OMCeO Udine

Il paziente di aspetto “strano”

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Regole per tutte le stagioni

① Tratti peculiari del volto possono associarsi ad anomalie congenite multiple e/o a disordini del neurosviluppo. In particolare nei casi di disabilità intellettiva e di ritardo globale dello sviluppo, siano essi isolati o sindromici e ricorrenti o singoli, oggigiorno la moderna genetica di laboratorio consente di giungere a una diagnosi eziologica più o meno una volta su due.

② La buona pratica (ma anche le norme di legge vigenti in Italia) vorrebbe che i test genetici richiesti per le indicazioni appena menzionate, al pari della gran parte degli altri scenari clinici, siano preceduti e/o seguiti o da una visita di genetica clinica o da un counseling mirato, in rapporto al preciso quesito diagnostico e alla locale disponibilità di idonee figure professionali.

③ Alcuni test genetici forniscono quasi sempre risposte di interpretazione immediata e chiara. Il più delle volte, però, l'interpretazione dei risultati delle analisi di laboratorio di più recente introduzione richiede un vasto background tecnico e un notevole impegno di tempo. Ci limiteremo, per semplicità, a sottolineare che l'equazione "presenza all'interno di un referto di varianti genetiche non specificate" = "diagnosi certa e definitiva di malattia genetica" è sbagliata.

Definizioni

The term *dysmorphology* was first coined by David Smith (USA) in 1960s. It implies the study of human congenital defects and abnormalities of body structure. The term *dysmorphic* is used to describe individuals whose physical features are not usually found in other individuals of the same age, sex and ethnic background. "Dys" = disordered or abnormal and "Morph" = shape.

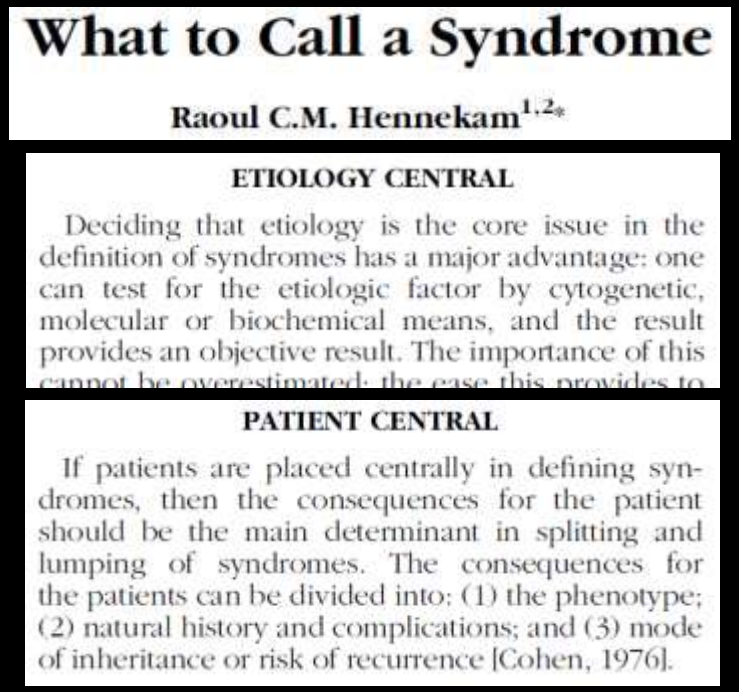
dys·mor·phic (dis-mor'fik) 1. pertaining to dysmorphology. 2. characterized by dysmorphism (def. 1); malformed.

dys·mor·phism (dis-mor'fiz-əm) [*dys-* + *morph-* + *-ism*] 1. an abnormality in morphologic development, such as a malformation in an organ. 2. allomorphism. 3. ability to appear in different morphological forms.

dys·mor·phol·o·gist (dis"mor-fol'ə-jist) a specialist in dysmorphology.

dys·mor·phol·o·gy (dis"mor-fol'ə-je) [*dys-* + *morpho-* + *-logy*] a branch of clinical genetics concerned with the diagnosis and interpretation of patterns of the three types of structural defects—malformation, disruption, and deformation (qq.v.)

Dorland's Illustrated Medical Dictionary, 32nd ed.



What to Call a Syndrome

Raoul C.M. Hennekam[1,2]*

ETIOLOGY CENTRAL

Deciding that etiology is the core issue in the definition of syndromes has a major advantage: one can test for the etiologic factor by cytogenetic, molecular or biochemical means, and the result provides an objective result. The importance of this cannot be overestimated; the case this provides to

PATIENT CENTRAL

If patients are placed centrally in defining syndromes, then the consequences for the patient should be the main determinant in splitting and lumping of syndromes. The consequences for the patients can be divided into: (1) the phenotype; (2) natural history and complications; and (3) mode of inheritance or risk of recurrence [Cohen, 1976].

About 3% of all children born will have a significant congenital malformation (high burden of morbidity, mortality, disability and hospital admissions).

Single minor anomaly: 15% of all newborns, 3% have an associated major anomaly. Two minor anomalies: less common, 11% have an associated major anomaly.

Three or more minor anomalies: unusual (1%), 90% have an associated major anomaly

40% of idiopathic ID is associated w/ 3 or more anomalies (80% minor).

External minor anomalies in the head and neck region and in the hands = 70% of all minor anomalies.

Definizioni: terminologia standard(izzata)

Volume 149A, Issue 1

Special Issue: Elements of Morphology: Standard Terminology

Pages: 1-127

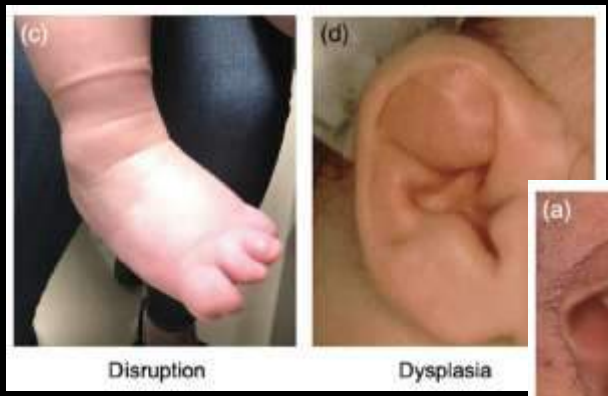
January 2009

Elements of morphology: Standard terminology for the teeth and classifying genetic dental disorders

Elements of morphology: Standard terminology for the external genitalia

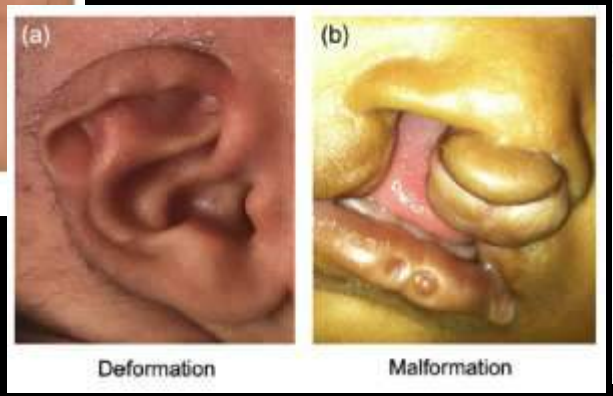
TABLE I. Nomenclature Subgroups and Their Members (the Chair of Each Group Is in Italics)

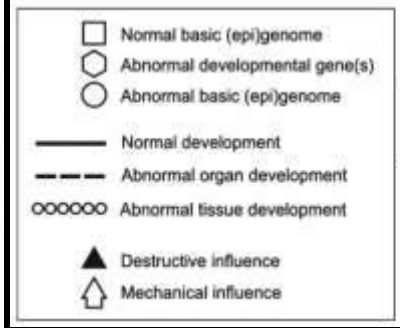
Head and Face: *Judith E. Allanson*, Chris Cunniff, Gene Hoyme, Julie McGaughran, Max Muenke, Giovanni Neri
Hands and Feet: *Leslie G. Biesecker*, Jon M. Aase, Carol Clericuzio, Fiorella Gurrieri, Karen Temple, Helga Toriello
Mouth: *John C. Carey*, M. Michael Cohen Jr, Cynthia Curry, Koen Devriendt, Lewis Holmes, Alain Verloes
Ear: *Alasdair G. W. Hunter*, Jaime Frias, Gabrielle Gillessen-Kaesbach, Ken Jones, Helen Hughes, Louise Wilson
Periorbital structures: *Bryan D. Hall*, John M. Graham Jr, Suzanne B. Cassidy, John M. Opitz
Nose and Philtrum: *Raoul C. M. Hennekam*, Valerie Cormier-Daire, Judith G. Hall, Karoly Méhes, Michael Patton, Roger Stevenson

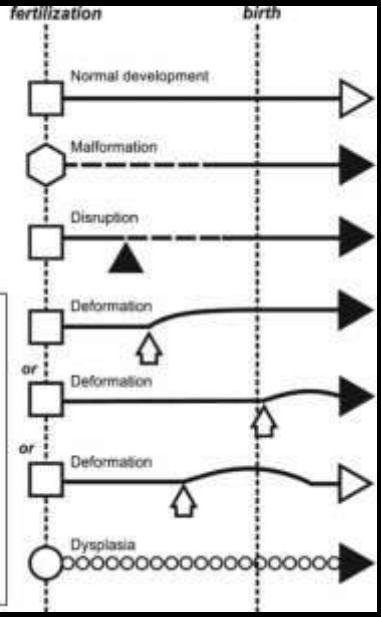


Elements of Morphology: General Terms for Congenital Anomalies

Raoul C. Hennekam,[1]* Leslie G. Biesecker,[2] Judith E. Allanson,[3] Judith G. Hall,[4] John M. Opitz,[5] I Karen Temple,[6] John C. Carey,[5] and Elements of Morphology Consortium







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Human Malformation Terminology

- Human Malformation Terminology Home Page
- Head and Face Terminology
- Periorbital Region Terminology
- Ear Terminology
- Nose and Philtrum Terminology
- Lips, Mouth, and Oral Region Terminology
- Hands and Feet Terminology
- References

Epicanthus

Definition:

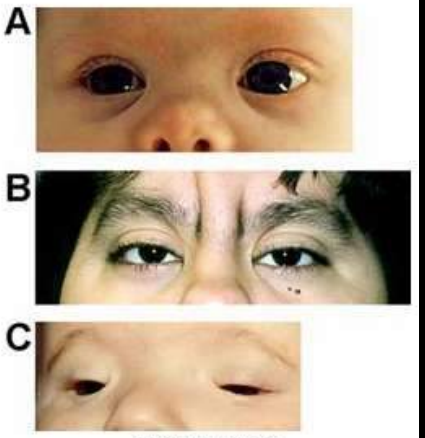
Subjective: A fold of skin starting above the medial aspect of the upper eyelid and arching downward to cover, pass in front of and lateral to the medial canthus

Comments:

In extreme cases, the skin fold can start as high as the eyebrow [Hall et al., [2007]]. This is called epicanthus superciliaris.

