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Encyclopaedia of tumour-associated familial disorders. Part I: from AIMAH to CHIME syndrome

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Abstract

Cancer is associated with a wide range of hereditary disorders. Recognizing these disorders in cancer patients may be of great importance for the medical management of both patients and their relatives. Conversely, recognizing the fact that cancer may develop as a complication of a particular hereditary disorder which has already been diagnosed may be important for the same reason. The Familial Cancer Database (FaCD) is a web-based application (www.facd.info) which has been developed at our department with the intention to assist clinicians and genetic counsellors in making a genetic differential diagnosis in cancer patients, as well as in becoming aware of the tumour spectrum associated with hereditary disorders that have already been diagnosed in their patients. This encyclopaedia is published in parts and discusses the disorders included in the FaCD database in alphabetical order. It lists names, synonyms, OMIM number, mode of inheritance, associated genes, phenotype, clinical discussion and references. The purpose of presenting this encyclopaedia in paper format is simply that we hope that you as clinicians and researchers find it helpful to browse through it and familiarize yourself even better with the scope of genetic disorders that have been associated with increased tumour risk.

Introduction

Cancer is associated with a wide range of hereditary disorders. Recognizing these disorders in cancer patients may be of great importance for the medical management of both patients and their relatives. Conversely, recognizing the fact that cancer may develop as a complication of a particular hereditary disorder which has already been diagnosed may be important for the same reason. The Familial Cancer Database (FaCD) is a web-based application (www.facd.info) which has been developed at the Department of Genetics of the University Medical Center Groningen, The Netherlands, with the intention to assist clinicians and genetic counsellors in making a genetic differential diagnosis in cancer patients, as well as in becoming aware of the tumour spectrum associated with hereditary disorders that have already been diagnosed in their patients. This encyclopaedia is published in parts and discusses the disorders included in the FaCD database in alphabetical order. It lists names, synonyms, genes involved, phenotype, brief clinical discussion and references. The following classes of disorders have been included in this paper: hereditary disorders certainly or

possibly associated with increased cancer risk (e.g. Lynch syndrome) and familial clustering of particular types of cancer *e.c.i.* (for example familial occurrence of salivary gland tumours). If some fields are not listed for a particular disorder, for example 'Non-tumour features', then those fields are empty for that disorder. Especially in rare syndromes it can be difficult to decide whether or not a particular tumour type truly belongs to the phenotype of that disorder. Those tumours have been classified below as '*Tumour features* (*possible*)' in the descriptions of the phenotypes. The purpose of presenting this encyclopaedia in paper format is that we hope that you as clinicians and researchers find it helpful to browse through it and familiarize yourself even better with the scope of genetic disorders that have been associated with increased tumour risk.

Abbreviations used:
AD – autosomal dominant
AR – autosomal recessive
CGD – contiguous gene deletion
CI – confidence interval
de novo – de novo mutation
Impr – subject to genomic imprinting
Multifact – multifactorial inheritance
OMIM number – the number of the disorder in Online Mendelian Inheritance in Men
Pat – paternal
RR – relative risc
SIR – standarized incidence ratio
Upd – uniparental disomy
XLR or XLD – X-linked recessive or dominant, respectively
? – reflects uncertainty with respect to mode of inheritance

ACTH-independent macronodular adrenal hyperplasia

Synonym: AIMAH, Cushing's disease, adrenal, familial
Mode of inheritance: spor/AD
OMIM number: 219080
Genes:
GNAS1, mapped to 20q13.2
Tumour features:
macronodular adrenal hyperplasia
Non-tumour features:
adrenal dysplasia
adrenal hyperplasia

Comment

AIMAH cases are usually sporadic, causing Cushing's disease generally in the 5th or 6th decade. Affected siblings with Cushing's disease caused by primary (ACTH independent) adrenal, often bilateral, nodular hyperplasia and dysplasia have been observed [1-5]. Somatic GNAS1 mutations have been observed in isolated AIMAH cases.

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Acute lymphoblastic leukaemia, familial clustering of

Synonym: familial ALL, including familial T-ALL
Mode of inheritance: AD?/multifact?
Genes:
CYP1A1, mapped to 15q22-q24
GSTM1, mapped to 1p13.3
HLA-DQB1, mapped to 6p21.3
Tumour features:
leukaemia, acute lymphoblastic (ALL)

Comment

Familial clustering of ALL has been observed [1-3]. Becker et al. [4] reported a 4-generation Irish family with childhood onset acute T-cell leukaemia/lymphoblastic T-cell lymphoma in 9 relatives, which to the authors suggested autosomal dominant inheritance with reduced penetrance.

Dearden et al. [5] studied HLA-DQB1 alleles in children with ALL because of the suggestion that ALL may be caused by HLA-regulated susceptibility to an unidentified neonatal infection. They observed a significant excess of the DQB1*05 allele (RR 2.5) and in particular of certain amino acid motifs (not restricted to that allele). Polymorphisms in the GSTM1 and CYP1A1 genes, encoding xenobiotic-metabolizing enzymes, have been found to be associated with an

increased relative risk of childhood ALL [6]. A germline heterozygous truncating mutation in the gene for Fanconi anaemia type C has been detected in 2 sibs with T-ALL; 1 of the sibs subsequently developed AML [7]. In general, there appears to be no increase in ALL risk to siblings of patients. Risk may even be decreased and it has been speculated that immunization of mothers to leukaemia-specific antigens may occur which can enhance elimination of pre-leukaemic cells in utero [8].

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Acute myelocytic leukaemia with polyposis coli and colon cancer

Mode of inheritance: AR?
OMIM number: 246470
Tumour features:
bladder polyps
colorectal cancer
leukaemia, acute myeloblastic (AML, M2)

Comment

Two brothers with consanguineous parents were reported by Greenberg et al. [1] to have developed multiple colorectal adenomatous polyps, early-onset colorectal cancer, acute myeloblastic leukaemia, and (in one of the brothers) papillary bladder tumours. This could have been a case of bi-allelic MMR gene mutations.

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Adenosine deaminase deficiency

Synonym: severe combined immunodeficiency (SCID) due to ADA deficiency
Mode of inheritance: AR
OMIM number: 102700
Genes:
ADA, mapped to 20q13.11
Tumour features:
Burkitt's lymphoma
Hodgkin's disease
leukaemia, acute
non-Hodgkin's lymphoma
Non-tumour features:
adenosine deaminase deficiency
agammaglobulinaemia
immunodeficiency
skeletal dysplasia

Comment

A substantial percentage of (apparently) autosomal recessive severe combined immunodeficiency is caused by deficiency of adenosine deaminase. Dysplastic skeletal changes (typically of costochondral junctions) occur frequently in patients with ADA deficiency. Most cases are diagnosed in the first year [1]. As in other types of severe combined immune deficiency, there is an increased risk of developing malignancies of the haemato-lymphoproliferative type [2-5]. There appears to be no increased cancer risk for heterozygotes of the mutant gene [6].

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Agammaglobulinaemia, X-linked

Synonym: Bruton type agammaglobulinaemia
Mode of inheritance: XLR
OMIM number: 300300, 300310
Genes:
BTK, mapped to Xq21.3-q22
Tumour features:
colorectal cancer
Hodgkin's disease
leukaemia, acute lymphoblastic (ALL)
leukaemia, chronic myeloid (CML)
non-Hodgkin's lymphoma
thymoma
Tumour features (possible):
gastric cancer
lung/bronchial cancer
Non-tumour features:
agammaglobulinaemia
immunodeficiency

Comment

This infantile immunodeficiency in males is characterized by an isolated B-cell defect and these cells are absent in the vast majority of patients. Lymphoid tissue (adenoid, tonsils) is either absent or hypoplastic. There is approximately an incidence of 1.5-6% of malignancies in this disorder, mainly involving the haematopoietic-lymphoid system [1-9]. Patients also have an increased risk of developing colorectal cancer [10,11]. Lung cancer was diagnosed in a 32-year-old non-smoking male with the disorder [12]. Gastric cancer associated with chronic atrophic gastritis [13, 14].

