Inherited Tumour Syndromes

The study of familial cancer syndromes has led to the discovery of key genes that are important not only for the understanding of the mechanisms of genetic susceptibility but also for giving new insights into genetic and signaling pathways involved in sporadic cancers. Investigations into the rare skin disease xeroderma pigmentosum has led to the discovery of 7 DNA repair genes involved in the nucleotide excision repair pathway. Studies of these patients allowed us to understand the mechanism of DNA repair in the general population. Eventually, the in-depth analysis of the activity of these repair genes may allow us to define a subpopulation of individuals at higher risk of developing cancers in different organ sites. This chapter contains a detailed description of clinical, pathological and genetic data of some major, well characterized inherited syndromes associated with skin cancer or other skin disorders.
### Table 7.1

**Inherited disorders associated with skin abnormalities**

<table>
<thead>
<tr>
<th>OMIM</th>
<th>Disease</th>
<th>Inheritance</th>
<th>Tumour types</th>
<th>Locus</th>
<th>Gene</th>
<th>Protein</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>278700</td>
<td>Xeroderma Pigmentosum</td>
<td>AR</td>
<td>BCC SCC MM</td>
<td>9q22.3</td>
<td>XPA</td>
<td>XPA</td>
<td>Damaged DNA-binding interaction with TFIIH and XPF/XPG endonucleases</td>
</tr>
<tr>
<td>133510</td>
<td>Complementation group B</td>
<td>2q11</td>
<td>XPB/ERCC3 XPB</td>
<td>3p25.1</td>
<td>XPC</td>
<td>XPC</td>
<td>Damaged DNA-binding only involved in global genomic repair. Heterodimer with HHR23B</td>
</tr>
<tr>
<td>278720</td>
<td>Complementation group C</td>
<td>19q13.2-3</td>
<td>XPD/ERCC2 XPD</td>
<td>11q12-13</td>
<td>DDB1</td>
<td>XPE P127</td>
<td>Damaged DNA-binding only involved in global genomic repair. Heterodimer with DDB2</td>
</tr>
<tr>
<td>600811</td>
<td>Complementation group E</td>
<td>11p11-12</td>
<td>DDB2</td>
<td>XPE P48</td>
<td>16p13-13</td>
<td>XPF/ERCC4 XPF</td>
<td>5' structure-specific endonuclease heterodimer with ERCC1</td>
</tr>
<tr>
<td>27860</td>
<td>Complementation group G</td>
<td>13q32-33</td>
<td>XPG/ERCC5 XPG</td>
<td>12q14</td>
<td>CDK4</td>
<td>CDK4</td>
<td>3' structure-specific endonuclease. Stabilization of the open complex</td>
</tr>
<tr>
<td>603968</td>
<td>Xeroderma pigmentosum variant</td>
<td>6p21.1</td>
<td>POLh POL h</td>
<td>9p21</td>
<td>CDKN2A</td>
<td>P16/INK4</td>
<td>Inhibits CDKs from phosphorylating Rb, thereby freezing cell cycle</td>
</tr>
<tr>
<td>600160</td>
<td>Familial melanoma</td>
<td>AD</td>
<td>M M</td>
<td>1p36(?)</td>
<td>unknown</td>
<td>unknown</td>
<td>Activated protein kinase resistant to p16 inhibition; overphosphorylates Rb, thereby driving cell cycle</td>
</tr>
<tr>
<td>109400</td>
<td>Naevoid basal cell carcinoma syndrome</td>
<td>AD</td>
<td>BCC</td>
<td>9q22.3</td>
<td>PTCH1</td>
<td>PTCH1</td>
<td>Development gene; regulates the Sonic Hedgehog signaling pathway</td>
</tr>
<tr>
<td>158350</td>
<td>Cowden disease b</td>
<td>AD</td>
<td>M H</td>
<td>10q23</td>
<td>PTEN/MMAC1</td>
<td>PTEN/MMAC1</td>
<td>Lipid/protein phosphatase</td>
</tr>
<tr>
<td>158320</td>
<td>Muir-Torre syndrome</td>
<td>AD</td>
<td>CSN</td>
<td>2p22</td>
<td>hMSH2</td>
<td>hMSH2</td>
<td>Involved in DNA mismatch repair</td>
</tr>
<tr>
<td>175100</td>
<td>Gardner syndrome a</td>
<td>AD</td>
<td>EC</td>
<td>5q21</td>
<td>APC</td>
<td>APC</td>
<td>Negatively regulates β-catenin, a cytoskeletal and growth-promoting protein, and the WNT signaling pathway</td>
</tr>
<tr>
<td>131100</td>
<td>Multiple endocrine neoplasia 1</td>
<td>AD</td>
<td>M FA</td>
<td>11q13</td>
<td>MEN1</td>
<td>menin</td>
<td>Inhibitor of JH D-activated transcription</td>
</tr>
<tr>
<td>171400</td>
<td>Multiple endocrine neoplasia 2</td>
<td>AD</td>
<td>CLA</td>
<td>10q11.2</td>
<td>RET</td>
<td>RET</td>
<td>Tyrosine kinase receptor involved in signal transduction</td>
</tr>
<tr>
<td>605284</td>
<td>Tuberous sclerosis 1</td>
<td>AD</td>
<td>M SL</td>
<td>9q34</td>
<td>TSC1</td>
<td>hamartin</td>
<td>Interacts with tuberin and exhibits growth-inhibitory activity</td>
</tr>
<tr>
<td>191092</td>
<td>Tuberous sclerosis 2</td>
<td>AD</td>
<td>M SL</td>
<td>16p13.3</td>
<td>TSC2</td>
<td>tuberin</td>
<td>GTPase-activating protein for RAP1 and RAB5; interacts with hamartin</td>
</tr>
<tr>
<td>162200</td>
<td>Neurofibromatosis 1 b (von Recklinghansen disease)</td>
<td>AD</td>
<td>FTK</td>
<td>17q11.2</td>
<td>NF1</td>
<td>neurofibromin</td>
<td>Negatively regulates ras-family of signal molecules through GAP function: Tumour suppressor activity</td>
</tr>
<tr>
<td>101000</td>
<td>Neurofibromatosis 2 b</td>
<td>AD</td>
<td>ST</td>
<td>2q12.2</td>
<td>NF2</td>
<td>merlin</td>
<td>Integrates cytoskeletal signaling</td>
</tr>
<tr>
<td>210900</td>
<td>Bloom syndrome b</td>
<td>AR</td>
<td>ST</td>
<td>15q26.1</td>
<td>BLML/REQL3</td>
<td>BLML</td>
<td>DNA helicase; unwinds DNA at blocked replication forks</td>
</tr>
<tr>
<td>175200</td>
<td>Peutz-Jeghers syndrome</td>
<td>AD</td>
<td>M ML</td>
<td>19p13.3</td>
<td>STK11</td>
<td>STK11</td>
<td>Serine/threonine protein kinase; Tumour suppressor activity</td>
</tr>
<tr>
<td>268400</td>
<td>Rothmund-Thomson syndromeb</td>
<td>AR</td>
<td>D</td>
<td>8q24.3</td>
<td>REQL4</td>
<td>REQL4</td>
<td>DNA helicase; unwinds DNA at blocked replication forks/recombination sites</td>
</tr>
<tr>
<td>277700</td>
<td>Werner syndrome b</td>
<td>AR</td>
<td>SSC</td>
<td>8p12</td>
<td>WRN/REQL2</td>
<td>WRN</td>
<td>DNA helicase; unwinds DNA at blocked replication forks/recombination sites</td>
</tr>
<tr>
<td>135150</td>
<td>Birt-Hogg Dubé Syndrome</td>
<td>AD</td>
<td>HFH</td>
<td>17p11.2</td>
<td>BHD</td>
<td>folliculin</td>
<td>Unknown</td>
</tr>
<tr>
<td>132700</td>
<td>Cylindromatosis familial</td>
<td>AD</td>
<td>C</td>
<td>16q12-13</td>
<td>CYLD1</td>
<td>CYLD1</td>
<td>Tumour suppressor gene. Protein with 3 cytoskeletal-associated-protein-glycine-conserved domains implicated in the attachment of organelles to microtubules</td>
</tr>
</tbody>
</table>
Familial cutaneous melanoma