Synonyms:

- Epicanthal Fold
- Epicanthus Palpebralis



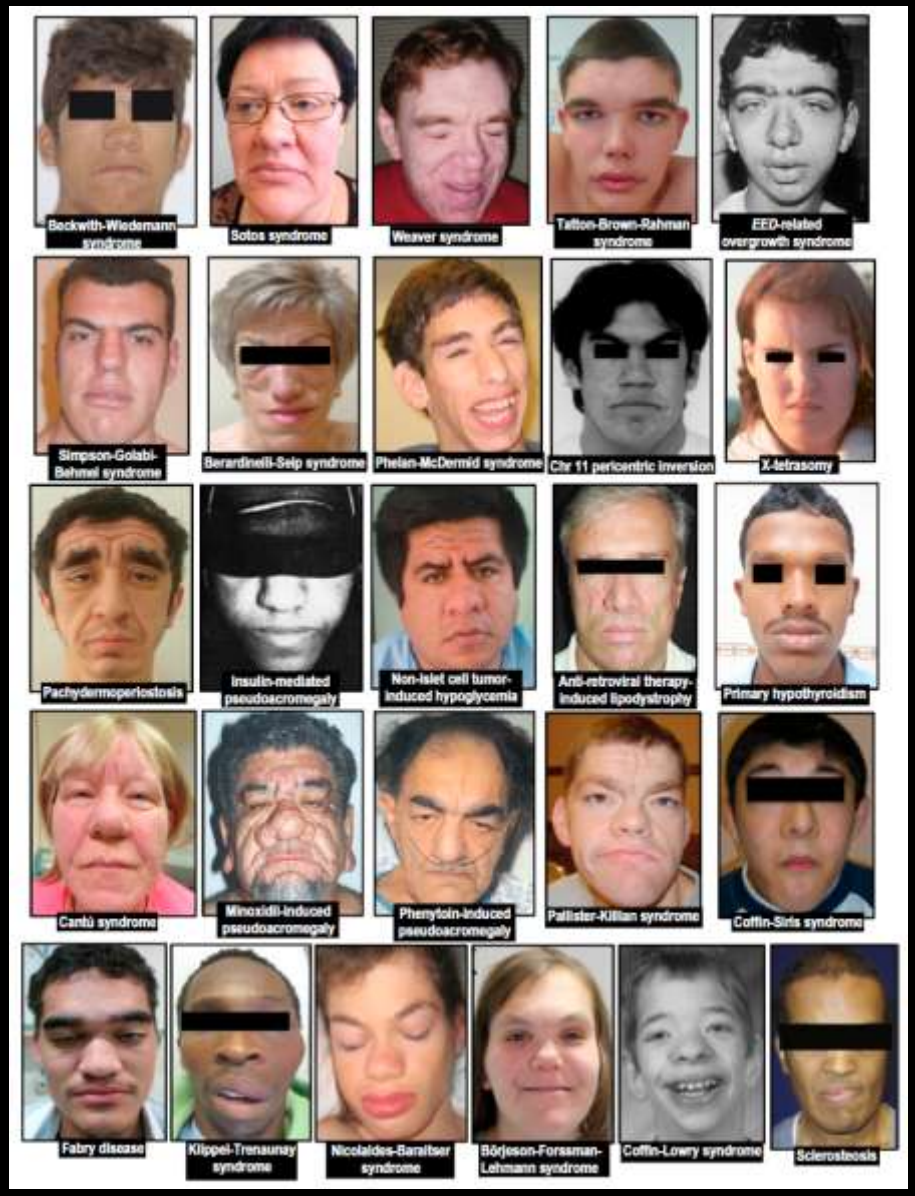
Epicanthal Fold

Table 1 Epicanthal fold classification

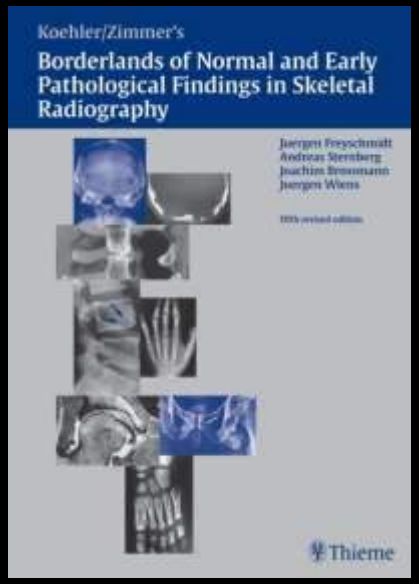
	Types	Description	Patterns
Type I	Epicanthus supraciliaris	The pretarsal fold runs parallel to the upper eyelid margin	
Type II	Epicanthus tarsalis	The upper eyelid skin covers the tarsal border and the lacrimal lake partially as it converges at the medial canthus	
Type III	Epicanthus palpebralis	The upper eyelid skin completely covers the lacrimal lake and the medial angle of the palpebral fissure	
Type IV	Epicanthus inversus	The lower eyelid skin covers the lacrimal lake, creating a reverse epicanthal fold	

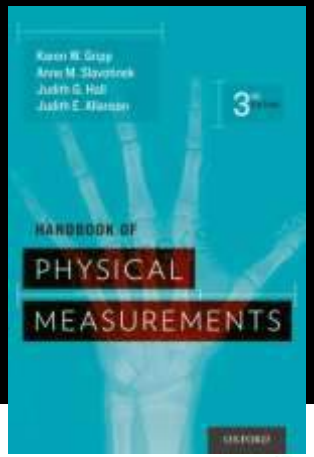
Duke-Elder, 1952

Coarse face: what's in a name?



Tracciare i confini della normalità





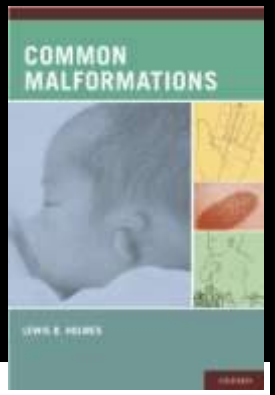
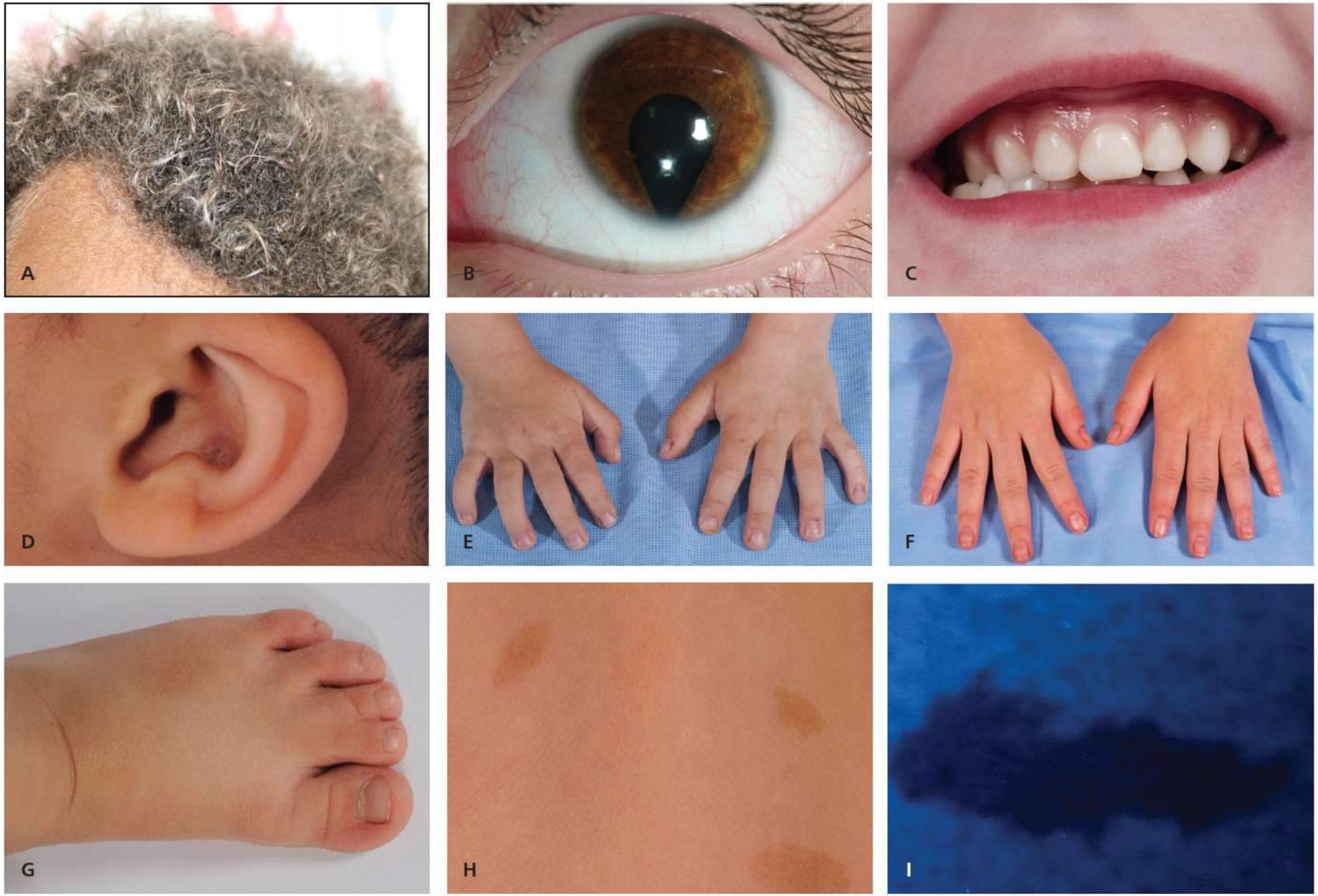