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Aicardi syndrome

Mode of inheritance: XLD
OMIM number: 304050
Genes:
AIC, mapped to Xp22
Tumour features (possible):
angiosarcoma
choroid plexus papilloma
colorectal polyps
gastric polyps
hepatoblastoma
lipoma
medulloblastoma
palate, benign teratoma of
parapharyngeal embryonal cell cancer

Non-tumour features:
chorioretinal lacunae
cleft lip
cleft palate
corpus callosum agenesis
facies, asymmetric
gross motor delay
mental deficiency
plagiocephaly
rib anomalies
seizures
vertebral anomalies

Comment

Clinical hallmarks are infantile spasms, corpus callosal agenesis, chorioretinal abnormalities (lacunae) and severe psychomotor retardation. Other findings include plagiocephaly, facial asymmetry, cleft lip and palate and costovertebral anomalies. A number of tumours have been reported in association with Aicardi syndrome [1-7]: choroid plexus papilloma (the most frequent tumour), medulloblastoma, gastric hyperplastic polyps, rectal polyps, soft palate benign teratoma, hepatoblastoma, parapharyngeal embryonal cell cancer, limb angiosarcoma and scalp lipoma.

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Alagille syndrome

Synonym: ALGS1, ALGS2, Alagille-Watson syndrome
Mode of inheritance: AD/AR?
OMIM number: 118450
Genes:
JAG1, mapped to 20p12
NOTCH2, mapped to 1p13-p11
Tumour features:
hepatocellular cancer
Tumour features (possible):
thyroid cancer, papillary
Wilms' tumour (nephroblastoma)
Non-tumour features:
bile ducts, paucity of intrahepatic
chin, triangular
embryotoxon posterior
eyes, deeply set
frontal bossing/prominent forehead
hypertelorism
midface, flat/hypoplastic
nose, long straight
philtrum, short
pulmonary artery stenosis
vertebral anomalies

Comment

Hallmarks of this disorder are: paucity of intrahepatic bile ducts leading to cholestasis, peripheral pulmonary artery stenosis, vertebral arch defects, poor linear growth, a characteristic facies and embryotoxon posterior in the eye [1]. Hepatocellular cancer has been reported in a number of cases [2-5], and papillary thyroid cancer [6] and Wilms' tumour in one case [7].

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Alpha-1-antitrypsin deficiency

Mode of inheritance: AD
OMIM number: 107400
Genes:
PI, mapped to 14q32.1
Tumour features:
hepatocellular cancer
Tumour features (possible):
colorectal cancer
lung/bronchial cancer
Non-tumour features:
liver cirrhosis
lung emphysema

Comment

This disorder is caused by deficiency of alpha-1-antitrypsin (= protease inhibitor = anti-elastase) and is characterized by emphysema and juvenile or adult liver cirrhosis. The severity of the disease depends on the specific combination of alleles and very likely also on the influence of exogenous factors such as smoking. The homozygous null allele combination causes the most severe disease, followed by the ZZ combination. Risk of hepatocellular cancer is increased, possibly only in males [1, 2] and depending on allele type [3]. It has been reported in children [4]. Alpha-1-antitrypsin deficiency/haplosufficiency may also act as a co-risk factor for lung cancer [5]. Yang et al. [6] estimated a 20-fold increase in risk of developing colorectal cancer (with microsatellite instability, MSI-H) among smokers who carry alpha-1-antitrypsin deficiency alleles.

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Alpha-fetoprotein, hereditary persistence of

Synonym: HPAFP
Mode of inheritance: AD
OMIM number: 104150
Genes:
AFP, mapped to 4q11-q13
Tumour features (possible):
non-seminoma
seminoma
Non-tumour features:
increased/persistent serum AFP

Comment

This disorder is characterized by the persistence of high AFP, due to a mutation in the AFP gene [1, 2]. Staples et al. [3] reported high serum AFP in a 23-year-old man with a testicular seminoma as well as in his 3 sisters, mother and maternal aunt. He also had hereditary spherocytosis. Hart et al. [4] and Cochran et al. [5] reported a yolk sac tumour in a 20-year-old male and a 20-month-old male with HPAFP, respectively. Although the association is probably purely coincidental, it is important to stress that HPAFP may confuse management in patients with testicular or liver tumours, or other conditions where AFP levels are of diagnostic or screening importance. If HPAFP is not recognized in these conditions, then this may lead to inappropriate medical decisions. Testing parental levels of AFP has been advised for cases where persistent (mild) elevation of AFP following resection of localized germ cell tumours has been observed, before deciding on chemotherapy [5].

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Alport syndrome with diffuse leiomyomatosis

Mode of inheritance: XLD/cgd
OMIM number: 308940
Genes:
COL4A5, mapped to Xq22-q24
COL4A6, mapped to Xq22-q24
Tumour features:
bronchioli, leiomyoma of the
oesophageal leiomyoma
gastric leiomyoma
leiomyoma of the clitoris
leiomyoma of the urethra
trachea, leiomyoma of the
uterine leiomyoma
vulvar leiomyoma
Non-tumour features:
cataract, congenital
deafness, neurosensory
nephropathy

Comment

Alport syndrome is characterized by haematuric nephropathy, in most cases leading to renal failure (usually progressive), sensorineural deafness and ocular anomalies (maculopathy and anterior lenticonus). Some patients with Alport syndrome develop diffuse leiomyomatosis (especially of the oesophagus and less often the vulva and other anatomical sites). These patients also frequently have severe cataracts. The oesophageal leiomyomas appear to develop earlier among boys (average age 6 years compared to 14 years in girls) [1-4].

Alport syndrome is genetically heterogeneous. The specific subset of patients/families with Alport syndrome and leiomyomatosis is associated with deletions extending from within the COL4A5 gene to the neighbouring COL4A6 gene [5, 6]. Multiple giant gastro-oesophageal leiomas have been reported in the absence of such a detectable deletion [7].

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Amenorrhoea-galactorrhoea syndrome

Mode of inheritance: AD?
OMIM number: 104600
Tumour features:
pituitary adenoma

Comment

Familial cases of galactorrhoea and amenorrhoea, due to a pituitary gland tumour, have been reported [1, 2]. Possibly these cases represent in fact multiple endocrine neoplasia type 1 or another type of hereditary pituitary gland tumours.

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Androgen insensitivity syndrome

Synonym: AIS, testicular feminisation, Reifenstein syndrome
Mode of inheritance: X-linked
OMIM number: 300068
Genes:
AR, mapped to Xq11-q12

Tumour features:
non-seminoma
seminoma
testicular gonadoblastoma
testicular Sertoli-Leydig cell tumour
Non-tumour features:
male (46,XY) pseudohermaphroditism

Comment

Mutations in the androgen receptor coding gene on the X chromosome cause pseudo-hermaphroditism in the XY individual through androgen insensitivity. External genitals are female. The gonads are undescended testes and may be intra-abdominal, inguinal, or labial. Mullerian structures (including uterus) are absent, because of AMH production by the testicles [1].

Sex cord hamartomas and Sertoli cell adenomas are common findings in AIS, with a prevalence of 63 and 23%, respectively, observed in one series of 43 patients [2]. Patients with AIS show an increased frequency of testicular malignancies with risks estimated between 2 and 33%; 2-10% might be the most realistic estimate. Seminoma [3-8] and sex-cord stromal tumours (particularly Sertoli-cell tumours) [9-14] are the most common tumour types observed. Gonadoblastoma [15] and non-seminomas (yolk sac tumour [16], embryonal carcinoma [17]) have been reported as well.

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Angiolipomatosis, familial

Mode of inheritance: AD?/AR?
OMIM number: 206550
Tumour features:
angiolipoma
Non-tumour features (possible):
iris, Lisch nodules

Comment

Familial clustering of multiple (non-infiltrating) angiolipomas has been reported a few times, the most extensive family being that published by Kumar et al. [1]. In that family the angiolipomas were well encapsulated and located on the upper part of the body. Hapnes et al. [2] reported on a case with angiolipomas located close to joints and extending deep between muscle, tendons and joint capsules. Abbasi et al. reported an 80-year-old man with a 50-year history of asymptomatic, subcutaneous masses on the arms, trunk, and legs. His father and maternal grandmother had a history of similar lesions [3]. The distinction from familial multiple lipomatosis is not completely certain. Familial angiolipomatosis may

sometimes be clinically confused with neurofibromatosis type 1 (NF1). Interestingly, Cina et al. [4] reported the occurrence of Lisch nodules (a typical feature of NF1) in familial angiolipomatosis.

