Thomas A. Traill 16.11 Cardiac involvement in gene

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ESSENTIALS Many clinicians find themselves faced, from time to time, with a pa- tient who has a family history of a known disorder, such as Marfan syndrome, or who has noncardiac features that suggest a syndrome. Syndromic congenital heart disease Down's syndrome—25–50% have congenital heart disease, most char- acteristically atrioventricular canal defect. Turner's syndrome—causes coarctation of the aorta and congenital abnormalities of the aortic valve (usually bicuspid). Noonan's syndrome—the most common heritable syndrome that characteristically causes congenital heart disease. Mutations in an intracellular signalling molecule protein tyrosine phosphatase SHP- 2 account for 40% of cases. Characteristics include short stature, with a facies that is variously described as elfin or triangular, ocular hypertelorism, ears that are set low and rotated forwards, and web- bing of the neck (the most obvious of the features that may lead to confusion with Turner's syndrome). The most typical cardiac lesion is pulmonary stenosis. Williams' syndrome—caused by macrodeletions of chromosome 7 that include the elastin gene; includes the cardiovascular features of familial supravalvar aortic stenosis along with a characteristic facial appearance, with round, blue eyes, a distinctive stellate pattern of the irises, depression of the nasal bridge, outwards tilting of the nostrils, abnormal dentition, and big lips. Other conditions—many other genetic syndromes have significant cardiac and vascular manifestations. Connective tissue disorders Marfan syndrome—caused by mutations of the fibrillin-1 gene (FBN1); characteristic cardiovascular findings are aneurysmal dilatation of the aorta, and occasionally other large arteries, and floppy mitral valve. Diagnosis is based on the presence of particular major or minor criteria, the major criteria being (1) aortic aneurysm, (2) lens subluxation, (3) characteristic skeletal abnormalities, and (4) dural ectasia. Aortic dissection and

rupture are the commonest causes of death in untreated cases. β-Blockers are commonly given to slow the progression to aneurysm, but the benefit is probably modest; recent work suggests that angiotensin-II receptor blockers may be equally more effective. Surgical replacement of the aortic root is generally recommended when the maximum measurement across the aorta reaches 5 cm. Other conditions—the Ehlers–Danlos syndromes and many other genetic disorders have significant cardiac and vascular manifestations. Introduction The online catalogue of heritable disorders and their causes, Mendelian Inheritance in Man (OMIM), is expanding week by week, and with it the long list of candidates for inclusion in a chapter such as this. The following pages deal only with a few of the more commonly seen heritable syndromes that affect the heart and blood vessels, and which are seen in adult patients. Mendelian conditions that affect only the heart, that are 'nonsyndromic', are considered in the chapters of this textbook dealing with their pathologic effects (e.g. cardiomyopathies in Chapter 16.7.2, familial hypercholester- olemia in Chapter 12.6). Other heritable conditions whose main pathologic significance lies outside of the heart are also discussed elsewhere (e.g. metabolic and neuromuscular disorders). Left to be considered here are conditions which many clinicians face from time to time, in the form of a patient who has a family history of a known disorder, such as Marfan's syndrome, or who has non- cardiac features that suggest a syndrome, perhaps Noonan's. They may wonder how to make the diagnosis, what else to look for, and how to screen family members. It is no longer given that there is a clean distinction between men- delian, single-gene disorders on the one hand and, on the other, polygenic disease such as high blood pressure and atherosclerosis. Increasingly we recognize the role of epigenetic factors in mono- genic disorders, and of likely oligogenic inheritance in conditions with suggestive family patterns. Familial aortic aneurysm disease and its relationship to bicuspid aortic valve seem to be an important example of an oligogenic pattern, as is pulmonary arterial hyper- tension. Both of these influences—oligogenic inheritance and epigenetics—contribute to phenotypic variation and to our impres- sion of penetrance. They also contribute to an important phenom- enon that affects our assessment of severity and prognosis. When a 16.11 Cardiac involvement in genetic disease Thomas A. Traill