TABLE 25-3 *Incidence of minor physical features among 7,157 newborn infants*

		White		Black		Latin		Mixed Racial	
Physical Feature	All Races	Males	Females	Male	Female	Male	Female	Male	Female
HEAD									
Frontal bossing	0.4% 25/7112	0.3% 7/2191	0.4% 9/2091	0.2% 1/469	0.5% 2/443	0.5% 1/223	0.5% 1/188	0 0/691	0.6% 4/659
Keel-shaped brow	0.01 1/7110	0 0/2192	0 0/2089	0 0/469	0 0/443	0 0/223	0.5 1/188	0 0/619	0 0/658
Flat brow	0.01 1/7114	0.05 1/2191	0 0/2090	0 0/469	0 0/443	0 0/223	0 0/189	0 0/619	0 0/661
Prominent occiput	3.4 246/7148	3.9 86/2199	3.4 71/2100	3.2 15/470	2.9 13/447	2.7 6/224	1.6 3/189	4.3 27/623	3.3 22/666
Flat occiput	0.1 7/7112	0.05 1/2189	0.1 3/2091	0 0/469	0 0/442	0 0/223	0.5 1/189	0.2 0/619	0 0/661
Metopic suture palpable	59.8 4072/6813	63.7 1340/2105	65.3 1319/2020	41.7 187/449	43.4 183/422	53.3 112/210	46.1 83/180	58.6 340/580	60.3 377/625
Metopic suture open to glabella	1.0 71/6856	1.0 21/2120	0.4 8/2030	1.8 8/451	3.5 15/424	1.0 2/210	1.7 3/182	0.7 4/584	1.3 8/632
Metopic fontanel	0.2 13/6809	0.3 6/2099	0.3 5/2024	0 0/450	0 0/420	0.5 1/210	0 0/181	0 0/579	0.2 1/625
Third sagittal fontanel	6.0 306/5122	4.0 65/1616	4.9 79/1542	13.6 48/352	13.8 40/290	7.8 13/167	6.5 9/139	3.6 15/413	7.0 30/430
Scalp defect	0.06 4/7110	0.05 1/2189	0.1 2/2090	0 0/469	0 0/443	0 0/220	0.5 1/189	0 0/619	0 0/660
Double whorl of hair	7.4 523/7111	7.4 161/2190	7.0 140/2089	6.2 29/469	6.1 27/443	10.8 24/222	10.6 20/189	8.4 52/619	7.9 52/661
Triple whorl of hair	0.4 19/4833	0.3 5/1534	0.2 3/1456	0.6 2/338	0 0/275	0.6 1/159	2.2 3/134	0.5 2/379	0.8 3/395
Absent whorl	0.9 43/4826	0 0/1531	0 0/1455	5.3 18/337	8.4 23/275	0 0/159	0 0/134	0 0/378	0.3 1/394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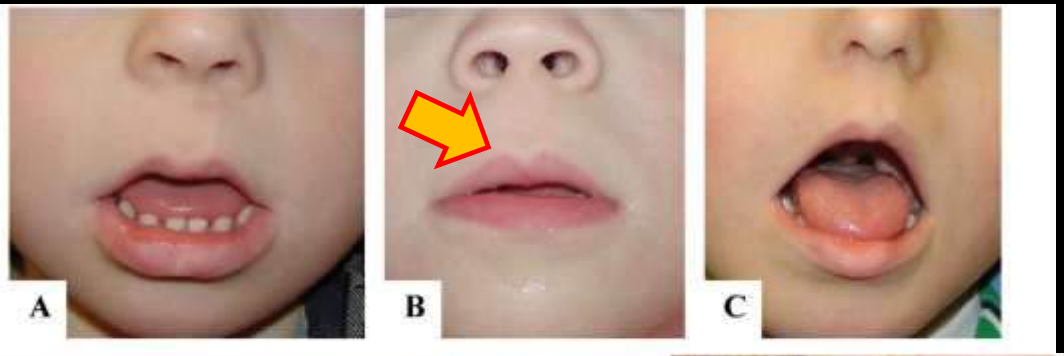
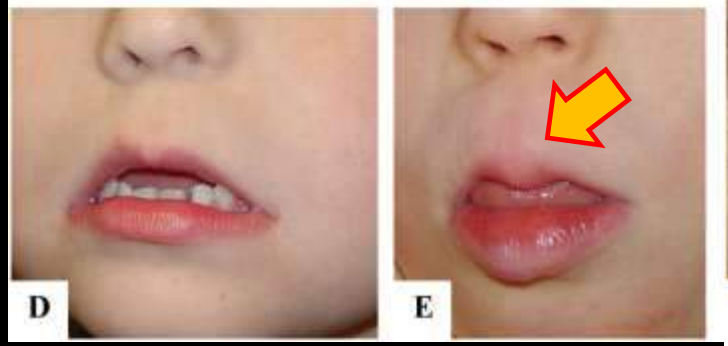
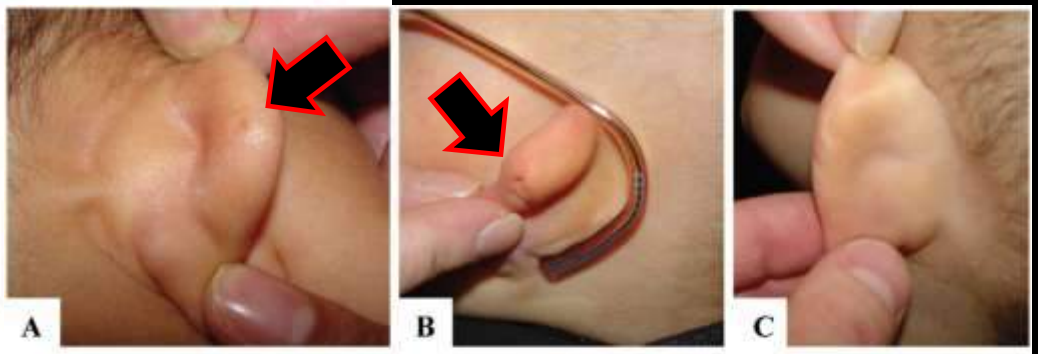
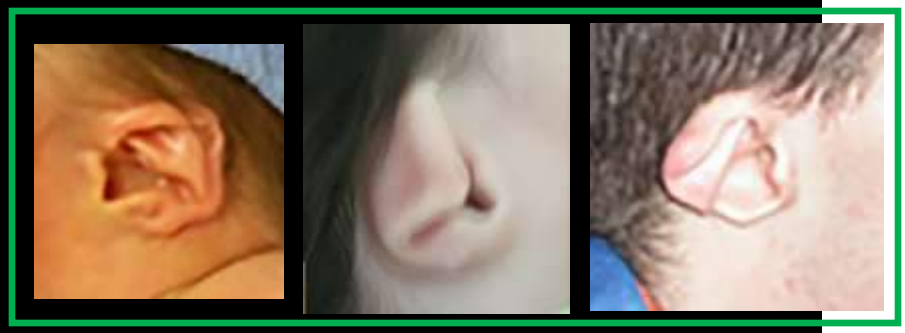








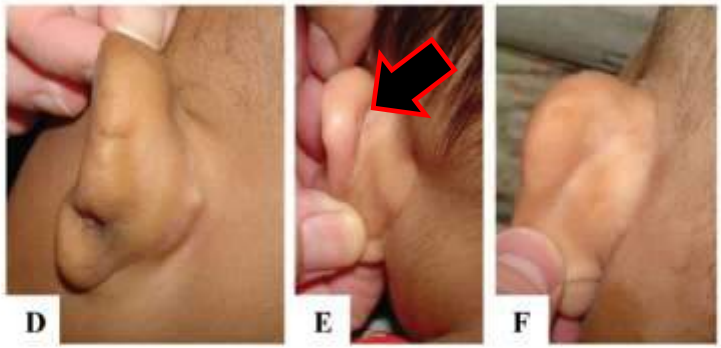
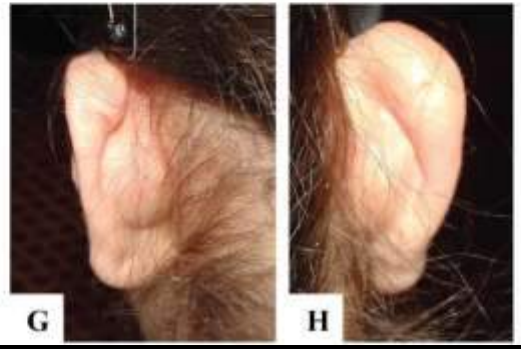
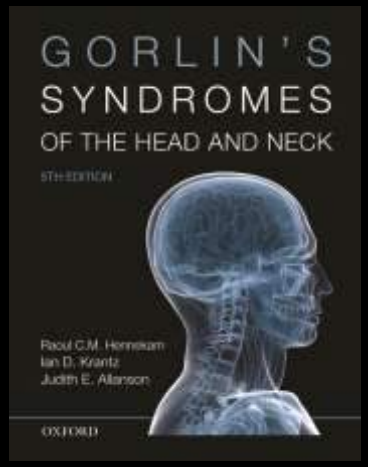