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Arrhenoblastoma and thyroid adenoma, familial

Synonym: including arrhenoblastoma, familial clustering
Mode of inheritance: AD
OMIM number: 107950
Tumour features:
ovarian Sertoli-Leydig cell tumour
thyroid adenoma
Tumour features (possible):
hamartomatous polyps in small intestine
ovarian mucinous cystadenoma
Wilm's tumour
Non-tumour features:
thyroid hyperplasia/goitre

Comment

A number of families with multiple cases of ovarian Sertoli-Leydig cell tumours (arrhenoblastomas) have been reported. In some of these families (multiple) thyroid adenomas were also present in some of the relatives with ovarian tumours as well as in relatives without these tumours [1, 2]. A mucinous cystadenoma was reported twice in these families and one case of Wilms' tumour was reported [1]. In the proband published by O'Brien et al. [2], a hamartous polyp was removed from the small intestine at the age of 3 months. Could this disorder be a variant of Cowden syndrome or Peutz-Jeghers syndrome?

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Ataxia pancytopenia syndrome

Synonym: myelocerebellar disorder
Mode of inheritance: AD
OMIM number: 159550
Tumour features:
lung haemangioma
Non-tumour features:
bone marrow monosomy 7 karyotype
cerebellar ataxia
nerve conduction velocity, reduced
pancytopenia

Comment

This condition is characterized by pancytopenia, progressive cerebellar ataxia, reduced nerve conduction speed and acute myelomonocytic leukaemia, which all develop in early childhood. The hypoplastic bone marrow shows cells with a monosomy 7 karyotype [1-3].

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Ataxia telangiectasia

Synonym: AT, Louis-Bar syndrome
Mode of inheritance: AR
OMIM number: 208900
Genes:
ATM, mapped to 11q22.3
Tumour features:
astrocytoma
breast cancer
colon cancer
gastric cancer
glioma of the brain
hepatocellular cancer
histiocytosis (reticuloendotheliosis), malignant
Hodgkin's disease
laryngeal cancer
leukaemia, acute lymphoblastic (ALL)
leukaemia, chronic lymphocytic (CLL)
non-Hodgkin's lymphoma
ovarian cancer (i.e. epithelial origin)

parotid gland cancer
skin cancer, basal cell
skin cancer, squamous cell
thyroid cancer

Tumour features (possible):

leiomyosarcoma of the uterus
ovarian dysgerminoma
ovarian fibroma
ovarian gonadoblastoma
seminoma
uterine leiomyoma

Non-tumour features:

café-au-lait spots
cerebellar ataxia
growth deficiency
hypogonadism
immunodeficiency
increased chromosomal breakage
increased/persistent serum AFP
ionizing radiation sensitivity, increased
mutagen sensitivity, increased
oculocutaneous telangiectasia
strabismus
thymus hypoplasia/aplasia

Comment

Progressive ataxia usually develops during infancy. Telangiectasia occurs usually first in the bulbar conjunctivae and later over the bridge of the nose, auricles and other areas. Growth deficiency commonly presents during late infancy/childhood. Mental deficiency is a feature in about half of cases [1]. Neoplasms develop in approximately 10 percent of patients, especially lymphoid tumours. Many patients do not survive to adulthood, lung infections and neurological complications being the main cause of death. Non-Hodgkin's lymphoma (mostly of the histological subtype associated with 14q translocations), acute lymphoblastic leukaemia and Hodgkin's disease (mostly of lymphocytic depletion type) are the most frequent neoplasms in AT patients [2]. Myeloid tumours are absent [3]. The increase in lymphoid malignancy is caused by both B- and T-cell tumours [3, 4]. T-cell tumours may develop at any age and may be T-ALL, T-cell lymphoma or T-cell prolymphocytic leukaemia [3]. The recognition of lymphomas may be delayed due to confusion with known infectious complications in AT [5]. A wide range of other neoplasms have been reported, including gastric cancer, colon cancer, chronic lymphoblastic leukaemia, brain tumours, craniopharyngioma, liver cancer, laryngeal cancer, leiomyoma and leiomyosarcoma of the uterus, dysgerminoma, fibroadenoma and gonadoblastoma of the ovaries, testicular seminoma and basal cell and squamous cell skin cancer [5-13].

Inheriting one mutated copy of the AT gene (ATM) increases breast cancer risk in females, and may turn out to contribute significantly to the total breast cancer burden. However, data are inconclusive as to the magnitude of this contribution and strength of this risk factor [14-25]. Broeks et al. [26] found the relatively high percentage of 8.5% ATM mutation carriers in a group of 82 breast cancer patients selected for early onset (<45 years), long-term survival and bilaterality. Baynes et al. showed that it is unlikely that common ATM variants increase breast cancer risk [27]. Johnson et al. confirmed this and argued that it is rather a combination of variants in different genes (ATM, BRCA1, BRCA2) that confers an increased breast cancer risk [28]. However, single rare ATM alleles may still confer a substantially increased breast cancer risk [29]. Balleine et al. reported that breast cancer occurring in carriers of ATM variants is not associated with distinctive histopathological features [30].

Fibroblast cultures of AT heterozygotes show increased radiosensitivity and given the fact that breast cancer is a complication well known to occur in long-term survivors of Hodgkin's disease who received mantle-field irradiation, it has been questioned whether germline mutations in ATM contributed to this increase of breast cancer risk. Studies by Broeks et al. [31] and Nichols et al. [32] did not support a major contribution of germline ATM mutations to the breast cancer risk in these types of patients. The same was true for contralateral breast cancer risk after radiation therapy for the first breast tumour, as reported by Shafman et al. [33].

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Autoimmune lymphoproliferative syndrome, type I

Synonym: Canale-Smith syndrome, ALPS type I (including: ALPS1A, ALPS1B), including autoimmune lymphoproliferative disease (ALD)
Mode of inheritance: AD
OMIM number: 601859, 134637
Genes:
APT1/FAS, mapped to 10q24.1
Tumour features:
Burkitt lymphoma
Hodgkin's disease
non-Hodgkin's lymphoma
Tumour features (possible):
hepatocellular cancer
Non-tumour features:
autoimmune disease

Comment

This disorder develops in early childhood because of a defective lymphocyte apoptosis. It is characterized by non-malignant lymphadenopathy, splenomegaly and autoimmune disease [1]. In the majority of patients a heterozygous mutation in APT1 has been detected. APT1 encodes the Fas protein, which is a mediator of lymphocyte apoptosis. Of 46 ALPS1 patients with APT1 mutations studied at the NIH, 6 (13%) developed a lymphoma: Hodgkin's, Burkitt's, follicular lymphoma or non-Hodgkin's lymphoma [2, 3]. A case of hepatocellular carcinoma has also been reported. In general, risk for non-Hodgkin's lymphoma and Hodgkin's disease is increased.

Ramenghi et al. [4] reported an ALPS-like disorder, which they referred to as autoimmune lymphoproliferative disease (ALD), associated with decreased Fas function in the absence of detectable Fas mutations. Hodgkin's disease was reported by them to have occurred in one of these ALD families and the frequency of cancer in general was increased in the families' maternal lines.

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Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy

Synonym: APECED
Mode of inheritance: AR
OMIM number: 240300
Genes:
AIRE, mapped to 21q22.3
Tumour features:
oesophagus, squamous cell cancer of the
intraoral squamous cell cancer
Non-tumour features:
alopecia
autoimmune disease
candidiasis
cataract
dental abnormalities
diabetes mellitus
hypogonadism
hypoparathyroidism
hypothyroidism
keratopathy
nails, dystrophic

Comment

This rare autoimmune disorder mainly affects the endocrine glands [parathyroid glands (85%), adrenal cortex (72%) and ovaries (60%)] and is associated with enamel hypoplasia (77%), nail dystrophy (52%), keratopathy (22%) and candidiasis (100%). Oral squamous cell cancer and severe autoimmune hepatitis are the most life-threatening complications [1-3]. Perheentupa reported oral or oesophageal squamous cell carcinoma in 10% of patients older than 25 years in a relatively large Finnish series [4].