section 16 Cardiovascular disorders 3552 syndrome is first identified as an inherited condition, it is usually in people whose phenotype is quite extreme. As a genetic condition or syndrome becomes easier to detect and more widely diagnosed, including in people whose findings are less egregious than in the ori- ginal description, so the expanding denominator of less severe cases makes for a smaller percentage risk that any given complication will occur, which means that our perception of the danger posed by a particular diagnosis generally evolves over the years in a favourable direction. The first part of this chapter deals with developmental syn- dromes that include congenital cardiac defects, with coverage re- stricted to a few relatively common disorders that are seen in adult patients. The second part describes the two common connective tissue disorders—Marfan's and Ehlers–Danlos syndromes—and the more recently described Loeys–Dietz syndrome that shares some pathogenetic mechanisms with Marfan's. Some other her- itable diseases that affect the heart are listed in a table, without discussion in the text: though they are important to other organ systems, they offer little opportunity to the cardiologist for diag- nosis or management. Syndromic congenital heart disease Aneuploidy disorders The two commonest chromosomal disorders in adult patients are Down's and Turner's syndromes, and each includes characteristic cardiac abnormalities. A third, Klinefelter's syndrome, does not. Some 25–50% of patients with Down's syndrome (OMIM 190685) have congenital heart disease. The characteristic lesion, present in about one-half of the affected hearts, is atrioventricular canal defect. This ranges

from the relatively simple primum atrial septal defect to the complete type, in which the defect involves both the atrial and ventricular septa, between which there lies a single atrioventricular valve ring. In other patients, ventricular septal defect, tetralogy of Fallot, and persistent ductus arteriosus are seen in roughly equal numbers. Patients with Down's syndrome undergo heart surgery most easily when they are infants, and the tendency has shifted from the nihilistic approach of past years to correcting serious cardiac malformations early in life. Turner's syndrome causes coarctation of the aorta, and congenital abnormalities of the aortic valve, usually a bicuspid valve. These are lesions that commonly accompany one another, even in the absence of an identifiable genetic cause. Patients with either lesion frequently have aortic ectasia. In some patients with Turner's syndrome, the whole aorta is abnormal—either hypoplastic or weakened by the presence of cystic medial necrosis. Aortic dissection may occur, and aortic surgery (e.g. to repair coarctation), can sometimes be very dif- ficult, owing to the fragile nature of the aortic wall. Other congenital heart abnormalities are not common in Turner's syndrome, except for anomalies of pulmonary venous return. Mendelian syndromes that include congenital heart disease Noonan's syndrome Noonan's syndrome (OMIM 163950) is the most common heritable syndrome that characteristically causes congenital heart disease. The syndrome shares some features with the Turner phenotype, and the two were confused between 1930 and the 1960s. In 1963, Noonan described a small series of patients with pulmonary stenosis who shared a characteristic facial appearance. Since then, the expanded phenotype has been well described and shown to be associated with a normal karyotype and autosomal dominant inheritance. The con- dition is genetically heterogeneous, with causative mutations shown in eight proteins, all members of the RAS-MAPK growth-regulating pathway that links extracellular signalling proteins to gene tran- scription factors. Mutations in the intracellular signalling molecule protein tyrosine phosphatase SHP-2 (the gene is called PTPN11) are the most common, and account for 50% of cases. The pathogenetics are complicated by both clinical and genetic overlap. Another syndrome—LEOPARD syndrome (OMIM 151100)— is also caused by PTPN11 mutations, and the Noonan phenotype is closely related to disorders caused by mutations affecting other members of the RAS-ERK intracellular signalling cascade. Within Noonan's syndrome there is some suggestion that mutations of par- ticular proteins within the signalling cascade may predict particular phenotypic features. Patients with Noonan's syndrome are of short stature, with a facies that is variously described as elfin or triangular (Fig. 16.11.1), em- phasized by ocular hypertelorism. The palpebral fissure may slope (a) (b) (c) Fig. 16.11.1 Two patients with Noonan's syndrome: (a, b) patient 1 aged 18 and 40; (c) patient 2—note scars at site of plastic surgery for pterygium colli.