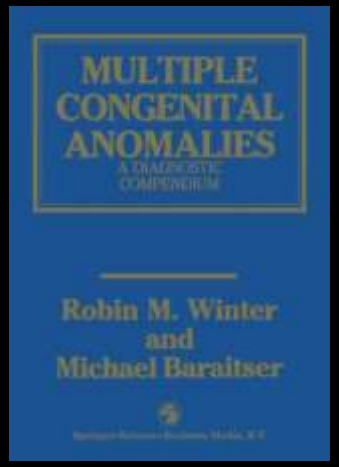
TABLE 1 Top distinguishing features or trigger words of common conditions seen in genetics

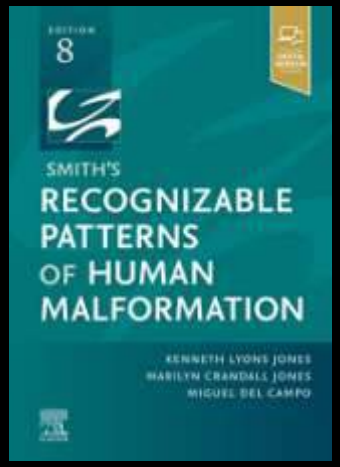
Voice	
Cat-like cry	Cri Du Chat
Harsh, brassy, or hoarse voice	Williams syn
Hypernasal voice	22q11.2 Del
Head/face	
Triangular facies	Russell-Silve

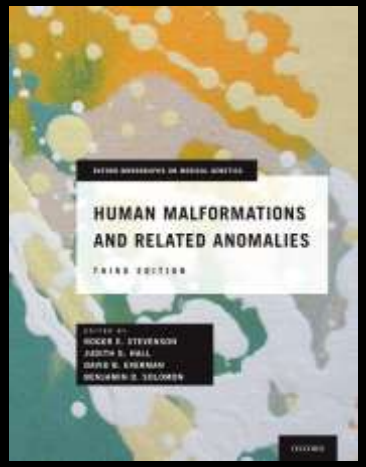


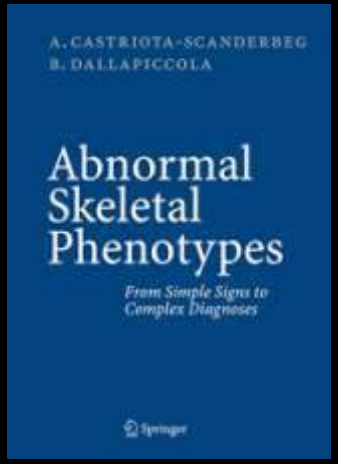
Delineare la malattia

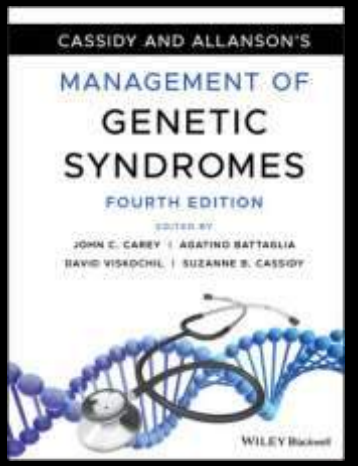


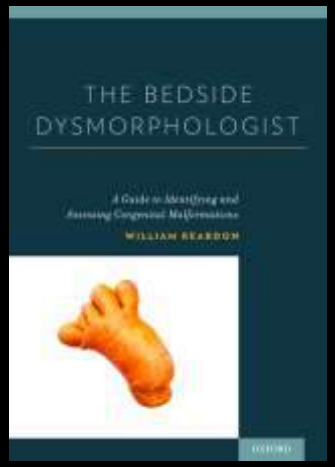


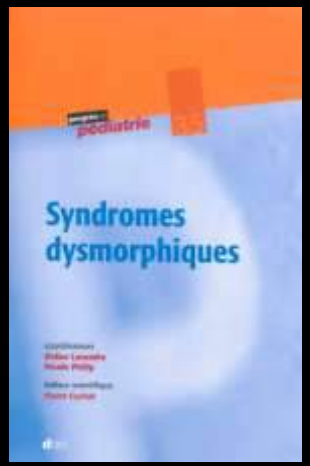


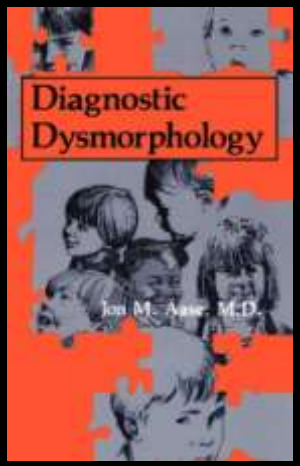


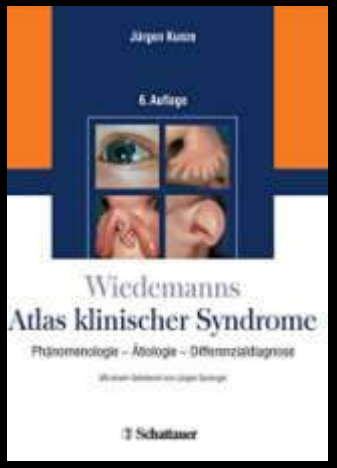


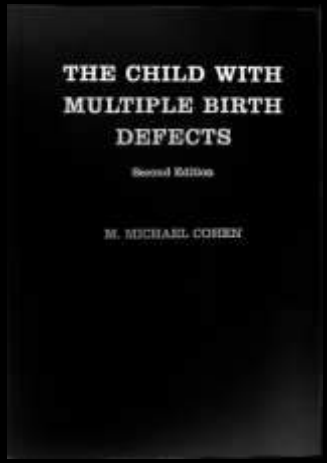


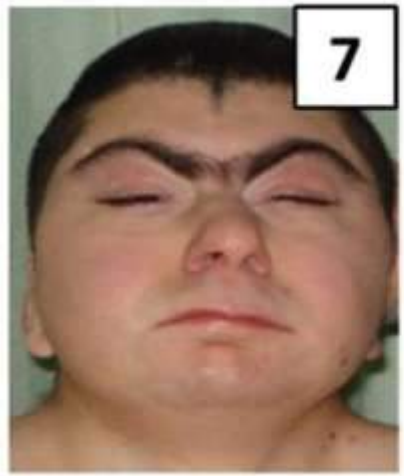








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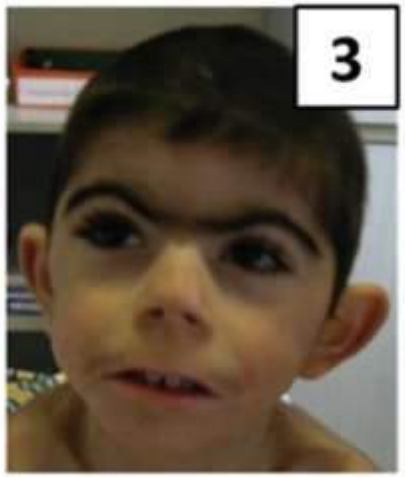
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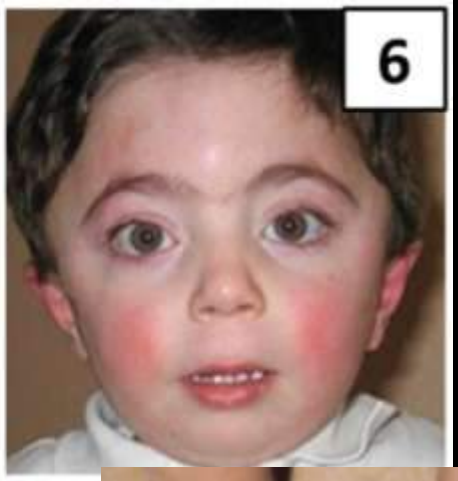
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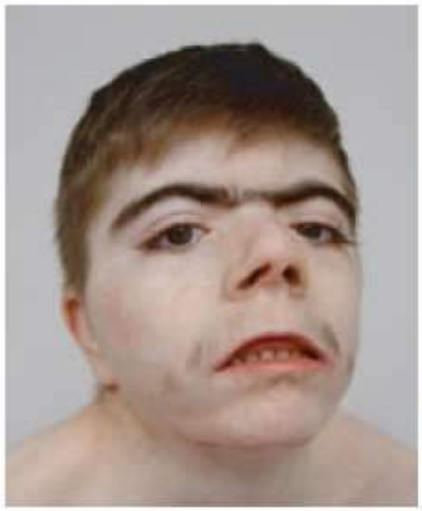
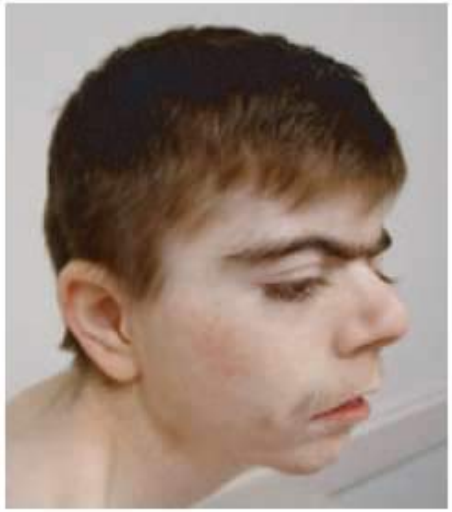
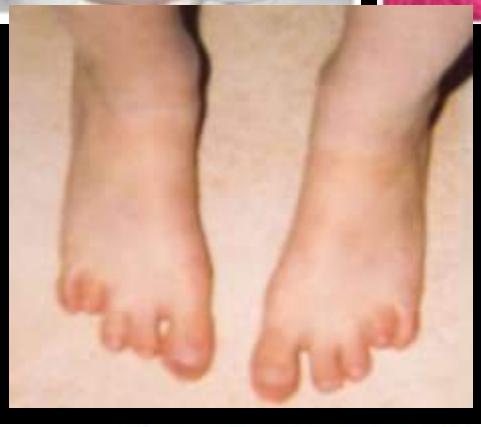
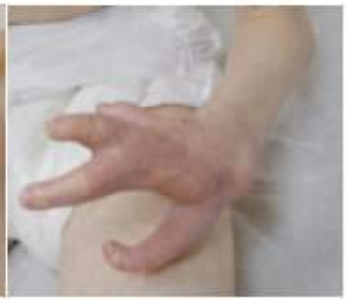
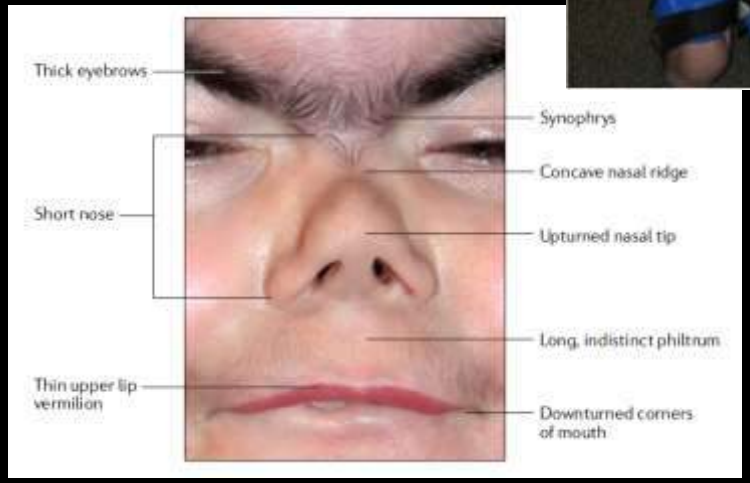
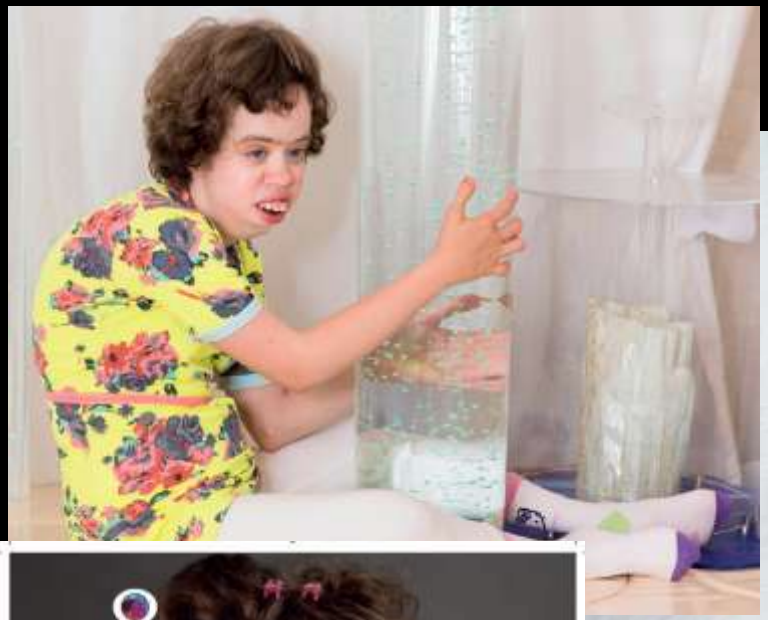