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Bannayan-Riley-Ruvalcaba syndrome

Synonym: subset of PTEN-MATCH, including Ruvalcaba-Myhre-Smith syndrome
Mode of inheritance: AD
OMIM number: 153480
Genes:
PTEN, mapped to 10q23.3
Tumour features:
facial papules
hamartomatous polyps in colon/rectum
hamartomatous polyps in small intestine
haemangioma
lipoma
oral papules
trichilemmoma

Tumour features (possible):
breast cancer
meningioma
thyroid adenoma
thyroid cancer
Non-tumour features:
cornea, prominent nerves
deafness
gross motor delay
high birth weight
hypotonia
joint laxity
lipid storage myopathy of proximal muscles
macrocephaly
mental deficiency
pectus excavatum
pigmented macules on glans and shaft of penis
scoliosis
seizures
vulvar lentigines

Comment

Lipid storage myopathy, pigmented macules on glans and shaft of penis and vulva, intestinal hamartous (juvenile type) polyps and neurodevelopmental delay are the typical features [1-9]. A clinical overlap with Cowden disease has been noted and indeed germline mutations in the PTEN gene, involved in Cowden disease, have been detected in this disorder. It should therefore be considered as a variant of Cowden syndrome [10-15]. DiLiberti [10] has recently proposed the nomenclature PTEN-MATCHS (macrocephaly, autosomal dominant, thyroid disease, cancer, hamartomata, skin abnormalities) to cover the clinical spectrum associated with germline PTEN mutations.

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Bardet-Biedl syndrome

Synonym: BBS, Bardet-Biedl syndrome, type 1-12: BBS1-12
Mode of inheritance: AR
OMIM number: 209901, 209900, 600151, 600374, 603650, 605231
Genes:
BBS1, mapped to 11q13
BBS10, mapped to 12q
BBS11, mapped to 9q33.1
BBS12, mapped to 4q27
BBS2, mapped to 16q21
BBS3, mapped to 3p12-q13
BBS4, mapped to 15q22.3
BBS5, mapped to 2q31

BBS6/MKKS, mapped to 20p12
BBS7, mapped to 4q27
BBS8, mapped to 14q32.11
BBS9, mapped to 7p14
Tumour features (possible):
renal cell cancer, clear-cell
Non-tumour features:
brachydactyly, of feet
brachydactyly, of hands
deafness, conductive
dental abnormalities
hypogonadism
mental deficiency
obesity
polydactyly, postaxial
renal anomalies
renal dysplasia
rod-cone dystrophy

Comment

This disorder (BBS) is characterized by postaxial polydactyly, central obesity, rod-cone dystrophy, mental retardation and renal dysfunction. Beales et al. [1] observed 3 cases of clear cell renal cell carcinoma (diagnosed at age 37, 40 and 52, respectively) among 180 parents of BBS patients. This is more than expected in the normal population (p=0.0007). The authors calculated that parents of BBS children have a relative risk of 17 (95% CI=3.6-49.9) of developing clear cell renal cell cancer before the age of 55 years. One of the tumours showed loss of heterozygosity at the BBS1 locus. The authors suggest that the BBS genes may be implicated in the development of renal cancer (and renal malformation). In contrast, Hjortshøj et al. found no evidence for an increased cancer risk in BBS patients and their relatives [2].

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Barrett's oesophagus, familial

Mode of inheritance: AD?/multifact?
OMIM number: 109350
Tumour features:
oesophagus, adenocarcinoma of the
Tumour features (possible):
colorectal cancer
colorectal polyps
gastric cancer
tongue cancer
Non-tumour features:
oesophagus, Barrett's

Comment

Barrett's oesophagus and oesophageal adenocarcinoma are complications of gastroesophageal reflux [1], which may show familial clustering, as has been demonstrated by Romero et al. [2]. These authors reported that reflux symptoms were significantly more prevalent among parents and siblings of patients with oesophageal adenocarcinoma and/or Barrett's oesophagus than among controls. Other authors have reported familial cases as well. Hampel et al. [3] reported on 3 families and suggested that Barrett's oesophagus families possibly are at an increased risk of developing extra-oesophageal cancer (notably of the digestive tract) as well. More recently more familial clusters have been reported [4-8] and family history is an acknowledged risk factor. Chak et al. showed that a family history of Barrett's oesophagus can be confirmed in 7.3% of persons presenting with Barrett's oesophagus, adenocarcinoma of the oesophagus, or adenocarcinoma of the gastroesophageal junction [5]. Linkage analyses are underway [9].

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Basal cell nevus syndrome

Synonym: Gorlin syndrome, Gorlin-Golz syndrome, naevoid basal cell carcinoma syndrome
Mode of inheritance: AD
OMIM number: 109400
Genes:
PTCH, mapped to 9q22.3
Tumour features:
cardiac fibroma
infundibulocystic basal cell cancer
medulloblastoma
ovarian fibroma
skin cancer, basal cell
Tumour features (possible):
astrocytoma
breast cancer
dermoid cyst, nasal
ependymoma
Hodgkin's disease
leiomyoma
leiomyosarcoma
leukaemia, acute lymphoblastic (ALL)
leukaemia, chronic lymphocytic (CLL)
lung/bronchial cancer
malignant melanoma, cutaneous
meningioma
multiple myeloma
nasopharyngeal rhabdomyosarcoma
non-Hodgkin's lymphoma
ovarian fibrosarcoma
ovarian sarcoma (including pPNET of ovary)
renal cell cancer
renal fibroma
rhabdomyoma, fetal
rhabdomyosarcoma
salivary gland tumour
salivary gland, adenoid cystic carcinoma
seminoma
teratoma, benign cystic (dermoid cyst) of the ovary
thyroid adenoma
urinary bladder cancer
Wilms' tumour (nephroblastoma)
Non-tumour features:
café-au-lait spots
epidermoid cysts
falx cerebri, calcification of
frontoparietal bossing
hypertelorism
ionizing radiation sensitivity, increased
jaw, odontogenic keratocysts of the
nasal bridge, broad
palate, high arched
palmar pits
pectus excavatum/carinatum
plantar pits
prognathism
rib anomalies
sloping shoulders
strabismus
vertebral anomalies

Comment

In this disorder, multiple nevoid basal cell cancers (NBCC) typically start to appear at the age of puberty, although they have been reported to occur as early as 3 years of age. The NBCCs may manifest anywhere on the skin, but mainly on the face, neck and upper trunk. A typical facies is often present (70%), featuring frontoparietal bossing, broad nasal bridge and prognathism. Skeletal anomalies are often detected (e.g. 80% of patients are diagnosed with keratocysts of the jaw before the age of 30), as well as palmoplantar skin pits (87% of patients [1]). Mental deficiency occurs in a few cases [1-4].

A wide range of tumours has been reported in basal cell nevus syndrome in addition to basal cell carcinomas: ovarian fibromas occur in frequencies ranging from 14 to over 50%. Medulloblastoma, ages at diagnosis ranging from 2 months to 7 years and of the desmoplastic subtype [5], is considered to be part of the tumour spectrum [6] and has been included as a minor criterion for the disorder (see below). However, it is still relatively rare: 4 out of 105 patients studied by Kimonis et al. [1]. Cardiac fibromas [7, 8] have been included as a minor criterion as well. Other reported tumours include: rhabdomyosarcoma [9, 10], (malignant) meningioma [1, 11], astrocytoma [4, 12, 13], cerebellar ependymoma [1], hamartous polyps of the stomach [14], fetal rhabdomyoma [15], nasal dermoid cyst [16], NHL [4], ovarian dermoid cyst [4], CLL [4], ALL [13], breast cancer [4], lung cancer [4], ovarian fibrosarcoma [2] and ovarian leiomyosarcoma [17], leiomyosarcoma of the extremities [18], seminoma [19], carcinoma of the vulva

[20], adenoid cystic carcinoma of the salivary glands [21] and others [2]. Rhabdomyosarcoma and Wilms' tumour were diagnosed in a girl with a deletion of 9q22-q32 which included the PTCH gene [22].