 downwards and outwards, and display ptosis and an epicanthal fold. The ears are set low and rotated forwards so that the lobes are prominent, and there is characteristic webbing of the neck— the most obvious of the features that may lead to confusion with Turner's syndrome. Pectus deformities are common, as are other miscellaneous skeletal abnormalities, including cubitus valgus. Patients with Noonan's syndrome are prone to develop keloid scars. Cryptorchidism is common, as is delayed sexual maturation, but not infantilism as in Turner's syndrome. Unlike Turner's syndrome, many patients with Noonan's syndrome have a degree of mental handicap, but this is quite variable. Among the author's patients with Noonan's syndrome are a physician, an architect, a certified ac- countant, and a high-school mathematics teacher. The frequency of cardiac involvement in Noonan's syndrome is high, estimated as more than 80%, but because the diagnosis is so easily missed in the absence of congenital heart disease the true fre- quency may be less. The most characteristic lesion is

pulmonary stenosis, but in contrast to the almost stereotypical cardiovascular findings in Turner's syndrome, the range in Noonan's syndrome is broad. In many patients, the stenotic pulmonary valve leaflets are not simply fused, as in nonsyndromic pulmonary stenosis, but may be dysplastic, thickened, and immobile—unsuitable for simple balloon or surgical valvotomy. Other congenital lesions found in Noonan's syndrome are ventricular and atrial septal defects, tricuspid atresia, single ventricle, and abnormalities of the left ventricle, including congenital mitral stenosis, subaortic stenosis, and a combination of these two lesions. The electrocardiogram often shows a superior axis (left-axis deviation), even when there is pulmonary stenosis and right ventricular hypertrophy. The most ominous complication of Noonan's syndrome is cardio- myopathy, taking the form of myocardial hypertrophy complicated by progressive fibrosis. This leads, over the course of 5–15 years, to low cardiac output with very high ventricular diastolic pressures— the pathophysiology of restrictive cardiomyopathy. Since the valvular abnormalities are for the most part correctable, this hyper- trophic restrictive cardiomyopathy is the main factor limiting life expectancy. Familial supravalvar aortic stenosis and Williams' syndrome Familial supravalvar aortic stenosis is caused by loss-of-function mutation or deletion affecting the gene for elastin located on chromosome 7. Affected patients develop a tight, fleshy constric- tion of the aorta, or sometimes the pulmonary artery, at the level of the sinotubular junction above the semilunar valve (Fig. 16.11.2). In some patients, both great arteries are affected. Supravalvar aortic stenosis can lead to severe left ventricular outflow obstruction, with left ventricular failure or even sudden death. This is not a setting for balloon dilation or stenting, but the results of surgery are good, for either lesion or for both. Williams' syndrome (OMIM 194050) is one of the best-documented examples of a contiguous gene phenomenon seen in adult medicine. It is caused by macrodeletions of chromosome 7 that include the elastin gene. Hence, Williams' syndrome includes the cardiovas- cular features of familial supravalvar aortic stenosis described in the previous paragraph. In addition, more far-reaching effects caused by deletion of contiguous genes accompany these vascular abnor- malities. The full syndrome includes a characteristic facial appear- ance, with round, blue eyes, a distinctive stellate pattern of the irises, (a) (b) (c) Fig. 16.11.2 Supravalvar aortic stenosis: (a) contrast angiogram of the thoracic aorta showing normal sinuses of Valsalva (broad arrow) with constriction at the sino–tubular junction (narrow arrow). (b) Operative photograph. The patient's head is to the right. Arrows as in panel (a). (c) Fluorescence in situ hybridization (FISH) showing two markers for chromosome 7 (bright fluorescence), but only one for the elastin gene (orange fluorescence).

section 16 Cardiovascular disorders 3554 depression of the nasal bridge, outwards tilting of the nostrils, ab- normal dentition, and big lips, together with small stature, mental retardation, and a history of infantile hypercalcaemia. Mental re- tardation in Williams' syndrome takes on very individual forms, the patients often being articulate and socially adept: several purported idiot savants have had Williams' syndrome. As in the purely cardiac syndrome, surgery may be required to relieve severe left (or right) ventricular outflow obstruction. DiGeorge and velocardiofacial syndromes (chromosome 22 deletion syndrome) DiGeorge syndrome (OMIM 188400), described in 1965, comprises abnormalities of the parathyroid glands, absence or hypoplasia of the thymus, and conotruncal abnormalities of the heart such as pul- monary atresia and severe forms of tetralogy of Fallot. Some affected patients have learning disabilities or schizophrenia. It was recog- nized soon after the original description that the syndrome is gener- ally caused by deletions in a region of chromosome 22. Velocardiofacial syndrome (OMIM 192430), or Shprintzen's syn- drome, described in 1981, comprises similar cardiac abnormalities along with cleft palate, a characteristic facies, and

