Multiple lentigines syndrome (LEOPARD syndrome or progressive cardiomyopathic lentiginosis)

Brian D Coppin, I Karen Temple

The multiple lentigines syndrome is an autosomal dominant condition which has many similarities to Noonan syndrome, except in the most striking feature from which its name is derived. The less neutral but very apt mnemonic, LEOPARD syndrome, was first used by Gorlin et al to whom the major debt in the definition of this syndrome lies, that is, Lentigines, ECG abnormalities, Ocular hypertelorism/Obstructive cardiomyopathy, Pulmonary valve stenosis, Abnormalities of genitalia in males, Retardation of growth, and Deafness. Not previously included in the mnemonic is cardiomyopathy which is an important feature because it is associated with significant mortality.

Keywords: cardiomyopathy; deafness; lentigines; pulmonary stenosis

The first documented case was probably that described in 1936 by Zeisler and Becker, who presented a 24 year old woman with lentigines and pectus carinatum to the American Dermatology Association. Photographs show hypertelorism and proasis. In 1966 Walther et al described a family with ECG abnormalities, systolic murmurs, and lentigogenesis. In 1968 Matthews described lentigo with electrocardiographic changes. In 1972, after the 1969 publication of Gorlin et al established the condition as a distinct entity, Polani and Moynahan re-reported a sibship previously reported by themselves in an article involving eight patients in a total of six families. In 1975, Voron et al presented a new case and reviewed the subject, pointing out the highly variable manifestations and suggesting criteria for the diagnosis. Many others have contributed to the more than 80 cases reported to date.

Clinical presentation
Lentigines and other pigmentedary changes
Classically, thousands of lentigines appear in childhood and increase in number until puberty. They are flat, dark brown to black in colour, and 1 to 2 millimetres in size, although they can be larger and are then described as café noir patches (fig 1). These may be congenital, but are present on the palms, soles, face, scalp, and external genitalia, but less so in these areas than the rest of the body. The irides may be involved but not the fundi. The mucosae are spared. The colour and density of the lentigines are not related to sun exposure, which differentiates them from freckles. Some patients lack lentigines but this makes the diagnosis difficult in the absence of deafness or a family history of lentigines. Additional cases presented by Gorlin et al in 1971 included a mother and son who both lacked lentigines but whose other features included sensorineural deafness, ocular hypertelorism, pulmonary stenosis, and (in the son) undescended testes. They also presented a cousin of a previously reported family who had dysplastic pulmonary valve stenosis and the typical ECG changes, but in contrast to the proband lacked lentigines.
Multiple lentigines syndrome

On histological examination of the lentigines there is pigment accumulation in the dermis as well as the deeper layers of epidermis. There is an increase in melanocytic density owing to corru- 
gation of the dermoepidermal junction. There are no naevus cells and the rete ridges are prominent. 10,11,19,20

Café au lait patches as well as axillary freckling have been described. 10,21 Localised hypo-
pigmentation (in one case in places where pre-
vious lentigines existed) is also a known feature. 22,23

CARDIOVASCULAR ABNORMALITIES

The frontal plane QRS axis is rotated anti-
clockwise so as to be superiorly orientated and 
generally lies between –60° and –120°. This fea-
ture is not present in all cases and conversely 
may be the only cardiovascular feature, and is a 
useful diagnostic clue. 5,10,24

Valvular pulmonary stenosis is the common-
est anomaly, occurring in 40% of reported 
cases. 25 It is usually mild. It occurs either as 
typical valvular pulmonary stenosis 18 or more 
commonly as a dysplastic pulmonary valve. 2,3,4,7 In 
a dysplastic pulmonary valve, three leaflets 
are present with no fusion of commissures, but 
the leaflets are poorly mobile owing to dysplas-
tic myxomatous deposits. 17 No ejection click 
is present in this instance. Infundibular and sup-
ravalval pulmonary stenosis have also been 
described. 25

Hypertrophic obstructive cardiomyopathy (HOCM) is a major concern in these patients and echocardiography to exclude this should be 
offered to all patients regardless of symp-
toms. It may be progressive and commonly 
involves the intraventricular septum. 11 In 30%, 
right ventricular outflow tract obstruction is 
also present. Muscular subaortic stenosis may 
or may not be part of HOCM. 10 Heart block, 
bundle branch block, hemiblock, atrial sepal 
defects, arrhythmias, and endocardial fibroelas-
tosis have all been described in multiple 
lentigines syndrome. 7,10,12,24,26

DYSMORPHIC FEATURES

The principal facial features include ocular 
hypertelorism, broad, flat nose, low set, poste-
rionally rotated ears, and ptosis. 2,10,25 These 
patients often have a short neck which may be 
webbed. Pectus excavatum and carinate are 
common and 10% of patients have a 
scoliosis. 10,27 A prognathic mandible is charac-
teristic. 2 Joint hypermobility is an occa-
sional feature, as is winging of the scapula. 
These patients are usually growth retarded, 
their adult height being below the 25th centile, 
despite having normal or above average birth 
weights. 10,25,28

UROGENITAL ABNORMALITIES

A few isolated renal anomalies have been described. 9,29 Genital hypoplasia in males, 
including a small penis and small, often unde-
scended testicles, are the commonest 
association. 10 Hypospadias, delayed puberty, 
absence or hypoplasia of an ovary, and late 
menarche are also listed. 7,10,18 In the reported 
pedigrees, the affected parent is more often the 

mother, suggesting that the affected male 
population may have diminished fertility. Many 
affected fathers have however been reported, 
thus ruling out an imprinted gene.