Patients with the syndrome have an increased risk of developing secondary tumours in the field of radiation treatment. A conservative estimate of the new mutation rate in basal cell nevus syndrome is 14% [4]. Fukushima et al. [23] reported the occurrence of a meningioma after radiation treatment for a medulloblastoma.

The gene for basal cell nevus syndrome has been identified as the human homologue of the Drosophila patched gene [24, 25].

Diagnostic criteria:

two major criteria or one major + two minor criteria should be present.

Major:

- multiple basal cell carcinomas, or one under the age of 30 years, or >10 basal cell nevi; in a sunny climate these numbers should be higher (not further specified),
- histologically proven odontogenic keratocyst, or polyostotic bone cyst,
- >3 palmar and/or plantar pits,
- calcification of the falx cerebri: lamellar or early (<20 years),
- first-degree relative with nevoid basal cell carcinomas.

Minor:

- congenital skeletal anomaly: bifid, fused, splayed or missing rib or fused vertebrae,
- macrocephaly (occipitofrontal circumference > 97th centile) with bossing,
- cardiac or ovarian fibroma,
- medulloblastoma,
- lymphomesenteric cysts,
- congenital malformation: cleft lip and/or palate, polydactyly, eye anomaly (cataract, coloboma, microphthalmia).

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Basal or squamous cell skin cancer, familial clustering of

Synonym: familial non-melanoma skin cancer
Mode of inheritance: multifact?
Genes: many low penetrant gene mutations have been reported, we do not list them separately here
Tumour features:
skin cancer, basal cell
skin cancer, squamous cell
Tumour features (possible):
malignant melanoma, cutaneous
melanoma, uveal (choroidal, ciliary body, iris)/ocular

Comment

The influence of a family history of skin cancer on basal cell skin cancer (BCC) risk is controversial. Two studies could not demonstrate a familial risk factor [1, 2]. However, Wallberg et al. [3] found a family history of skin cancer (not further specified) among siblings and/or parents to be the strongest risk factor (RR 10.9) of 12 factors tested. The authors could not explain this risk by correcting for hereditary pigmentary characteristics, such as skin type, eye and hair colour, which are known to be associated with melanoma as well as non-melanoma skin cancer risk [4]. Hogan et al. [5] also found that a family history of skin cancer was associated with an increased risk of developing BCC (RR 1.22). In their series of 538 BCC patients and matched controls, they also observed a significantly lower age at diagnosis in those BCC patients with a family history of skin cancer compared with those who did not. In a case-control study of similar size, Naldi et al. [6] confirmed the significant association of BCC and a family history of skin cancer (odds ratio 6.7). In a population-based cohort study of twins, the co-twin of a twin affected with BCC cancer was shown to have an increased BCC risk (RR 7-8); however, zygosity did not influence this risk [7, 8]. In general, BCC in children in the absence of known genetic conditions is rare, but has been diagnosed at the age of 4 years and older [9].

Polymorphisms of members of the glutathione-S-transferase and cytochrome P450 enzyme families have been associated with an increased risk of developing (multiple) BCC [10-12].

For squamous cell skin cancer (SCC), a positive family history of skin cancer in general also increases SCC risk, as has been calculated by Hogan et al. [13], Gamble et al. [14] and Hemminki and Dong [15]. The latter study from the Swedish Family-Cancer Database reported SIRs of 2.4 for invasive SCC and 2.8 for invasive SCC in the offspring of parents with SCC. SIR for SCC in offspring of parents with multiple SCC was 70% higher than in offspring of parents with single SCC. The authors also reported a familial association between SCC and skin and ocular melanoma.

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Bazex syndrome

Synonym: Bazex-Dupré-Christol syndrome
Mode of inheritance: XL
OMIM number: 301845
Genes:
BZX, mapped to Xq24-q27
Tumour features:
skin cancer, basal cell
Non-tumour features:
atrophoderma, follicular (ice pick marks)
facial hyperpigmentation
hair shaft dystrophy
hypotrichosis
milia

Comment

This syndrome is characterized by multiple basal cell cancers developing mainly on the face, from the second decade. The skin shows follicular atrophoderma (resembling ice pick marks), especially on the face, hands, elbows and feet. Sweating is decreased and hypotrichosis is another characteristic. The term follicular atrophoderma appears inappropriate because the skin histology does not show atrophy [1-7]. The disorder has been mapped to Xq [8].

Confusingly, the name Bazex syndrome is also used for the sporadic disorder acrokeratosis paraneoplastica, which mainly occurs in males and is characterized by psoriasiform skin lesions of predominantly ears, fingers, nose and toes, associated with squamous cell cancer of the upper aerodigestive tract [9].

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Beckwith-Wiedemann syndrome

Synonym: BWS, exomphalos-macroglossia-gigantism (EMG) syndrome, Wiedemann-Beckwith syndrome, WBS
Mode of inheritance: AD/spor/impr (UPDpat11)
OMIM number: 130650
Genes:
H19, mapped to 11p15.5
LIT1/KCNQ1OT1, mapped to 11p15.5
NSD1, mapped to 5q35
p57/kip2/CDKN1C, mapped to 11p15.5
Tumour features:
adrenal adenoma
adrenocortical cancer
hepatoblastoma
pancreatoblastoma
Wilms' tumour (nephroblastoma)
Tumour features (possible):
carcinoid of the small intestine
cardiac tumour
ganglioneuroma (tosis)
gastric teratoma
glioblastoma (multiforme)
leukaemia, acute lymphoblastic (ALL)
leukaemia, acute myeloid (AML, including ANLL)
lipoma
lymphoma, malignant (Non-Hodgkin and/or Hodgkin)
mesenchymal hamartoma of the liver
neuroblastoma, extra-adrenal
ovarian gonadoblastoma
perineurioma
pheochromocytoma
rhabdomyosarcoma
testicular gonadoblastoma
umbilical myxoma

Non-tumour features:
ear-lobe grooves
flame nevus
gigantism/overgrowth
heart, congenital defect
helix, indentations on posterior rim
hemihypertrophy
omphalocele
seizures
skeletal anomalies
tongue, macroglossia
transitory hypoglycaemia

Comment

Gigantism, macroglossia, omphalocele and ear creases are the typical features of the syndrome [1-4]. Pancreatic hyperplasia often occurs and leads to neonatal hypoglycaemia in 30-50% of cases. Approximately 5% of children with this disorder develop tumours before the age of 8 years, mainly Wilms' tumour (60%), hepatoblastoma and neuroblastoma, but a range of other tumours have been reported [2, 5-19]. Limb asymmetry/hemihypertrophy is associated with an increased risk of tumours [10, 11] and nephromegaly appears to be a predictor of Wilms' tumour, particularly in these patients [12].

The genetics of BWS are relatively complex. Cooper et al. analysed genotype-cancer phenotype associations and concluded that the risk of neoplasia was significantly higher in UPD and IC1 defect cases than in IC2 defect and CDKN1C mutation cases. Cancer risk for all patients was estimated at 9% at age 5 years, and 24% in the UPD subgroup. UPD including WT1 was associated with renal neoplasia. In contrast, Wilms' tumour risk in the IC2 defect subgroup appears to be small [20]. Rump et al. concluded that increased tumour risk in BWS is typically associated with loss of imprinting of H19 [21].

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Biallelic mismatch repair gene mutations associated early onset cancer

Synonym: childhood cancer syndrome
Mode of inheritance: AR

Genes:
MLH1, mapped to 3p21.3
MSH2, mapped to 2p21-p22
MSH6, mapped to 2p16
PMS2, mapped to 7p22
Tumour features:
astrocytoma
colorectal cancer
endometrial cancer
glioblastoma (multiforme)
leukaemia, acute
leukaemia, acute lymphoblastic (ALL)
leukaemia, acute myeloid (AML, including ANLL)
leukaemia, chronic myeloid (CML)
medulloblastoma
non-Hodgkin's lymphoma
oligodendroglioma
Tumour features (possible):
ovarian sarcoma (including pPNET of ovary)
Wilms' tumour (nephroblastoma)
Non-tumour features:
axillary freckling
café-au-lait spots
Non-tumour features (possible):
immunodeficiency

Comment

Multiple café-au-lait spots, axillary freckling and early onset colorectal cancer, oligopolyposis, leukaemia (ALL, AML, AL-not specifed, CML), non-Hodgkin's lymphoma, brain tumours (glioblastoma, astrocytoma, oligodendroglioma medulloblastoma), Wilms' tumour, ovarian neuroectodermal tumour, endometrial cancer and sometimes IgA-deficiency have been observed in patients with biallelic mutations of the mismatch repair (MMR) genes MLH1, MSH2, MSH6 and PMS2 [1-11].

