American Journal of Medical Genetics 29:581–594 (1988)

International Nosology of Heritable Disorders of Connective Tissue, Berlin, 1986

P. Beighton, A. de Paepe, D. Danks, G. Finidori, T. Gedde-Dahl, R. Goodman, J.G. Hall, D.W. Hollister, W. Horton, V.A. McKusick, J.M. Opitz, F.M. Pope, R.E. Pyeritz, D.L. Rimoin, D. Sillence, J.W. Spranger, E. Thompson, P. Tsipouras, D. Viljoen, I. Winship, and I. Young

Cape Town, South Africa, (P.B., D.V., I.W.); Ghent, Belgium (A. de P.); Melbourne, Australia (D.D.); Paris, France (G.F.); Oslo, Norway (T. G-D.); Tel-Hashomer, Israel (R.G.); Vancouver, Canada (J.G.H.); Portland, Oregon, U.S.A. (D.W.H.); Houston, Texas, U.S.A. (W.H.); Baltimore, Maryland, U.S.A. (V.A. McK., R.E.P.); Helena, Montana, U.S.A. (J.M.O.); London, U.K. (F.M.P., E.T.); Torrance, California, U.S.A. (D.L.R.); Sydney, Australia (D.S.); Mainz, West Germany (J.W.S.); Farmington, Connecticut, U.S.A. (P.T.); Leicester, U.K. (I.Y.)

INTRODUCTION

The heritable disorders of connective tissue have proven to be very heterogeneous and problems have arisen concerning syndromic boundaries, nomenclature, and classification. In an attempt to resolve these dilemmas, a group of experts participated in a Workshop held during the 7th International Congress of Human Genetics, Berlin, in September, 1986. The program for this Workshop had been drawn up at a planning meeting held in 1985 at the Ciba Foundation, London (Beighton, Hollister, Pope, Pyeritz).

At the Workshop, overviews were given of the uses and limitations of nosology (McKusick), diagnostic criteria (Pyeritz), and practical issues in biochemical and molecular diagnosis (Hollister). Invited speakers then gave brief comments on the current

Received for publication June 24, 1987; revision received August 3, 1987.

Address reprint requests to Prof. Peter Beighton, MRC Unit for Inherited Skeletal Disorders, Department of Human Genetics, University of Cape Town, Medical School, Observatory 7925, Cape Town, South Africa.

status of the nosology of specific categories of inherited connective tissue disorders and made recommendations for possible modification.

The Workshop was followed by two closed committee meetings at which the participants attempted to reach agreement on syndromic definition and a standardized nomenclature. The final proposals, with brief comment where relevant, form the subject of this communication.

GENERAL COMMENTS

1. This "Berlin Nosology" is not intended to intrude upon or cut across the existing Paris Nomenclature for constitutional disorders of the skeleton [Maroteaux et al., 1986]. Inevitably, there is some overlap, but wherever possible this has been avoided.

2. In some conditions current problems revolve around diagnostic criteria or syndromic boundaries, while in others nomenclature and classification are the main issues. For these reasons, the style of presentation in this article is not necessarily uniform.

3. Some heritable connective tissue disorders can be subclassified on a clinical basis or through biomolecular abnormalities; in others the basic defect is still unknown. The nosology represents a synthesis of these factors, based on current knowledge, and future modification is foreseen. The Committee plans to meet at regular intervals for updating.

4. A number of conditions, including heteroglycanoses, overlap syndromes and tight joint syndromes were also discussed at the Workshop and Committees. There was general consensus that disorders in these categories were outside the scope of this document.

5. Key references are provided for each disorder. The catalogue of inherited disorders "Mendelian Inheritance in Man" [McKusick, 1986] and the classical monograph "Heritable Disorders of Connective Tissue" [McKusick, 1972] are additional rich sources of references and information. Other relevant reviews have been published by Byers [1983], Maroteaux et al. [1986], and Pope and Nicholls [1987].

6. Where relevant the numbers allocated to entities in "Mendelian Inheritance in Man" [McKusick, 1986] have been cited in the titles of the disorders mentioned in this nosology.

7. A need for a register of researchers, projects, and affected persons was recognized and a subcommittee has been established under the chairmanship of Dr. Reed Pyeritz. A report on conclusions and proposals is appended.

