Neurofibromatosis type 1

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Definition

Type 1 neurofibromatosis (NF1) makes up 90% of the genetic disorders known clinically as the neurofibromatoses. NF1 is inherited in an autosomal dominant manner and gene penetrance is such that almost all cases show sufficient evidence of the disorder to allow diagnosis in childhood {945}. The condition is characterised by tumour and pigmentary involvement of the neural crest and bony dysplasia. Neurofibromas occur widely throughout the body, but characteristically in the skin. *Café au lait* patches and axillary/groin freckling are near constant. Other tumours include optic nerve and other brain stem gliomas, phaeochromocytoma, carcinoid and malignant peripheral nerve sheath tumours.

MIM No.   162200

See: http://www.ncbi.nlm.nih.gov/omim {1468}.

Synonyms

Von Recklinghausen disease, peripheral neurofibromatosis, NF1

Incidence/prevalence

NF1 has a birth incidence of 1 in 2,500-3,300 {434,945} and a prevalence of 1 in 4,150-4,950 {945}. Several major studies have addressed this. A study in South Wales (UK) found the above frequency in a population of 280,000 people. A large US study by Crowe and colleagues esti-

Fig. 5.28 Café au lait spots and subcutaneous neurofibromas in a 44 year old man with neurofibromatosis type 1 who had a benign adrenal phaeochromocytoma.

mated incidence at 1 in 2,500 {434}, but this was contaminated with NF2 patients. The highest frequency was reported in an Israeli study of military recruits with a prevalence of around 1 per thousand {794}.

Diagnostic criteria

The diagnostic criteria for NF1 (see table 5.10) are unlikely to lead to misdiagnosis or confusion {2}. They were originally laid out at the 1986 National Institutes of Health (NIH) consensus conference and have since been ratified by the National Neurofibromatosis Foundation (NNFF) working party. Patients with segmental neurofibromatosis can fulfil these criteria and clinicians should note any segmental involvement. Our own use of these criteria in over 740 patients and in a large North American database has lent further support for them {474,1462}.

Skin lesions

Age distribution and penetrance

Skin lesions are critical in the diagnosis of NF1, with *café au lait* patches being present from birth and nearly every affected child has 6 or more by 5 or 6 years of age {947,1462}. *Cafe au lait* patches are usually the first feature of NF1 in most affected patients. They are usually seen in the first year of life and increase in number and size until the early teens {947,1462}. Axillary and inguinal freckling usually follows some time afterwards although it may be present as early as 3 years of age. Around 90% of patients show freckling by adulthood {1462}. Plexiform tumours are often visible from birth with diffuse involvement of the skin and underlying structures. Externally visible plexiform neurofibromas occur in approximately 25% of cases {947,1462}. Cutaneous tumours typically start to occur at puberty but may well be present before that, and are present in >95% of adult patients. Subcutaneous tumours are less frequent, but show a similar age-dependent progression to their cutaneous counterparts.

Clinical features

In childhood, *café au lait* patches are smaller, as reflected in the diagnostic criteria, but they become larger and may merge with one another. They have a straight rather than ragged border, the so called "coast of California" as opposed to "Coast of Maine" seen in McCune-Albright syndrome. They often fade in later life against the generally darker "dirtier" looking skin and may be less easy to recognise. They are flat and not associated with hair or malignant transformation. Freckling occurs in non-sun exposed skin typically in the axilla more frequently than the groin, and this usually appears later than the *café au lait* spots. Neurofibromas on and under the skin are the characteristic feature of NF1. Plexiform tumours are often visible from birth with diffuse involvement of the skin and underlying structures. About 2-3% of patients have unsightly plexiform tumours affecting the head and neck. The overlying skin is often hyperpigmented and loses its elasticity. Cutaneous tumours usually start as soft, often purplish coloured areas on the skin, but can

Table 5.10
Diagnostic criteria for NF1. Two or more must be present.

| |
|---|
| 1. Six or more *cafe au lait* macules, the greatest diameter of which is more than 5 mm in pre-pubertal patients and more than 15 mm in post-pubertal patients. |
| 2. Two or more neurofibromas of any type, or one plexiform neurofibroma. |
| 3. Axillary or inguinal freckling. |
| 4. Optic glioma. |
| 5. Two or more Lisch nodules. |
| 6. A distinctive osseous lesion such as sphenoid dysplasia or pseudarthrosis. |
| 7. A first-degree relative with NF1 according to the preceding criteria. |
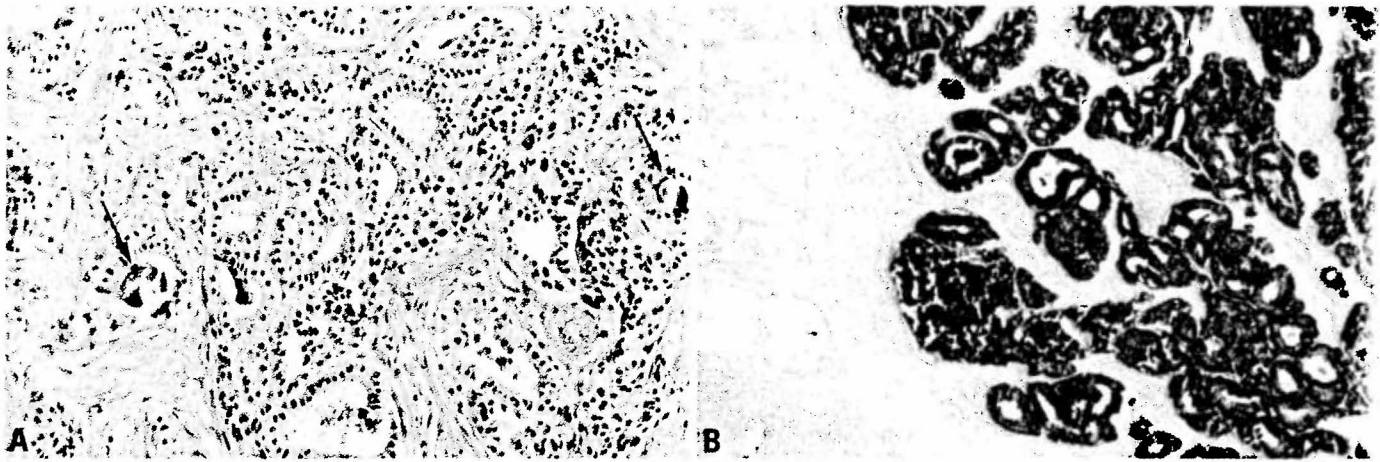
Fig. 5.29 Type 1 neurofibromatosis. **A** Somatostatinoma in a patient with neurofibromatosis type 1. Note the glandular structure of the tumour and the psammoma-like bodies (arrows). PAS stain. **B** Same tumour as illustrated in A stained for somatostatin.

evolve into unsightly warty outgrowths. Subcutaneous tumours occur as fusiform swellings on more major nerve routes and can be painful to touch. The deeper fusiform subcutaneous and plexiform tumours may undergo malignant change to malignant peripheral nerve sheath tumour (MPNST). Lifetime risk could be as high as 10% {1360,1462}. About 5% of patients develop xanthogranulomas aged 2-5 years, and these are associated with an increased risk of juvenile chronic myeloid leukaemia. Although the risk of malignant change in visible cutaneous tumours is probably small, it likely warrants monitoring of skin lesions. Although not strictly skin lesions, iris Lisch nodules (benign hamartomas) occur early in childhood and usually precede the appearance of cutaneous neurofibromas {587}. Ophthalmic slit lamp examination is therefore a useful diagnostic aid in equivocal cases.

Pathology
Café au lait macule
Macroscopically, *café au lait* macules vary greatly in size, millimetres to many centimetres. Flat and smooth bordered, they vary in colour from light to dark brown. *Café au lait* macules spots are not diagnostic of neurofibromatosis. Solitary examples are common in normal individuals. Histologically, they feature basilar hyperpigmentation with or without super-basilar melanosis. A minor degree of melanocytic hyperplasia may be seen. The macules are characterized by the presence of giant (2-6 micron) melanosomes within the melanocytes and at times in keratinocytes as well. Such

melanosomes are not limited to neurofibromatosis but may also be seen in Albright syndrome, in occasional examples of lentigo simplex and nevus spilus as well as in dysplastic nevi. Microscopically, they appear as markedly pigmented, rounded cytoplasmic bodies derived by fusion of primary melanosomes or secondary lysosomal residual bodies {1005}.

Neurofibroma
Neurofibromas are benign nerve sheath tumours composed largely of Schwann cells in the various neurofibroma types. All can be seen in NF1 including localized cutaneous, diffuse cutaneous, localized intraneural, plexiform, massive soft tissue, and visceral examples. Their clinicopathologic features have recently been summarized {1968}.

Localised cutaneous neurofibromas are common in NF1 and affect the dermis and subcutis and show no site predilection. Nodular or polypoid and unencapsulated, they infrequently exceed 2 cm. Whether sporadic or syndrome-associated, the microscopic features are similar. They consist mainly of uniform, spindle-shaped Schwann cells with barely discernible processes and delicate elongate or sinuous nuclei. Such neurofibroma show no tendency to malignant change.

Diffuse cutaneous neurofibroma.
This uncommon variant presents in children, and 10% are NF1 associated. They consist of sizable, diffuse plaque-like thickenings of dermis and subcutaneous tissue often of the head and neck region. They tend to nondestructively infiltrate

the dermis with extention into subcutaneous tissue. Pseudo-Meissnerian corpuscles are commonly seen as are minor plexiform components. Such tumours rarely undergo malignant change.

Localized intraneural neurofibroma infrequently involve skin. They affect spinal, cranial, or autonomic nerves. The neurofibroma cells grow within the nerve, transforming it into a fusiform mass. Such neurofibromas infrequently undergo malignant change.

Plexiform neurofibroma.
This characteristic tumour occurs almost exclusively in NF1 and generally affects sizable nerves. Cutaneous lesions are often part of diffuse neurofibromas, but they may occur in pure form. Occasional, usually small, tumours lack an NF1 association; these presumably result from a local mutation. Involvement of branching nerves often form worm-like tangles. Approximately 2-5% of plexiform neurofibromas undergo malignant change.

Neurofibromas vary in cellularity and in content of stromal mucin. The cells feature ovoid to elongate, often curved nuclei, scant cytoplasm and indiscernible processes. Accompanying mast cells are commonly seen. Melanin-containing cells are rare. Variations in the cell pattern include structures resembling Wagner-Meissner corpuscles or Pacinian corpuscles. Nodules of pure Schwann cells may be seen in plexiform tumours. Neurofibromas are generally diploid {1912}. All neurofibromas are S-100 protein immunoreactive. Leu-7 and collagen IV or laminin staining is frequent. As a rule, MIB-1 labelling indices are low.

often less than 1% {1087}. Ultrastructurally, the neoplastic Schwann cells are well-differentiated {578}.

Malignant peripheral nerve sheath tumour

Malignant peripheral nerve sheath tumours (MPNST) are uncommon tumours varying greatly in clinicopathologic features {1968}, about 50% are NF1-associated. Cutaneous MPNST is very rare {444,698,1510}; skin involvement is usually secondary to larger underlying tumours. Grossly, MPNST as a whole form globoid or fusiform masses, not all of which are nerve-associated. Approximately half of the tumours originate in neurofibromas of intraneural or plexiform type. Pathologically, they show a broad spectrum. Most are high grade, poorly differentiated and aneuploid. Only half can be shown to exhibit schwannian differentiation by immunohistochemical methods. The minority show perineurial features {893}. The epithelioid subtype shows no NF1 association. Particularly associated with NF1, however, are tumours exhibiting mesenchymal primarily rhabdomyosarcomatous differentiation ("Triton tumour") {2416} or differentiation toward mucinous, squamous, or neuroendocrine epithelium ("glandular MPNST") {2416}. As a rule, MPNSTs are highly aggressive tumours with a poor prognosis.

Prognosis and prognostic factors

Life expectancy in NF1 is reduced by an average of around 15 years partly due to excess deaths due to MPNST {1798, 2102}. Early detection and complete excision of MPNST is essential. They usually present with rapid growth or pain. The vast majority of skin tumours remain benign and usually become dormant after a period of fairly rapid evolution. Excision of tumours is often undertaken for cosmetic reasons, but is particularly problematic for plexiform tumours due to the indistinct borders and poor healing of the involved skin.