DEAFNESS

This is the rarest of the mnemonic features, 
occurring in 15-25% of reported cases. 7,10,22,25,30 
Deafness is sensorineural in nature, may be 
unilateral, but can be profound. Most cases 
have deafness diagnosed in childhood, but some 
are reported to have developed this in adult life.

OTHER FEATURES

Mild learning difficulty occurred in 23 of the 
80 cases reviewed by Voron et al. 10 Oculomotor 
defects were present in 16/80 and EEG abnor-
malities in 11/80 patients in this series.

Genetics

This condition is clearly autosomal dominant 
in its inheritance. Penetrance is high but may 
be incomplete. One of the additional cases pre-
 

Case reports (table 1)

Case 1 presented with HOCM following the 
discovery of a murmur in infancy. Long term 
propranolol was prescribed and apart from the 
development of mild right ventricular outflow 
tract obstruction he has remained haemody-
namically stable. The pulmonary valve was 
normal on echocardiography. At the age of 2 
years he developed dark lentigines diffusely 
over his whole body, including his scalp, palms, 
and soles. Relative sparing of his back was 
noted. There was no involvement of fundi or 
mucoas membranes. The anterior fontanelle 
closed late (at 2 years of age). He had severe 
unilateral right nerve deafness with normal 
hearing on the left. When last reviewed at 9 
years, he was noted to have mandibular 
prognathism, mild ptosis, posteriorly rotated 
ears, anteverted nares, mild joint hypermobil-
ity, winged scapulae, and hypertelorism with 
both the inner and outer canthal distances 
being on the 90th centile. He also had pectus 
excavatum (fig 2A).

His parents had a previous child who died at 
birth. The cause of death was thought to have 
been cardiac in origin but necropsy was not 
performed and there was no further informa-
tion. There was no family history of lentigi-
 
 

FAMILY K

Case 2 was noted to be dysmorphic in infancy. 
He had a large anterior fontanelle, hypertele-
Table 1  Case report features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lentigines</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>OFC, centile</td>
<td>85-95</td>
<td>90</td>
<td>&gt; 95</td>
<td>Large</td>
<td>50-75</td>
</tr>
<tr>
<td>Hypertelorism, centile</td>
<td>90</td>
<td>&gt; 95</td>
<td>&gt; 95</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Potosis</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Posteriorly rotated ears</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Superior ECG axis</td>
<td>(+90°)</td>
<td>(+130°)</td>
<td>(+105°)</td>
<td>(+70°)</td>
<td>(+55°)</td>
</tr>
<tr>
<td>Other ECG</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cardiac symptoms</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Hypertrophy - septal</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>RVOT obstruction</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>LVOT obstruction</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pulmonary stenosis</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>*</td>
<td>Normal</td>
</tr>
<tr>
<td>features</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latest height (cm)</td>
<td>3900</td>
<td>2980</td>
<td>3440</td>
<td>4000</td>
<td>?</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3900</td>
<td>2980</td>
<td>3440</td>
<td>4000</td>
<td>?</td>
</tr>
<tr>
<td>Deafness</td>
<td>Left sided</td>
<td>Mild,</td>
<td>Unilateral,</td>
<td>At 59</td>
<td></td>
</tr>
<tr>
<td></td>
<td>only</td>
<td>conduction</td>
<td>congenital years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormalities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* = feature present, = feature absent, ? = feature not ascertained, * = unilateral undescended testis, OFC = occipitofrontal circumference, RVOT = right ventricular outflow tract, LVOT = left ventricular outflow tract.

![Figure 2](A) The face of case 1 aged 9 years showing hypertelorism and lentigines. (B) Case 2 in infancy showing the typical faces. Lentigines became manifest later. (C, D) Case 3 in adulthood. Note the hypertelorism, multiple lentigines, and low set, posteriorly rotated ears.

Diagnosis

Diagnostic criteria were proposed by Voron et al. in 1976, which included lentigines plus two other recognised features or a first degree relative relation with lentigines plus three other features in the patient. This still seems reasonable pending clarification of the genetic defect.