There is overlap with HNPCC (associated with single inherited MMR mutations) and Turcot syndrome (brain tumours and colorectal polyps).

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Biliary tract cancer, familial clustering of

Synonym: including familial gallbladder cancer
Mode of inheritance: multifact?
Tumour features:
biliary tract cancer (including gallbladder)
Tumour features (possible):
pancreatic adenocarcinoma

Comment

A Spanish-Italian study demonstrated an association between a family history of gallbladder cancer and the development of this tumour in a relative (RR 13.9) [1]. Hemminki et al. [2] studied the occurrence of cancer in relatives of patients with liver or biliary tract cancers. The authors demonstrated a high risk for familial gallbladder cancer (SIR 5.21 [95% CI 2.07-10.80]) and for familial hepatocellular cancer (SIR 4.69 [95% CI 1.48-11.04]). For

gallbladder and hepatocellular cancer, maternal transmission appeared to be more prevalent. Gallbladder cancer was associated with pancreatic cancer (SIR 2.39 [95% CI 1.23-4.18]).

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Birt-Hogg-Dubé syndrome

Synonym: fibrofolliculomas with trichodiscomas and acrochordons, including Hornstein-Knickenberg syndrome, perifollicular fibromatosis
Mode of inheritance: AD
OMIM number: 135150
Genes:
FLCN, mapped to 17p11.2
Tumour features:
acrochordons
fibrofolliculomas
perifollicular fibromas
trichodiscomas
Tumour features (possible):
chromophobe renal cell cancer
colon cancer
colorectal polyps
renal cell cancer, clear-cell
renal cell cancer, papillary
renal oncocytoma
thyroid cancer, medullary
Non-tumour features:
lung cysts
pneumothorax, spontaneous

Comment

This condition is characterized by the presence of 3 types of benign skin tumours: fibrofolliculomas, trichodiscomas and acrochordons [1-4], although its has been questioned whether acrochordons truly belong to this hereditary disorder [5]. Spontaneous pneumothorax and cystic lung disease is another feature of BHD [6].

In one large family with this disorder, medullary thyroid cancer was diagnosed in several relatives, 2 of them also presenting with skin tumours. It may have been a coincidental co-segregation of familial medullary thyroid cancer (see that entry) and Birt-Hogg-Dubé syndrome. Benign and malignant adenomatous colon polyps have been reported in patients with this disorder and with what some consider to be a variant of Birt-Hogg-Dubé syndrome: Hornstein-Knickenberg syndrome, which is characterized by multiple perifollicular fibromas [7-10]. Renal tumours (single or multiple, unilateral or bilateral) of various histology have been observed in Birt-Hogg-Dubé syndrome: oncocytoma, chromophobe carcinoma and clear cell as well papillary renal cell carcinomas [11-13].

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Bladder, ureter, renal pyelum cancer, familial clustering of

Mode of inheritance: multifact?
Genes: many low penetrant gene mutations have been reported, we do not list them separately here
Tumour features:
renal pyelum cancer
ureter cancer
urinary bladder cancer
Non-tumour features (possible):
t(5;20)(p15;q11) (constitutional)

Comment

Familial clustering of bladder cancer has been reported [1-5] and may occur in approximately 4% of cases [6]. Kantor et al. [6] demonstrated that having an affected first-degree relative increases the risk of bladder cancer. These authors reported relative risks of 2.7, 1.7 and 1.3 depending on the age at diagnosis of the tumour: below age 45, ages 45-64 and 65 and older, respectively. Cigarette smoking in the setting of a family history of bladder cancer was shown to strongly increase the risk of developing this tumour. Relative risks of up to 28.1 in heavy smokers (60 + cigarettes/day) were calculated as compared to a RR of 2.1 in heavy smokers with a negative family history. Non-smokers with a positive family history still had a RR of 1.5 and this observation of a familial component independent of smoking was supported by the findings of Kramer et al. [7], who reported a RR of 1.8 for a similar group. Piper et al. [8] found bladder or renal cancer in first-degree relatives not to be a risk factor for bladder cancer in young women (<50 years). A family history of cancer in general has been reported to be a risk factor in the development of bladder cancer [2].

Having blood type A or HLA types Cw4 and B5 increases the risk of developing this tumour [9]. Inherited variation in the metabolism of (pro)carcinogens, related to smoking and other environmental exposures, also influences the risk of bladder cancer, e.g. activities of glutathione-S-transferase, N-acetyltransferase and those of the cytochrome P450 group [10-13]. Also, certain alleles of the Hras1 minisatellite locus are associated with an increased tumour risk at this anatomical site [14]. More mutations have been reported, not listed in this brief overview. A small number of published families suggest the existence of a rare autosomal dominant predisposition to urinary tract cancer [3, 5, 15]. Familial clustering of transitional cell carcinomas (TCC) at different sites of the urinary tract has been observed [5, 16, 17], including familial cancer of the ureter [18]. A germline translocation (5;20)(p15;q11) has been observed in a 29-year-old man with TCC bladder cancer. His mother had been diagnosed with a similar tumour (she was not karyotyped) [19].

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Bloom syndrome

Mode of inheritance: AR
OMIM number: 210900
Genes:
BLM, mapped to 15q26.1

Tumour features:
breast cancer
cervical cancer
colon cancer
gastric cancer
hepatocellular cancer
laryngeal cancer
leukaemia, acute lymphoblastic (ALL)
leukaemia, acute myeloid (AML, including ANLL)
lymphoma, malignant (non-Hodgkin's and/or Hodgkin's)
oral cancer
skin cancer, basal cell
Wilms' tumour (nephroblastoma)
Tumour features (possible):
colorectal adenomatous polyps
external auditory canal cancer
medulloblastoma
myelodysplastic syndrome (MDS)
osteosarcoma
skin cancer, squamous cell
vaginal cancer
Non-tumour features:
clinodactyly
growth deficiency
hyperpigmentation of the skin
hypopigmentation of the skin
immunodeficiency
increased chromosomal breakage
increased sister chromatid exchange
long small facies
mutagen sensitivity, increased
UV hypersensitivity
UV radiation sensitivity, increased
Non-tumour features (possible):
bone marrow monosomy 7 karyotype

Comment

Clinical features of this disorder are [1-4]: short stature, dolichocephaly, excessive number of neoplasms (see below), characteristic facies (malar hypoplasia, prominent nose, small mandible, protuberant prominent ears), UV hypersensitivity of the skin (lesions appear mainly in the face and back of hand/forearms), patchy hyperpigmentation (café-au-lait spots) and areas of hypopigmentation of the skin (predominantly on the trunk), variable degree of vomiting and diarrhoea during infancy, diabetes mellitus, azoospermia and early menopause, immunodeficiency, average to low-average intelligence, sometimes mental retardation. Cytogenetic studies show increased sister-chromatid exchange and excessive number of chromatid gaps and breaks. Neoplasms reported in Bloom syndrome (in decreasing frequency): non-Hodgkin's lymphoma, skin cancer (predominantly basal cell type), acute lymphocytic and acute myelocytic leukaemia, breast cancer, colon (diagnosed as early as age 16 [5]) and rectal cancer, oesophageal cancer, tongue cancer, laryngeal cancer, cervical cancer and endometrial cancer, tongue cancer, external auditory canal cancer, Wilms' tumour, osteogenic sarcoma, medulloblastoma and meningioma, tonsillar cancer, retinoblastoma and myelodysplastic syndrome (associated with monosomy 7 [6]). Wang et al. [7] reported a 37-year-old man with ulcerative colitis complicated by colon cancer. Lowy et al. observed colonic polyposis in a Bloom syndrome patient [8]. More recently hepatocellular cancer and vaginal cancer were reported [9, 10].