Duodenal endocrine lesions (carcinoid)

Age distribution and penetrance

Carcinoid tumours occur in NF1 with a frequency of around 1% {947}. A series of 27 patients with NF1 and duodenal carcinoids showed a peak incidence in the fourth and fifth decades {777}. Many patients with carcinoid and NF1 have a co-existent phaeochromocytoma.

Clinical features

Carcinoid tumours while predominantly occurring in the duodenum in NF1 very rarely also occur in other organs derived from the embryonic foregut such as the stomach, pancreas, thyroid and bronchus as well as elsewhere in the small intestine. Carcinoid or "somatostatinoma" syndromes are extremely rare. Duodenal tumours may present with obstructive jaundice, intestinal obstruction and or bleeding. As many as 50% of all duodenal somatostatinomas occur in the context of NF1 {464} and an association with NF1 is especially observed when the tumour is located in the ampullary region.

Pathology

Neuroendocrine tumours of the duodenum in NF1 patients are usually solitary and are located in the periampullary region. They may display a polypoid growth but infiltration of the sphincter of Oddi, the duodenal wall or head of the pancreas may also occur {464,2115}. The tumours have a mean diameter of 2 cm.

Histologically, they typically exhibit well-formed tubulo-glandular structures with some evidence of luminal secretion {776} and contain characteristic PAS-positive psammoma bodies composed of calcium apatite crystals in 66% of cases {34}. Immunohistochemically, they express neuroendocrine markers (but in 50% are negative for chromogranin A), cytokeratins and label strongly with somatostatin (representing non-functioning "pure" somatostatinomas) with rare single cells expressing other hormones (e.g. calcitonin, pancreatic polypeptide, ACTH, insulin) {2115}. This is in contrast to sporadically occurring somatostatinomas, which frequently display a multihormonal expression pattern {264}.

By electron microscopy, the neoplastic cells show signs of intestinal differentiation (microvilli, glycocalyceal bodies, filamentous core rootlets) as well as of neuroendocrine differentiation (D-type secretory granules, whorls of neurofilaments). These tumours are seldom associated with a recognisable "somatostatin syndrome" (diabetes, diarrhoea and biliary lithiasis) {768}, but often present with obstructive jaundice, duodenal obstruction, weight loss or gastrointestinal bleeding.

A genomic examination of a single resected somatostatinoma of a NF1 patient showed neither *KRAS* nor *TP53* gene mutations {1019}.

Other tumours which may be encountered in the duodenum of NF1 patients include gastrointestinal stromal tumours, gangliocytic paragangliomas and ampullary adenocarcinomas {329,400, 421, 1039,1900,2124}.

Prognosis and prognostic factors

The endocrine tumours in the duodenum mostly remain localised but do metastasize in 27% of cases mainly to lymph nodes (88%) or the liver. However, they appear to be less aggressive than their pancreatic and sporadically occurring duodenal counterpart tumours which frequently exhibit a malignant clinical behaviour {813,2091}. The risk of metastasis significantly increases with tumours larger than 2.0 cm {2190}.

Phaeochromocytoma

Age distribution and penetrance

Phaeochromocytomas occur in <1% of NF1 patients, predominantly in the fourth and fifth decades, similar to carcinoids. About 5% of phaeochromocytoma patients have NF1 and inherited forms of these tumours are more frequently associated with MEN type 2 or VHL disease.

Clinical features

Headache is the most common presenting feature of phaeochromocytoma occurring in about 60% of patients. The headaches are usually frontal or occipital start suddenly and usually last about 15 minutes. Associated nausea, vomiting and neck ache are common if there is associated paroxysmal hypertension. Blurred vision and other visual features such as homonymous hemianopia occur in about 10% of patients. Visual scotomata scintillating in time with the heartbeat may also occur. Seizures and transient loss of consciousness due to cerebral ischaemia are later features. About a third of patients suffer from anxiety attacks, tremor and a feeling of impending doom. Cardiac complications due to catecholamine cardiomyopathy are the

most serious complication and account for 58% of deaths {1868}. Palpitations due to arrythmias and chest pain due to cardiac ischaemia are manifestations of this. Night or constant sweats often confined to the upper body occur in around 50% of patients and weight loss is a less common accompanying sign {619}. Other vascular effects include claudication and gangrene of limbs. Unusual sites of phaeochromocytoma may cause unusual symptoms such as haematuria from bladder neck tumours. Clinically sustained or paroxysmal hypertension may be detectable with actively secreting tumours, but this is not a totally reliable sign. Any NF1 patient with persistent hypertension refractive to treatment, especially if there is a narrow pulse pressure or where beta- blockers actually increase blood pressure should be actively assessed for phaeochromocytoma {1868}. Most NF1 specialists do not screen their patients with regular abdominal ultrasound and 24-hour urine catecholamines due to the very low yield annually. However, an annual check of blood pressure and suggestive symptoms should prompt a more complete search including MRI or CT {619}.

Pathology
There is no evidence that NF1 related phaeochromocytoma differs significantly from other sporadic or syndrome related tumours from a histologic point of view.

Prognosis and prognostic factors
Hypertensive crisis especially during pregnancy is a life-threatening complication in NF1 patients with phaeochromocytomas. The majority of phaeochromocytomas are benign {392}. Malignant tumours have been described in single case reports {1782,2181} including composite tumours {1573,1949}. Compiled data indicate a malignancy rate of 11.5%, which is somewat higher than in sporadically occurring phaeochromocytomas {2345}. As for sporadic tumours it is difficult to predict malignant behaviour by histology when no gross invasion or metastases are present {2229}.

CNS lesions

Age distribution and penetrance
Large studies where children with NF1 have been screened with MRI or CT scans indicate that around 15% have at least a unilateral optic glioma {898,1310}. It is unclear how many children who have a scan-detected glioma will ever develop symptoms as studies which have not specifically screened with imaging find much lower rates of between 0.7-5% {947,2062}. Tumours usually present between birth and 6 years of age peaking at around 3-4 years, but adult onset of symptoms does occur. Other brain stem gliomas are less frequent, affecting around 1-2% of patients, but are more frequent in those with optic gliomas {929}. Other CNS lesions include macrocephaly (45% above 97th centile), aqueduct stenosis (<1%) and "Unidentified Bright Objects" (UBOs) on T2-weighted MRI (33%). About 3% of NF1 patients have epilepsy.

Clinical features
Perhaps the most worrysome complication in NF1 is that of CNS tumours and malignancy. The area over which there is most current controversy is in the occurrence rate of optic gliomas and how or whether they should be screened for. The tumours themselves are often benign and vision may not deteriorate at all from presentation. Other features of optic glioma include precocious puberty with a rapid growth spurt or appearance of secondary sexual characteristics and ocular proptosis. It is also unclear whether treatment of even symptomatic cases is warranted {1311,1736}, although radiotherapy and chemotherapy have been shown to be beneficial in several series {1736}. The situation is made more confused by the appearance of focal hyperintensity or unidentified bright objects (UBOs) in many asymptomatic individuals on MRI scanning {249}. The full significance of these is not yet known, as even their association with learning disorders is controversial. Other CNS gliomas do occur but their frequency is probably below 5% even in neurological-based series {225}. Symptoms from these tumours will depend on their position in the brain stem or cerebellum, but signs of increased intracranial pressure may be the first manifestation. Meningiomas and vestibular Schwannomas probably do not occur in excess frequency in NF1 {474,947}. However, the old literature is littered with NF2 cases included in series with NF1. Spinal neurofibromas may cause weakness and wasting, paraes-

thesia or nerve root pain, but symptomatic tumours occur in only 1-2% {474, 947}. Nonetheless, MRI scans reveal evidence of spinal nerve root involvement in up to 60% of patients. A significant proportion of children with NF1 have learning difficulties particularly with reading and or minimal intellectual handicap. Although some studies have shown a large proportion (8-11%) with an IQ<70 indicating mental handicap {620,946, 1819}, population-based studies suggest that fewer children have moderate or severe handicap (3%) or need special schooling {620}. Learning difficulties improve with extra education and IQ in adulthood is better {620,946}.

Pathology
The medical literature describing gliomas in NF1 does so largely in topographic (optic nerve, chiasmal or visual pathway glioma, cerebellar astrocytoma, brainstem glioma) and radiologic, rather than histologic terms. Many reports of optic glioma are of small series and, as in the case of brainstem tumours, draw conclusions without the benefit of biopsy. Thus, it is difficult to critically discuss the pathology of NF1 associated CNS tumours and to meaningfully contrast them with sporadic lesions. Nevertheless, certain distinguishing features emerge.

Pilocytic astrocytoma, the common glioma in NF1, occurs in 15% of cases. It arises at any of the typical loci for this tumour type, but is especially prone to affect the optic nerve as a diffuse enlargement without cystic change. Bilateral involvement is typical. Optic pathway pilocytic astrocytomas in non-NF1 patients, on the other hand, are more likely to be cystic and situated more posteriorly, i.e. in the chiasm {355}. While it has been claimed that the NF1-associated optic nerve gliomas are more prone to massive leptomeningeal extension {2125}, this has not been the general experience. Pilocytic astrocytomas of the optic nerves in NF1 are notoriously indolent. At this location and others, NF1 and even sporadic pilocytic astrocytomas sometimes regress {1694}.

Gliomas of the brain stem in NF1 include focal contrast-enhancing masses consistent with classic pilocytic astrocytomas but also radiologically diffuse lesions whose histological correlates are unclear. In spite of the similarity to the most com-

mon form of brain stem glioma, infiltrating or "diffuse" astrocytoma, this NF1-associated process is unusually indolent {1527,1757}.

With respect to cerebellar astrocytomas in NF1, it has been suggested they may be more aggressive than those occurring sporadically {954}. Whether this is due to inability to clearly distinguish pilocytic from diffuse astrocytomas in all cases is unclear, but some NF-1 associated astrocytic tumours do show indeterminate histologic features.

Rare among other astrocytic tumours occurring in NF1 is pleomorphic xanthoastrocytoma {1642}.

Although there is little literature on the subject, diffuse astrocytomas, in some cases high grade, also occur in the setting of NF1.The same is true of rare cases of gliomatosis {1648}.

The genetic underpinnings of NF1 suggest that abnormalities in the NF1 tumour suppressor gene are likely to be critical in the genesis of pilocytic astrocytomas that arise within the syndrome, and possibly in the much more common counterparts that arise sporadically in the non-NF1 patient. Loss of NF1 alleles occurs in the syndrome-associated astrocytomas, although not the pilocytic neoplasms arising in patients without NF1 {1119}. Loss of staining for the product of the NF1 gene, neurofibromin, has been found in an NF1 associated pilocytic astrocytoma, but not in surrounding parenchyma {1244}.

Unidentified Bright Objects (UBO) are a frequent abnormality in NF1 patients in the brain stem, as well as in the cerebellum and deep cerebral grey matter. They are often multiple, bilateral, foci on MRI. While they are often referred to as hamartomas, they are evanescent in some patients. Little is known about their histological features. One study suggested a form of spongiosis, whose water content explains the brightness in T2-weighted images {500}.

Prognosis and prognostic factors

Prognosis of CNS lesions depends on type, age of onset and location. Simple megalencephaly is common and usually harmless but can lead to increased skull circumference. Hydrocephalus with or without associated tumours may present at any age and can become symptomatic. Nerve root and spinal cord neurofibromas can lead to deficits depend-

ing on location. Gliomas and meningiomas may compromise surrounding structures or nerves causing neurological symptoms. Optic nerve gliomas may lead to visual loss. Pilocytic astrocytomas are relatively benign while half of fibrillary astrocytomas exhibit malignant behaviour. Some gliomas may progress to anaplastic tumours which have a poor prognosis.

Overall, the prognosis of CNS tumours in NF1 patients appears to be slightly better than those of sporadic tumours {2322}. In a retrospective study on 104 NF1 patients with CNS tumours, the overall survival rate was 90% at 5 years. Extra-optic location, tumour diagnosis in adulthood and symptomatic tumours are independent factors associated with shorter survival time {786}. UBOs which commonly occur in children usually regress with age and seem to be benign, however, young children with a large number and volume of UBO should be followed closely with regular MR examinations because of an increased risk of proliferative change {778}.