Definition
Familial melanoma is defined as the occurrence in at least two affected blood-relatives up to the third degree on one side of the family. This genetic susceptibility is caused by germline mutations in the CDKN2A/p14ARF or CDK4 gene.

OMIM numbers
600160: Cyclin-dependant kinase inhibitor 2A; CDKN2A
Synonyms: CDK4 Inhibitor; multiple tumour suppressor 1, MTS1; TP16; p16(INK4); p16(INK4A); p19(ARF); p14(ARF).

123829 Cyclin-dependant kinase 4; CDK4
Synonyms: Cell Division Kinase 4; Cutaneous malignant melanoma 3, CMM3.

155600 Melanoma, cutaneous malignant; CMM

Synonyms: Melanoma, malignant; Familial atypical mole-malignant melanoma syndrome, FAMMM; Melanoma familial, MLM; Dysplastic naevus syndrome, hereditary, DNS; Melanoma, cutaneous malignant 1, CMM1; B-K Mole syndrome.

155755 Melanoma-astrocytoma syndrome
Synonyms: Melanoma and neural system tumour syndrome

155755 Melanoma-pancreatic cancer syndrome
Synonyms: Familial atypical multiple mole melanoma pancreatic carcinoma syndrome (FAMMMPC)

Epidemiology
Cutaneous melanoma is a typical example of a multifactorial disease, where both genetic and environmental factors are involved and interact. Genetic factors were first suspected through the existence of familial aggregations of CM. The proportion of familial cases varies from 4-15% across different studies. Within large families, familial aggregation of melanoma was consistent with autosomal, dominant inheritance. In addition to CM family history, numerous epidemiological studies have demonstrated that cutaneous and pigmentary characteristics (the presence of numerous naevi, naevi atypia, skin colour, red hair and freckles), sun exposure (particularly during childhood) and reactions to sun exposure (inability to tan and propensity to develop sunburns) are major CM risk factors. Some melanoma risk factors also show familial aggregations independent of melanoma, suggesting the existence of genetic factors specific to these phenotypes {309}. The various patterns of associations of these different phenotypes (phototype, naevus phenotypes and CM) across families are likely to result from complex interactions of genetic and environmental factors underlying these traits.

Clinical features and neoplastic disease spectrum
Cutaneous melanoma (CM)
Characteristics of familial melanoma include multiple cases of CM among blood-relatives on the same side of the family. Potential genetic predisposition may be suspected also in sporadic cases such as multiple primary CM in the same individual or early age of onset {1239}.

Pancreatic cancer
The existence of an increased risk of pancreatic cancer in a subset of CDKN2A families has been reported {286,859}.

Breast cancer
An excess of breast cancer has been described in two sets of families, Italian and Swedish {286,822}.

Table 7.2: Inherited tumour syndromes
<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>Gene Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR*</td>
<td>Autosomal Recessive</td>
</tr>
<tr>
<td>AD</td>
<td>Autosomal Dominant</td>
</tr>
<tr>
<td>BCC**</td>
<td>Basal Cell Carcinoma</td>
</tr>
<tr>
<td>SCC</td>
<td>Squamous Cell Carcinoma</td>
</tr>
<tr>
<td>M M</td>
<td>Malignant Melanoma</td>
</tr>
<tr>
<td>M H</td>
<td>Multiple Hamartomatous</td>
</tr>
<tr>
<td>CSN</td>
<td>Cutaneous Sebaceous Neoplasms</td>
</tr>
<tr>
<td>EC</td>
<td>Epidermoid Cysts</td>
</tr>
<tr>
<td>M FA</td>
<td>Multifocal Angiofibromas</td>
</tr>
<tr>
<td>CLA</td>
<td>Cutaneous Lichen Amyloidosis</td>
</tr>
<tr>
<td>M SL</td>
<td>Malignant Skin Lesions</td>
</tr>
<tr>
<td>FTK</td>
<td>Fibromatous Tumours of the Skin</td>
</tr>
<tr>
<td>ST</td>
<td>Skin Tumours</td>
</tr>
<tr>
<td>M ML</td>
<td>Malignant Macules of the Lip</td>
</tr>
<tr>
<td>D</td>
<td>Dermatosis</td>
</tr>
<tr>
<td>SSL</td>
<td>Scleroderma-like Skin Changes</td>
</tr>
<tr>
<td>HFF</td>
<td>Hair Follicle Hamartomas</td>
</tr>
<tr>
<td>C</td>
<td>Cyclinindroma</td>
</tr>
</tbody>
</table>

a Already described in the WHO Classification of Tumours of the Digestive System {944}
b Already described in the WHO Classification of Tumours of Soft Tissue and Bone {756}
Inherited tumour syndromes

Nervous system tumours

Rare families have been described displaying melanoma and neural system tumours (NSTs) over several generations {129,1230}. This has been termed melanoma-astrocytoma syndrome due to the presence of cerebral astrocytomas in the first family described.