learning difficulty. It has since proved to be caused by deletions in the same region of chromosome 22, now often referred to as the DiGeorge critical re- gion (DGCR). A third syndrome, known as ‘conotruncal anomalies face’, is also linked to this site. With a broad spectrum of phenotypic variation, and deletions that are often quite large, it was suspected for some time that these syndromes are related manifestations of a contiguous gene phenom- enon, just as in Williams’ syndrome. However, it has emerged that the size of the deletion does not predict the extent of the pheno- type, and that within a family the same (presumably stable) dele- tion can be the cause of a wide range of phenotypes. Two candidate genes lie within the DGCR—TBX1 and UFDIL; it remains to be seen whether either can be implicated as the cause of the entire group of phenotypes. Heart–hand syndromes The two commonly recognized heart–hand syndromes are Holt– Oram syndrome and Ellis–van Creveld syndrome. Holt–Oram syndrome Holt–Oram syndrome (OMIM 142900), inherited as an autosomal dominant trait, was described in 1960. It includes a secundum atrial septal defect and skeletal abnormalities, principally affecting the upper limbs and shoulder girdle, never the legs, and usually more pronounced in the left arm (Fig. 16.11.3). Within a family, affected individuals may have skeletal abnormalities, congenital heart dis- ease, or both. The limb abnormalities cover a wide spectrum from just a triphalangeal thumb to phocomelia. Abnormalities of the hand and forearm always involve the radial side and thumb (in con- trast to Ellis–van Creveld syndrome). The characteristic cardiac ab- normality is fossa ovalis (secundum) atrial septal defect, but affected patients may have other relatively simple lesions (e.g. ventricular septal defect or pulmonary stenosis). Holt–Oram syndrome is caused by mutation in a transcription factor, TBX5, a close homologue of a transcription factor seen as phylogenetically far away as the fruit fly, where mutations produce abnormalities of the wing. Ellis–van Creveld syndrome Ellis–van Creveld syndrome (OMIM 225500) is inherited as a re- cessive trait, hence the more complete clinical descriptions have come from studies in genetically circumscribed communities, notably the Old Order Amish of Pennsylvania where, thanks to a founder effect, the gene is common and homozygotes abound. The syndrome, described in 1940, includes dwarfism, caused mainly by shortening of the forearms and lower legs, and symmetrical polydactyly affecting the ulnar side with accessory sixth and even seventh digits attached to or beyond the little finger. Cardiac in- volvement is very common, present probably in three-quarters of homozygotes. The characteristic lesion is common atrium—a lesion that has the appearance, on echocardiography and to the surgeon, of a very large primum atrial septal defect. A few pa- tients have more complete forms of atrioventricular canal defect, and—at least among the Amish—there is a high perinatal mor- tality rate among affected infants, suggesting the possibility of still more extensive cardiac involvement. The gene has been mapped to chromosome 4, sequenced, and named EVC. The protein has been identified as playing a role in the hedgehog signal transduc- tion pathway. Connective tissue disorders Marfan’s syndrome Thanks principally to the work of McKusick and his collabor- ators, beginning in 1955, Marfan’s syndrome (OMIM 154700) has become the paradigm for the clinical, genetic, and molecular investigation of the heritable disorders of connective tissue. The importance of the syndrome is heightened by the fact that its recognition and treatment have had a dramatic impact on survival among those affected. Untreated, patients had a median survival into the fourth decade before death from aortic dissec- tion and rupture (Fig. 16.11.4). Today, affected patients have a near-normal lifespan, and there are reasons to hope that recent Fig. 16.11.3 Holt–Oram syndrome.

 advances in understanding the molecular pathogenesis may yet offer treatments of this genetic disease that can forestall its complications.