Bone and other lesions

Age distribution and penetrance

Bony abnormalities are frequently present from birth. While scoliosis typically advances at puberty, there are often underlying congenital bony abnormalities of the vertebrae. Scoliosis occurs in about 5-9% of cases, with about half requiring surgery {947}. Pseudoarthrosis of the tibia/fibula occurs congenitally in around 1-2% {474,947}. Sphenoid wing dysplasia and lamboid suture defects occur in about 1%. Less common non-bony lesions include gastrointestinal neurofibromas (2%), renal artery stenosis (1%) and congenital glaucoma in <1% {947,1462}.

Clinical features

Pseudoarthrosis is the development of a false joint in a long bone or the failure of a fracture to unite after 6 months to a year. It typically occurs in the upper tibia or fibula where 50-90% of such cases are due to NF1 {1541,1561}. However, it may occur in all other long bones. The tibial condition often presents with anterior bowing, and an hourglass appearance may be present at birth. Spontaneous fracture or fracture with minor trauma

often occurs by 2 years of age. Pseudoarthrosis may occur in relation to a bone cyst, sclerotic bone or even rarely, an intramedullary neurofibroma. Pseudoarthrosis can be managed with brace treatment {1768}, electrical stimulation {956} or free vascularised bone grafts {246}. The spine may be affected with scalloping of the posterior margins or dysplasia of vertebral bodies, enlargement of foramina, and defective pedicles. The above abnormalities give rise to a dystrophic scoliosis although idiopathic scoliosis is probably more common. Dystrophic scoliosis is relentlessly progressive involving a sequence of 4-6 vertebrae and cannot be managed by bracing. Surgical treatment with spinal fusion has a risk of paraplegia and pseudoarthrosis. Idiopathic scoliosis can be managed similarly to its sporadic counterpart. However, even in this form pseudoarthrosis may occur after surgery {2370}. Sphenoid wing dysplasia often presents with proptosis and can be associated with an orbital plexiform tumour.

Pathology

Although bony lesions are common in NF1, they show non-specific changes.

Prognosis and prognostic factors

Bony abnormalities may be clinically silent and only evident on x-ray. Congenital pseudarthrosis may be present at birth, with bowing of the tibia being the most typical presentation. Long bone abnormalities may be treated with limb-sparing procedures but sometimes necessitate amputation. Scoliosis in NF1 is often mild, but a subset of children younger than 10 years (especially young girls) develop a more rapidly progressive form of (kypho) scoliosis that requires aggressive intervention to prevent paraparesis. Scoliosis detected during adolescence is much less likely to require orthopedic intervention {428}. Sphenoid bone dysplasia is usually asymptomatic but occasionally can be associated with herniation through the bony defect. Massive osseous and soft tissue overgrowth may lead to facial deformity and disfigurement.

Stenosis of the renal artery (secondary to fibromuscular dysplasia) or coarctation of the aorta may lead to arterial hypertension. Vascular disease and cardiac involvement can cause early and sudden death.

Genetics

Chromosomal location

The *NF1* gene was mapped to 17q11.2 by family linkage studies {2003} and the gene was eventually cloned by the identification of 2 patients with balanced translocations involving the 17q locus.

Gene structure

The *NF1* gene was cloned in 1990 {2325}. It is a massive gene containing over 300 kilobases of DNA divided into more than 50 exons. The gene transcribes for a 327 kd GAP protein containing 2818 amino acids. It is unusual in having 3 embedded genes in one intron, which transcribe in the reverse direction.

Gene expression

The *NF1* gene is ubiquitously expressed in almost all tissues but most intensely in central and peripheral nervous systems {461,2421}. Mutations of the *NF1* gene lead to reduced levels of functional protein, which may not be sufficient for the proper function of the cell. Regulation of the *NF1* gene takes place at multiple levels: transcription, mRNA and protein stability, and mRNA targeting. The levels of *NF1* mRNA and protein, neurofibromin, can undergo rapid changes, and mRNA level may not always directly correlate with the protein level {242,775,894,2455}. During fetal development, the *NF1* gene is transiently expressed in many tissues and is needed for proper histogenesis. Mice homozygous for a mutation in the *Nf1* gene fail to develop the normal structure of heart and various neural crest derived tissues, and die *in utero* {984, 2421,2454}. Selected growth factors, such as basic fibroblast growth factor (bFGF), platelet derived growth factor (PDGF), and transforming growth factor β1 (TGFβ1) have been identified as upregulators of NF1 *in vitro* {894,1270}.

Gene function

The function of the gene encoding neurofibromin is not fully understood but it seems likely that the gene encodes a multifunctional protein. Neurofibromin has been referred to as a tumour suppressor since cells of malignant peripheral nerve sheath tumours of neurofibromatosis patients may display loss of heterozygosity of markers in and around the *NF1* gene {52}. Somatic mutations of *NF1* have also been found in malignant tissues of persons who do not have neurofibromatosis {98,495,1009,1292,2224}. In addition to playing a role in foetal development, expression of the *NF1* gene has been associated with normal tissue repair in man and mouse {1270, 2431}.

Neurofibromin contains a domain that is related to the GTPase activating protein (GAP). This domain accelerates the switch of active Ras-GTP to inactive Ras-GDP in various cell types {131,209, 475,2431}. However, GAP activity alone is apparently not sufficient to explain the entire function of neurofibromin. Interaction of neurofibromin with cytoskeletal microtubules, actin microfilaments, and intermediate filaments has been demonstrated {210,770,1127,1289, 2432}. For instance, neurofibromin associates with intermediate type cytoskeleton in differentiating keratinocytes during the short period of formation of cell junctions {1127}. Furthermore, a bipartite interaction takes place between neurofibromin and syndecan transmembrane heparan sulfate proteoglycans {932}. Mutations of the *NF1* gene can also lead to altered calcium-mediated cell signalling between cells {1149}.

Mutation spectrum

Mutations have been identified throughout the *NF1* gene. There was an initial concentration on the RAS-GAP domain and reports of the predominance of mutations at this site are self-fulfilling. Most mutations are protein truncating consisting of nonsense, frameshift and splice site mutations. However, some pathogenic missense mutations have been described. 5-10% of patients have large deletions, often involving the whole gene that are easily detectable with FISH. While initial reports of fairly extensive testing using a single technique such as SSCP identified a relatively small proportion (10-20%) of mutations {9}, newer techniques such as DHPLC have boosted detection to 68% {814} and exhaustive screening including a deletion strategy boosts this to 95% {1487}.

Genotype-phenotype correlations

The search for a link between mutation type or location and disease features was initially elusive due to the poor identification rate in most surveys. However, large deletions have now been correlat-ed with a greater neurofibroma burden, as well as dysmorphic features and more mental retardation {1059,1352}. There is also emerging evidence for an elevated risk of MPNST in those patients with *NF1* deletions {2425}. No clear correlation exists for other mutation type or site, although segmental disease has now been shown to be due to somatic mutation {403}.

Genetic counselling and preventive measures

NF1 can nearly always be diagnosed clinically using the NIH criteria. An individual fulfilling these criteria will have a 50% risk of transmitting the disease to their offspring, unless they show segmental involvement {403}, in which case offspring risks may be substantially below this. Disease severity varies a great deal within families and it is not possible to predict the disease course in an affected offspring unless they have a large deletion. It is likely that there are significant genetic modifiers for NF1 {538}. There are unfortunately no real preventive measures that can be taken in NF1, but early detection of hypertension by regular blood pressure checks may detect complications such as renal artery stenosis and phaeochromocytoma and regular skin checks could detect early malignant change in a plexiform.

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Carney complex

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Definition

Carney complex (CNC) is a multiple neoplasia syndrome featuring cardiac, endocrine, cutaneous and neural tumours, and a variety of mucocutaneous pigmented lesions {318}. CNC is inherited as an autosomal dominant trait {314} and may involve several endocrine glands simultaneously (adrenal cortex, gonads, pituitary and thyroid, but not the parathyroid glands, the adrenal medulla or the endocrine pancreas), as in the classic multiple endocrine neoplasia (MEN) syndromes {312}. CNC also has some similarities to McCune-Albright syndrome and shares skin abnormalities and some non-endocrine tumours with the lentiginoses and/or the hamartomatoses, including Peutz-Jeghers syndrome in particular, but also Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome (Bannayan-Zonana; Bannayan-Myhre-Smith), Birt-Hogg-Dubé and neurofibromatosis syndromes {589, 2139,2141}.

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See: http://www.ncbi.nlm.nih.gov/omim {1468}.

Epidemiology

Approximately four hundred patients with CNC from all races and with equal distribution between the sexes are listed in the National Institutes of Health (NIH)-Mayo Clinic (MC) Registry {2146}. Most of the patients (more than two-thirds) belong to families in which the disease is inherited

in an autosomal dominant fashion. The number of affected members in the majority of these families is small: in the NIH-MC registry, the maximum number of affected generations in a family was 5. CNC is a developmental disorder, occasionally diagnosed at birth {1468,2146}. Most commonly, however, the disease is diagnosed in late adolescence or young adulthood. Abnormal skin pigmentation may be present at birth and is usually the first manifestion of the disease; lentigines, however, do not assume their characteristic distribution, density and intensity until around and shortly after puberty. Heart myxomas or Cushing syndrome due to primary pigmented adrenocortical nodular disease (PPNAD) are the clinical conditions with which most CNC patients present {311,313,1468,2033}. Lentigines and other pigmented lesions, acromegaly, thyroid nodules, gonadal tumours and Schwannomas may be present at the time of diagnosis but are rarely the reason for which most patients seek medical attention initially {2146}.

Sites of involvement

Mucocutaneous involvement in CNC is extensive: lentigines and other pigmented lesions, including blue naevi, café-au-lait spots may be present at birth, and referred to as "birthmarks"; more frequently, however, these lesions develop in the early childhood years. The rare café-au-lait spots in CNC are usually smaller and less pigmented than those in McCune-Albright syndrome; they also

tend to fade with time. Their shape is more reminiscent of the neurofibromatosis (NF) syndromes; however, unlike those of NF, café-au-lait spots in CNC do not usually enlarge or merge with time. Depigmented lesions, often mimicking vitiligo, may also be present in patients with CNC. The skin and the mucosal myxomas may also develop at any age; characteristic locations include the eyelids, the external ear canal, the nipples, the external female genitalia. When the myxoma includes an epithelial element (as it occasionally does), it is reminiscent of tumours of the hair follicle in Cowden syndrome and Birt-Hogg-Dubé syndrome. The heart and the breast are the next two most common locations for myxomas in CNC. The cardiac tumours may occur in any of the chambers of the heart, at any age and without any gender predilection, unlike sporadic cardiac myxoma that usually occurs in the left atrium, and in older females. Breast myxomatosis may be extensive and rarely accompanied by another, unusual, benign tumour of the mammary gland: ductal adenoma {317,423}. The adrenal cortex almost always has histologic changes consistent with PPNAD, and commonly the testis and ovary feature lesions, large-cell calcifying Sertoli cell tumours (LCCSCT) and cysts, respectively {1769,2147}. Non-functioning nodules, and occasionally, follicular or papillary carcinoma may be present in the thyroid {1625,2144}. All of these tumours are easily detectable by ultrasonography: LCCSCT appear as micro-calcifications

Fig. 5.30 Carney complex (CNC). **A** Characteristic distribution of pigmented skin lesions in CNC: around the eyes, **B** around the inner canthus, and **C** on the vermilion border of the lips.

Fig. 5.31 Carney complex. Characteristic distribution of pigmented skin lesions on the helix (arrow) of the ear.

{1769}, and ovarian cysts and thyroid nodules as multiple hypoechoic lesions, the latter often within the first two decades of life {2144,2147}. The pituitary gland is affected in most patients with CNC; however, only 10% develop clinically significant acromegaly due to a growth hormone (GH)-producing adenoma {2146}. Finally, approximately 10% of patients with CNC develop a unique tumour of the peripheral nervous system, psamommatous melanotic schwannoma (PMS), which is often multicentric and may be found along the spine, in the esophagus or stomach, the mediastinum, the retroperitoneal space, and the pelvis {308, 2359}. PMS is one of the few tumours associated with CNC that may assume an aggressive clinical behaviour and metastasize to distant sites, primarily the lungs.