Uveal melanoma (UM)

Certain melanoma-prone kindred have members affected by either uveal and/or cutaneous melanoma. The first CDKN2A germline mutation was detected recently in a melanoma-prone family, where one carrier was affected by UM and the other by CM (Kannengiesser C. et al., Gene Chromosome and Cancer, pending).

Naevus: total number (TN), clinically atypical (AN), histologically dysplastic (DN)

These naevus phenotypes are major risk factors for CM but whether they represent precursor lesions in the course of tumour development is still unclear. There are several lines of evidence suggesting that distinct genetic factors may be involved in CM and number of naevi {309}. CDKN2A does not appear to be a “naevus” predisposing gene; this phenotype was found in only half of the subjects with a CDKN2A gene mutation and who had developed melanoma (2226) and a study of Australian twins has reported that a CDKN2A-linked gene may influence flat moles but has no effect on raised or atypical moles {2601}. Naevus phenotypes (TN, AN and/or DN) have been shown to influence the penetrance of CDKN2A in melanoma-prone North-American and French families (860,452A) with a greater effect of DN in non-carriers than in carriers of CDKN2A mutations in the American sample.

Genetics

Gene structure and mutations

Two genes (encoding three proteins) conferring a high risk of developing melanoma have been identified to date, CDKN2A/p14ARF and CDK4. In addition, a low-risk melanoma susceptibility gene has also been identified, the melanocortin-1 receptor gene (MC1R).

CDKN2A/p16INK4A gene

Linkage analyses, cytogenetic studies and loss of heterozygosity (LOH) studies in tumour cells have led researchers to suspect the existence of a CM susceptibility gene at 9p21 locus. The gene, p16INK4A/CDKN2A, was cloned in 1993 {2140} and formally identified as a melanoma susceptibility gene in 1994 {1088,1184}.

The CDKN2A transcript includes exons 1a, 2 and 3. It encodes the 156 amino-acid p16INK4A protein composed of four ankyrin repeats which are motifs involved in protein-protein interactions. P16INK4A binds to cyclin-dependent kinase 4 (CDK4) and 6 (CDK6), therefore preventing binding of cyclin D1 to the CDKs. Cyclin D1/CDK4/6 complexes participate in the phosphorylation of the retinoblastoma protein (RB), allowing the cell to progress beyond the G1 phase of the cell division cycle (2166). The p16INK4A protein inhibits RB-dependant cell cycle and therefore acts as a tumour suppressor.

The search for mutations of the CDKN2A gene in numerous familial studies around the world shows that the frequency of CDKN2A mutations is about 20% on average but varies from 5-50% depending on the criteria for family selection. Homozygotes for CDKN2A germline mutation have been described in relation to a Dutch founder effect; they display similar phenotypes than heterozygous individuals {912}. Mutations of the CDKN2A gene are detected in approximately 10% of sporadic multiple melanoma cases, without any evidence of de novo mutations up to date but in relation to the existence of a founder effect for some of them {115}. To date, no germ line mutations have been found in cases of childhood melanoma (<18-20 years of age) lacking a family CM context {2507}. Most CDKN2A mutations are missense mutations scattered throughout the coding sequences of exons 1a and 2. Functional studies of mutant p16INK4A proteins have been carried out using several assays displaying various sensitivity: CDK-binding, kinase activity inhibition, growth arrest and protein cellular localisation assays. Two more complex mutations have been also described: a mutation located within CDKN2A 5'UTR, creating an aberrant initiation codon {1435} and a deep intronic mutation (IVS2-105A/G) of CDKN2A, leading to aberrant mRNA splicing {956}. Recurrent mutations described in melanoma-prone families from different continents have been shown to be founder mutations {115,488}.

Within the International Melanoma Consortium, CDKN2A mutation penetrance was estimated to be, in a set of 80
families, 0.58 in Europe, 0.76 in the United States and 0.91 in Australia, by age 80 years ([251]). This variation of penetrance by geographical location was found to be similar to the variation of overall population incidence rates among these countries. This suggests that the same risk factors mediate CM risk to the same extent in CDKN2A mutation carriers as in non-carriers. Moreover, CM risk does not change according to whether or not the mutation can simultaneously alter the p16INK4A and p14ARF proteins.

Three MC1R variant alleles also act as modifiers of melanoma risk in families segregating CDKN2A mutations: MC1Rvar/var genotypes increased the melanoma penetrance in CDKN2A carriers from 50-84% in Australia (sunny country) and from 18–55% in the Netherlands (less sunny country) ([291,2410]).

**CDKN2A/p14ARF gene**

In 1995, it was discovered that part of CDKN2A gene was common to another transcript. This second transcript (exons 1b, 2 and 3) encodes the human p14ARF protein (ARF meaning "alternative reading frame") composed of 132 amino-acid, encoded by exons 1b and 2. According to the current state of knowledge, p14ARF is involved in regulation of the cell cycle and apoptosis via the p53 and RB pathways, by interacting with MDM2 (leading to p53 protein accumulation and to RB inactivation) and E2F1 proteins ([1437]).

Mutations in exon 2 potentially affect p16INK4A and p14ARF proteins at the same time. Despite this dual coding capacity of the INK4A/ARF locus, recent description of three p14ARF germ-line alterations involving only exon 1b suggests a direct role for p14ARF haploinsufficiency in melanoma predisposition: (1) a deletion restricted to exon 1b and segregating with melanoma and neural cell tumours within a family (1890), (2) a 16bp insertion in exon 1b in a sporadic multiple melanoma case (1945), (3) a splice mutation in exon 1b in a two melanoma-cases family (1022).

**A role for both p14ARF and p16INK4A/CDKN2A genes?**

Germ-line alterations presumably altering both p16INK4A and p14ARF functions, have been described in three CM and NSTs families: two large deletions involving the INK4A locus (128) and a CDKN2A splice point mutation, leading to p16INK4A and p14ARF transcripts lacking exon2 (1818). However, it cannot be concluded that both p16INK4A and p14ARF inactivation are necessary for melanoma-astrocytoma syndrome as a fourth such family has been also described with a germ line deletion apparently restricted to the p14ARF -specific exon 1b (1890).