In 1896, Marfan described a weak, generally hypotonic child, with what he termed arachnodactyly. In the ensuing 100 years it was appreciated that the syndrome is mendelian and pleiotropic, involving several apparently unrelated organs whose common feature seemed initially to be just the importance of elastic tissue to their structural integrity. Ocular involvement, with the lens subluxed because of failure of its suspensory ligament, was rec- ognized early in the 20th century. Cardiovascular involvement was noted incidentally in the 1940s, and studied systematically from the 1950s onwards. Skeletal involvement includes—besides long limbs and arachnodactyly—scoliosis and other abnormal- ities of the thoracic cage. The sternum may be pushed outwards or inwards by the abnormally long ribs, hence pectus carinatum and/or excavatum, often asymmetrical. Skin involvement is iden- tified by light-coloured striae, which should be looked for over the deltopectoral groove and the flanks. Less common findings are dural ectasia, which can sometimes be so marked as to cause ra- dicular symptoms, and pulmonary involvement with emphysema, spontaneous pneumothorax, or apical blebs. In severely affected children, like the one Marfan described, there may be generalized weakness and hypotonia. These last findings are hard to account for just on the basis of abnormal elastic tissue, and recognizing this led to an appreciation that the pathogenesis of Marfan involves ab- normal growth regulation, not simply a fixed physical abnormality of ground substance scaffolding. The characteristic cardiovascular findings in Marfan's syndrome are aneurysmal dilatation of the aorta, and occasionally other large arteries, and floppy mitral valve. The former was recognized in the 1920s, but not really addressed until McKusick showed that it was the principal cause of early death in the disease. Shortly afterwards, echocardiography became available to identify and follow these ab- normalities, and surgical techniques were developed by Bentall and Gott to repair the aneurysms. Until then, median life expectancy for men with Marfan's syndrome had been 45 years, for women a year or two longer. Fibrillin-1 mutations The syndrome (OMIM 134797) is caused by mutations of the fibrillin-1 gene (FBN1) on chromosome 15. It has recently emerged that besides a purely structural role, one that could hardly be re- placed by any form of treatment, fibrillin-1 acts to modulate cell-to- cell signalling during development and, at least in a mouse model, after birth. The dominant negative hypothesis, in which the mutated fibrillin protein was believed to have its effect by interfering with polymerization of the product of the nonmutated allele, thus proves to have been an oversimplification. Rather, the pleiotropic effects of FBN1 mutations prove to be mediated through upregulation of the signalling pathway transforming growth factor-β1 (TGFβ1), which is modulated by fibrillin-1. Such findings have led to the like- lihood of pharmacological treatment for the disease. Losartan, an angiotensin-II receptor blocker, which like other members of its class also blocks TGFβ1 signalling, has been shown dramatically to prevent aortic dilation in a mouse model, also in a small clin- ical cohort study. However, a larger randomized study in a group of children and young adults did not show benefit from losartan compared to traditional treatment with a β-blocking agent directed, not towards the molecular mechanism of disease, but just to redu- cing cardiac ejection rate and hence the rate of stress on the aortic wall. Only further experiment will reveal whether this unexpected result reflects differences between mice and humans with respect to signalling pathways, or whether it was related to some particular de- tail of the conduct of the trial. Diagnostic criteria The fibrillin molecule is large and some disease-causing mutations have yet to be described, hence genetic diagnosis by screening for known mutations is often not possible and diagnosis usually de- pends on clinical assessment. There are generally accepted major and minor criteria. In an index case, involvement of three organ systems is required, with major criteria in two. Major criteria are aortic aneurysm, lens subluxation, characteristic and severe skel- etal abnormalities, and dural ectasia. Minor criteria can be skin striae, mitral valve prolapse,

joint laxity, the facies, or moderate pectus excavatum. Characteristic skeletal abnormalities can be Fig. 16.11.4 Aortic ectasia and dissection in a patient with Marfan's syndrome. Note that the aortic root enlargement, to 7 cm, is not apparent from the chest radiograph.