Clinical features

At least two of the classic manifestations of CNC need to be present to make the diagnosis of CNC {2146}. Most patients with CNC present with spotty mucocutaneous pigmentation on the face, vermilion border of the lips, the bridge of the nose, the inner canthi and around the eyes, and elsewhere, particularly the female external genitalia, and one of the two most common types of tumours: myxoma or PPNAD. Heart myxoma may present with symptoms of cardiac insufficiency or embolisation {313}. Skin myxomas resemble neurofibromas clinically and are often misdiagnosed as such histologically. They often present in the form of simple skin tags or they may grow over

several years to a large size and become tender, fixed subcutaneous nodules or masses affecting the trunk and gluteal region.

In the "classic" patient with spotty skin pigmentation (in the characteristic distribution), skin myxoma(s) and symptoms of Cushing syndrome (facial plethora, central obesity, striae), the diagnosis of CNC is easily made {2146}. In a patient with skin pigmentation suggestive of CNC but without a heart tumour or Cushing syndrome, echocardiogarphy or biochemical screening by a dexamethasone-stimulation test may reveal a myxoma or PPNAD, respectively. Ultrasonography has been used to detect some of the other tumours associated with the complex: LCCSCT (multicentric, bilateral testicular microcalcifications), Leydig cell and adrenal rest tumours (these rare tumours may also be present in CNC and almost always are found together with LCCSCT), thyroid nodules and ovarian cysts (multiple, bilateral, hypoechoic lesions) {1769, 2144,2147}. LCCSCT in CNC, as in Peutz-Jeghers syndrome, may be hormone-producing, and cause gynaecomastia in prepubertal and peripubertal boys {1769}. Clinically evident acromegaly occurs in about 10% of patients with CNC {1671,2359}. However, asymptomatic elevated levels of GH and insulin-like growth factor type-1 (IGF-1) and/or subtle hyperprolactinemia may be present in up to 75% of the patients {1671,1788}. Biochemical acromegaly is often unmasked by abnormal results of oral glucose tolerance test (oGTT) or paradoxical responses to thyrotropin-releasing hormone (TRH) administration {2146, 2359}. Somatomammotropic hyperplasia, a putative precursor of GH-producing adenoma, may explain the insidious and protracted period of establishment of clinical acromegaly in CNC patients {1671}. CNC is the only genetic condition other than the NF syndromes and familial isolated schwannomatosis that is associated with schwannomas, the rare and characteristic psammomatous melanotic schwannoma (PMS) {308}. Depending on its location, this tumour may cause pain or neurologic deficits or be asymptomatic. Metastatic PMS to the lungs or brain may cause obstructive lung disease or increased cerebrospinal fluid pressure and death, respectively. Imaging of the brain, spine, chest, abdomen (in particular the
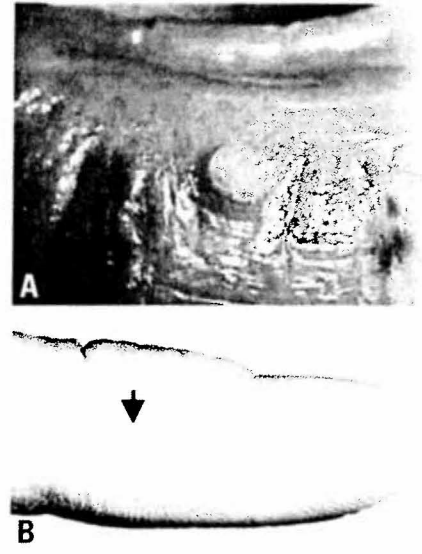
Fig. 5.32 Carney complex. **A** Lesions from a si[...] patient with CNC at presentation: a myxoma on [...] lip, and **B** pigmented spots on the index fi[...] (arrow).

retroperitoneum), and the pelvis, may [...] necessary for the detection of PM[...] there are suggestive symptoms. [...] most recently described tumour tha[...] probably associated with the comple[...] osteochondromyxoma {310}. The tum[...] has occurred in the nasal sinuses [...] long bones, causing painless swellin[...] may also be congenital. Rarely, a pa[...] may be diagnosed with CNC at auto[...] usually after a fatal embolus or str[...] due to a heart myxoma or, infreque[...] due to complications of hyperc[...] solemia or metastatic PMS {2146}.

Histopathology

Lentigines

A spectrum of abnormalities is see[...] the pigmented cutaneous macules {3[...] ranging from localised hyperpigme[...] tion of the basal epidermal layer, wit[...] without an increase in melanocytes [...] localised presence of coarse mel[...] granules throughout the epidermal [...] ers, to hyperplasia of the epidermis [...] elongation of the rete pegs.

Blue naevi

Two types of blue naevi are seen {3[...] the usual Jadassohn-Tièche type and [...] rare epithelioid type that was [...] described in connection with CNC. [...] usual blue naevus features elonga[...] melanin-laden, dendritic melanoc[...] located among the dermal collagen [...]

dies. The cells have spindle nuclei and inconspicuous nucleoli. The melanocytes of the epithelioid blue nevus are similarly located but differ cytologically from those of the usual blue naevus; they are large and polygonal (epithelioid), and have large vesicular nuclei with a clear chromatin pattern and a prominent nucleolus. The pigmented lesions are often combined naevi, that is, composed of two different melanocytic pigmented lesions that occur side-by-side or are intermingled.

Electron microscopy. The epithelioid blue naevus features cells that are heavily laden with type III and type IV melanosomes and cells in which these organelles are sparse {311}. Nuclei are mostly round and occasionally have indentations. Collagen bundles separate the cells.

Myxoma
The variously located myxoid lesions in CNC (skin, heart, breast and other) show sufficient histologic similarity to suggest that these apparently distinct tumours are the result of a widespread, specific abnomality of an as yet unidentified population of mesenchymal cells {313}. Histologically, the myxomas are typically hypocellular lesions. They feature scattered polygonal, stellate and spindle cells in pools of ground substance. Capillaries are usually prominent. The cutaneous lesions when in contact with the epidermis may induce downward proliferation of the epidermis, which becomes incorporated in the myxoma, resulting in a tumour with mesenchymal and epithelial components.

Electron microscopy. The cutaneous tumour features widely separated polygonal and spindle cells set in a pale-staining matrix containing scattered collagen bundles {313 The nuclei are oval or spindle and deeply indented with pale or peripherally condensed heterochromatin. Some nuclei contain a huge vacuole. The plasmalemma often has microvilli. A basal lamina is not present.

Primary pigmented nodular adrenocortical disease
The gross findings of this remarkable pathology, PPNAD, include 1) decreased, normal, or slightly increased total adrenal gland weight, 2) studding of the cut surface by small (less than 4 mm) black or brown, rarely yellow, nodules

and 3) atrophy of the cortex and loss of normal zonation between the nodules {2033}. Microscopically, the nodules are composed of enlarged, globular cortical cells with granular eosinophilic cytoplasm that contains lipochrome pigment.

Large-cell calcifying Sertoli cell tumour
This tumour ranges in size from microscopic to a mass that may replace the entire testis. It is usually bilateral, multicentric and calcified {1772}. Microscopically, it tends to be ill-defined peripherally. The tumour cells assume a number of patterns but usually have a trabecular or solid element. An intratubular (*in situ*) component may be present. The tumour cells are large and have abundant granular eosinophilic cytoplasm. Mitotic figures are rare. Laminated calcospherites, few to many, often with confluence are a characteristic feature. Two other tumours, Leydig cell tumour and adrenocortical rest tumour, may also be present {312}.

Electron microscopy. The cortical nodules are composed of polygonal cells that have a straight or interdigitating plasmalemma {2033}. Junctional complexes are uncommon. The most prominent organelles in the cells are smooth endoplasmic reticulum, mitochondria, lysosomes and lipid vacuoles. Pigment bodies are prominent in most cells.

Pituitary adenoma
Lesions in the pituitary gland range from invasive macroadenoma to multiple minute but grossly visible zones of abnormality evident at surgery, to microscopic foci of pituitary cell (sommatomammotroph) hyperplasia {1671}. Microscopically, the usual adenoma has a diffuse (solid) growth pattern and features round and polygonal cells with a variable amount of granular eosinophilic cytoplasm and a round or oval nucleus. Growth hormone or prolactin or both may be detected immunohistochemically in the tumours.

Electron microscopy. The pituitary adenoma features large, tightly packed somewhat irregular cells with complex interdigitations {1184}. Rough endoplasmic reticulum is abundant and may be disposed in parallel arrays and in short profiles. The Golgi apparatus is conspicuous. Secretory granules, ranging from 200 to 250 nm in diameter, are present in variable numbers.

Psammomatous melanotic schwannoma
This rare peripheral nerve sheath tumour was first recognised when it was found to be a component of CNC {308}. The neoplasm affects posterior spinal nerve roots, the alimentary tract (particularly esophagus and stomach), bone and skin. It is usually black grossly and may be multiple, and occur simultaneously or asynchronously at different sites. Microscopically, the tumour features spindle and epithelioid cells, melanin, psammoma bodies and fat. About 10% of the tumours are malignant and metastasize.

Electron microscopy. The fusiform, oval or stellate cells have long cell processes {308}. A continuous basal lamina that is sometimes reduplicated surrounds the cells. Scattered simple cell junctions may be present. Nuclei are round or oval and deeply indented. Premelanosomes and melanosomes in various stages of maturation are seen. There is long spacing collagen between the cells.

Genetics
Tumour studies have shown extensive genomic instability in CNC component tumour cells, an unusual finding among benign tumours {2145}. Linkage analysis in CNC families has shown genetic heterogeneity, with at least two main loci for candidate genes {326,2145}; others are likely to be found in the future.

2p15-16
A chromosome 2 (2p15-p16) locus was identified first {2142}, but the gene responsible for CNC in that region remains unknown. The most closely linked region on chromosome 2 centers around locus CA2/D2S123 {2142}.

17q22-24 / PRKAR1A
At the second locus, on chromosome 17 (17q22-24), mutations of the *PRKARIA* gene were recently identified {1094}. The *PRKARIA* gene encodes the regulatory 1-alpha (R1alpha) subunit of the protein kinase A (PKA), the main mediator of cAMP signaling in mammals. PRKAR1A is the most abundant subunit of the PKA tetramer {232,2143}.

The predominant type of PKA isoform (type-I versus type-II) in a cell depends on the differentiation and proliferation stage; hence, cellular PKA responses to cAMP can differ significantly depending on the predominant type of the PKA present {2143}. The expression of PRKARIA

has been shown to be altered in several sporadically occurring tumours and tumour-derived cell lines from non-CNC patients and the gene was a likely candidate for endocrine and non-endocrine tumourigenesis in CNC. Among the kindreds registered at NIH-MC, about half carried *PRKAR1A* mutations {1095}, although this percentage may be higher among patients presenting with PPNAD only {784}. In almost all mutations, the sequence change is predicted to lead to a premature stop codon {1095}. Both the mutant transcript and the predicted mutant *PRKAR1A* protein products were absent in these cells. The most frequent *PRKAR1A* mutation in CNC is a deletion in exon 4B that results in a frameshift, 578delTG; other frequent mutations are present in exons 2 and 6 {1094,1095}. Nonsense-mediated decay (NMD), in which the cells degrade the mRNA containing a deleterious, premature stop codon mutation prior to its translation, is apparently responsible for destruction of the abnormal mRNA in mutant *PRKAR1A*-carrying cells.

Preliminary data suggested that *PRKAR1A* functions as a tumour suppressor gene in CNC: tumours showed LOH of 17q22-24, and the wild-type allele was lost in associated tumours {1094,1095}. As a result of NMD of the pathogenic allele and LOH of the normal allele, the PRKAR1A protein was not present in CNC tumour cells {1094,1095}. This loss of the most important regulatory subunit of the PKA tetramer was associated with a greater PKA response to cAMP than in non-CNC tumours. Additional data indicate that the loss of PRKAR1A in CNC tumours leads to compensatory increases in the other PKA subunits, type I (PRKAR1B) and type II (PRKAR2A and PRKAR2B) depending on the tissue, the cell cycle stage, and perhaps other factors. This is not unlike the situation in mouse models in which one of the PKA subunits is knocked out {50}. Thus, it appears that the increased cAMP response of PKA activity in CNC tumours is due to the up-regulation of other possible components of the PKA tetramer, type-II regulatory subunits, in particular {2140}. Supportive of this notion also are data indicating that the presence of an abnormal PRKAR1A (complete loss may not be necessary) in CNC tumours is associated with increased PKA signalling in response to cAMP {785}. Interestingly.

in most tumours from the kindred that had this mutation, there was no LOH, indicating that even in the presence of haplo-insufficiency, tumours may develop, presumably due to the imbalance between type I and type II PKA in the affected cells {785}. It remains to be seen how these abnormalities fit in what is known about the effects of cAMP and PKA on growth and proliferation, and whether, indeed, in functional studies, PRKAR1A directly suppresses tumourigenesis, or has a more complicated role in the regulation of other signaling pathways, the cell cycle or, perhaps, chromosomal stability {1865,2143}.