Differential diagnosis (table 2)

NOONAN SYNDROME

The presence of lentigines and deafness in LEOPARD syndrome are the only distinguishing features between this and Noonan syndrome. The cardiovascular, growth, and dysmorphic findings are identical. Cases of lentiginosis sine lentigines are well described in families with LEOPARD syndrome and such patients would be indistinguishable from Noonan syndrome in the absence of a family history. It is speculative that the two conditions may be allelic.
Multiple lentigines syndrome has features in common with NF1. However, the skin findings differ and the number of true café au lait patches do not usually fulfil the diagnostic criteria for NF1. In 1996, Wu et al. reported a de novo missense mutation in exon 18 of the NF1 gene in a woman with possible LEOPARD syndrome. She had multiple lentigines, mild mental retardation, and both valvular and subaortic stenosis. In the review of 80 cases by Voron et al., valvular aortic stenosis was not described, hence this is atypical. In addition, the patient was not deaf. She lacked neurofibromas and Lisch nodules and therefore features were also not typical of NF1. This finding is yet to be repeated in a patient with classical LEOPARD syndrome.

Watson syndrome (cafe au lait spots, atypical pulmonary valve stenosis, and learning difficulties) has phenotypic features common to both NF1 and LEOPARD syndrome. Mutations in the NF1 gene have been shown in patients with this condition.

PEPTZ-JEGHER SYNDROME (PJ)

It is easy to confuse these two conditions because gastrointestinal symptoms are not always present, particularly in childhood, and the lentigines may appear similar. However, in Peutz-Jegher syndrome the lentigines are also present on mucosal surfaces. Patients with PJ syndrome, however, lack the coarse facial appearance and characteristic ECG seen in patients with LEOPARD syndrome.

NAME SYNDROME (NAEVI, ATRIAL MYXOMA, MYXOID NEUROFIBROMATA AND EPIPHILIDES/ENDOCRINE NEOPLASIA)

Multiple dark macules occur in this condition with a similar appearance to freckles (fig 3). Mucosal involvement and the lack of dysmorphic features characteristic of LEOPARD syndrome help the clinician to differentiate these diagnoses; 60% of patients manifest subcutaneous myxomas, most commonly on the eyelids, pinnae, and nipples. Half of patients develop intracardiac myxomas, usually biventricular, but some are intraventricular. Endocrine neoplasia occurs in 15-30%.

The authors were recently consulted by a family with NAME syndrome who were misdiagnosed as LEOPARD syndrome until routine cardiac follow up showed an atrial myxoma. Several features of LEOPARD syndrome were noticed in those who had lentigines; these included sensorineural deafness, valvular pulmonary stenosis, innocent heart murmurs, winged scapulae, glandular hypospadias, cafe au lait patches, moderate learning difficulties, hypermobile joints, kyphoscoliosis, pectus excavatum, and prognathism.

We would like to thank Dr L Mulligan for molecular investigation of patients with LEOPARD syndrome and Dr A P Salmon for discussions regarding the cardiac features.

Table 2 Differential diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Leopard</th>
<th>Noonan</th>
<th>NF1</th>
<th>PJ</th>
<th>NAME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin lentigines/freckling</td>
<td>+ (93%)</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Mucosal lentigines</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hypertelorism</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Deafness</td>
<td>+ (15-25%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Male genital abnormalities</td>
<td>+ (38%)</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HOCM</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pulmonary valve stenosis</td>
<td>+ (40%)</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cardiac tumour</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GIST polyposis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cafe au lait patches</td>
<td>+ (19%)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Growth retardation</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

+ = a well described association, - = not a recognised association, * one reported case, † not a previously reported feature but present in the family discussed under "Differential diagnosis".

NEUROFIBROMATOSIS TYPE 1 (NF1)

LEOPARD syndrome has features in common with NF1. However, the skin findings differ and the number of true café au lait patches do not usually fulfil the diagnostic criteria for NF1. In 1996, Wu et al. reported a de novo missense mutation in exon 18 of the NF1 gene in a woman with possible LEOPARD syndrome. She had multiple lentigines, mild mental retardation, and both valvular and subaortic stenosis. In the review of 80 cases by Voron et al., valvular aortic stenosis was not described, hence this is atypical. In addition, the patient was not deaf. She lacked neurofibromas and Lisch nodules and therefore features were also not typical of NF1. This finding is yet to be repeated in a patient with classical LEOPARD syndrome. In cases 1 to 5, mutations were looked for in 6.6 kb of the NF1 CDNA but were not found (Dr Lois Mulligan, CRC, Human Cancer Research Genetics Group, Cambridge, personal communication, 1993).

Watson syndrome (café au lait spots, atypical pulmonary valve stenosis, and learning difficulties) has phenotypic features common to both NF1 and LEOPARD syndrome. Mutations in the NF1 gene have been shown in patients with this condition.

Figure 3 Patient with NAME syndrome. The lentigines are very similar to those in multiple lentigines syndrome, but the distribution differs as buccal mucosa is involved.