**CDK4 gene**

The CDK4 gene on chromosome 12q13 is composed of 8 exons within a 5-kilo-bases (kb) segment. The initiation codon is located in exon 2, the stop codon in exon 8. This gene encodes the cyclin-dependant kinase 4 (CDK4), a 304 amino-acid protein. It has been identified as a melanoma predisposing gene in three families world-wide (2226,2607). Germline mutations affect Arg-24 residue in exon 2, which plays a key role in p16INK4A binding. The mutation induces the loss of the cell cycle down-regulation signal that p16INK4A exerts through RB phosphorylation. In a “knock-in” Cdk4R24C/R24C mouse model, constitutive Cdk4 activation is oncogenic (1891).

**Application of genetic testing in the clinical testing**

There is some evidence that non-carrier of CDKN2A mutations in melanoma-prone families may have a higher incidence of melanoma than the general population, presumably due to co-inheritance of other low-risk susceptibility genes and common environmental risk amongst family members. Therefore, genetic testing for melanoma is of limited clinical utility to date, mainly because a negative genetic test may give dangerously false security. Testing should be done in research protocols and first-degree relatives of high-risk individuals should be engaged in the same programs of melanoma prevention and surveillance, irrespective of the results of any gene testing. However, in countries of low melanoma incidence such as most European countries, DNA testing may improve compliance with sun protection and surveillance in identified mutation carriers. In such situations, CDKN2A testing could be proposed after careful genetic counselling ([1238]).
Xeroderma pigmentosum

Definition
Xeroderma pigmentosum (XP) is an autosomal recessive disease with sun sensitivity, photophobia, early onset of freckling, and subsequent neoplastic changes on sun-exposed surfaces (284, 778). There is cellular hypersensitivity to UV radiation and to certain chemicals in association with abnormal DNA repair (2419). Some of the patients have progressive neurologic degeneration. The XP syndrome is genetically heterogeneous. Patients with defective DNA nucleotide excision repair (NER) have defects in one of 7 NER genes, while XP variant patients have normal NER and a defect in a polymerase gene (316,500).

OMIM Numbers
278700 - XPA
133510 - XPB
278720 - XPC
278730 - XPD
278740 - XPE
278760 - XPF
278780 - XPG
278750 - XP variant

Synonyms
De-Sanctis Cacchione syndrome, pigmented xeroderma, xeroderma pigmentosum variant

Epidemiology
Incidence
Xeroderma pigmentosum occurs with an estimated frequency of 1:1,000,000 in the United States (1322). It is more common in Japan, the Middle East and North-Africa. Patients have been reported worldwide in all races including Whites, Asians, Blacks, and Native Americans. Consanguinity is common. There is no significant difference between the sexes.

Clinical features
Abnormalities may be present in the skin, eyes, or nervous system. There is a greatly increased frequency of cancer on sun-exposed sites.

Skin
Approximately half of the patients with XP have a history of acute sunburn reaction on minimal UV exposure (1322). The other patients give a history of normal tanning without excessive burning. In all patients, numerous freckle-like hyperpigmented macules appear on sun-exposed skin.

The median age of onset of the cutaneous symptoms is between 1 and 2 years (1321). Repeated sun exposure results in dry and parchment-like skin with increased pigmentation, hence the name xeroderma pigmentosum (“dry pigmented skin”). Pre-malignant actinic keratoses may develop at an early age.

Eyes
Ocular abnormalities are almost as common as the cutaneous abnormalities (801,871,2424). Clinical findings are strikingly limited to the anterior, UV-exposed structures. Photophobia is often present and may be associated with prominent conjunctival injection. Continued UV exposure of the eye may result in severe keratitis leading to corneal opacification and vascularization. The lids may develop loss of lashes and atrophy of the skin of the lids results in the lids turning out (ectropion), or in (entropion), or complete loss of the lids in severe cases. Benign conjunctival inflammatory masses or papillomas of...
the lids may be present. Basal and squamous cell carcinoma, and melanoma of UV-exposed portions of the eye are common.

**Nervous system**

Neurologic abnormalities have been reported in approximately 30 percent of the patients. The onset may be early in infancy (the De-Sanctis Cacchione syndrome) or delayed until the second decade. The neurologic abnormalities may be mild (e.g., isolated hyporeflexia) or severe, with progressive mental retardation, sensorineural deafness (beginning with high-frequency hearing loss), spasticity, or seizures. In clinical practice, deep tendon reflex testing and routine audiometry can usually serve as a screen for the presence of XP-associated neurologic abnormalities. The predominant neuropathologic abnormality found at autopsy in patients with neurologic symptoms was loss (or absence) of neurons, particularly in the cerebrum and cerebellum (1894).

**Cancer**

Patients with XP under 20 years of age have a greater than 1000-fold increased risk of skin cancer (basal cell or squamous cell carcinoma or melanoma) (1321). Multiple primary skin cancers are common. The median age of onset of non-melanoma skin cancer reported in patients with XP was 8 years. This 50-year reduction in comparison to the general population is an indication of the importance of DNA repair in protection from skin cancer in normal individuals. There is a greatly increased frequency of cancer of the anterior portion of the eye and of the oral cavity, particularly squamous cell carcinoma of the tip of the tongue. These are presumed sun-exposed sites.

Brain (sarcoma and medulloblastoma), central nervous system (astrocytoma of the spinal cord), lung, uterine, breast, pancreatic, gastric, renal, and testicular tumours and leukaemias have been reported in a small number of XP patients. Overall, these reports suggest an approximate ten to twenty-fold increase in internal neoplasms (1321).

**Diagnosis**

There have been no consistent routine clinical laboratory abnormalities in patients with XP. Diagnosis is based on clinical features and confirmed by tests of cellular hypersensitivity to UV damage along with a defect in nucleotide excision repair for classical XP (778).

**Cellular hypersensitivity**

Cultured cells from patients with XP generally grow normally when not exposed to damaging agents. The population growth rate or single-cell colony-forming ability is reduced to a greater extent than normal, however, following exposure to UV radiation. A range of post-UV colony-forming abilities has been found with fibroblasts from patients, some having extremely low post-UV colony-forming ability and others having nearly normal survival. XP fibroblasts are also deficient in their ability to repair some UV-damaged viruses or plasmids to a functionally active state. XP variant cells are specifically sensitive killing by UV-irradiation in the presence of caffeine.

**DNA repair**

Cells from most XP patients have a defect in one of 7 genes (XPA through XPG) involved in the nucleotide excision repair (NER) system (500). The NER pathway is described in Figure 7.6 (2253). The DNA repair defect can be measured by post-UV unscheduled DNA synthesis. Host cell reactivation assays can be used to determine the complementation group by use of a panel of cloned DNA repair genes. Cells from XP variant patients have normal NER but have a defect in an error-prone polymerase (pol eta) (316).