Prognostic factors

Most tumours associated with CNC are characterised by slow growth and show no malignant potential. However, lifespan is decreased in patients with CNC, due to an increased incidence of sudden death caused by heart myxoma or its complications. Other causes of early death in patients with CNC include complications of severe or chronic Cushing syndrome, malignant PMS, and metastatic pancreatic, ovarian and thyroid carcinoma.

Genetic counselling and preventive measures

Clinical and biochemical screening for CNC and medical surveillance for affected patients remain the gold standard for the care of patients with CNC {2146}. While the diagnosis of CNC can be made clinically in classic presentations, mutation analysis for *PRKAR1A* may be used as a molecular diagnostic adjunct when clinical diagnosis is difficult. Further, once a family-specific mutation is established in a known affected, it is advised that other family members be offered testing for that mutation so that relatives who are truly non-carriers can avoid unnecessary medical intervention {2140, 2146}.

In brief, for post-pubertal paediatric and for adult patients of both sexes with established CNC, the following annual studies are recommended: echochardiogram, measurement of urinary free cortisol levels (which may be supplemented by diurnal cortisol or the overnight 1 mg dexamethasone testing) and serum IGF-1 levels {2146}. Male patients should also have testicular ultrasonography at the initial evaluation: microscopic LCCSCT

may be followed by annual ultrasound thereafter {1769}. Thyroid ultrasonography should be obtained at the initial evaluation, and may be repeated, as needed {2144}. Transabdominal ultrasonography in female patients is recommended during the first evaluation but need not be repeated, unless there is a detectable abnormality, because of the relatively low risk of ovarian malignancy {2147}. More elaborate clinical and imaging studies may be necessary for the detection of PPNAD and pituitary tumours in affected patients who do not have overt clinical manifestations of Cushing syndrome or acromegaly {1671,2148}. For the former, a dexamethasone-stimulation test {785} is recommended, in addition to adrenal computed tomography and diurnal cortisol levels {1940,2148}. For the latter, oGTT may be obtained in addition to IGF-1 levels and pituitary magnetic resonance imaging {1671,2359}. Paediatric patients with CNC should have echocardiography during their first six months of life and annually thereafter; bi-annual echocardiographic evaluation may be necessary for patients with history of an excised myxoma {318,2146}. Most endocrine tumours in CNC do not become clinically significant until the second decade in life (although they might be detectable at a much earlier age) and imaging or biochemical screening in young, prepubertal children are not considered necessary, except for diagnostic purposes. However, paediatric patients with LCCSCT (or a micro-calcification upon testicular ultrasonography) should have growth rate and pubertal status closely monitored; some might need bone age determination and further laboratory studies {2146}.

McCune-Albright syndrome (MAS)

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Definition

McCune-Albright syndrome (MAS) is defined by the triad of polyostotic fibrous dysplasia (POFD), *café-au-lait* skin lesions, and sexual precocity., caused by activating mutations in the complex *GNAS* locus at 20q13.2-13.3. MAS patients may also develop nodular hyperplasia or adenomas of endocrine glands with associated endocrinopathies or other, nonendocrine manifestations. Some MAS patients only develop a subset of the full syndrome. Mazabraud syndrome is the co-occurrence of POFD and intramuscular myxomas.

MIM No. 174800 {1468}

Synonyms

McCune-Albright syndrome, Albright syndrome, fibrous dysplasia (polyostotic and monostotic); Mazabraud syndrome.

Diagnostic criteria

The diagnosis of MAS is usually clinically obvious and is confirmed by excess circulating levels of one or more hormones (thyroid hormone, cortisol, growth hormone, or estrogen) in the absence of the respective stimulating hormones. FD is usually diagnosed by its characteristic ground glass (but occasionally sclerotic) appearance on X-ray, although it can be confused with osteofibrous dysplasia {1390,1902} or hyperparathyroid-jaw tumour syndrome {319,549,632,809}. In Mazabraud syndrome, FD is associated with intramuscular (but not juxtaarticular) myxomas {1643}.

Endocrine hyperfunction

Age distribution/penetrance

MAS/FD generally is diagnosed within the first decade of life. Penetrance is high but is primarily affected by the specific extent and distribution of mutant cells in each individual.

Clinical features

The classical clinical triad, which has generally defined the syndrome, is the co-occurrence of sexual precocity, POFD, and areas of skin hyperpigmentation (*café-au-lait* spots). However, multiple other endocrine and nonendocrine abnormalities may be present or patients may present with only 1 or 2 manifestations. In girls, sexual precocity usually presents as premature menses followed by breast development and is associated with gonadotropin-independent secretion of estrogen from large ovarian follicles {406,623,642,1442,1827}. Usually, females undergo normal development during adolescence and show normal reproductive function in adult life. Boys present with precocious puberty less commonly than girls. Testicular enlargement often results from maturation and growth of seminiferous tubules {424, 722}. MAS patients can develop nodular or multinodular thyroid disease detectable by ultrasound associated with increased radioiodine uptake and often associated with suppressed thyrotropin levels and varying levels of hyperthyroxinemia {625,1202,1426}. Acromegaly due to growth hormone-secreting pituitary adenomas may occur in 20% of MAS patients and is often associated with hyperprolactinemia {21}. Another less common endocrine manifestation is adrenocorticotropin-independent hypercortisolism, which can lead to decreased growth rate and many other severe problems in young children {457,1442}. Hyperphosphaturic hypophosphatemic rickets or osteomalacia can also occur in MAS and POFD patients and is usually associated with a more general renal tubulopathy {402}. This may result from a phosphaturic factor secreted from FD lesions {402,2441}.

A few severely affected patients (often with extensive POFD and hypercortisolism) also develop other nonendocrine manifestations. Liver abnormalities include severe neonatal jaundice and elevated liver enzymes {2032,2052}. Cardiac abnormalities, which may be associated with MAS include cardiomegaly, persistent tachycardia and unexplained sudden death in young patients. Other abnormalities, which are rarely associated with MAS include thymic hyperplasia, myelofibrosis with extramedullary haematopoiesis, gastrointestinal polyps, pancreatitis, breast and endometrial cancers, microcephaly and other neurological abnormalities {35, 457,1375,1459,2032}.

Pathology

Affected endocrine tissues generally have nodular hyperplasia or in some cases, adenomas that are hormone-secreting {457,1442,2371}. The ovaries have large follicular cysts with no evidence of ovulation. Acromegaly is associated with pituitary adenomas, which may be small {21}, or nodular hyperplasia {1158}. Hypercortisolism is generally associated with macronodular adrenal cortical hyperplasia although adrenal adenoma has also been reported {165,1093}. In some patients the liver shows atypical cholestatic and biliary abnormalities and the heart shows atypical myocyte hypertrophy {2032,2052}. Other pathological findings that have been found in MAS include hypertrophy of the thymus and spleen, myeloid metaplasia with extramedullary haematopoiesis, subtle brain abnormalities, gastrointestinal polyps, and breast and endometrial cancer {457,2032}.

Prognosis

While the vast majority of MAS patients have an excellent prognosis {457,837, 1267}, there are a small number of severely affected patients (often with extensive POFD and hypercortisolism) who present with one or more nonendocrine abnormalities which may lead to markedly increased morbidity and mortality {2032}. These patients may die of sudden death during surgery or illness, perhaps secondary to cardiomyopathy and arrythmia {2032}. MAS patients have the same morbidity from bone disease as those with POFD alone. Often, the endocrine abnormalities are treated medically or by surgical removal of the enlarged endocrine glands. Cypro-

heptadine, testolactone, tamoxifen, and ketoconazole have been used for sexual precocity with mixed success {581, 623,624,2165} Thyroid disease can be managed with surgery, antithyroid medications, or radioiodine therapy. Hypercortisolism is usually treated with bilateral adrenalectomy. Pituitary tumours are treated with surgery if possible, but can often be managed with a dopamine agonist, long-acting somatostatin analogue, or both {21}. Surgery may be impossible if FD is present in the base of the skull. Radiotherapy in these cases may increase of risk of malignancy in the surrounding bone.

Fibrous dysplasia

Fibrous dysplasia (FD) is a benign focal bone lesion composed of fibrous connective tissue, immature woven bone and, occasionally, cartilaginous tissue. FD may occur in multiple bones (polyostotic FD; POFD) or at a single site (monostotic fibrous dysplasia; MOFD).

Clinical features
MOFD is a common disorder that is often a clinically silent, incidental radiological finding. One study suggested the relative incidence among FD patients to be 70% MOFD, 30% POFD and less than 3% MAS {1570}.
FD lesions are most commonly found in the femur (femoral neck and intertrochanteric region), tibia, humerus, ribs, and craniofacial bones (most often the maxilla) {837,1570,1973}. Other long bones such as the radius, ulna and fibula are involved less frequently while the bones of the hands, feet and spine are usually spared. MOFD is often clinically silent and diagnosed as an incidental radiological finding, which does not require follow-up. More extensive FD can lead to deformities (often producing a limp), pathological fractures, pain and nerve compression {457,837,1973}. Deformities may include leg length discrepancy, outward bowing of the proximal femur (shepherd's-crook deformity), facial asymmetry, orbital displacement and visible or palpable bony enlargement. Deformity of the chest wall may lead to restrictive pulmonary disease {1570,1973}. Pathologic fractures occur frequently and are often recurrent. Pain can result from pathological fractures and
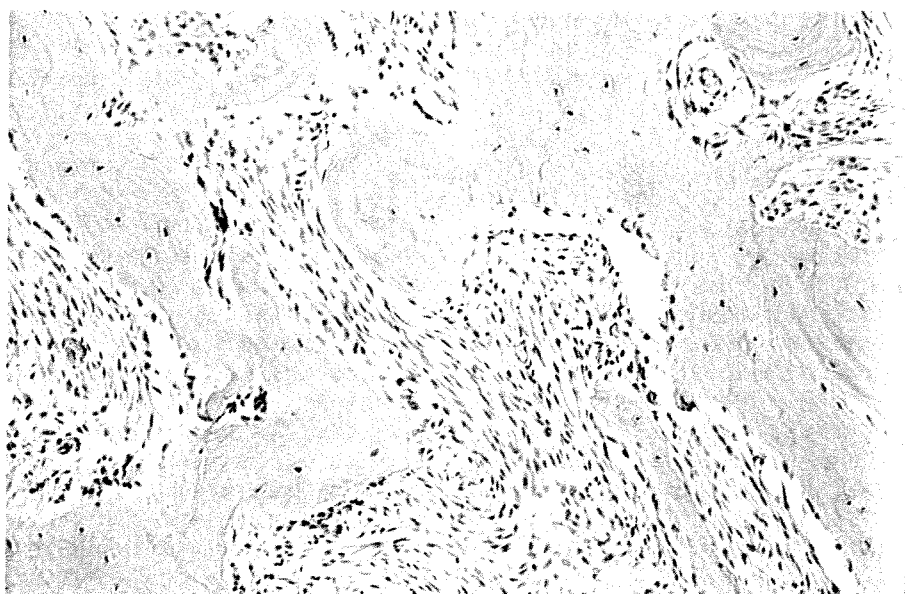
Fig. 5.33 McCune-Albright syndrome. An iliac crest biopsy showing the characteristic 'Chinese writing' pattern of fibrous dysplasia containing whirls of fibrous tissue interspersed with spicules of immature woven bone. Courtesy of Dr. Michael Collins, NIDCR/NIH.

secondary arthritic changes in nearby joints. The most common neurological complications include blindness, deafness and equilibrium disturbances due to compression of the occipital and auditory nerves. High output cardiac failure due to arteriovenous shunting through bone lesions has also been reported {633}. FD lesions occur in the metaphysis or diaphysis and on radiographs appear as radiolucent cysts expanding from the medullary cavity with thinning of the surrounding cortex. Often, there is a ground glass appearance but sclerosis and calcifications may also be present {1361}. Nuclear bone scanning and magnetic resonance imaging {732,964,998} are also useful for determining extent of disease. Active disease is associated with increased serum alkaline phosphatase and other biochemical markers of bone turnover. Extensive POFD may also be associated with hypophosphatemia and renal tubulopathy {402}. Coexistent intramuscular myxomas in Mazabraud syndrome tend to be large and are often located in the vicinity of the FD, usually in the thigh.