1. MARFAN SYNDROME (15470)

Diagnostic manifestations (Listed in approximate order of decreasing specificity. Major manifestations indicated by an asterisk)

Skeletal

- anterior chest deformity, especially asymmetric pectus excavatum/carinatum
- dolichostenomelia not due to scoliosis
- arachnodactyly
- vertebral column deformity
  - scoliosis
  - thoracic lordosis or reduced thoracic kyphosis
- tall stature, especially compared to unaffected 1° relatives
- high, narrowly arched palate and dental crowding
- protrusio acetabulae

abnormal appendicular joint mobility
congenital flexion contractures
hypermobility
Ocular
*ectopia lentis
flat cornea
elongated globe
retinal detachment
myopia
Cardiovascular
*dilatation of the ascending aorta
*aortic dissection
aortic regurgitation
mitral regurgitation due to mitral valve prolapse
calcification of the mitral annulus
mitral valve prolapse
abdominal aortic aneurysm
dysrhythmia
endocarditis
Pulmonary
spontaneous pneumothorax
apical bleb
Skin and integument
striae distensae
inguinal hernia
other hernia (umbilical, diaphragmatic, incisional)
Central nervous system
*dural ectasia
lumbosacral meningocele
dilated cisterna magna
learning disability (verbal-performance discrepancy)
hyperactivity with or without attention deficit disorder

Genetics

Autosomal dominant inheritance
25–30% of cases are sporadic; paternal age effect

Requirements for diagnosis

In the absence of an unequivocally affected 1° relative:
Involvement of the skeleton and at least 2 other systems; at least one major manifestation
In the presence of at least one unequivocally affected 1° relative:
Involvement of at least 2 systems; at least one major manifestation preferred, but this will depend somewhat on the family's phenotype
Urine amino acid analysis in the absence of pyridoxine supplementation confirms absence of homocystinuria

Conditions most often considered in differential diagnosis

homocystinuria
familial or isolated mitral valve prolapse syndrome
familial or isolated annuloaortic ectasia (Erdheim disease)

congenital contractural arachnodactyly
Stickler syndrome

Comments

The syndromic status of congenital contractural arachnodactyly is uncertain; most patients so diagnosed likely have the Marfan syndrome.
The Marfanoid hypermobility syndrome is not a distinct entity.

2. STICKLER SYNDROME (10830)

Alternative designation: Hereditary arthrophthalmopathy.
Excludes: Marshall and Wagner syndromes, which are apparently different entities.
Weissenbacher-Zweymüller syndrome, which is a severe early form of the Stickler syndrome in some familites. This eponym should be discarded.

Manifestations

Stickler syndrome is a common pleiotropic autosomal dominant syndrome with the following variable manifestations:

Myopia and retinal detachment, rarely congenital cataracts
Arthropathy, mild, with skeletal manifestations sometimes called mild spondyloepiphyseal dysplasia
Deafness
Physique, normal or "Marfanoid habitus," with joint hypermobility
Short midface
Cleft palate
Cardiac defects, rare

The condition is an "iceberg trait" in many families; severely affected propositi may have mildly affected relatives with minor stigmata. The condition should be suspected in all cases of apparently isolated congenital cleft palate, of Pierre Robin anomaly, all Kniest-like cases in infancy, and autosomal dominant myopia with retinal detachment. Recent tight linkages between the Stickler syndrome and the COL2A1 locus in one large pedigree suggests that the basic defect is in the primary structure of alpha 1(II) procollagen. Genetic heterogeneity must be investigated before using DNA probes for COL2A1 in diagnosis.

3. EHLERS-DANLOS SYNDROME (EDS)

Redundant synonym "cutis hyperelastica"
Excludes "cutis laxa" and "familial joint hypermobility syndrome"

Type			
EDS I	Gravis type	AD	(13000)
EDS II	Mitis type	AD	(13001)
EDS III	Hypermobile type	AD	(13002)
EDS IV	Vascular	Heterogeneous	
	IV-A Acrogeric type	AD	(13005)
	IV-B Acrogeric type	AR	(22535)
	IV-C Ecchymotic type	AD	(13005)
	IV-D Others	AD	(AR?)[1]
	(All forms have defect of type III collagen)		

[1]The existence of these subtypes is unproven.