section 16 Cardiovascular disorders 3556 arachnodactyly (encircling the wrist with the thumb and little finger, the 'wrist sign', and making a fist with a protruding thumb, the 'thumb sign'), marked pectus deformity, wingspan increased to 5% more than the height, and scoliosis. In the relative of an index case, the positive family history becomes another major criterion. In clinical practice, determining whether a patient satisfies these criteria may be fairly subjective and requires experience with the syndrome. Often, it is enough to know whether or not there is car- diovascular involvement, and there are numerous families with aortic aneurysms or ectasia who do not satisfy clinical criteria for Marfan syndrome, yet whose long-term management is identical. Indeed, in a busy cardiac surgery practice with expertise in aortic root replacement, such 'nonsyndromic' familial aortopathy repre- sents a significant proportion of patients treated, and some of these families have yielded other loci as sites for the cause of their disease. On the other hand, a lanky patient who has a normal aorta needs only infrequent follow-up, even though there may be a suspicion that he or she has a mild case of the syndrome. Clinical management Patients with Marfan syndrome should be followed up with annual or 6-monthly echocardiograms to examine the aortic root. If there is reason to suspect that the aorta may be dilated above the echo plane, then CT scanning or MRI is required at least once to validate the echo measurement. When the maximum measurement across the aorta reaches 5 cm, we generally recommend surgical replacement of the aortic root, to prevent aortic dissection (see Chapter 16.14.1), which becomes a real risk once the dimension reaches 6 cm. The traditional and very successful approach is with the composite graft, whereby a mechanical aortic valve prosthesis—to which is indissol- ubly attached a tubular vascular prosthesis—is used to replace the entire aortic root and annulus. The coronary artery ostia are excised from the native aorta and reattached to the prosthetic root. Recently, to avoid anticoagulation in certain patients, there has been interest in a valve-sparing technique of root replacement in which a vascular prosthesis is fitted snugly over the aortic valve commissures, with the native leaflets suspended in their normal anatomical arrange- ment. Long-term success with this approach will depend on the de- gree to which the valve leaflets themselves degenerate because of the connective tissue abnormality. The Ross (pulmonary autograft) pro- cedure is not appropriate in Marfan syndrome. After surgery, and especially in patients whose surgery was done as an emergency for dissection, follow-up is with periodic imaging by CT or MRI to keep the remaining aorta under surveillance. Management of mitral pro- lapse and regurgitation in Marfan syndrome is the same as in other patients. Surgery is required for severe or symptomatic regurgita- tion; mitral valve repair has proved surprisingly successful. It is usual to treat patients who have aortic involvement with β- adrenergic blockers to slow the progression to aneurysm, but the benefit is probably modest. In mice with fibrillin-1 mutations in which the Marfan phenotype is well reproduced, β-adrenergic blockade had only slight effect on aortic ectasia. This was in contrast to the dramatic effect of losartan, alluded to in a previous paragraph, and many clinicians now recommend use of this drug. We generally advise against excessively demanding sports, particularly competi- tive basketball, but in all affected children it is important to balance the risks of aortic disease against the importance of normal psycho- logical development. Pregnancy is not contraindicated in all women with Marfan syndrome, but genetic counselling should be offered, and it is advised that women not become pregnant if the aorta is en- larged to over 4 cm. Indeed, aortic dissection has been reported in a very few affected patients during pregnancy, even when they did

not previously have aortic enlargement. In this autosomal dominant condition with high penetrance, the risk for the offspring of affected mothers or fathers is 50%. This can be mitigated, when the disease- causing mutation has been identified, by preimplantation genetic diagnosis. Loeys–Dietz syndrome If the pathogenesis of Marfan syndrome lies with abnormal TGFβ signalling, then it should not come as a surprise that mutations in the TGFβ receptors also cause abnormalities of vascular and other tissues. Recently, this was confirmed in the description of Loeys– Dietz syndrome (OMIM 609192, 610380, 610168, 608967), a disease that shares some aspects of the Marfan phenotype and is associated with mutations of either of the two TGFβ receptors. Patients with Loeys–Dietz syndrome have more diffuse vascular involvement than those with Marfan, and may have dissection even in vessels that are only mildly dilated. In this, they resemble patients affected by the vascular form of Ehlers–Danlos syndrome, and the pheno- types may be very difficult to distinguish. Prominent nonvascular features include ocular hypertelorism with malar hypoplasia, bifid or broad uvula (Fig. 16.11.5), cleft palate, arachnodactyly, scoliosis, and pectus excavatum, yet excessive height is uncommon. Ehlers–Danlos syndromes In the early part of the 20th century, Ehlers and Danlos independ- ently described an association between hyperextensibility of the skin, atrophic scarring, and hypermobility of the large joints. In the
Fig. 16.11.5 Loeys–Dietz syndrome, illustrating the characteristic bifid uvula.