Histopathology
FD lesions are thought to be secondary to increased proliferation and decreased osteoblastic differentiation of bone marrow stromal cells resulting from elevated intracellular cAMP levels. FD lesions are primarily composed of fibrous tissue that expands concentrically from the medullary cavity to the cortical bone. Long spindle-shaped fibroblasts are arranged in parallel arrays or in whirls {767}. These cells are of the osteoblastic lineage, as they express proteins associated with osteoblast differentiation {1832}. The matrix is composed of parallel collagen fibres and in some areas is more myxomatous. Spicules of immature woven bone are embedded within the fibrous tissue. These spicules are surrounded by flat lining cells with retracted cell bodies forming pseudo-lacunar spaces {1832, 1833}. This retraction is probably due to increased intracellular cAMP, as cAMP produces similar changes in cultured osteoblasts. Unlike normal woven bone, the collagen fibrils at the surface are arranged perpendicular to the bone forming surface (so-called Sharpey's fibres) {186,1832,1833}. The osseous components in FD contain osteonectin but not osteopontin or bone sialoprotein, proteins that are present in the matrix of normal woven bone {1832}. The osteocytic lacunae are large with each containing multiple osteocytes (hyperosteocytic bone) {1832}. Changes consistent with osteomalacia may or may not be present within the bony component of FD lesions {186,2213}. The border between FD and normal bone is usually sharp and well demarcated.

The histology of FD lesions varies depending on the location of the affected bone {1833}. Lesions in the axial and appendicular skeleton have a 'Chinese writing' pattern, characterised by thin and disconnected bone trabeculae with interspersed fibrous tissue. Cranial bone lesions generally have a 'sclerotic/Pagetoid' pattern, with dense, sclerotic trabecular bone forming an uninterrupted network and the presence of cement/arrest lines similar to those observed in Pagetic bone. Gnathic bone lesions have a 'sclerotic/hypercellular' pattern, characterised by large trabeculae arranged in a parallel array with osteoblasts lining one side of the trabeculae. However, all FD lesions have retracted osteoblasts and Sharpey's fibers, which appear to be hallmarks for FD.

Occasionally, islands of hyaline cartilage are present in FD, probably due to a metaplastic process {767}. Rarely, the cartilaginous component may be a dominant feature (fibrocartilaginous dysplasia {968}). The cartilage may undergo endochondral ossification and, if prominent, may result in the presence of stippled or ring-like calcifications on radiographs. Some lesions of FD contain calcified spherules, a typical feature of cemento-ossifying fibroma. Other lesions, which appear histologically similar to FD, are osteofibrous dysplasia, osteitis fibrosa cystica (which is usually associated with hyperparathyroidism or chronic renal failure), and Paget disease (which develops in older adults). In osteitis fibrosa cystica and Paget disease, there is more active osteoclastic bone resorption within the lesions and no evidence of cartiginous islands.

FD often invades the outer cortical bone through the action of increased numbers of surrounding multinucleated osteoclasts {1832,2442}, resulting in cortical thinning and in some cases, concentric bulging of the cortex. Osteoclast activation is most likely the result of increased interleukin 6 secretion from FD cells. Rarely, these lesions are more aggressive, resulting in exophytic protuberances {524} or soft tissue invasion {1240}. FD is benign and does not metastasize. Rarely, it undergoes malignant progression, most often to osteosarcoma and less commonly to chondrosarcoma, fibrosarcoma or malignant fibrohistiosarcoma {1055,1883, 2435}.

Prognosis

POFD is usually diagnosed in the first decade of life, either due to symptoms or the presence of other MAS manifestations. It usually progresses in early life and then becomes quiescent after the third decade {457,837}, although in some cases FD continues to progress or may be initially diagnosed during puberty, pregnancy or the use of oral contraceptives {1973,2128}. FD rarely undergoes malignant degeneration, most often to osteosarcoma and occasionally to chondrosarcoma, fibrosarcomas or other types of sarcoma {1055,1883,2197, 2435}. Radiotherapy may increase the risk of malignant transformation. Generally, fractures heal well with conservative management {837} although surgery may be required for nonhealing fractures, severe pain or deformity, particularly on weight-bearing bones, or imminent signs of nerve compression {545,756,837,1062,1378,1570}. A recent study concluded that orbital decompression is not required in patients who do not have clinical symptoms due to optic nerve compression {1266}. Bisphosphonates, such as pamidronate, can also lead to clinical and radiological improvement of FD in some patients {352,967,1203,1299,2473}.

Skin lesions

Clinical features
Café-au-lait lesions in MAS are hyperpigmented flat macules that can be extensive but generally do not cross the midline and follow a segmental pattern following the distribution of the developmental lines of Blaschko {818}. Often, these lesions are on the same side affected by POFD. The borders of these lesions tend to be very irregular, as opposed to the *café-au-lait* lesions associated with neurofibromatosis {35}. The pigmentation becomes more obvious with age and may darken after sun exposure. These lesions likely result from Gsα activating mutations and increased intracellular cAMP in melanocytes, which leads to increased melanin production {1077}. Alopecia is rarely associated with MAS {1991}.

Histopathology
The skin lesions in MAS histologically appear similar to those in neurofibromatosis, with no change in the number of melanocytes but an increase in the number of melanin-containing pigment granules. Melanocytes cultured from these lesions have increased numbers of dendrites and melanosomes and increased levels of tyrosinase, the rate-limiting enzyme for the production of melanin {1077}.

Prognosis
The hyperpigmentation lesions in MAS are totally benign and do not lead to any complications beyond their cosmetic effect.

Genetics

Chromosomal location and gene structure
MAS/FD results from activating mutations of *Gsα*, one of several transcripts encoded by the complex *GNAS* locus at 20q13.2-q13.3. *GNAS* was originally described as a gene comprising only the 13 exons that encode Gsα, {1161}, but more recently, additional upstream exons have been described, designated 1A (or A/B), XLαs and NESP55 {848,849,1313}. Transcription of *Gsα*, XLαs, NESP55, and exon 1A mRNAs is initiated from distinct promoters and first exons that share a common set of downstream exons (exons 2-13). NESP55 contains a stop codon in its first exon and so exons 2-13 are not translated, whereas XLαs is identical to *Gsα* except at their amino-termini, which are encoded by their unique first exons. Exon 1A mRNAs are untranslated.

Mutation spectrum
Like all heterotrimeric G proteins, Gsα is activated by ligand-bound receptors through the release of bound GDP and binding of ambient GTP, which allows Gsα to bind to and activate the cAMP-generating enzyme adenylyl cyclase. The turn-off mechanism is an intrinsic GTPase activity that hydrolyzes bound GTP to GDP. Residues Arg201 and Gln227 are catalytically important for the GTPase reaction and therefore missense mutations leading to their substitution lead to constitutive activation of Gsα and its downstream effectors. MAS/FD and Mazabraud syndrome are associated with Arg201 mutations (most commonly R201H and R201C, more rarely R201G, R201L, and R201S. {186,290,1520,1644,
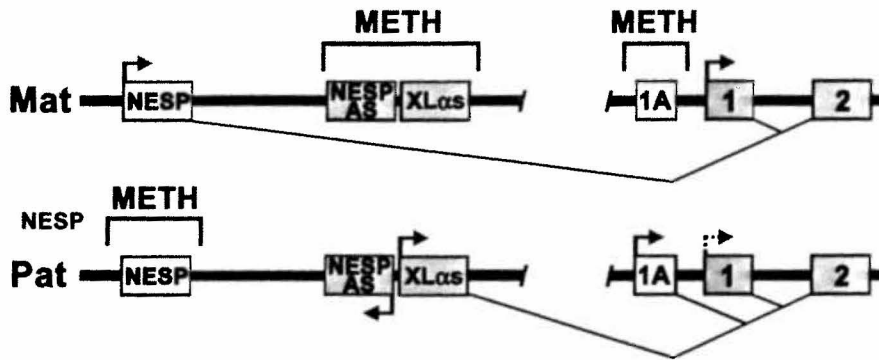
Fig. 5.34 Organization and imprinting of *GNAS*. The maternal (Mat) and paternal (Pat) alleles of *GNAS* are depicted with alternative first exons for NESP55, XLαs, 1A (untranslated), and Gsα (exon 1) mRNAs splicing to a common exon (exon 2). Exons 3-13 are not shown. Differentially methylated regions (METH) are shown above and splicing patterns are shown below each panel. Horizontal arrows show direction of transcription of active promoters. Transcription from the paternal Gsα (exon 1) promoter is suppressed in some tissues (indicated with dashed arrow). The first exon of antisense transcripts (NESPAS) is also shown.

1831,1992,2371}). The mutations arise post-zygotically and affected individuals are therefore somatic mosaics, which accounts for the significant variability observed in the extent and severity of clinical presentation. Germ-line transmission of these activating mutations has not been observed, suggesting they are embryonic lethal if present in non-mosaic form. Somatic Arg201 (R201H, R201C, R201S, R201L) or Gln227 (Q227H, Q227R) mutations are also in some sporadic hyperfunctioning endocrine tumours, including pituitary adenomas, thyroid adenomas, thyroid carcinomas, parathyroid adenomas and phaeochromocytomas {748,1224,1373, 2446} and in isolated intramuscular myxomas {1644}. Inactivating *Gsα* mutations lead to Albright hereditary osteodystrophy (with or without multihormone resistance) and progressive osseous heteroplasia.

Gene expression

Gsα is expressed in virtually all tissues while XLαs and NESP55 expression is restricted to neuroendocrine tissues. All products are subject to genomic imprinting as described below.

Gene function

Gsα is the heterotrimeric G protein α-subunit that couples seven-transmembrane receptors to the cAMP-generating enzyme adenylyl cyclase, and is, therefore, required for the intracellular cAMP response to hormones and other extracellular signals. Activating *Gsα* mutations lead to their pleiotrophic effects primarily by raising cAMP levels in affected tissues. XLαs is a Gsα isoform that has also been shown to be capable of coupling receptors to cAMP generation while NESP55 is a chromogranin-like neurosecretory protein. The biological functions of both of these latter proteins are presently unknown.

Imprinting

GNAS is subject to a complex pattern of imprinting. NESP55 is expressed only from the maternal allele while XLαs and the exon 1A transcripts are expressed only from the paternal allele {848,849, 1313}. Loss of exon 1A imprinting causes pseudohypoparathyroidism type Ib {1313}. *Gsα* is biallelically expressed in most human tissues, but shows exclusive or preferential expression from the maternal allele in some tissues, including pituitary, thyroid and ovary {699,847,1403}. In pituitary tumours that harbour an activating *Gsα* mutation, the mutation almost always occurs on the maternal allele {847}. Therefore, the clinical manifestations observed in each MAS patient might possibly be affected by which parental allele harbours the *Gsα* mutation.

Genetic counselling and preventive measures

MAS and FD both result from somatic rather than germline, *GNAS* mutations. These disorders are virtually never inherited, presumably due to the fact that the mutations are lethal in the germline. There are no known measures that can prevent their occurrence. Patients with FD should not be treated with radiation, as it is ineffective and may increase the risk for malignant transformation. POFD patients should be screened for endocrine manifestations of MAS.

Familial non-medullary thyroid cancer

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Definition

There is no widely accepted definition for familial non-medullary thyroid cancer (FNMTC), but its existence is now accepted, mainly as a result of single-kindred linkage studies, which have identified several candidate regions. No 'site-specific' genes have yet been identified, but autosomal dominant inheritance is presumed for most of the currently identified loci. Under a broad classification of FNMTC, one could also include inherited thyroid-specific syndromes where non-medullary thyroid cancer (NMTC) is an occasional feature, such as familial multinodular goiter. Other syndromes that feature NMTC include Cowden syndrome, familial adenomatous polyposis (FAP), Carney complex and Werner syndrome.