EDS V	X-linked type	XL	(30520)
EDS VI	Ocular-scoliotic type	AR	(22540)
	VI-A Decreased lysyl hydroxylase activity		
	(VI-B Normal lysyl hydroxylase activity ?)[1]		
EDS VII	Arthrochalasis multiplex congenita	Heterogeneous	
	VII-A Structural defect of pro-α 1(1)	AD	(13006)
	VII-B Structural defect of pro-α 2(1)	AD	(13006)
	(VII-C Procollagen N-Proteinase deficiency ?)[1]	AR	(22541)
EDS VIII	Periodontitis type	AD	(13008)
EDS IX	Vacant (formerly occipital horn syndrome, or X-linked cutis laxa, now recategorized as a disorder of copper transport)		(30415)
EDS X	Fibronectin abnormality	AR	(22531)
EDS XI	Vacant (formerly familial joint instability, now recategorized with the familial articular hypermobility syndromes)		(14790)

Cardinal manifestations

	Skin—hyperextensible with soft, velvety, doughy texture
	Dystrophic scarring
	Easy bruising
	Joint hypermobility
	Connective tissue fragility
EDS I	Cardinal manifestations in severe degree
EDS II	Cardinal manifestations in mild degree
EDS III	Marked articular hypermobility
	Moderate dermal hyperextensibility
	Minimal scarring
EDS IV	Variable stigmata
	Severe bruising, hyperpigmentation and/or scarring
	Thin skin with prominent venous plexus
	Vascular rupture
	Colonic perforation
	Characteristic facial appearance
EDS V	Cardinal manifestations in moderate degree
	X-linked inheritance
EDS VI	Cardinal manifestations in severe degree
	Eye involvement (microcornea, scleral perforation, retinal detachment)
	Scoliosis
EDS VII	Cardinal manifestations with marked articular hypermobility
	Short stature
	Micrognathia
EDS VIII	Cardinal manifestations in moderate degree
	Aggressive periodentitis, gingival recession, early tooth loss
EDS X	Cardinal manifestations but skin texture normal
	Petechiae
	Striae distensae
	Platelet aggregation defect corrected by fibronectin

4. FAMILIAL ARTICULAR HYPERMOBILITY SYNDROME (14790)

Excludes:
EDS group of disorders, notably EDS III (Hypermobile type) and VII (Arthrochalasis multiplex congenita)
Skeletal dysplasias with joint hypermobility, notably the Larsen syndrome

Cardinal manifestations
Generalized articular hypermobility, with or without subluxation or dislocations
No skin involvement

4-1 *Familial articular hypermobility*, uncomplicated type — AD/AR
4-2 *Familial articular hypermobility*, dislocating type (formerly EDS XI, familial joint instability syndrome) — AD
(The basic defect in these disorders is unknown.)

5. SKELETAL DYSPLASIAS WITH PREDOMINANT JOINT LAXITY

5-1 **Larsen Syndrome** — Mild form: AD (15025); Severe form: AR (24560)

Cardinal manifestations:
Joint laxity, especially at the knees
Flattened nasal bridge
Short stature
Broad terminal phalanges
Radiographic changes:
Supernumerary ossification centres in the carpus and calceneus

5-2 **Desbuquois Syndrome** — AR (heterogeneous?)

Cardinal manifestations:
Joint laxity
Short stature
Prominent eyes
Broad terminal phalanges
Supernumerary phalanges
Radiographic characteristics:
Supernumerary carpal ossification centres
Prominent lesser trochanter of femur

5-3 **Spondyloepimetaphyseal Dysplasia With Joint Laxity (SEMDJL)** — AR (27164)

Clinical manifestations:
Gross joint laxity with progressive spinal mal-alignment and multiple dislocations
Dwarfism
Characteristic facial appearance
Variable cardiac defects and palatal clefts
Radiographic changes:
Skeletal dysplasia with changes in the vertebrae, epiphyses, and metaphyses

Skeletal dysplasia with changes in the vertebrae, epiphyses, and metaphyses

6. CUTIS LAXA

Excludes:
Ehlers-Danlos syndrome (syn. cutis hyperelastica)

Ehlers-Danlos syndrome (syn. cutis hyperelastica)
Cutis laxa with joint mobility and developmental delay
Occipital horn syndrome (formerly EDS IX, X-linked cutis laxa)

Cardinal manifestations:

Loose skin folds
Characteristic "mournful" face with beaked nose and long upper lip
Variable systemic involvement (pulmonary emphysema, diverticula of the gut, hernia)
Joints not hypermobile
Skin not fragile

6-1 *Cutis laxa, benign form* AD (12370)
6-2 *Cutis laxa, severe form* AR (21910)

7. PSEUDOXANTHOMA ELASTICUM

Cardinal changes:

Skin—yellow infiltrated lesions, maximal in the flexures
Eyes—angioid streaks, retinal hemorrhage
Cardiovascular—calcification of the media of medium-sized arteries, with progressive occlusion and occasional rupture

7-1 *Pseudoxanthoma elasticum (PXE)*—AD form (probably heterogeneous) (17785)
7-2 *Pseudoxanthoma elasticum (PXE)*—AR form (probably heterogeneous) (26480)

Elastic fibres are characteristically fragmented and calcified in skin biopsy specimens but the basic defect is unknown.