Thick eyebrows
Synophrys
Concave nasal ridge
Short nose
Upturned nasal tip
Long, indistinct philtrum
Thin upper lip vermilion
Downturned corners of mouth

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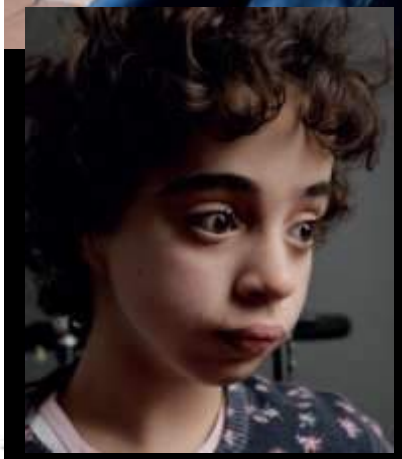
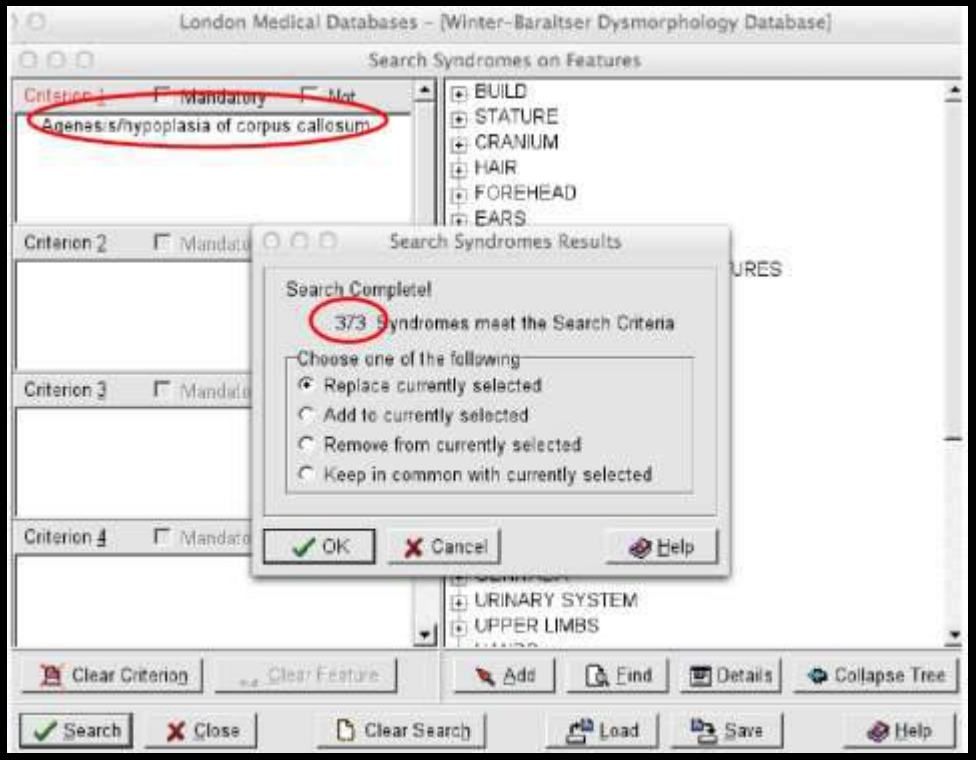
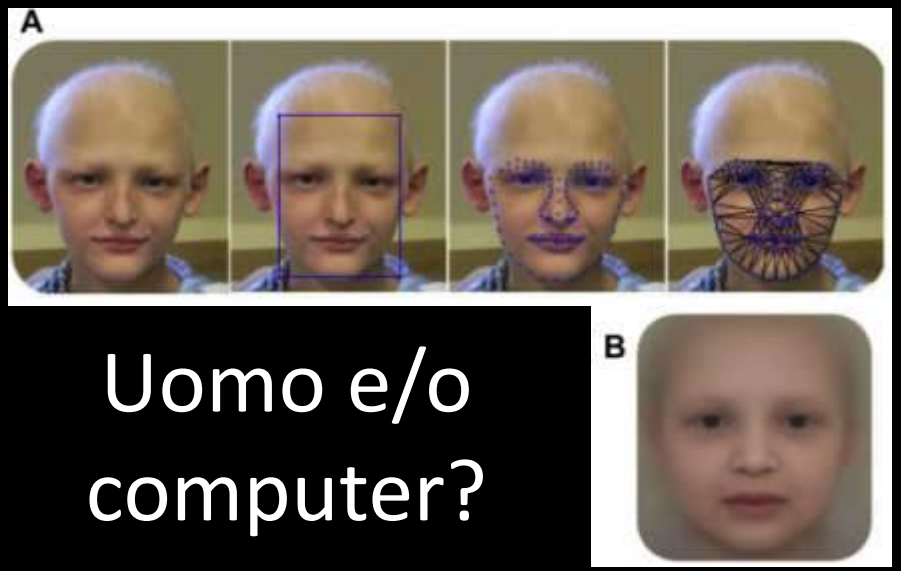
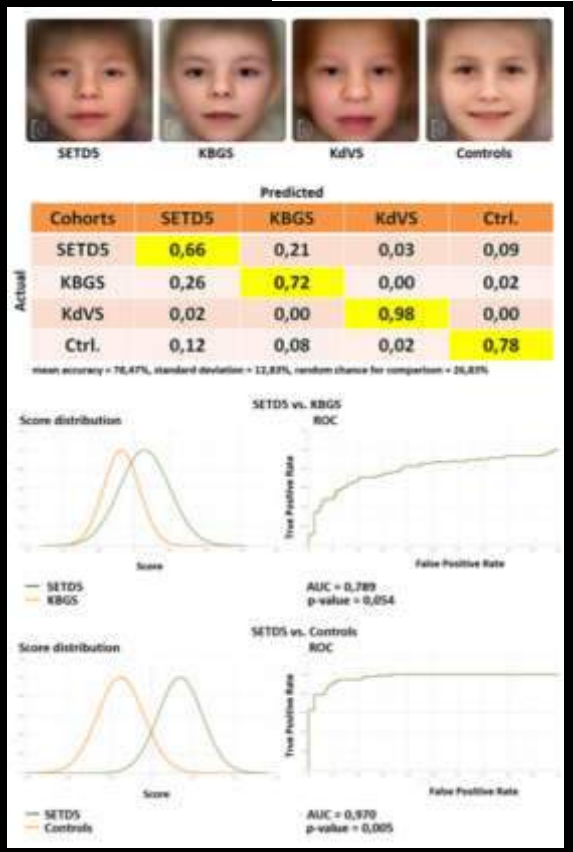
Information on caring for children and adults with the Marshall-Smith Syndrome

