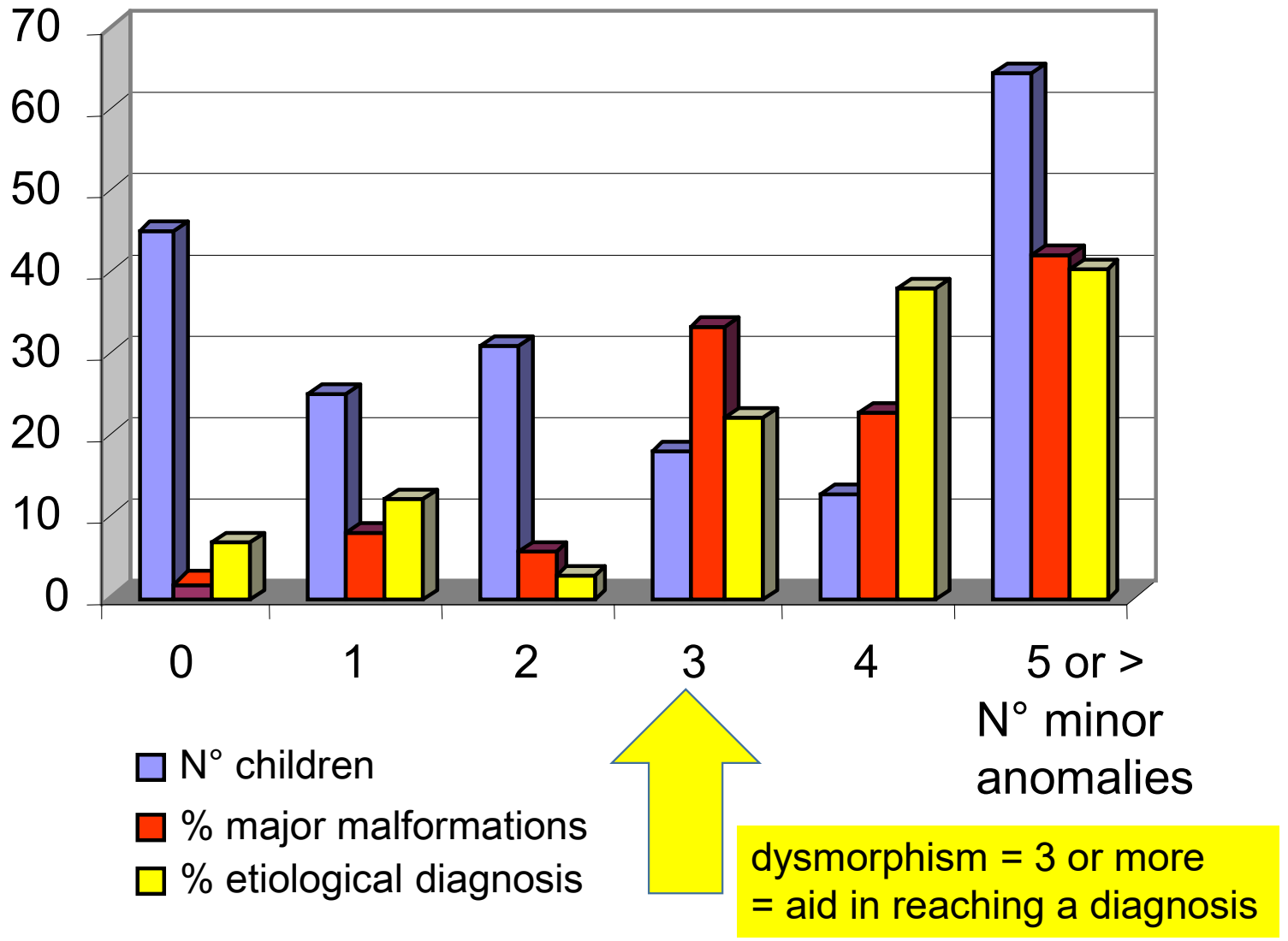


Risk for a major malformation depends on number of minor anomalies



Hennekam R. Seminar Fetal Neonat Medicine 2011:109-13.

minor anomalies and major malformations : chance of reaching an etiological diagnosis



“No one supposes that all the individuals of the same species are cast in the very same mould. These individual differences are highly important for us, as they afford materials for
natural selection to accumulate.”

Charles Darwin *: The Origin of Species*, 1859

*“ These individual differences are highly important for us, as they afford the dysmorphologist
to reach an etiological diagnosis”*

Klinisch Geneticus 2024

Array Comparative Genomic Hybridization as a Diagnostic Tool for Syndromic Heart Defects

Jeroen Breckpot, MD,* Bernard Thienpont, PhD,* Hilde Peeters, MD, PhD, Thomy de Ravel, MD, PhD, Amihood Singer, MD, Maissa Rayyan, MD, Karel Allegaert, MD, PhD, Prof, Christine Vanhole, MD, PhD, Prof, Benedicte Eyskens, MD, PhD, Prof, Joris Robert Vermeesch, PhD, Prof, Marc Gewillig, MD, PhD, Prof, and Koenraad Devriendt, MD, PhD, Prof*

Objectives To investigate different aspects of the introduction of array comparative genomic hybridization (aCGH) in clinical practice.

Study design A total 150 patients with a syndromic congenital heart defect (CHD) of unknown cause were analyzed with aCGH at 1-Mb resolution. Twenty-nine of these patients, with normal results on 1Mb aCGH, underwent re-analysis with 244-K oligo-microarray. With a logistic regression model, we assessed the predictive value of patient characteristics for causal imbalance detection. On the basis of our earlier experience and the literature, we constructed an algorithm to evaluate the causality of copy number variants.

Results With 1-Mb aCGH, we detected 43 structural variants not listed as clinically neutral polymorphisms, 26 of which were considered to be causal. A systematic comparison of the clinical features of these 26 patients to the remaining 124 patients revealed dysmorphism as the only feature with a significant predictive value for reaching a diagnosis with 1-Mb aCGH. With higher resolution analysis in 29 patients, 75 variants not listed as clinically neutral polymorphisms were detected, 2 of which were considered to be causal.

Conclusions Molecular karyotyping yields an etiological diagnosis in at least 18% of patients with a syndromic CHD. Higher resolution evaluation results in an increasing number of variants of unknown significance. *(J Pediatr 2010;156:810-7)*.

two children with autism spectrum disorder

Who is most likely to get an etiological diagnosis ?

The science behind the art of dysmorphology