8. EPIDERMOLYSIS BULLOSA (EB)

Epidermolysis bullosa is the descriptive term used for the mechano-bullous genodermatoses. The 26 subtypes are characterized by traumatically induced blistering of the skin, while the nails and mucous membranes are variably affected.

EB is traditionally divided into three major subgroups depending on the presence or absence of scarring of the skin and on the ultrastructural changes. These are:

Simplex (nonscarring)
Atrophicans (nonscarring with skin atrophy)
Dystrophica (scarring)

The *dystrophica* subgroups are inherited connective tissue disorders; some of these conditions are associated with absence or abnormality of type VII collagen. The *atrophicans* forms, with basement membrane defects, may turn out to be disorders of connective tissue, but at present their status is uncertain. In the *simplex* forms, the defect is in the epidermis, and they cannot, therefore, be regarded as connective tissue disorders. The 8 dystrophic subtypes are listed below. In accordance with conventional terminology, eponyms have been retained.

8-1 Epidermolysis Bullosa Dystrophica, Cockayne-Touraine AD (13180)
8-2 Epidermolysis Bullosa Dystrophica, Pasini AD (13175)
8-3 Epidermolysis Bullosa Dystrophica, Pretibial type AD (13185)
8-4 Epidermolysis Bullosa Dystrophica, Hallopeau Siemens (localized and mutilans forms) AR (22660)
8-5 Epidermolysis Bullosa Dystrophica Inversa AR (22645)
8-6 Epidermolysis Bullosa Dystrophica, Winship AR
8-7 Epidermolysis Bullosa Dystrophica, Fine AR
8-8 Epidermolysis Bullosa Progressiva AR (22650)

9. HERITABLE DISORDERS OF CONNECTIVE TISSUE SECONDARY TO METABOLIC DEFECTS

9-1 Alcaptonuria (Homogentisic acid oxidase deficiency) AR (20350)

9-2 Homocystinuria AR
Pyridoxine responsive form (23620)
Pyridoxine unresponsive form (23625)

10. DISORDERS OF COPPER TRANSPORT

10-1 **Occipital Horn Syndrome** (formerly EDS IX, X-linked cutis laxa) XL (30415)

Diagnostic clinical criteria:
- Skin lax and mildly hyperextensible
- Hypermobile digits
- Bony protuberances of the occiput (evident as bony nubbins in the first decade)
- Limitation of extension of the elbows and knees due to bone modeling defects
- Carpal bone coalescences
- Short clavicles
- Bladder diverticulae
- Osteomalacia
- Chronic diarrhea (variable)
- Postural hypotension (occasional)

Diagnostic biochemical criteria:
- Moderate decrease in serum copper and ceruloplasmin levels
- Excess copper and increased ^{64}Cu accumulation (attached to metallothionein) in cultured fibroblasts

10-2 **Menkes Syndrome** XL (30940)

(Classical and mild forms)

Diagnostic clinical criteria:

(Classical and mild forms)

Diagnostic clinical criteria:
- Lax skin
- Hypermobile joints
- Severe brain dysfunction
- Vascular rupture
- Abnormal hair

Diagnostic biochemical criteria:
- Decreased serum copper and ceruloplasmin levels
- Excess copper and increased ^{64}Cu accumulation (attached to metallothionein) in cultured fibroblastic cells

11. OSTEOGENESIS IMPERFECTA

Information concerning biochemical and molecular defects in OI is accumulating rapidly but a nosology based on a synthesis of these factors, together with clinical and genealogical data is not yet possible. The current classification of OI on a basis of clinical and radiological changes is given below.