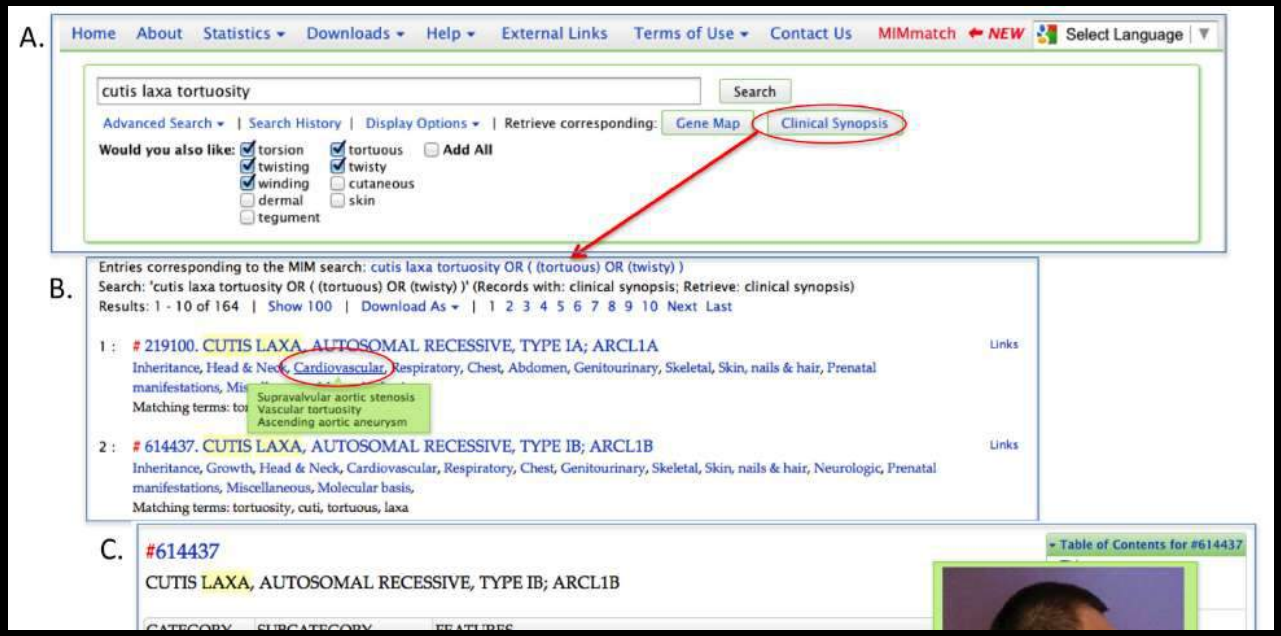


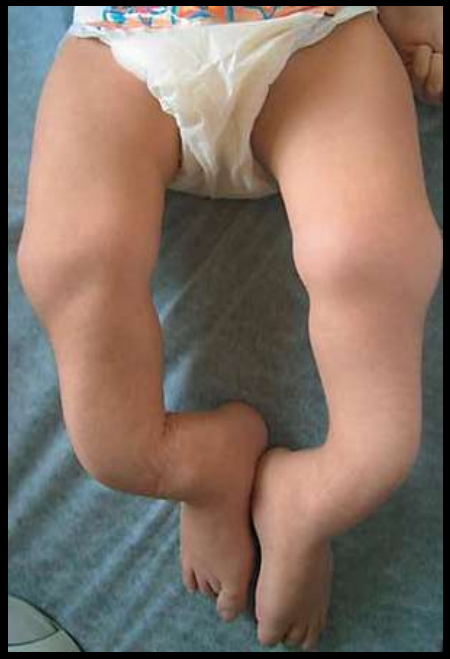


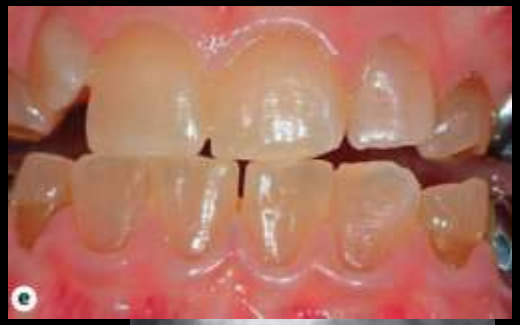


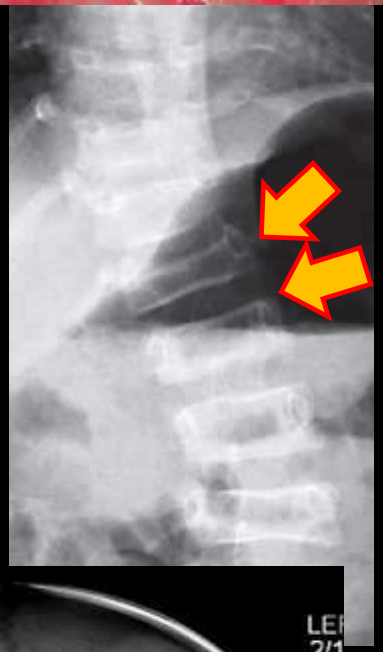
Uomo e/o computer?

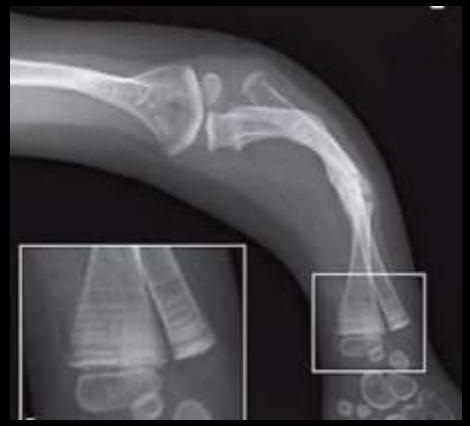


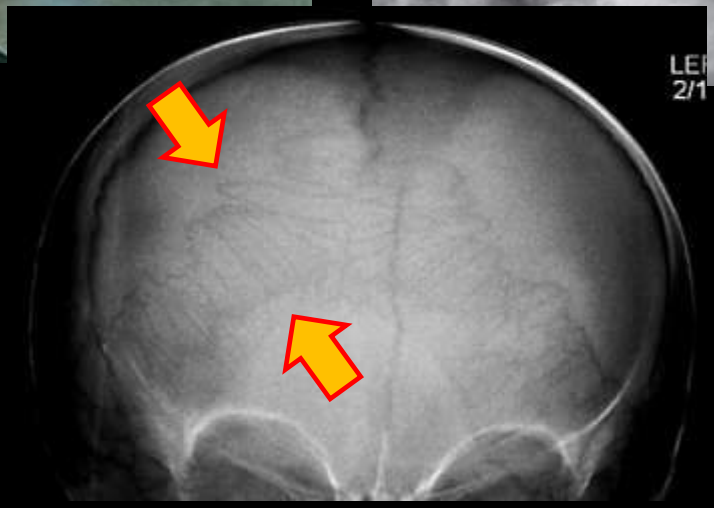












Prevalence:
2.5-10/100000 worldwide

Incidence:
0.5-1/10000 live births

Performing a systematic assessment: algorithms & checklists

Summary of bone fracture during infancy

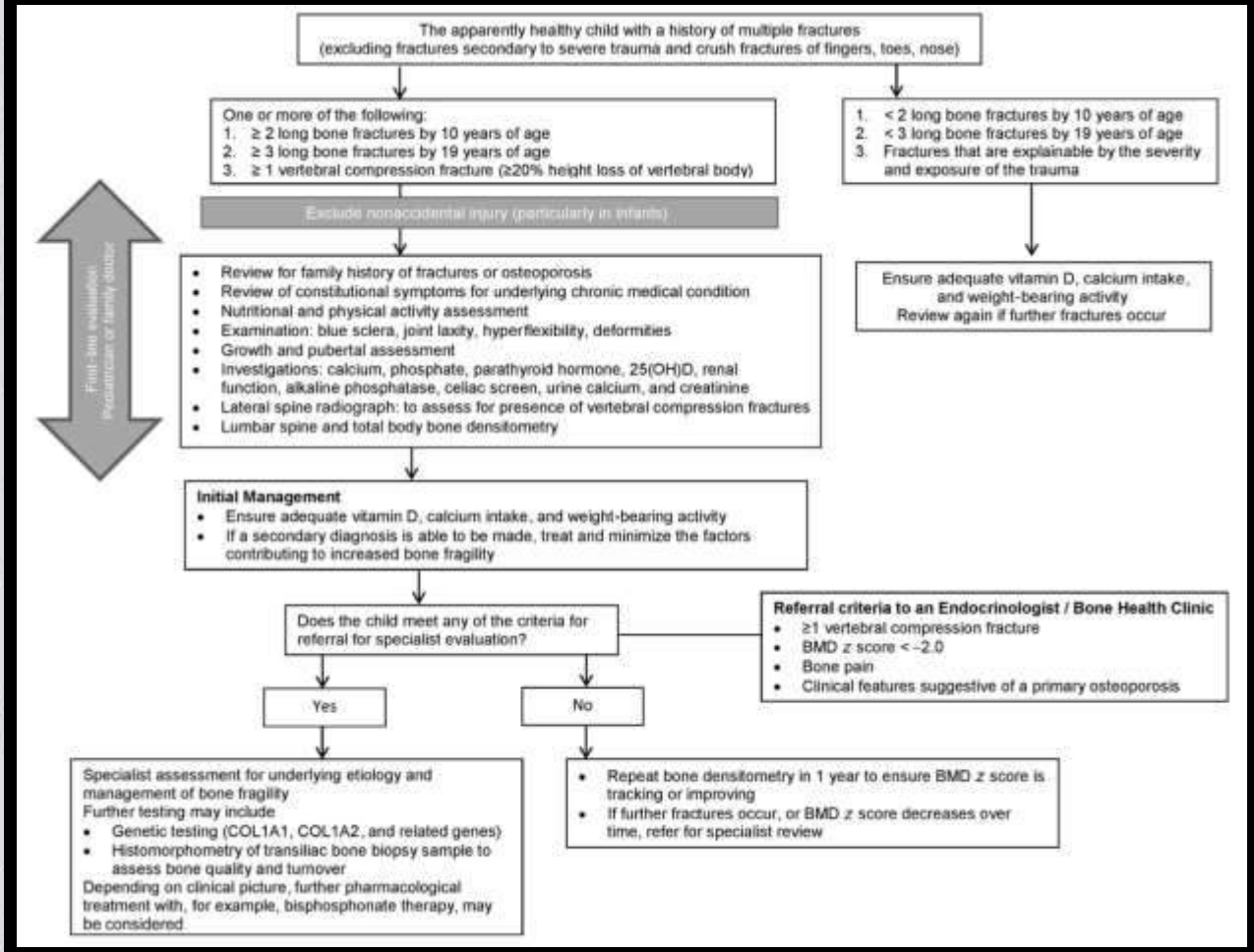
Features of bone disease in infancy—history