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Blue rubber bleb nevus syndrome

Synonym: Bean syndrome
Mode of inheritance: AD/spor
OMIM number: 112200
Tumour features:
gastrointestinal polypoid haemangioma
hepatic haemangioma
joint capsules, haemangioma in
lung haemangioma
splenic haemangioma
subcutaneous haemangioma
Tumour features (possible):
leukaemia, chronic lymphocytic (CLL)

medulloblastoma
renal cell cancer
Non-tumour features:
cutaneous nevi, haemangiomatous (blue rubber blebs)

Comment

The hallmarks of this disease are the presence of multiple bladder-like haemangiomas (blue rubber blebs) on the skin, especially on the trunk and arms. The intestinal polypous haemangiomas may cause bleeding. Haemangiomas may be found in a wide range of tissues (spleen, lungs, joint capsules etc.) [1-3]. Chronic lymphocytic leukaemia (at age 66) and renal cell cancer (at age 57) were reported in a male with this disorder [4]. Medulloblastoma was reported in a 21-year old affected woman [5]. This condition may be identical to familial venous malformation syndrome.

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Bone dysplasia with malignant change, hereditary

Synonym: hereditary bone dysplasia with malignant fibrous histiocytoma, diaphyseal medullary stenosis with malignant fibrous histiocytoma, DMS-MFH
Mode of inheritance: AD
OMIM number: 112250
Genes:
DMSMFH/BDMF, mapped to 9p21-p22
Tumour features:
bone, malignant fibrous histiocytoma of the
Non-tumour features:
cataract
skeletal dysplasia

Comment

This disorder is characterized by bone dysplasia presenting with diaphyseal medullary stenosis of bone with overlying cortical bone thickening. The epiphysis is not affected. The bone changes may not appear until the 3rd or 4th decade of life. Other features are fractures after minimal trauma and malignant transformation (typically in 2nd-5th decade). The neoplasms were originally classified as fibrosarcomas, but later reclassified as malignant fibrous histiocytomas. Approximately 35% of gene carriers develop these malignant tumours. Early-onset cataract was documented in some of the patients and mental retardation was seen in a minority of cases [1, 2]. This syndrome maps to 9p21-22 [3, 4].

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Brain tumours, familial clustering of

Synonym: including familial medulloblastoma
Mode of inheritance: multifact?/AR?/AD?
OMIM number: 137800
Genes:
CYP2D6, mapped to 22q13.1
GSTM1, mapped to 1p13.3
GSTT1, mapped to 22q11.2
TP53, mapped to 17p13.1
Tumour features:
astrocytoma
brain, sarcoma of the
choroid plexus papilloma
ependymoma
Ewing sarcoma
glioblastoma (multiforme)
glioma of the brain
medulloblastoma
meningioma
prostate cancer

Tumour features (possible):
breast cancer
colon cancer
gastric cancer
Hodgkin's disease
leukaemia
malignant melanoma, cutaneous

Comment

Familial occurrence of brain tumours has predominantly been reported in sibs, but in some cases the tumours have been found in successive generations [1-5]. The most frequent tumours in these clusters are astrocytoma, medulloblastoma [6, 7] and glioblastoma [8]. Less frequently, choroid plexus papillomas [9], ependymomas [10] and sarcomas [11] have been reported. Figures on the percentage of brain tumours that are familial are rare. Estimates for astrocytomas range from less than 1 to 14% [12]. In the Swedish Family-Cancer Database, which included 2060 childhood brain tumours, 1.3% of brain tumour patients had a parent with nervous system cancer. Some studies conclude that a family history of brain tumours or cancer in general does not significantly contribute to glioma risk in adults and brain tumour risk in children [13-17]. Others found that the occurrence of childhood brain tumour is associated with an increased risk of developing central nervous system tumours, leukaemia and childhood tumours in relatives [18-20]. One study found a particularly strong association between parental meningioma and brain astrocytoma in the offspring [20]. Malmer et al. [26] studied cancer risk in the first-degree relatives of Swedish astrocytoma patients and found an increased risk for astrocytomas (relative risk 2.1) but not for other primary brain tumours in these relatives.

Hill et al. reported that in individuals with a family history of a brain cancer or a brain tumour, risk of glioma was 1.6 and 3.0, respectively, in comparison with those without such family histories. Increased risks were also reported for a family history of stomach (RR 2.2), colon (RR 1.4), or prostate cancer (RR 2.1) or Hodgkin's disease (RR 2.4) [21]. In another paper they reported that risk of meningioma was increased among those with a family history of a benign brain tumour (RR 4.5) or melanoma (RR 4.2). A family history of breast cancer was associated with an elevated meningioma risk among participants aged 18 to 49 years (RR 3.9) but a reduced risk among older individuals [22].

In general, the familial clustering of gliomas may be associated with a range of congenital malformations and is a genetically heterogeneous group [2]. Relatives of patients with Ewing sarcoma or prostate cancer are at increased risk of developing brain tumours [23, 24]. Significantly more colon cancer was observed in first-degree relatives of children with brain tumours, although absolute numbers were small [25]. Interestingly, another study reported a significant decrease in colon (and breast) cancer risk for first-degree relatives of astrocytoma patients [26]. Certain variants of enzymes involved in (pro)carcinogen metabolism have been found to be associated with an increased risk of astrocytomas and meningiomas, e.g. GSTT1, GSTM1 and CYP2D6 [27]. A small fraction of familial clustering of gliomas may be attributed to germline TP53 mutations [28-31].

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Breast cancer, familial clustering of

Mode of inheritance: multifact?
OMIM number: 114480
Genes many low penetrant gene mutations have been reported, we do not list them separately here
Tumour features:
breast cancer
colorectal cancer
endometrial cancer
ovarian cancer (i.e. epithelial origin)
prostate cancer
Non-tumour features:
breast, proliferative disease
mutagen sensitivity, increased

Comment

Given the high risk of breast cancer in women [1], familial occurrence of breast cancer is not rare. A family history of breast cancer has been reported in 14 to 30% of female breast cancer patients [2, 3]. Familial male breast cancer is rare [4-6]. Having a relative with breast cancer is one of the strongest risk factors for this tumour [7-10]. A RR of 34.7 of developing breast cancer has been reported in monozygotic twins of women in whom breast cancer had occurred before age 35 [11]. In general, the risk of breast cancer in relatives does not appear to depend heavily on the gender of their affected family member [12-15]. Compared with the general population, breast cancer is also found more frequently in women with family history of ovarian, endometrial, colorectal and/or prostate cancer and vice versa [16-24]. One study reported a RR of 5.6 for parotid cancer in first-degree relatives of breast cancer patients [25].

Depending on the number of affected relatives, the degree of kinship and the age at onset of the tumours, the empirical risk of developing breast cancer in a female relative may be close to 50% (even higher if she already has children with breast cancer). Several models have been developed to estimate breast cancer risk in a specific family situation. Those by Gail et al. [26-30], focussing on white females who are being examined annually, and by Claus et al. [21, 31, 32] are the ones most widely used in clinical practice. Users should be aware of the specific limitations of these models [33]. For example, the risk tables may need to be adapted for use in different countries and or ethnic groups to account for differences in genetic background and exogenous risk factors [34]. The Claus model includes first- and second-degree relatives, as opposed to the Gail model, which looks at first-degree relatives only. However, the latter method also takes into account the risk factors of age at menarche, age at first live birth and number of previous biopsies.