OI type I	Osseous fragility (variable from minimal through moderately severe), distinctly blue sclerae (at all ages), presenile hearing loss	AD (16620) (heterogeneous)

OI type II	Lethal perinatal OI. Extremely severe osseous fragility, stillbirth or neonatal death		
	Sub-group A) Radiographs show broad, crumpled long bones and broad ribs with continuous beading	AD new mutation	(16621)
	Sub-group B) Radiographs show broad, crumpled long bones, ribs show discontinuous beading or are not beaded	AR?	(25940)
	Sub-group C) Radiographs show thin, fractured long bones and thin, beaded ribs	AR?	(25940)
OI type III	Moderately severe to severe osseous fragility, normal sclerae (sometimes blue in infancy), variable but severe deformity of long bones and spine, stunted stature. Generally nonlethal in the newborn infant	AR	(25942)
OI type IV	Osseous fragility with normal sclerae (blue in infancy), variable deformity of long bones and spine	AD	(16622)
Note:	i. The value of opalescent dentin (DI) for subcategorization is uncertain.		
	ii. In families with OI-I, linkage has been demonstrated with the pro-α 1(1) (COL1A1) and pro-α 2(1) (COL1A2) collagen gene loci. In a few families with OI-IV, linkage with pro-α 2(1) (COL1A2) has been recorded.		

12. MISCELLANEOUS INHERITED CONNECTIVE TISSUE DISORDERS

12-1	*Cutis laxa with joint hypermobility and developmental delay* excludes Ehlers-Danlos syndrome, classical cutis laxa, and X-linked cutis laxa (now occipital horn syndrome)	AR	(21920)
12-2	*Wrinkly skin syndrome* Diagnostic criteria: Joint laxity Low birth weight Wrinkled skin over hands and feet	AR	(27825)
12-3	*Dermatofibrosis lenticularis disseminata* with osteopoikilosis (Buschke-Ollendorff syndrome)	AD	(16670)
12-4	*Familial cutaneous collagenoma*	AD/AR	(11525)
12-5	*Keloid formation*	AD?	(14810)
12-6	*Elastosis perforans serpiginosa*	AD?	(13010)
12-7	*Reactive perforating collagenosis*	AR?	(21670)

ACKNOWLEDGMENTS

We thank Gillian Shapley for typing the manuscript with her usual enthusiasm and efficiency. This research was supported by grants from the South African Medical Research Council, the Mauerberger Foundation, the Harry Crossley Foundation, and the University of Cape Town Staff Research Fund.

Beighton P, Curtis D (1985): X-linked Ehlers-Danlos syndrome type V: The next generation. Clin Genet 27:472–478.

EDS VI:

Beighton P (1970): Serious ophthalmological complications in the Ehlers-Danlos syndrome. Brit J Ophthal 54:263–267.

Krane SM (1982): Hydroxylysine-deficient collagen disease: A form of Ehlers-Danlos syndrome type VI. In Akeson WH (ed): "Symposium on Heritable Disorders of Connective Tissue." Am Acad of Ortho Surg. St Louis: CV Mosby, pp 61–81.

Pinnell SR, Krane SM, Kenzora JE, Glimcher MJ (1972): Heritable disorder with hydroxylysine-deficient collagen: Hydroxylysine-deficient collagen disease. N Engl J Med 286:1013–1020.

EDS VII:

Cole WG, Chan D, Chambers GW, Walker ID, Bateman JF (1986): Deletion of 24 amino acids from the pro 1(I) chain of type I procollagen in a patient with the Ehlers-Danlos syndrome type VII. J Biol Chem 261:5496–5503.

Eyre DR, Shapiro FD, Aldridge GF (1985): A heterozygous collagen defect in a variant of the Ehlers-Danlos syndrome type VII. J Biol Chem 260:11322–11329.

Steinmann B, Tuderman L, Peltonen L, Martin GR, McKusick VA, Prockop DJ (1980): Evidence for a structural mutation of procollagen type I in a patient with the Ehlers-Danlos syndrome, type VII. J Biol Chem 255:8887–8893.

EDS VIII:

Hollister DW (1982): Clinical features of Ehlers-Danlos syndrome type VIII and IX. In Akeson WH (ed): "Symposium on Heritable Disorder of Connective Tissue." St Louis: CV Mosby, pp 102–113.

Nelson DL, King RA (1981): Ehlers-Danlos syndrome type VIII. J Am Acad Dermatol 5:297–303.

EDS X:

Arneson MA, Hammerschmidt DE, Furcht LT, King RA (1980): A new form of Ehlers-Danlos syndrome. JAMA 244:144–147.

4. FAMILIAL ARTICULAR HYPERMOBILITY SYNDROMES

Carter CE, Sweetnam R (1960): Familial joint laxity and recurrent dislocations of the patella. J Bone Joint Surg 42B:721–727.

Beighton PH, Horan FT (1970): Dominant inheritance in familial generalized articular hypermobility. J Bone Joint Surg 52B:145–147.