Prenatal diagnosis can be performed by use of unscheduled DNA synthesis assays on cultured amniotic fluid cells and by molecular analysis of trophoblast biopsies (52,1309). Most XP cells have a normal response to treatment with x-rays, indicating the specificity of the DNA repair defect.

**Genetics**

The seven complementation groups found for the classical XP correspond to...
seven genes involved in NER (2253, 2419); XPC, XPE and XPA code for proteins able to recognize DNA lesions produced by various DNA damaging agents, including UV-radiation. XPB and XPD are two helicases necessary to open the double helix at the site of the lesion. XPF and XPG are two endonucleases able to cut the damaged strand at the 5’ and 3’ sites, respectively. Numerous other enzymes are necessary to complete the error-free repair but defects have not yet been identified in these genes in association with human diseases.

There is marked clinical and molecular heterogeneity in XP. Patients in XP complementation groups A, B, D, and G may have neurological abnormalities in addition to skin involvement. Patients with defects in XP complementation group D may have one of at least 5 different clinical phenotypes: XP with skin disease, XP with neurological disease, the XP/Cockayne syndrome complex (1894), trichoithiodystrophy (TTD - a disorder with sulphur deficient brittle hair) (1113) or XP/TTD (315).

**Treatment**

Management of patients with XP is based on early diagnosis, life-long protection from UV radiation exposure, and early detection and treatment of neoplasms (778).
Naevoid basal cell carcinoma (Gorlin) syndrome

**Definition**
The naevoid basal cell carcinoma syndrome (NBCCS) is a genodermatosis caused by germline mutations of the PTCH gene. It is characterized by numerous basal cell cancers and epidermal cysts of skin, odontogenic keratocysts of jaws, palmar and plantar pits, calcified dural folds, various neoplasms or hamartomas (ovarian fibromas, medulloblastoma, lymphomesenteric cysts, fetal rhabdomyomas, etc.) and various stigmata of maldevelopment (rib and vertebral abnormalities, Sprengel anomaly, enlarged head circumference, cleft lip and/or palate, cortical defects of bones and other lesions.

**OMIM number**
109400

**Synonyms**
Naevoid basal cell carcinoma syndrome, Gorlin syndrome, Gorlin-Goltz syndrome, basal cell naevus syndrome.

**Epidemiology**
The frequency of NBCCS has been variously estimated. It constitutes about 0.4% of all cases of basal cell carcinomas. Evans et al (698) suggested that the minimal prevalence was 1 per 57,000.

**Clinical features**
Although the syndrome is remarkably variable in sites of involvement, the most persistent problems are the odontogenic keratocysts and the inordinate number of basal cell carcinomas, only a fraction of which become aggressive (867, 868, 1273).

**Skull**
The head appears large (>60 cm in adults). Relative macrocephaly (occipito-frontal circumference greater than 95th centile for height) is found in 50%. Mild mandibular prognathism, noted as "pouting lower lip", is seen in 35%.

**Basal cell carcinomas**
These may appear as early as 2 years of age, especially on the nape, most often proliferate between puberty and 35 years. There appears to be a relationship to increased sun exposure. The basal cell cancers, which vary in number from a few to literally thousands, range in size from 1-10 mm in diameter. They are pearly to flesh coloured to pale brown and may be mistaken for skin tags or naevi. The basal cell carcinomas which most often involve the face and upper chest may become aggressive and invade locally. Increase in size, ulceration, bleeding and crusting indicate invasion. Radiation therapy causes proliferation of basal cell carcinomas and invasion several years later.

**Milia**
Small keratin-filled cysts (milia) are found intermixed with basal cell carcinomas in 30-50%. Larger, often multiple, epidermal cysts arise on the limbs and trunk in about 35-50% of whites. Multiple cysts are located on the palpebral conjunctiva in about 40%.

**Pits**
Palmar and, somewhat less often, plantar...
Inherited tumour syndromes

...should be carefully examined for signs of the syndrome. Radiation therapy of medulloblastoma results in produce numbers of invasive basal cell carcinomas appearing in the radiation field (from nape to base of spine).

**Medulloblastoma**
This embryonal neoplasm is present in 3-5% of NBCCS patients and characteristically presents during the first 2 years of life as opposed to 7-8 years in the general population (698). Because medulloblastoma presents early (mean 2.5 years) in patients with NBCCS, children who present with the tumour, especially those less than 5 years, should be carefully examined for signs of the syndrome.

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**Fibromas**
Cardiac fibromas occur in 3% (698). Conversely, about 5% of patients with cardiac fibromas have NBCCS. Presentation time has varied from birth to 60 years. Most have been found incidentally. Ovarian fibromas are noted in 25% (698). The ovarian fibromas associated with NBCCS are most often bilateral (75%). Minor kidney anomalies and hypogonadotropic hypogonadism are found in roughly 5%. Gorlin (868) reviewed examples of fetal rhabdomyoma.

**Imaging**
Lamellar calcification of the falx cerebri is found in 55-95% (normal-5%). Calcification of the tentorium cerebelli has been noted in 20-40%, the pteroclinoid ligament in 20%, and the diaphragma sellae in 60-80%. Radiographically, this appears as if the sella turcica is bridged, i.e., as if there were fusion of the anterior and posterior clinoid processes (1897,1898). Odontogenic keratocysts first appear at about 7-8 years of age and increase in number from puberty onward. They peak during the second and third decades. The cysts cause marked tooth displacement. They may invade the paranasal sinuses and, in the mandible, extend from the molar-ramus area to the coronoid processes.

**Table 7.3**
Diagnostic findings in adults with naevoid basal cell carcinoma syndrome. Modified, from R.J. Gorlin (868).