- Age at first fracture
- Number of fractures, sites and timing
- Apparent causation: mechanism and force
- Associated features: swelling and pain
- Infantile hernia
- Family history of recurrent fractures with minor trauma, dislocations, hernia, early-onset deafness, dentinogenesis imperfecta (discoloured, translucent teeth, cracking or chipping of teeth), late walking in siblings, osteoporosis in older family members (especially when apparent before the age of 50 years), eye disease (retinopathy, early blindness)
- Pregnancy/delivery/neonatal course: prematurity, gestation, birth weight, necrotising enterocolitis, time to establish full enteral feeds, conjugated hyperbilirubinaemia, use of furosemide, chronic lung disease and metabolic bone disease of prematurity

Features of bone disease in infancy—examination (apply to the infant and any available family members)

- Brachycephaly/plagiocephaly/dolicocephaly
- Large anterior fontanelle/sutural diastasis without hydrocephalus
- Craniotabes
- Blue sclerae: scleral hue variable in infancy but blue sclerae persist in cases of mild osteogenesis imperfecta
- Harrison's sulcus
- Translucent skin
- Ligamentous laxity: use the Beighton scale for children and adults. In infants, check whether the knees and elbows extend beyond 180° and whether the thumbs can be apposed to the forearm.
- Hernia(s)
- Bowing deformity of limbs
- Easy bruising is reported in some cases of osteogenesis imperfecta, but is not a universal finding
- Dentinogenesis imperfecta (translucent teeth that chip or crack easily, and may wear excessively, more so in primary dentition) may not be clinically apparent.[47]

Arch Dis Child. 2007 Mar; 92(3): 251–256



Pediatr Clin North Am. 2015 Aug;62(4):841-55

Name of Disorder	MOI	OMIM No.	Gene	Molecular Diagnosis OMIM
OI type 1	AD	166200	*COL1A1, COL1A2*	OI type I
OI type 2	AD	166200	*COL1A1, COL1A2*	OI type II
	AR	610854	*CRTAP*	OI type VII
	AR	610915	*LEPRE1*	Oi type VIII
	AR	259440	*PPIP*	OI type IX
	AR	607723	*SUCO*	SUN1
OI type 3	AD	259240	*COL1A1, COL1A2*	OI type III
	AR	613982	*SERPINF1*	OI type VI
	AR	610682	*CRTAP*	OI type VII
	AR	610915	*LEPRE1*	OI type VIII
	AR	259440	*PPIB*	OI type IX
	AR	613848	*SERPINH1*	OI type X
	AR	610968	*FKBP10*	OI type XI
	AR	615066	*TMEM38B*	OI type XIII
	AR	112264	*BMP1*	OI type XIV
	AR/AD	615220	*WNT1*	OI type XV
	AR	616229	*CREB3L1*	OI type XVI
	AR	616507	*SPARC*	OI type XVII
	AR	617952	*TENT5A(FAM24A)*	OI type XVIII
	AR	607783	*MESD*	OI type XX
OI type 4	AD	166220	*COL1A1, COL1A2*	OI type IV
	AD	615220	*WNT1*	OI type XV
	AR	610854	*CRTAP*	OI type VII
	AR	259440	*PPIB*	OI type IX
	AR	610968	*FKBP10*	Oi type XI
	AR	606633	*SP7*	OI type XII
OI type 5	AD	610967	*IFITM5*	OI type V
Osteoporosis X-linked form	XL		*PLS3*	
	XL	300294	*MBTPS2*	OI type XIX
Osteoporosis AD form	AD	615220	*WNT1*	OI type XV
	AD		*LRP5*	

ILLUMINA HiSeq 4000 DNA Genome Sequencer Analyzer

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Dalla clinica al laboratorio di genetica e viceversa

Diagnosi clinica
(entità clinica)

gestaltica/euristica

sistematica/algoritmica

→ Indagine genetica
(entità clinico-molecolare)

Indagine genetica → Definizione di casi non diagnosticati, non diagnosticabili, atipici, composti

Defining the Phenotype in Human Genetic Studies: Forward Genetics and Reverse Phenotyping

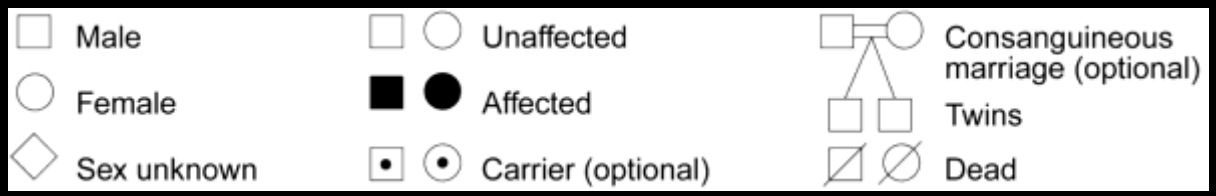
Hum Hered 2004;58:131–138

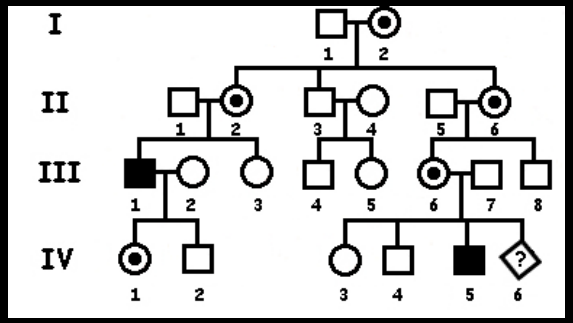
Gli ambiti di interesse cambiano ma il metodo clinico è universale

Diagnosis	*Salient features*	*Comment*
Clinical	H/O repeated fractures with minimal trauma, positive family history, blue sclera, hypermobility, dentinogenesis imperfecta, pre-senile hearing loss, short stature, long bone deformities	Mild cases have subtle signs and family history may be missed unless specifically asked for
Genetic	1 Linkage analysis: 2 Direct mutation detection	Large family with clear separation in normal and abnormal subjects is needed for linkage analysis. Mutation analysis is labour intensive, expensive and not 100% sensitive
Routine and "Bone" Biochemistry	1 Routine investigations (serum calcium, phosphorous, alkaline phosphatase etc.) 2 Biochemical markers of bone turnover: serum osteocalcin, urinary collagen cross links, n-telopeptides, etc	Routine bone biochemistry is always normal, except increased urinary calcium excretion in nearly half. Bone turnover (osteocalcin) and resorption (collagen cross links) is increased
Specialised collagen biochemistry	Fibroblast culture and collagen biochemistry	Studies on collagen produced by cultured fibroblasts are "gold standard" but can be normal in 10%–15%
Bone histomorphometry	Double tetracycline labelled iliac crest biopsy	Reduced trabecular and cortical volume, reduction in new bone formation
Radiological	Osteopenia, under-ossified calvarium, concertina appearance of long bones, basilar invagination, cod-fish vertebra, wormion bones, popcorn ossification	Plain radiographs can be normal and hence cannot be used for "ruling out" OI
Bone densitometry	Lumbar spine, femoral neck and whole body bone densitometry by dual energy x ray absorptiometry	Very useful test. Most patients have low BMD, but sensitivity unclear

…più anamnesi familiare

Standardized Human Pedigree Nomenclature: Update and Assessment of the Recommendations of the National Society of Genetic Counselors





specialties will benefit from these developments. However, it has been suggested that one medical discipline may instead be a victim of this technology: medical genetics, specifically dysmorphology. During a plenary session of the 2011 Meeting of the European Society of Human Genetics, an expert and well-respected speaker made this prediction, and one of the topics of a public debate in the 2011 International Congress of Human Genetics in Montreal was "...medical genetics will disappear as a separate specialty." To paraphrase Mark Twain, the rumors of the death of dysmorphology and medical genetics are greatly exaggerated. So if the rumored death is not imminent, what is afoot?

Next-Generation Sequencing Demands Next-Generation Phenotyping, RCM Hennekam & LG Biesecker, 2011

Sindromologia, e genetica clinica più in generale = attività specialistica!