Shapiro SD, Jorgenson RJ, Salinas CF (1976): Recurrent dislocation of the patella versus generalized joint laxity. In Bergsma D, Schimke RN (eds): "Cytogenetics, Environment and Malformation Syndromes." New York: Alan R. Liss, Inc., for The National Foundation—March of Dimes, BD:OAS V:287–291.

Horton WA, Collins DL, De Smet AA, Kennedy JA, Schimke RN (1980): Familial joint instability syndrome. Am J Med Genet 6:221–228.

5. SKELETAL DYSPLASIAS WITH PREDOMINANT JOINT LAXITY

LARSEN SYNDROME:

Kiel EA, Frias JL, Victoria BE (1983): Cardiovascular manifestations in the Larsen syndrome. Pediatrics 71:942–946.

Larsen LJ, Schottstaedt ER, Bost FD (1950): Multiple congenital dislocations associated with a characteristic facial abnormality. J Paediatr 37:574–581.

Maroteaux P (1975): Heterogeneity of Larsen's syndrome. Arch Franc Pediatr 32:597–603.

Stanley D, Seymour N (1985): The Larsen syndrome occurring in four generations of one family. Int Orthopaed 8:267–272.

Striscuiglio P, Sebastio G, Andria G (1983): Severe cardiac anomalies in sibs with Larsen syndrome. J Med Genet 20:422–424.

DESBUQUOIS SYNDROME:

Desbuquois G, Grenier B, Michel J, Rossignol C (1966): Nanisme chondrodystrophique avec ossification anarchique et polymalformations chez deux soeurs. Arch Franc Pediatr 23:573–587.

SPONDYLO-EPIMETAPHYSEAL DYSPLASIA WITH JOINT LAXITY:

Beighton P, Kozlowski K (1980): Spondylo-epimetaphyseal dysplasia with joint laxity and severe, progressive kyphoscoliosis. Skel Radiol 5:205–212.

Beighton P, Kozlowski K, Gericke G, Wallis G, Grobler L (1983): Spondyloepimetaphyseal dysplasia with joint laxity and severe, progressive kyphoscoliosis. SA Med J 64:772–775.

Beighton P, Gericke G, Kozlowski K, Grobler L (1984): The manifestations and natural history of spondylo-

epimetaphyseal dysplasia with joint laxity. Clin Genet 26:308–317.
Kozlowski K, Beighton P (1984): Radiographic features of spondyloepimetaphyseal dysplasia with joint laxity and progressive kyphoscoliosis. Fortschr Röntgenstr 141(3):337–341.

6. CUTIS LAXA

Beighton P (1972): The dominant and recessive forms of cutis laxa. J Med Genet 9:216–222.
Fitzsimmons JS, Fitzsimmons EM, Guibert PR, Zaldua V, Dodd KL (1985): Variable clinical presentation of cutis laxa. Clin Genet 28:284–295.
Goltz RW, Hult AM, Goldfarb M, Gorlin RJ (1965): Cutis laxa. Arch Dermatol 92:373–387.
Weir EK, Joffe HS, Blaufuss AH, Beighton P (1977): Cardiovascular abnormalities in cutis laxa. Eur J Cardiol 5:255–261.
Brown FR III, Holbrook KA, Byers PH, Steward D, Dean J, Pyeritz RE (1982): Cutis laxa. Johns Hopkins Med J 150:148–153.

7. PSEUDOXANTHOMA ELASTICUM

Goodman RM, Smith EW, Paton D, Bergman RA, Siegel CL, Ottesen OE, Shelley WM, Pusch AL, McKusick VA (1963): Pseudoxanthoma elasticum, a clinical and histopathological study. Medicine 42:297–334.
Pope FM (1974): Autosomal dominant variants of pseudoxanthoma elasticum. J Med Genet 11:152–157.
Pope FM (1974): Two types of autosomal recessive pseudoxanthoma elasticum. Arch Dermatol 110:209–212.
Pope FM (1975): Historical evidence for the genetic heterogeneity of pseudoxanthoma elasticum. Br J Dermatol 92:493–509.
Viljoen DL, Beighton P, Mabin T, Woods K, Saxe N, Bonafede P (1984): Pseudoxanthoma elasticum in South Africa: Genetic and clinical implications. S Afr Med J 66:813–816.