<table>
<thead>
<tr>
<th>50% or greater frequency</th>
<th>49-15% frequency</th>
<th>14% or less but not random</th>
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</thead>
<tbody>
<tr>
<td>Enlarged occipitofrontal circumference (macrocephaly, frontal-parietal bossing)</td>
<td>Brain ventricle asymmetry</td>
<td>Medulloblastoma</td>
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<tr>
<td>Multiple basal cell carcinomas</td>
<td>Calcification of tentorium cerebelli and pteroclinoid ligament</td>
<td>True ocular hypertelorism</td>
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<tr>
<td>Odontogenic keratocysts of jaws</td>
<td>Calcified ovarian fibromas</td>
<td>Lymphomesenteric cysts</td>
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<td>Epidermal cysts of skin</td>
<td>Short fourth metacarpals</td>
<td>Cardiac fibromas</td>
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<td>High-arched palate</td>
<td>Kyphoscoliosis or other vertebral anomalies</td>
<td>Fetal rhabdomyoma</td>
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<td>Palmar and/or plantar pits</td>
<td>Lumbarization of sacrum</td>
<td>Ovarian fibrosarcoma</td>
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<td>Rib anomalies (splayed, fused, partially missing, bifid, etc.)</td>
<td>Narrow sloping shoulders</td>
<td>Marfanoid build</td>
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<td>Spina bifida occulta of cervical or thoracic vertebrae</td>
<td>Prognathism</td>
<td>Anosmia</td>
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<tr>
<td>Calcified falx cerebri</td>
<td>Pectus excavatum or carinatum</td>
<td>Agenesia of corpus callosum</td>
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<td>Calcified diaphragma sellae (bridged sella, fused clinoids)</td>
<td>Pseudocystic lytic lesion of bones (hamartomas)</td>
<td>Cyst of septum pellucidum</td>
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<td>Hyperpneumatization of paranasal sinuses</td>
<td>Strabismus (exotropia)</td>
<td>Cleft lip and/or palate</td>
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<td></td>
<td>Syndactyly</td>
<td>Low-pitched female voice</td>
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<td></td>
<td></td>
<td>Polydactyly, postaxial - hands or feet</td>
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<td></td>
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<td>Sprengel deformity of scapula</td>
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<td></td>
<td></td>
<td>Vertebral body fusion</td>
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<td></td>
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<td>Congenital cataract, glaucoma, coloboma of iris, retina, optic nerve, medullated retinal nerve fibers</td>
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<td></td>
<td></td>
<td>Subcutaneous calcifications of skin (possibly underestimated frequency)</td>
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<td></td>
<td></td>
<td>Minor kidney malformations</td>
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<tr>
<td></td>
<td></td>
<td>Hypogonadism in males</td>
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<td></td>
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<td>Mental retardation</td>
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**Table 7.4**
Diagnostic criteria for NBCCS

**Major criteria**
1. More than 2 BCCs or one under age of 20 yrs
2. Odontogenic keratocyst
3. Three or more palmar pits
4. Bilamellar calcification of falx cerebri
5. Bifid, fused or splayed ribs
6. First degree relative with NBCCS

**Minor criteria**
1. Macrocephaly adjusted for height
2. Frontal bossing, cleft lip/palate, hypertelorism
3. Sprengel deformity, pectus, syndactyly of digits
4. Bridging of sella turcica, hemivertebrae, flame-shaped radiolucencies
5. Ovarian fibroma
6. Medulloblastoma

Based on V.E. Kimonis et al (1273).
Naevoid basal cell carcinoma (Gorlin) syndrome involvement may give the impression that medulloblastoma has spread to bone. Histologically, the flame-like lesions are hamartomas consisting of fibrous connective tissue, nerves and blood vessels. Subcutaneous calcification of fingers and scalp has been rare. Sclerotic bone lesions have been reported occasionally. Ovarian fibromas are found in about 25% of females. They are bilateral and often calcified, at times overlapping medially. Prenatal diagnosis by sonography has been accomplished (235).

Genetics
The first link between the SONIC HEDGEHOG (SHH) signalling pathway and tumour formation in humans was in familial cancers, as 30-40% of NBCCS patients harbour loss-of-function mutations in the PATCHED1 (PTCH1) gene (514,939,1992). That disruption of the SHH signalling pathway is a major determinant of tumour formation, particularly for BCCs, was established from the discovery that PTCH1 is mutated in 10-38% of sporadic BCCs (514,1992). Inactivation of both PTCH1 alleles also results in the formation of cysts (1408). Consistent with its pivotal role in embryonic development, aberrant SHH signalling is associated with a range of human developmental anomalies (2434). In NBCCS, tumours (BCCs, keratocysts, meningiomas, ovarian fibromas, odontogenic keratocysts) exhibit loss of heterozygosity (LOH) in the PTCH1 locus (9q22.3) (514). Various physical anomalies (bifid rib, macrocephaly, cleft lip, etc.) apparently need but one-hit (1407). LOH in the PTCH1 locus was observed in 89% of hereditary BCCs. The majority (61-71%) of germline PTCH1 mutations are rearrangements. Most mutations (>80%) are likely to represent null mutations since they are predicted to result in truncation of the PTCH1 protein (133, 514,1408,1992).

The PTCH1 tumour suppressor gene comprises 23 exons which encode 12 putative transmembrane domains and two large extracellular loops. The function of PTCH1 is to silence the SHH signalling pathway in absence of active SHH ligand (2308). In presence of SHH, the pathway acts in at least two ways to regulate target genes. One is to activate GLI 1/2 transcription factors and the other is to inhibit the formation of GLI repressors, mostly from GLI3, to derepress target genes (1992).

Prognosis and predictive factors
New keratocystic odontogenic tumours (odontogenic keratocysts) and basal cell carcinomas continue for life. Limitation of sun exposure reduces the appearance of the skin cancers. The medulloblastoma appears before the age of 4 years, the ovarian fibromas after puberty. Therapeutic radiation should be avoided whenever possible due to the high occurrence of basal cell carcinomas in the radiation field.

Fig. 7.10 Model of Sonic Hedgehog (SHH) signaling pathway. The function of the pathway is to stimulate cellular proliferation and inhibit apoptosis. The PTCH-1 gene is predicted to encode a 12-transmembrane receptor with high affinity for the SHH secreted 19 kDa protein ligand. In presence of SHH, the pathway releases the 7-transmembrane protein. Smoothed (SMO) from its inhibition by PTCH-1, thus activating target genes through the glioma (GLI) family of zinc-finger transcription factors (GLI1 is the most studied of the three GLI factors). GLI1 may control the G1/S transition checkpoint through activation of the transcription of Cyclin D2 and E genes, and apoptosis through activation of BCL2 expression. PTCH-1 may also be involved in a G2/M transition checkpoint via Cyclin B1 which localizes to the nucleus upon SHH binding (232). PTCH-1 transcription is induced by GLI1, thus generating a negative feedback loop. Abbreviations : Cyc, cyclin ; CDK, cyclin-dependent kinase.
Inherited tumour syndromes

Cowden syndrome

**Definition**
Cowden syndrome (CS) is an autosomal-dominant disorder with age-related penetrance and variable expression, characterized by multiple hamartomas arising in tissues derived from all three embryonic germ cell layers and with a high risk of developing benign and malignant neoplasms in many organ systems, especially in the skin, breast, and thyroid gland. The condition was described in 1963 by Lloyd and Dennis (1439). It is caused by germline mutations in the tumour suppressor gene PTEN located on chromosome 10q23 (1424).