(ed è più viva che mai)

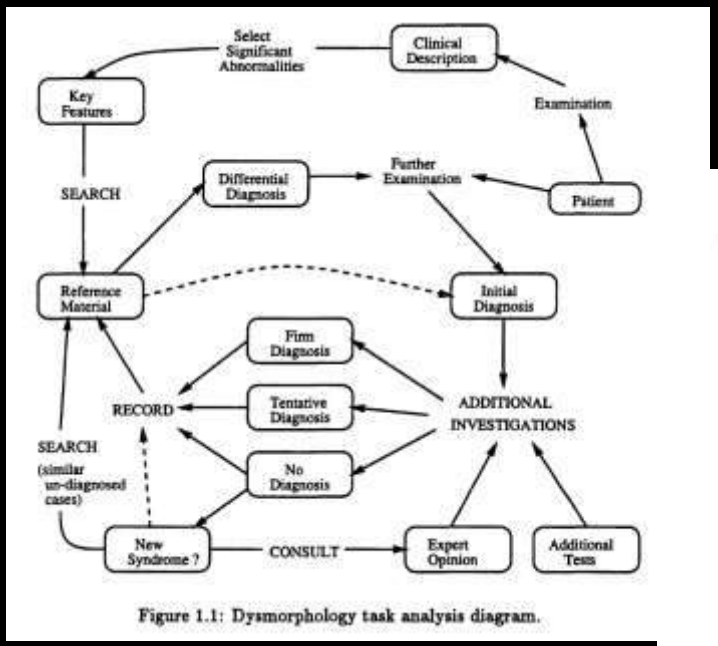


Figure 1.1: Dysmorphology task analysis diagram.

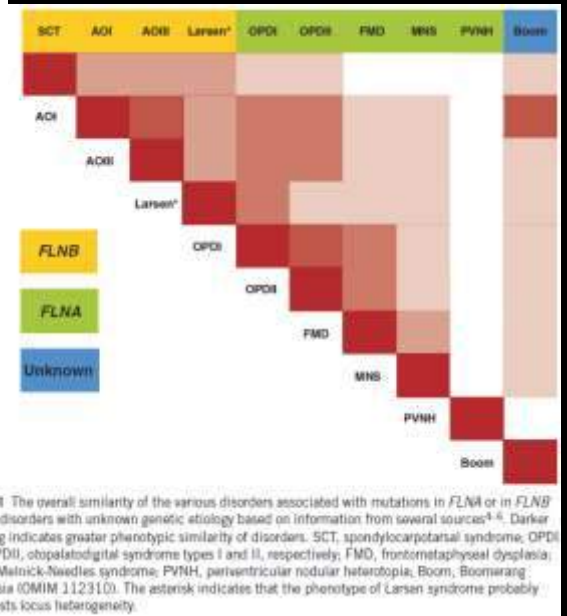


Figure 1 The overall similarity of the various disorders associated with mutations in *FLNA* or in *FLNB* and of disorders with unknown genetic etiology based on information from several sources[4–6]. Darker shading indicates greater phenotypic similarity of disorders. SCT, spondylocarpotarsal syndrome; OPDI and OPDII, otopalatodigital syndrome types I and II, respectively; FMD, frontometaphyseal dysplasia; MNS, Melnick-Needles syndrome; PVNH, periventricular nodular heterotopia; Boom, Boomerang dysplasia (OMIM 112310). The asterisk indicates that the phenotype of Larsen syndrome probably manifests locus heterogeneity.

Labels (diagnoses) tend to stick, and it is important that the techniques used in genetic counselling clinics are applied in dealing with patients, both in those cases in which a diagnosis has been made as well as those many situations in which no diagnosis has been possible. It is perhaps in this latter situation that most skill is needed. To put our own experience into perspective, about a half of the patients we see at our tertiary referral genetic counselling clinics leave without a diagnosis. It is at least comforting for both patient and doctor to know that by using a database or a book such as this a reasonably thorough search of the literature has been made, and important for the doctor, that this has been achieved in a short time.

What is clear is that syndrome identification by using purely clinical criteria is likely to be a necessary, but essentially preliminary step which anticipates newer methods of making definitive diagnoses, by cytogenetic, biochemical or molecular techniques.

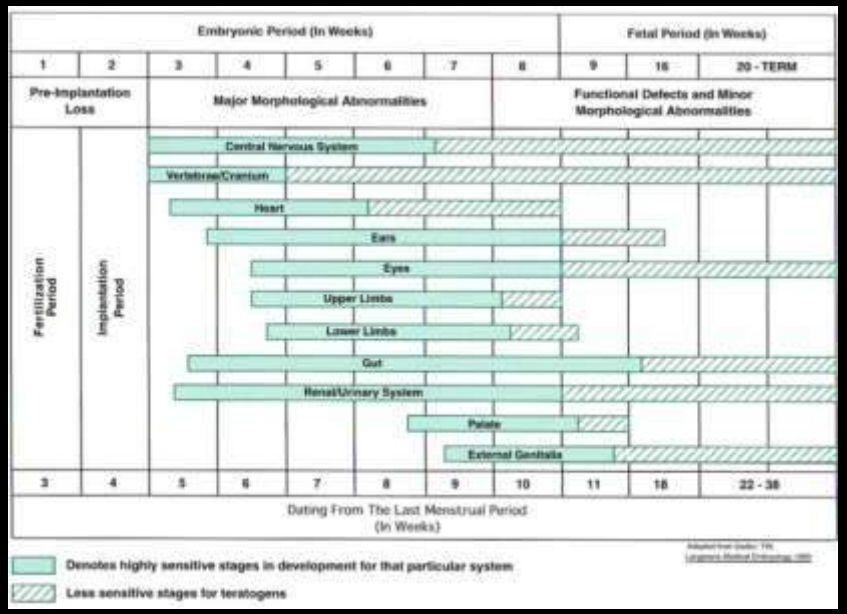
Robin M. Winter & Michael Baraitser, 1991

Profilo minimo del genetista clinico

- Diagnosi delle malattie genetiche
- Prescrizione e interpretazione delle indagini genetiche e stima del ‘rischio genetico’
- Informazioni sulla malattia per le persone interessate:
  - che presentano la malattia
  - i familiari, che rischiano di avere la stessa malattia o di trasmetterla
- Liaison con i laboratori dedicati
- Indirizzamentoo alle (varie)

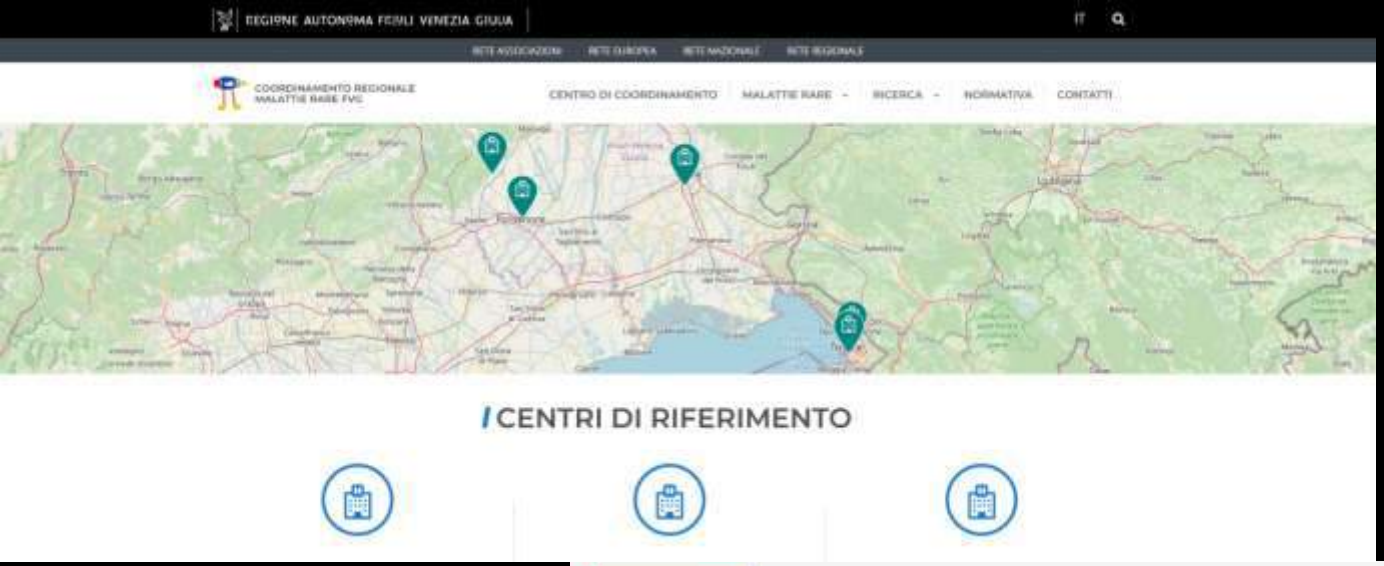
  prese in carico specialistiche
- … … …

Role of the clinical geneticist, BSHG
(tratta da F. Forzano, Genova 2007)

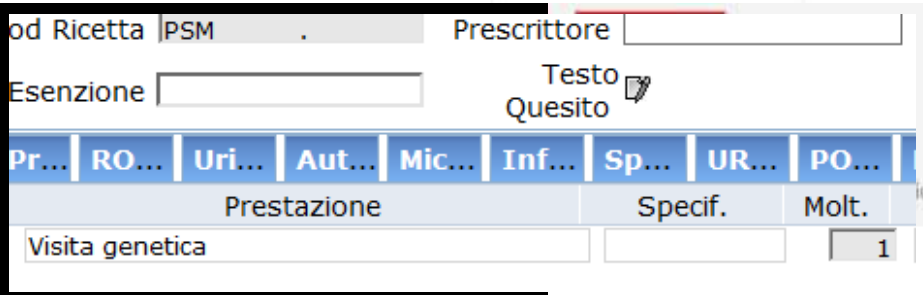


Who needs a clinical genetics evaluation?

- A history of intrauterine growth retardation or failure to thrive
- Abnormal growth (short, excessive)
- Abnormal or unusual facial features
- Abnormal body and limb proportions or asymmetry
- Major and/or minor congenital anomalies
- Microcephaly, macrocephaly or craniosynostosis
- Ambiguous or abnormal genitalia, early or late onset of puberty
- Developmental delay or intellectual disability
- Hypotonia, hypertonia
- A relative with problems similar to those of patient
- Metabolic problems
- Bleeding tendency
- Vision or hearing loss
- A significant regression in developmental progress
- An unusual body odor
- Excessive unexplained vomiting
- Unusual behaviors, especially when associated with minor malformations



Dove si nascondono i genetisti?



Come ci arrivo?