8. EPIDERMOLYSIS BULLOSA

Anton-Lamprecht I, Hashimoto I (1976): Epidermolysis bullosa dystrophica dominans (Pasini): A primary structural defect of the anchoring fibrils. Hum Genet 32:69–76.
Bauer EA, Eisen AZ (1978): Recessive dystrophic epidermolysis bullosa: Evidence for increased collagenase as a genetic characteristic in cell culture. J Exp Med 148:1378–1387.
Briggaman RA, Wheeler CE (1975): Epidermolysis bullosa dystrophica recessiva: A possible role of anchoring fibrils in the pathogenesis. J Invest Dermatol 65:203–211.
Heagerty AHM, Kennedy AR, Gunner DB, Eady RAJ (1986): Rapid prenatal diagnosis and exclusion of epidermolysis bullosa using novel antibody probes. J Invest Dermatol 86:603–605.
Gedde-Dahl T Jr, Anton-Lamprecht I (1983): Epidermolysis bullosa. In Emery AEH, Rimoin DL (eds): "Principles and Practice of Medical Genetics," Vol I. Edinburgh: Churchill Livingstone.
Winship I (1986): Epidermolysis bullosa in South Africa. S Afr Med J 69:743–746.

9. HERITABLE DISORDERS OF CONNECTIVE TISSUE SECONDARY TO METABOLIC DEFECTS

9.1 *Alcaptonuria*

Christensen K, Manthorpe R (1983): Alkaptonuria and ochronosis: A survey and 5 cases. Hum Hered 33:140–144.
LaDu BN (1972): Alcaptonuria. In Stanbury JB, Wyngaarden JB, Fredrickson DS, Goldstein JL, Brown M (eds): "The Metabolic Basis of Inherited Disease," 4th ed. New York: McGraw-Hill, pp 268–282.
Srsen S, Cisarik F, Pasztor L, Harmecko L (1978): Alkaptonuria in the Trencin district of Czechoslovakia. Am J Med Genet 2:159–166.
Srsen S (1979): Alkaptonuria. Johns Hopkins Med J 145:217–226.

9.2 *Homocystinuria*

Hill-Zobel RL, Pyeritz RE, Scheffel U, Malpica O, Engin S, Camargo EE, Abbott MH, Guilarte TR, Hill J, McIntyre PA, Murphy EA, Tsan M-F (1982): Kinetics and biodistribution of ^{111}In-labeled-platelets in homocystinuria. N Engl J Med 307:781–786.
Mudd SH, Levy HL (1983): Disorders of transsulfulation. In Stanbury JB, Wyngaarden JB, Fredrickson DS, Goldstein JL, Brown M (eds): "The Metabolic Basis of Inherited Disease," 5th ed. New York: McGraw-Hill, pp 522–559.
Mudd SH, Skovby F, Levy HL, Pettigrew KD, Wilcken B, Pyeritz RE, Andria G, Boers GHJ, Bromberg IL, Cerone R, Fowler B, Grobe H, Schmidt H, Schweitzer L (1985): The natural history of homocystinuria due to cystathionine beta-synthase deficiency. Am J Hum Genet 36:1–31.

10. DISORDERS OF COPPER TRANSPORT

10.1 *Occipital Horn Syndrome*

Byers PH, Siegel RC, Holbrook KA, Narayanan AS, Bornstein P, Hall JG (1980): X-linked cutis laxa. N Engl J Med 303:61–65.

Peltonen L, Kivaniemi H, Palotie A, Horn N, Kaitila I, Kivirikko K (1983): Alterations in copper and collagen metabolism in the Menkes syndrome and a new subtype of the Ehlers-Danlos syndrome. Biochemistry 22:6146–6163.

Satoris DJ, Luzzatti L, Weaver DD, MacFarlane JD, Hollister DW, Parker BR (1984): Type IX Ehlers-Danlos syndrome. Radiology 152:665–670.

10.2 *Menkes Syndrome*

Danks DM (1986): Of mice and men, metals and mutations. J Med Genet 23:99–106.

Danks DM (1983): Hereditary disorders of copper metabolism in Wilson's disease and Menke's disease. In Stanbury JB, Wyngaarden JB, Fredrickson DS, Goldstein JL, Brown M (eds): "The Metabolic Basis of Inherited Disease," 5th ed. New York: McGraw-Hill, pp 1251–1268.

Danks DM, Camakaris J (1983): Mutations affecting trace elements in humans and animals: A genetic approach to the understanding of trace elements. Adv Hum Genet 13:149–216.

Menkes JH (1972): Kinky hair disease. Pediatrics 50:181–182.