**OMIM number** 158350

**Synonyms**
Multiple hamartoma syndrome, Cowden disease

**Epidemiology**

**Incidence**
The incidence of CS, after PTEN was identified as the gene, was found to be 1 in 200,000 (1693). The latter may be an underestimate, since CS has variable expression and often manifests itself only with subtle skin changes, so that this condition may be difficult to recognize (688). Although the exact proportion of isolated and familial cases is not known, previous and on-going observations suggest that 40-60% are familial (1521, 2448, 688A).

**Clinical features**
CS is classically characterized as a multiple hamartoma syndrome with a high risk of breast and thyroid cancers. Although the reported age at onset varies from 4–75 years (1451), CS usually manifests in the second or third decade. More than 90% of individuals affected with CS are likely to manifest a phenotype by the age of 20 years, and 99% develop at least mucocutaneous lesions by the age of 30 years (1694, 2448). CS is characterized by the development of hamartomas, benign and malignant tumours in multiple organ systems including the skin, soft tissues, breast, thyroid gland, gastrointestinal tract, genitourinary tract, and central nervous system. The most common lesions are trichilemmomas (90-100%), breast fibroadenomas (70%), thyroid adenomas (40-60%), multinodular goiter (40-60%), and multiple gastrointestinal polyps (35–40%) (688, 1451). Macroccephaly is seen in 35–40% of cases. Malignant neoplasms develop in the breast in 25–50% of CS females, in the thyroid gland in 3–10% (usually follicular adenocarcinoma) and in the uterus in 3-6%. The most common malignant neoplasm in the breast is ductal adenocarcinoma, which is bilateral in one third of cases (2098). The average age of CS patients at diagnosis of breast cancer is 10 years younger than in those with sporadic disease (2252). Male breast cancers also occur, but with unknown frequency (704, 1519). A feature that distinguishes CS from other breast cancer susceptibility syndromes is the occurrence of benign breast disease prior to the development of breast cancer (2098, 2099).

Many other internal malignancies have been reported to occur in individuals affected with CS. There are no data to state whether they are true components of this syndrome or merely coincidental.

**Bannayan–Riley–Ruvalcaba syndrome (BRRS)**
This pediatric disorder characterized by congenital macrocephaly, multiple lipomatosis and angiomyomatosis involving the skin and visceral tissues, intestinal hamartomatous polyposis, and pigmented penile lesions, shows a partial clinical overlap with CS (711, 1519).

**Diagnostic criteria**
The International Cowden Consortium originally proposed a set of operational diagnostic criteria in 1996 (1694). Because of new data, the Consortium revised the criteria in 2000 (688), which...
Cutaneous and mucosal lesions
Cutaneous lesions are the most important hallmarks for CS, since they are present in almost every patient and frequently appear prior to the development of any internal disease (1030). Facial papules are the most frequent lesions (85-90%). They are mainly located in periorificial regions, sometimes extending into the nostrils. Histopathologically, the papules frequently show non-specific changes, with prominent compact orthokeratosis, hypergranulosis, and acanthosis, in some cases with trichilemmal differentiation. Involvement of the oral mucosa is present in over 80% of cases. Coalescent lesions produce the characteristic cobblestone-like pattern in 40% of patients. Histopathologically, these lesions are composed of acellular collagen fibres, with a predominantly whorl-like arrangement (2251). Mucosal papules and nodules with trichilemmoma-like histopathological features are also common. A scrotal tongue is another common finding. Usually mucocutaneous lesions are present in multiple locations, and extension to the oropharynx, larynx, tongue, and nasal mucosa may occur.

Other cutaneous lesions reported to occur in individuals affected with CS include lipoma, angiolipoma, multiple sclerotic fibromas, squamous cell carcinoma, melanoma, basal cell carcinoma, Merkel cell carcinoma, haemangiomata, xanthoma, vitiligo, neuroma, apocrine hidrocystoma, café au lait spots, periorificial and acral lentigines and acanthosis nigricans (reviewed in (748,1030))

Genetics
PTEN/MMAC1/TEP1 on 10q23.3, is the susceptibility gene for CS (1424,1694).

Gene structure and function
PTEN comprises 9 exons spanning 120-150 kb of genomic distance. It encodes a 1.2 kb transcript and a 403 amino acid lipid dual-specificity phosphatase (it dephosphorylates both protein and lipid substrates) (1419,1421,2256). A classic phosphatase core motif is encoded within exon 5, which is the largest exon, constituting 20% of the coding region (1419,1421,1519,2256).

PTEN is the major 3-phosphatase acting in the phosphatidylinositol-3-kinase (PI3K)/Akt pathway (1478,2241). To date, virtually all naturally occurring missense mutations tested abrogate both lipid and protein phosphatase activity, and one mutant, G129E, affects only lipid phosphatase activity. Overexpression of PTEN results, for the most part, in phosphatase-dependent cell cycle arrest at G1 and/or apoptosis, depending on cell type (reviewed in (687,2448)). There is also growing evidence that PTEN can mediate growth arrest independent of the PI3K/Akt pathway and perhaps independent of the lipid phosphatase activity (460,1564,2448,2495,2496).

Mutation spectrum
Approximately 70-85% of CS cases, as strictly defined by the Consortium Criteria, have a germline PTEN mutation (1424,1519,2599). If the diagnostic criteria are relaxed, then mutation frequencies drop to 10-50% (1464,1695,2382). A
formal study which ascertained 64 unrelated CS-like cases revealed a mutation frequency of 2% if the criteria are not met, even if the diagnosis is made short of one criterion (1519). A single research centre study involving 37 unrelated CS families, ascertained according to the strict diagnostic criteria of the Consortium, revealed a mutation frequency of 80% (1519).

As with most other tumour suppressor genes, the mutations found in PTEN are scattered throughout all 9 exons. They comprise loss-of-function mutations including missense, nonsense, frameshift and splice-site mutations (1519, 1521,2448). Approximately 30-40% of germline PTEN mutations are found in exon 5. Further, approximately 65% of all mutations can be found in one of exons 5, 7 or 8 (1519,1521).