 following 75 years, numerous accounts were published of what we now recognize to be a group of related conditions, so that by 1988 a new classification of the Ehlers–Danlos syndrome included 10 sep- arate phenotypes in an unwieldy classification. For practical pur- poses, clinicians distinguish ‘classical’ Ehlers–Danlos, formerly types I and II, from the potentially fatal ‘vascular’ form, previously type IV. Classical Ehlers–Danlos The classical Ehlers–Danlos syndrome (OMIM 130000, 130010) is characterized by skin elasticity, abnormal scars, and joint hypermobility, and is inherited as a dominant trait. Skin hypere xtensibility is obvious (e.g. on tugging at the side of the neck or face. Joint laxity is much more marked than in Marfan syndrome, and allows for tricks like placing the feet behind the head or other con- tortionist performances, besides permitting a remarkable span on the piano or violin. It also leads eventually to severe degenerative arthritis, often with considerable deformity of the hands. Ability to touch the nose with the tip of the tongue may also provide a clue to the diagnosis. The third aspect of the phenotype, atrophic scarring, if not immediately apparent, may be sought by inspecting the knees for the results of minor childhood injuries: there one may find char- acteristic wide, atrophic (‘cigarette paper’) scars still obvious from bygone years. Cardiovascular findings in classical Ehlers–Danlos are for the most part benign. Affected patients frequently have mitral valve prolapse, as do many people with joint laxity who do not have diagnosable Ehlers–Danlos syndrome. Relatively few progress to develop severe mitral reflux or to the point of requiring surgery. Enlargement of the aortic sinuses of Valsalva may occur, but only rarely is this severe or progressive. Surgical replacement of the aortic root, as is performed in Marfan syndrome, is unusual in Ehlers–Danlos syndrome. Vascular Ehlers–Danlos Unlike classical Ehlers–Danlos, vascular Ehlers–Danlos syndrome (OMIM 130050) is a potentially fatal condition, with a natural his- tory worse than Marfan syndrome. It is genetically and biochem- ically well characterized: patients have mutations in the COL3A1 gene which encodes for type III procollagen, with inheritance as a dominant trait. The collagen defect leads to excessive fragility of blood vessels, bowel, and uterus, and the natural history of the con- dition is to present with spontaneous rupture of one of these three (in the case of the uterus, during pregnancy). Because of the intrinsic weakness of the affected tissues, surgical repair is challenging and these complications frequently prove fatal.

Furthermore, in patients who have once undergone vascular or bowel rupture, the likelihood of a second event is high. Table 16.11.1 Rare mendelian disorders affecting the cardiovascular system Biochemical abnormality Noncardiac features Cardiovascular features Osteogenesis imperfecta (OMIM 166200, and others) Heterogeneous, abnormalities of type 1 procollagen Bony fractures and deformity, blue scleras (four types described) Mitral valve prolapse and regurgitation Aortic root enlargement and aortic regurgitation Pseudoxanthoma elasticum (OMIM 264800) Areas of thickened skin and pseudoxanthomas Vascular fragility and haemorrhage Fundus: angioid streaks Extensive vascular narrowing and calcification with angina, claudication, and limb ischaemia Hunter's syndrome (MPS II) (OMIM 309900) Iduronate sulphate sulfatase X-linked usually severe with dwarfing, mental retardation, gargoylism Cardiomyopathy, coronary narrowing, valve lesions Scheie's syndrome (MPS IS) (OMIM 607016) α-Iduronidase (as in the much more severe, allelic, Hurler's syndrome, MPS IH) Arthropathy, hepatosplenomegaly, corneal clouding Aortic regurgitation Abnormal valve leaflets Morquio's syndrome (MPS IV) (OMIM 253000 and others) Galactosamine-6-sulphate sulfatase or α-galactosidase Dwarfism, deafness, spinal cord compression, and injury Aortic regurgitation and stenosis Homocystinuria (OMIM 236200) Cystathionine-α-synthase Osteoporosis, sternal deformity, lens subluxation, mental retardation Vascular thrombosis, precocious coronary atherosclerosis Fabry's disease (OMIM 301500) α-Galactosidase A Painful neuropathy, CNS disease, renal failure, corneal opacity Coronary artery disease, myocardial infarction, mitral valve dysfunction Friedreich's ataxia (OMIM 229300) Frataxin Spinocerebellar degeneration Cardiomyopathy with increased wall thickness and restrictive physiology Ventricular arrhythmias Duchenne's muscular dystrophy (OMIM 310200) Dystrophin X-linked muscular dystrophy with rapid progression during childhood and adolescence Dilated cardiomyopathy, characteristic ECG Becker's muscular dystrophy (OMIM 300376) Dystrophin X-linked muscular dystrophy, less severe than Duchenne's Dilated cardiomyopathy, variable severity Dystrophia myotonica (OMIM 160900) Myotonin protein kinase Weakness and myotonia, ptosis, cataracts, frontal balding, intellectual slowing Bundle branch block, bradyarrhythmias, less frequently VT Haemochromatosis (OMIM 235200 and others) HFE protein Diabetes, liver disease, pigmentation, arthritis, pituitary dysfunction Dilated or restrictive cardiomyopathy Arrhythmogenic right ventricular dysplasia (OMIM 107970 and others) Desmosomes, Transforming growth factor-β-3 (and others) None Palpitations, syncope, sudden death CNS, central nervous system; MPS, mucopolysaccharidosis; VT, ventricular tachycardia.