MIM Numbers

See: http://www.ncbi.nlm.nih.gov/omim {1468}.
Multinodular goiter
    MNG1:   *138800
    MNG2:   *300273
Familial non-medullary thyroid cancer
    NMTC1:   *606240
Familial non-medullary thyroid cancer
with cell oxyphilia: *603386
Papillary thyroid carcinoma with papillary
renal neoplasia: *605642
Cowden Syndrome: #15830
    PTEN: *601728
Familial adenomatous polyposis (FAP)
              *175100
Carney Complex
    Type 1:   #16980
    Type 2:   *605244
Werner syndrome   #277700

Synonyms

Familial site-specific non-medullary thyroid cancer (FNMTC); Familial papillary thyroid cancer (FPTC); Familial micro-papillary thyroid cancer; Familial non-medullary thyroid cancer with cell oxyphilia (TCO); Familial Adenomatous Polyposis (FAP) / Gardner syndrome; Cowden syndrome / Multiple hamartoma syndrome

Incidence / prevalence

The annual incidence of thyroid cancer is between 0.9 and 5.2 per 100,000 people, with a ratio of women to men of 2-3:1 {380,656,864,1011,1854}. In 1955, twins with FNMTC were described {1845}. Approximately 4% of patients with PTC have at least one affected first degree relative {380,783,930,1146,1278,1344, 1676,2276}. A 4.2-10.3 fold excess risk of NMTC is seen in first relatives of patients with NMTC and this cancer risk among relatives is one of highest recorded {738,863,1676,1854}.

Like most known inherited cancer syndromes, there is age-related penetrance for Familial Papillary Thyroid Cancer (FPTC) {1344,1393}. Also similar to other inherited syndromes, an earlier age at diagnosis of NMTC (usually PTC) is more likely to be associated with potential genetic etiology {862}. It is unknown if penetrance is different between the sexes, and thus, if the sex ratio in FPTC is different from sporadic PTC. Some have suggested an unaltered sex ratio {1278,1345,2176,2276} while others have reported low penetrance in men {1676}, while others have suggested that it is high {783,862,930}.

Diagnostic criteria

Non-medullary thyroid cancer (NMTC) refers to primary thyroid malignancies derived from the thyroid follicular cells. A familial predisposition to NMTC is a component of several familial tumour syndromes. Diagnosis of familial NMTC (FNMTC) requires familial inheritance, including a first degree relative (parent, sibling, or offspring) {930} with papillary thyroid cancer (FPTC) or follicular thyroid cancer (FFTC) outside of a tumour syndrome where NMTC is an infrequent component. It is estimated that 47% of FNMTC patients from families with 2 affected members, and 99.9% of patients from families with 3 or more affected members, have an inherited form of the disease {353}. Around 90% of FNMTC is FPTC {1278}. The existence of familial follicular thyroid cancer (FFTC)

outside of an associated familial tumour syndrome is not established, but there are several case reports (see FFTC section). It can be appreciated from this that there are no universally accepted diagnostic criteria for FNMTC. Many families are rather small, and sometimes contain only 2 affected sibs, nonetheless, they have been counted as FNMTC. Operationally, two affected first-degree relatives could be regarded as sufficient to consider FNMTC. Common exposures, such as ionising radiation, could mimic a Mendelian genetic effect, particularly if there is a strong temporal relationship to a putative common exposure. The diagnostic criteria for Cowden syndrome includes follicular thyroid cancer as a major, but not pathognomonic criterion {561}. Any thyroid lesion, such as adenoma or goiter, is accepted as a minor criterion. NMTC is not regarded as a cardinal feature of familial adenomatous polyposis (FAP) as it is seen in less than 3% of all individuals with FAP {260}. Similarly, it is not a part of the diagnostic features of either Carney complex (see section on Carney complex) or Werner syndrome, but does occur at increased frequency in these syndromes, at least in some geographical areas (suggesting that environmental factors may be triggering a latent susceptibility {971,972, 1528,2144}.

Papillary thyroid cancer

Age distribution/penetrance

The penetrance of FPTC is high, although even in large kindreds used for linkage studies, there were unaffected obligate carriers. Similarly, the kindreds have been selected for early-onset cases, as these are more likely to be sampled than late-onset cases. Until specific genes have been identified and tested in the population, it will not be possible to accurately assess the penetrance of FPTC-related alleles. The situation for PTEN and APC is much clearer. The lifetime risk for thyroid cancer in
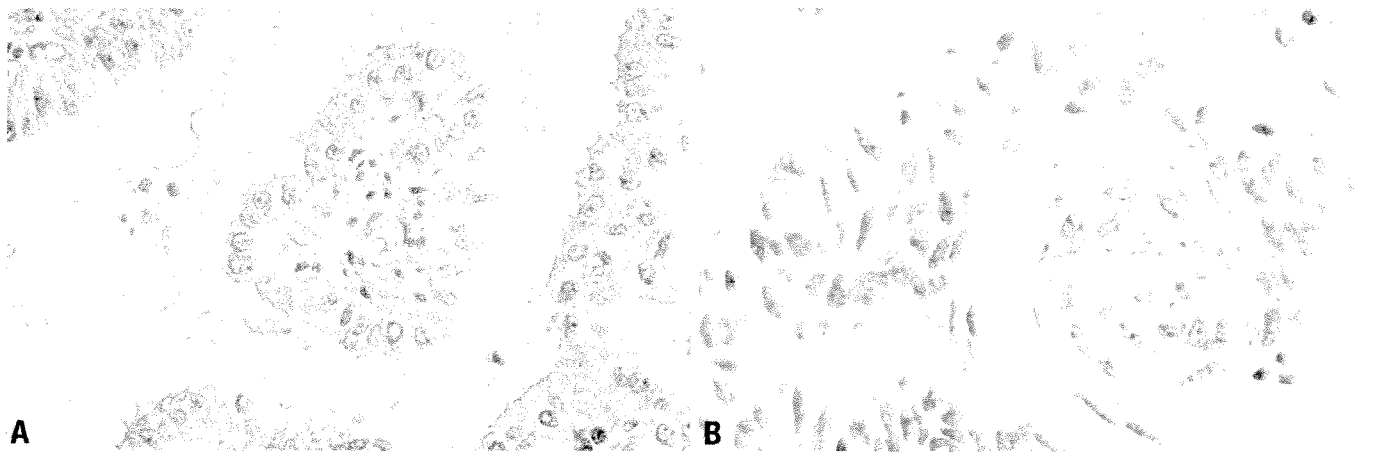
Fig. 5.35 Familial non-medullary thyroid cancer. **A** Oncocytic papillary carcinoma linked to chromosome 19p13.2. Papillae lined by oncocytic cells with abundant eosinophilic granular cytoplasm containing irregular grooved overlapping nuclei with prominent nucleoli. **B** Familial adenomatous polyposis associated thyroid carcinoma. Tumour cells show whorling and a trabecular growth pattern.

Cowden syndrome, caused by germline mutations in *PTEN*, has been estimated at approximately 10%. It is thought to be 1-3% in FAP. The average age of onset of thyroid cancer in Cowden syndrome is 26 years (range 9-43 years) {1879}, and in FAP, it is also 26 years (range 9-69 years) {337}, with the vast majority of the latter cases occurring in women {1879}. In Werner syndrome occurring in Japanese, the average age of onset has been reported to be 39 years (range 27-60) with an approximately 2:1 F:M ratio {971}. The lifetime risk is not known. Incidence of PTC in Carney complex is greater than expected, but the precise lifetime risks are unknown.

Clinical features
The age of diagnosis in FPTC may not be different from sporadic PTC {656,783, 930,1186,1676,2276}, while others have reported a peak incidence in the 4th decade of life, possibly a decade earlier than for sporadic PTC {1344,1368}. No given phenotype for FNMTC has been identified {1278,2276}, although an increased rate of intrathyroidal tumour multifocality, and an association with multiple benign nodules is reported {2276}. The onset of FPTC may be related to both genetics and an increased susceptibility to environmental factors such as radiation exposure {600,1391,1719,2134}. Women with FPTC may be at increased risk of breast cancer {930,2305}. Patients of both sexes with FPTC may be at increased risk of kidney cancer and CNS tumours {930}. An increased number of benign thyroid conditions, including nod-

ules, may be present in affected families {261,924,1278,1394,2134}, but this has not been a universal finding {1344,1676}. Members of families with FNMTC may be at increased risk of leukemia {738} and hormone-related cancers {1676}, although this has not been confirmed by others {656,862,930}. Specifically, the risks of breast and prostate cancer are uncertain {656,680,738,783,862,930, 1676,1854}.

Pathology of site-specific FPTC
In families with cellular oxyphilia
Both sporadic and familial NMTC with cell oxyphilia have been studied pathologically. In familial cases, there was a mixture of features, in particular a characteristic multiple adenomatous goiter, with or without PTC with oxyphilic features. Other affected individuals have only oxyphil PTC. Essentially, this is a variant form of multinodular goiter susceptibility, with prominent oxyphilic features. Multicentricity is a common feature and these adenomas are often encapsulated structures with variable oxyphilia. The oxyphil papillary carcinomas are characterised by irregular, grooved nuclei, occasional nuclear cytoplasmic inclusions and conspicuous nucleoli {293,827,1051}.

In families linked to 2q
Recently, linkage to chromosome 2q21 has been identified in one large Tasmanian family with FPTC and multinodular goiter (MNG) {261}. Interestingly, linkage to 2q21 was only obtained when it was observed that 7 of 8 family mem-

bers with PTC shared the same haplotype on 2q21 {1465}. The pathology of these PTCs was interesting: on review of the 8 PTC-affected individuals had the follicular variant of PTC (fvPTC). This variant accounts for less than 10% of all PTC's. Other families with at least one case of fvPTC appear also to be linked to this region.

In families with the papillary microcarcinoma
Microscopic papillary thyroid cancer is defined as a PTC that is 1 cm or less in size. It has been reported that, when familial, these cancers behave more aggressively {1368,1879}. The papillary microcarcinoma is common in the general population: nearly one quarter of those aged 45 years have papillary thyroid microcarcinoma {652}.

FPTC and papillary renal neoplasia
One large single pedigree has been reported with FPTC and papillary renal neoplasia. Linkage to 1q has been obtained {1393}. The PTC that occurs in this family appears to be "typical" PTC with no special features. Some individuals have thyroid nodules.

Pathology of syndromic FPTC
PTEN-related FPTC
Thyroid cancer in Cowden syndrome is usually follicular, rather than papillary in type (see section below). However, these carcinomas can often have an important papillary component {1028}. However in these cases, classical features of PTC such as psammoma bodies, are absent

Table 5.11
Familial tumour syndromes predisposing to non-medullary thyroid cancer.

Syndrome	Gene or chromosomal location	Thyroid cancer histology and incidence (%)
Cowden	PTEN	FTC and PTC(3-21%) {924,1412,2116}
Familial adenomatous polyposis, (also Gardner syndrome, Turcot syndrome, hereditary desmoid disease)	APC	PTC (2%) {160,706}
PTC with cell oxyphilia	TCO, 19p13.2	Oncocytic PTC {293}
PTC without oxyphilia	19p13.2	PTC {183}
Multinodular goiter	MNG1, 14q31	2 PTC-like lesions in the MNG1 kindred, none
	MNG2, Xp22	in the MNG2 kindred {189,298}
PTC, nodular thyroid disease, and papillary renal cell carcinoma	1q21	PTC {1393}
PTC and clear cell renal cell carcinoma	t(3;8)(p14.2;q24.1)	PTC {397,560}
Carney complex	PRKAR1A	FTC (2%) and PTC (2%) {1625,2144}
Werner syndrome	WRN	PTC, FTC, anaplastic {972}
FNMTC	NMTC1, 2q21	fvPTC {1465} [such as CK 5/6])

FAP-related FNMTC

Thyroid tumours associated with familial adenomatous polyposis are detected in 2% of affected individuals by palpation alone and up to 25% in selected series by ultrasonography {979,1879}. While traditionally classified as a papillary thyroid carcinoma or a cribiform subtype, a growing number of pathologists and thyroidologists believe that FAP-related thyroid carcinomas are histologically distinct {343,830}. Distinct histological patterns of growth include cribriform, morular (squamoid whorling) and short fascicles of spindle cells. Other frequent cytoarchitectural patterns include eosinophilic to amphophilic cuboidal to columnar sometimes stratified epithelium lining papillae and follicles with angular or tubular shapes, as well as trabecular or solid structures with occasional adamantinomatous and hyalinizing trabecular adenoma – like features. Microscopic hypercellular foci with similar cytoarchitecture to large tumours may occur admixed with normal looking background thyroid parenchyma. The tumours are usually well circumscribed and/or encapsulated, fibrosis is often prominent in the tumour capsule or stroma, and evidence of capsular, lymphatic or vascular invasion may not be present. Notably, FAP associated thyroid tumours, in contrast to classic papillary carcinoma, do not show the typical fir tree branching papillary pattern, psammoma bodies are rare or non-existent, nuclei lack the pale dusty 'ground glass' chromatin, show inconstant grooving and occasional, if any, cytoplasmic inclu-

sions. Only 5% show regional lymph node metastasis {830,1727,1879}. It should be noted that the distinct architecture seen in FAP-related thyroid carcinomas is very unusual in sporadic PTC {343}.