Although PTEN is the major susceptibility gene for CS, one CS family, without PTEN mutations, was found to have a germline mutation in the bone morphogenic protein receptor type 1A gene (BMPR1A, MIM 601299), which is one of the susceptibility genes for juvenile polyposis syndrome (1066,2600).

Whether BMPR1A is a minor CS susceptibility gene or whether this family with CS features actually has occult juvenile polyposis is yet unknown.

Genotype-phenotype associations
Clinically useful genotype–phenotype correlations are being intensively investigated. Exploratory genotype-phenotype analyses revealed that the presence of a germline mutation was associated with a familial risk of developing a malignant breast disease. Further, missense muta-

tions and/or mutations 5’ of the phosphatase core motif seem to be associated with a surrogate for disease severity (multiorgan involvement) (1519).

Previously thought to be clinically distinct, BRRS is likely allelic to CS (1519). Approximately 65% of BRRS families and isolated cases combined carry a germline PTEN mutation (420,1520,1521,2599). Interestingly, there were 11 cases classified as true CS-BRR overlap families in this cohort, and 10 of the 11 had a PTEN mutation. The overlapping mutation spectrum, the existence of true overlap families and the genotype-phenotype associations which suggest that the presence of germline PTEN mutation is associated with cancer, strongly indicate that CS and BRR are allelic and are along a single spectrum at the molecular level. The aggregate term “PTEN hamartoma tumour syndrome” (PHTS) has therefore been proposed (688,1521). The clinical spectrum of PHTS has recently been expanded to include also subsets of Proteus syndrome and Proteus-like (non-CS, non-BRR) syndromes (2203,2598).

Genetics of Cowden syndrome is also reviewed in detail in the WHO Classification of the Tumours of the Nervous System, Tumours of the Digestive System, as well as in the WHO Classification of Tumours of the Breast and Female Genital Organs.
Carney complex

**Definition**
Carney complex (CNC) is a lentiginosis-multiple endocrine neoplasia syndrome caused by at least two distinct mutations and characterized by multiple often unique tumours including myxomas and schwannomas, endocrine abnormalities, and cutaneous pigmentary lesions [397].

**OMIM numbers**
CNC1 160980; CNC2 605244

**Synonyms**
NAME syndrome [111], LAMB syndrome [1926].

**Epidemiology**
Carney complex is an uncommon disorder, inherited in an autosomal dominant fashion. More than 350 cases are known involving more than 65 families. The penetrance is high but the expressivity is highly variable. Patients may present with cutaneous, cardiac, or endocrine lesions; often the diagnosis is delayed until multiple manifestations are present.

**Localization**
The most commonly involved organs are the skin (75%), heart (50%) and adrenal glands (25%).

**Clinical features**
The cutaneous findings in CNC are often most dramatic. Patients may have multiple flat pigmented lesions that have been described both as ephelides (freckles) with an increased amount of melanin [111] and as lentigines with an increased number of melanocytes [1926]. Blue naevi are another marker of the syndrome; many exhibit epithelioid features on microscopic examination [396]. Pigmented lesions are also common on mucosal surfaces, such as the lips, mouth, conjunctiva and genital mucosa [1244]. Some patients have no pigmentary changes. Another highly specific cutaneous finding is myxomas, especially when they affect the eyelids and the external ear canal [734]. Histologically, these benign tumours often feature strands of lacy epithelium [398].

The most dramatic systemic finding is cardiac myxoma(s). The CNC-associated myxomas have important differences from sporadic cardiac myxomas; they are more likely to be familial, multiple, occur at a younger age, involve the ventricles and recur [2433]. Recurrent cardiac myxoma(s) may require multiple surgical resections that may result in postoperative arrhythmias and increased mortality.

The most common endocrine finding is primary pigmented nodular adrenal disease, a very rare ACTH-independent cause of Cushing syndrome (25%) [2164]. The adrenal glands show bilateral small, pigmented nodules with internodular cortical atrophy (881,2571). One of Cushing’s first patients, Minnie G., may well have had CNC [395]. Acromegaly and thyroid tumours [2275] are each seen in around 10% of patients. About one-third of male patients have large-cell calcifying Sertoli cell tumours of the testes, often bilateral and sometimes leading to precocious puberty [1734]. Two other uncommon tumours which should suggest the presence of CNC are psammomatous melanotic schwannomas (20%) of the GI tract, sympathetic chain and skin [394], and myxoid mammary fibroadenomas (25% of women) [400].

**Diagnostic procedures**
Both epithelioid blue naevi and myxomas (the latter sometimes with a characteristic epithelial component) may be identified on skin biopsies and suggest the diagnosis of CNC. When investigation for Cushing syndrome reveals low or undetectable ACTH levels and no adrenal tumour, a diagnosis of primary pigment-
ed nodular adrenal disease should be considered and the patient evaluated for CNC, particularly if the patient is young or has multiple pigmented skin spots or lumps. Echocardiography is particularly important (2276).

Differential diagnosis
When multiple pigmented lesions are present, LEOPARD syndrome should be considered but myxomas are absent in this condition and the systemic manifestations more protean. Mucosal pigmentation strongly resembles that of Peutz-Jeghers syndrome, but intestinal polyps are not part of the usual spectrum of Carney complex.

Genetics
Carney complex is inherited in an autosomal dominant fashion. The gene for CNC1, known as PRKAR1A, normally encodes the protein kinase A regulatory subunit R1a (408,1284). When the mutated gene is present, the regulatory subunit is no longer produced. The patients are heterozygous for the mutation: the tumours tend to have LOH of the wild type allele for this regulatory gene. The CNC2 gene is less well characterized but appears to be involved in regulating genomic stability, perhaps via the telomeres.

Prognosis and predictive factors
The prognosis depends on detecting cardiac myxoma, the most serious complex of CNC. The average age of 22 patients who died as the result of cardiac causes (cardiac failure from myxoma, cardiac myxoma emboli or cardiac arrhythmia) was 31 years. Timely diagnosis of the neoplasms requires an awareness of the possible significance of the pigmented skin spots, skin tumours, primary pigmented nodular adrenal disease and psammomatous melanotic schwannoma. Patients with lesions suggestive of CNC should be advised to have a general medical evaluation and an echocardiogram. Primary relatives of CNC patients should be similarly advised.

Fig. 7.15 A Eyelid myxoma in a young man with CNC and no cutaneous pigmentary changes. B Microscopic view of the same lesion, showing lacy epithelial strands amidst deposits of mucin.