 The joint and skin features of the vascular phenotype are less ob- vious than those of the classical form. Joint hypermobility is not seen, nor the resulting arthropathy. However, the skin feels soft and thin, and is abnormally translucent such that the veins are easily seen through it as one examines the shoulders and upper chest. The face is often thin and bony, and the nose pinched. Vascular complications are hard to anticipate. Aortic ectasia and aneurysm occur only in a few patients. Moreover, arterial rupture— as common as dissection—may occur in medium-sized vessels of the brain, thorax, or abdomen just as often as the aorta. In these regards, the vascular complications of this disease are comparable to those of the Loeys–Dietz syndrome. In affected patients and their families, detailed genetic evaluation is important and should in- clude screening of COL3A1 and biochemical analysis of type III col- lagen obtained from skin biopsy and cultured fibroblasts as well as screening the TGFβ receptor genes.

Other heart-related connective tissue and metabolic disorders Osteogenesis imperfecta causes aortic and mitral regurgitation, as do several of the mucopolysaccharidoses (Table 16.11.1). It is striking, particularly in the case of osteogenesis imperfecta, how healing is almost nonexistent where there is foreign material. If the

opportunity arises, even years later, to inspect the operative result in a patient who has undergone valve replacement, the sutures look as though they had only just been placed, with minimal endothelial reaction and scar-tissue formation. FURTHER READING Brooke BS, et al. (2008). Angiotensin II blockade and aortic-root dila- tion in Marfan’s syndrome. N Engl J Med, 358, 2787–95. D’Asdia MC, et al. (2013). Novel and recurrent EVC and EVC2 mu- tations in Ellis-van Creveld syndrome and Weyers acrofacial dysostosis. Eur J Med Genet, 56, 80–7. Groenink M, et al. (2013). Losartan reduces aortic dilatation rate in adults with Marfan syndrome: a randomized controlled trial. Eur Heart J, 34, 34913–500. Habashi JP, et al. (2006). Losartan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. Science, 312, 117–21. Judge DP, Dietz HC (2005). Marfan’s syndrome. Lancet, 366, 1965–76. Lacro RV, et al. (2014). Atenolol versus losartan in children and young adults with Marfan’s syndrome. N Engl J Med, 371, 2061–71. Lowery MC, et al. (1995). Strong correlation of elastin deletions, de- tected by FISH, with Williams syndrome: evaluation of 235 patients. Am J Hum Genet, 57, 49–53. McKusick VA (2000). Ellis–van Creveld syndrome and the Amish. Nat Genet, 24, 203–4. Oderich GS, et al. (2005). The spectrum, management and clinical outcome of Ehlers–Danlos syndrome type IV: a 30-year experience. J Vasc Surg, 42, 98–106. Prendiville TW, et al. (2014). Cardiovascular disease in Noonan syn- drome. Arch Dis Child, 99, 629–34. Pyeritz RE (1983). Cardiovascular manifestations of heritable dis- orders of connective tissue. Progr Med Genet, 5, 191–302. Roberts AE, et al. (2013). Noonan syndrome. Lancet, 381, 333–42.

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