11. OSTEOGENESIS IMPERFECTA

Beighton P, Versfeld GA (1985): On the paradoxically high relative prevalence of osteogenesis imperfecta Type III in the Black population of South Africa. Clin Genet 27:398–404.

Levin LS, Brady JM, Melnick M (1980): Scanning electron microscopy of teeth in autosomal dominant osteogenesis imperfecta: Support for genetic heterogeneity. Am J Med Genet 5:189–199.

Paterson CR, McAllison S, Miller R (1983): Heterogeneity of osteogenesis imperfecta type I. J Med Genet 20:203–205.

Sillence DO, Senn A, Danks DM (1979): Genetic heterogeneity in osteogenesis imperfecta. J Med Genet 16:101–116.

Sillence DO, Barlow KK, Garber AP, Hull JG, Rimoin DL (1984): Osteogenesis imperfecta type II. Delineation of the phenotype with reference to genetic heterogeneity. Am J Med Genet 17:407–423.

Sillence DO, Barlow KK, Cole WG, Dietrich S, Garber AP, Rimoin DL (1986): Osteogenesis imperfecta Type III. Delineation of the phenotype with reference to genetic heterogeneity. Am J Med Genet 23:821–832.

Sykes B, Ogilvie D, Wordsworth P, Anderson J, Jones N (1986): Osteogenesis imperfecta is linked to both type I collagen structural genes. Lancet 2:69–72.

Tsipouras P, Børresen A-L, Dickson LA, Berg K, Prockup DJ, Ramirez F (1984): Molecular heterogeneity in the mild autosomal dominant forms of osteogenesis imperfecta. Am J Hum Genet 36:1172–1179.

Wallis G, Beighton P, Boyd C, Mathew CG (1986): Mutations linked to the pro-α 2(I) collagen gene are responsible for several cases of osteogenesis imperfecta type I. J Med Genet 23:411–416.

12. MISCELLANEOUS INHERITED CONNECTIVE TISSUE DISORDERS

12.1 *Cutis laxa with joint hypermobility and developmental delay*

Agha A, Sakati MC, Higginbottom KL, Jones KL Jr, Bay C, Nyhan WL (1978): Two forms of cutis laxa presenting in the newborn period. Acta Paediatr Scand 67:775–780.

Sakati NO, Nyhan WL, Shear CS, Kattan H, Akhtar M, Bay C, Jones KL, Schackner L (1983): Syndrome of cutis laxa, ligamentous laxity and delayed development. Pediatrics 72:850–856.

Danks DM, Rogers JG (1985): Cutis laxa with delayed development. Aust Paediatr J 21:281–283.

12.2 *Wrinkly Skin Syndrome*

Gazit E, Goodman RM, Bat-Miriam Katznelson M, Rotem Y (1973): The wrinkly skin syndrome: A new heritable disorder of connective tissue. Clin Genet 4:186–191.

12.3 *Dermatofibrosis lenticularis disseminata* with osteopoikilosis (Buschke-Ollendorff syndrome) AD

Lagier R, Mbakop A, Bigler A (1984): Osteopoikilosis: A radiological and pathological study. Skeletal Radiol 11:161–168.

Verbov J, Graham R (1986): Buschke-Ollendorf syndrome: Disseminated dermatofibrosis osteopoikilosis. Clin Exper Dermatol 11:17–26.

12.4 *Familial cutaneous collagenoma*

Sacks HN, Crawley IS, Ward JA, Fine RM (1980): Familial cardiomyopathy, hypogonadism and collagenoma. Ann Intern Med 93:813–817.

Uitto J, Santa-Cruz DJ, Eisen AZ (1979): Familial cutaneous collagenoma: Genetic studies on a family. Br J

Dermatol 101:185–195.

12.5 *Keloid formation*

Bloom D (1956): Heredity of keloids: Review of the literature and report of a family with multiple keloids in five generations. NY J Med 56:511–519.

12.6 *Elastosis perforans serpiginosa*

Ayala F, Donofrio P (1983): Elastosis perforans serpiginosa: Report of a family. Dermatologica 167:111.

12.7 *Reactive perforating collagenosis*

Kanan MW (1974): Familial reactive perforating collagenosis and intolerance to cold. Br J Dermatol 91:405–414.

Mehregan AH, Schwartz OD, Livingood CS (1967): Reactive perforating collagenosis. Arch Dermatol 96:277–282.

Nair BKH, Sarojini PA, Basheer AM, Nair CHK (1974): Reactive perforating collagenosis. Br J Dermatol 91:399–403.

Edited by James F. Reynolds