Carney complex-related FPTC

There has been no systematic analysis of thyroid lesions in Carney complex, but up to 11% may have some form of thyroid disease {2144}. Case reports of PTC have suggested that the fvPTC (see above) and FTC (see below) may be seen. The lesions are usually multifocal.

Werner syndrome-related FPTC

No increase in PTC has been seen in non-Asian kindreds with Werner syndrome. It is not clear whether the incidence of thyroid cancer in Japanese affected by WRN is due to differences in mutation spectrum {971,972}, or reflects differences in iodine levels, and hence is more related to environmental factors than any observed differences in mutation spectrum {1528}. In Japanese kindreds, PTC (35%), FTC (48%) and anaplastic carcinoma (13%) have all been reported {971}. Detailed pathological description of these cases is awaited.

Prognosis and prognostic factors

The performance of prognostic factors that predict outcome in sporadic PTC is unknown in FPTC. The overall prognosis of FPTC is not well established, but may be the same as for sporadic tumours {1146,1186,1278,1344,1391}. Some have suggested a more aggressive tumour

behaviour in FPTC {783,1355,1666,2176, 2276}, perhaps surprisingly, including those with microcarcinoma (< 1 cm) {1368}. Thyroid cancer occurring as a part of FAP seems to have a favourable prognosis {1879}.

Follicular thyroid carcinoma

Clinical features

Familial FTC may be inherited as part of a syndrome with additional associated phenotypic features such as Cowden Syndrome, Carney Complex or Werner Syndrome {1879}. Inheritance of isolated FTC outside of a well-defined syndrome has not been clearly established {656, 863,1392,1854}, especially given the possibilities of chance occurrence and misclassification of PTC as FTC. FTC comprises approximately 6% of thyroid cancer cases from FNMTC series {1344}.

Pathology
PTEN-related FTC

Thyroid cancer is an important aspect of Cowden syndrome {561}. Up to 10% of Cowden individuals develop non-medullary thyroid (usually follicular) carcinoma. The lesions seen in this syndrome are usually multicentric and follicular, rather than papillary. The follicular adenomas tend to have classic follicular architecture. Follicular carcinomas that are seen in Cowden syndrome are believed to progress from pre-existing follicular adenomas {1879}.

Werner syndrome-related FTC

FTC is more common in Japanese Werner syndrome patients than is PTC. Detailed comparisons of FTC occurring in Werner syndrome and in the general Japanese population would be of interest.

Other FFTC

One study reported an African American family with congenital goiter in which two children with goiter also developed metastatic FTC {411}. The metastatic thyroid cancer occurred many years after subtotal thyroidectomy without thyroid hormone replacement therapy. This family has not been studied from a molecular standpoint. Another study described a small Ashkenazi Jewish family with MNG, FTC and alveolar rhabdomyosarcoma. The pathology of the thyroid glands did not reveal any special features {530}. A positive LOD score was obtained for chromosome 14q markers {189}.

Follicular neoplasms, and classic thyroid papillary carcinoma and microcarcinoma (1.0 cm or less in diameter) have been occasionally described in FAP patients {830,1727,1879}. This is probably due to chance occurrence since, for instance, small papillary cancers show a prevalence of up to 22%/24% in subjects aged 16-30/45 years, respectively {1879}.

Prognosis and prognostic factors

It appears that FTC has a slightly worse prognosis than PTC {763}, but this is largely due to the higher percentage of cases with FTC who present with metastatic disease, and when these are excluded, there are no differences {1451}. As FFTC is somewhat rarer than FTPC, there have been no systematic studies of outcome, but is not thought to be a common cause of death in Cowden syndrome (C. Eng, personal communication).

Multinodular goiter

Familial euthyroid multinodular goiter (MNG) occurs with or without intrathyroid calcification.

Clinical features

Several families have been reported where the dominant feature is multinodular goiter, and thyroid cancer either occurs rarely, or not at all {422,1562, 1591}. In other families, PTC has been reported, but the relationship between

the linked locus and MNG is much less clear in these cases, particularly as goiter may be endemic in countries with high iodine exposure {261,1465}. It may be that the MNG is attributable to another locus. In most of the families reported, the age of onset of MNG was adolescence or earlier.

Pathology

In general, the MNG seen in these families is typical (multiple nodules, epithelial hyperplasia, calcification and haemorrhage) and by definition, there is no evidence of altered thyroid function. The pathological description of the MNG does not provide evidence for a different etiology of the goiter in these families {298,422,1591}. In a Scottish family, a notable feature was the extensive calcification, but this probably results from the haemorrhage, infarction, necrosis and subsequent fibrosis {1562}.

Prognosis and prognostic factors

The prognosis in those with MNG is usually excellent. If PTC arises in a MNG, then the prognosis will be determined by the PTC. Death related to the thyroid gland disorder has very rarely, if ever, been reported in euthyroid MNG kindreds.
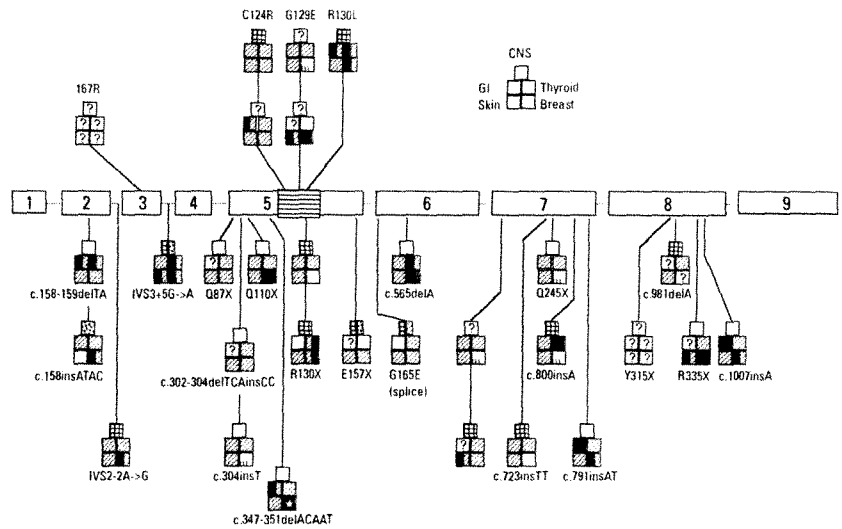

Genotype-Phenotype Associations in CS

Fig. 5.36 Familial non-medullary thyroid cancer. Genotype-phaenotype correlations of *PTEN* mutations, the cause of Cowden syndrome (CS), Bannayan-Ruvalcaba-Riley-Smith syndrome and related hamartomatous conditions.

Genetics

Chromosomal locations

Multinodular goiter

MNG1:	*138800	14q
MNG2:	*300273	Xp22

Familial non-medullary thyroid cancer

NMTC1:	*606240	2q

Familial non-medullary thyroid cancer with cell oxyphilia: *603386 19p

Cowden Syndrome: #15830 10q

PTEN:	*601728	10q

Familial adenomatous polyposis

	*175100	5q

Carney Complex

Type 1:	#16980	17q
Type 2:	*605244	2p

Werner syndrome #277700 8p

Gene structure, expression and function

PTEN

This tumour suppressor gene encodes a lipid and protein phosphatase that lies in the Protein Kinase B (PKB, Akt) and PI3K pathways, and is therefore implicated in many cytoplasmic signaling pathways. Of note, loss of PTEN function results in escape from programmed cell death and G1 arrest. *PTEN* is composed of 9 coding exons, and mutations are spread across the exons {563}. Cowden syndrome is inherited in an autosomal dominant fashion.

APC

This tumour suppressor gene which has multiple functions, but is mainly implicated in the Wnt pathway. The Armadillo region is of particular interest as it is also present in B-catenin, and interacts with protein phosphatase 2A, which in turn binds axin. B-catenin can accumulate when APC is inactivated, and translocation of B-catenin to the nucleus can activate the Tcf/Lef system. APC has 15 coding exons, the last of which occupies more than three-quarters of the coding region. The site of mutations can have functional significance (see below) {611,643}. FAP is inherited in as an autosomal dominant trait.

PRKAR1A

This is probably a tumour suppressor gene. It encodes a protein kinase A type 1a regulatory subunit, and therefore, like PTEN, has a crucial role in intracellular signalling pathways. It is placed downstream of cAMP, and its presence is a vital component of cAMP-dependent signalling. PRKAR1A has 10 coding exons {2140}. Carney complex is an autosomal dominant trait.

WRN

This gene is a member of the RecQ-type DNA helicase family, which includes BLM. It encodes a protein whose role is to assist in the control of the unwinding of intermediates of recombination. Loss of WRN results in elevated levels of recombination, and results in the characteristic cancer and premature ageing phenotype of Werner syndrome. It is a large gene with 35 exons {1438,1575}. Werner syndrome is an autosomal recessive trait.

Mutation spectrum and genotype / phenotype correlations
PTEN

Germline mutations have been reported throughout PTEN, although there is a paucity of mutations in exons 1, 4 and 9 {1412}. Classic Cowden probands found to have intragenic germline PTEN mutations may have a higher likelihood of developing breast cancer compared to those without mutation {1412}. Mutations within and 5' of the PTPase, core motif may be associated with multi-organ involvement. The relatively large number of missense mutations in the PTPase core motif suggests its biological importance, and these mutations likely act in a dominant negative manner {1412}. With regard to NMTC, mutations in families associated with this cancer site have been reported in most exons and are not limited to missense mutations.

APC

Most disease-associated mutations in APC are predicted to truncate the protein. There are fairly clear genotype-phenotype associations but their clinical usefulness is fairly limited {705}. The cribriform type of thyroid carcinoma is seen in FAP {830}. A large European study showed that mutations 5' of codon 1220 were significantly more likely to be associated with thyroid cancer than were mutations 3' of this point (P = .005) {336} but this requires confirmation.

PRKAR1A

As Carney complex is rare, and NMTC is not common in this syndrome, there are no reliable data on the role of mutations in this gene and thyroid cancer risk.

WRN

It is debatable whether there truly is an excess of thyroid cancer in Werner syndrome {1528}. The Japanese group has argued for a genotype-phenotype correlation between mutation position and thyroid cancer, in that all the affected individuals had mutations that were outside the helicase domain, and all 4 FTC cases were seen in those with 3' mutations, but the numbers are too small to make more definitive statements {971}.

Genetic counseling and preventive measures

Genetic counselling for non-syndromic FNMTC is not widely practised, partly because such families are rare, but also because they may not come to the attention of medical geneticists. Often, affected individuals from FNMTC families are seen only by their treating endocrinologist or surgeon.

Unlike the situation in medullary thyroid cancer, preventive thyroidectomy is rarely, if ever, recommended in FNMTC. This is partly because in the absence of identified genes, it can be difficult to identify individuals at risk. Individuals with adenomas, multinodular goiters or other possible pre-cancerous lesions may elect to have thyroidectomies for relatively minor symptoms because of the known family history and the possibility of malignant transformation. The discovery of specific susceptibility genes for FNMTC may lead to a change in counselling practice. An illustration is from Cowden syndrome where germline PTEN mutations have been identified. Because benign thyroid disease, e.g. multinodular goiter, is quite common (approximately 70%) and thyroid carcinoma, a true component in Cowden syndrome, thyroid surveillance is recommended starting in the teens {561,563}. Similarly, if thyroidectomy is to be performed for either benign or malignant conditions, a total thyroidectomy is recommended because of the high likelihood of developing further benign and malignant disease in the thyroid.