Given a positive or negative family history of breast cancer, other known risk factors may differ in their contribution to overall risk. Colditz et al. [35] reported on an adverse effect of first pregnancy among women with a family history of breast cancer that was

approximately 50% greater in magnitude than among women without a family history. Past use of oral contraceptives and use of postmenopausal hormones and history of benign breast disease showed similar relative risks between the two groups. Sellers et al. concluded the same with regard to hormone replacement therapy in women with a family history of breast cancer [36]. However, with respect to benign breast disease, Dupont et al. [37] found that fibroadenomas have an increased effect on breast cancer risk in patients with a family history of breast cancer compared to patients without a family history of breast cancer. In addition, Skolnick et al. [38] analyzed families with a clustering of breast cancer and suggested that genetic susceptibility may cause both proliferative benign breast disease and breast cancer in those kindreds. Among women aged 30-49 years, a family history of breast cancer was associated with an increased risk of ductal carcinoma-in-situ (DCIS), and among those aged 50 and older it was associated with an increased risk of both DCIS and invasive breast cancer [39]. Egan et al. [40] demonstrated a stronger inverse association of high parity with breast cancer risk in women who reported first-degree relatives with breast cancer compared with women who did not have affected first-degree relatives. In a study by Schouten et al. [41], family history of breast cancer was not correlated with survival.

Chromosomes of breast cancer patients (and some of their unaffected relatives) with a family history of breast cancer are more sensitive to the action of the mutagen bleomycin compared with sporadic breast cancer patients [42], hinting at the involvement of genes responsible for DNA repair.

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Byler disease

Synonym: PFIC-1, including Byler syndrome, progressive familial intrahepatic cholestasis
Mode of inheritance: AR
OMIM number: 211600
Genes:
FIC1/ATP8B1, mapped to 18q21
Tumour features:
hepatocellular cancer
Non-tumour features:
intrahepatic cholestasis
liver cirrhosis

Comment

Byler disease is characterized by intrahepatic cholestasis with an onset in infancy, leading to hepatic fibrosis and death. It was originally described in an Amish kindred. A similar disorder in children who are not members of that kindred is referred to as Byler syndrome. Both disorders are a subtype of progressive familial intrahepatic cholestasis (another type is Alagille s.) [1]. Bull et al. [2] concluded that Byler syndrome is heterogeneous from a clinicopathological point of view and is distinct from Byler disease (which has been linked to 18q).

Hepatocellular cancer may develop as a complication of Byler disease/syndrome [3-5].

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Carcinoid, familial clustering of

Synonym: including carcinoid, intestinal
Mode of inheritance: multifact?/AD?
OMIM number: 114900
Tumour features:
carcinoid of the lung
gastrointestinal carcinoid

Comment

Anderson reported a father and daughter both diagnosed with carcinoid of the appendix (at age 42 and 15 years, respectively) [1]. Moertel and Dockerty [2] reported on a 2-generation family with (multiple) intestinal carcinoids. One of the affected women developed breast cancer at age 53 while her mother had done so at age 47. Other tumours in that family included nasopharyngeal fibrosarcoma (age 5) and lung cancer (age 42), possibly suggesting Li-Fraumeni-

like syndrome (see that entry). Additional cases of familial intestinal carcinoids have been published [3-8] . An unknown proportion of these and other cases of familial carcinoid might very well be caused by germline mutations in MEN1, the gene associated with multiple endocrine neoplasia type 1. Perkins et al. [9] studied the family history of patients with carcinoid tumours of the lung and demonstrated that the proportion of distant metastasis in these patients was significantly higher among those with a positive family history of cancer (in general). Babovic-Vuksanovic et al. [10] studied the occurrence of cancer in first-degree relatives of 245 gastrointestinal carcinoid patients. For first-degree relatives, only the risk for carcinoid was increased ($p<0.0001$, life-time risk 1.5%).

Oliveira et al. reported pulmonary carcinoid in two affected sibs and in a mother and daughter. No other signs of MEN1 were present in these two families [11].

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Cardiac myxomas, familial clustering of

Mode of inheritance: AR?/AD?
OMIM number: 255960
Genes:
PRKAR1A, mapped to 17q22-q24
Tumour features:
cardiac myxoma

Comment

Familial cases of cardiac myxomas without further signs of Carney complex (see that entry) have been reported. A high rate of recurrence is associated with these cases [1]. Some families may carry a germline mutation in PRKAR1A, the gene involved in Carney complex [2, 3] and may be regarded as having a variant of that disorder.

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Cardiofaciocutaneous syndrome

Synonym: CFC
Mode of inheritance: sporadic (*de novo*)
OMIM number: 115150
Genes:
BRAF, mapped to 9q34
KRAS, mapped to 12p12.1
MEK1, mapped to 15q21
MEK2, mapped to 7q32
Tumour features:
hepatoblastoma
Tumour features (possible):
leukaemia, acute lymphoblastic (ALL)
rhabdomyosarcoma
Non-tumour features:
growth deficieny
heart, congenital defect
high forehead
hyperkeratosis
nasal bridge, depressed
palpebral fissures, downward slanting
woolly, sparse and friable hair

Comment

Hallmarks of CFC are a typical facies, congenital heart defects (predominantly pulmonary stenosis and ASD), growth failure and ectodermal anomalies. There is clinical and molecular overlap with Noonan syndrome and Costello syndrome. These disorders share disruption of the RAS/MAPK signalling pathway [1-3].

Van den Berg and Hennekam [4] reported a 5-year-old girl with CFC who was diagnosed with ALL and Makita reported another case [5]. Bisogno et al. [6] described a 20-month-old boy with CFC and an (embryonal) rhabdomyosarcoma. A hepatoblastoma was reported by Al-Rahawan [7].

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Carney complex

Synonym: Carney syndrome, NAME syndrome, LAMB syndrome, familial myxoma syndrome
Mode of inheritance: AD
OMIM number: 160980
Genes:
CNC2, mapped to 2p15-p16
PRKAR1A, mapped to 17q22-q24

Tumour features:
adrenocortical disease, primary pigmented nodular (PPNAD)
breast myxoma
cardiac myxoma
ductal adenoma of the breast
ear canal myxoma
gastrointestinal schwannoma
pituitary gland tumour
schwannoma (neurilemmoma), peripheral nerve
schwannoma of the bone
schwannoma, psammomatous melanotic
schwannomas of the (posterior) spinal nerve roots
skin myxoma
testicular Sertoli-Leydig cell tumour
thyroid cancer, follicular
uterine leiomyoma
Tumour features (possible):
cervical mesenchymal tumour, atypical
colorectal adenomas
peripheral nerve tumour
pheochromocytoma
teratoma, benign cystic (dermoid cyst) of the ovary
vestibular schwannoma
Non-tumour features:
blue nevi,
café-au-lait spots
lentiginosis (spotty pigmentation)
lips, pigmentation of
oral mucosa, pigmentation of
Non-tumour features (possible):
oesophagus, Barrett's

Comment

More than 200 patients have been reported, half of them familial cases. Patients present with spotty multiple small brown to black macules (lentiginosis) on the skin and mucosae (67% of patients). Other pigmented lesions are cafe-au-lait spots, (epithelioid) blue nevi (19% of patients) and less frequently psammomatous melanotic schwannoma (neurilemmoma) [1]. Primary pigmented nodular adrenocortical disease (PPNAD) leading to Cushing's disease is also typical for the syndrome (found in 33% of patients).

A range of tumours can be found in Carney complex, including myxomas of the heart (in 30-61% of patients), breasts (20%), skin (37%) (of the eyelids in 25%) and external ear canal, testicular tumours (30%): testicular large cell calcifying Sertoli tumours (LCCST) and (less frequently) Leydig cell tumours, growth hormone producing pituitary adenomas (11%) and schwannomas of the upper GI tract, bone,

sympatic chain and the skin (as mentioned above) (total % schwannomas found in Carney complex: 11). Thyroid gland involvement is common (11%), ranging from follicular hyperplasia to cancer [2-4]. Nwokoro et al. [5] reported an affected 34-year-old woman from a Carney complex family, who in addition to features typical for this disorder also developed an atypical mesenchymal tumour of the cervix, neoplastic colonic polyps and Barrett's oesophagus.

There is evidence for genetic heterogeneity in Carney complex [4, 6-8]. In some families, linkage analysis may help in identifying affected relatives [9]. Germline mutations in the PRKAR1A gene have been detected in approximately 45% of Carney complex cases and can also be found in isolated familial myxoma and familial or isolated cases of PPNAD [10-12].

Criteria [4, 5, 13] – 2 of the following should be present:

a) heart myxoma,
b) breast myxoma (myxoid mammary fibroadenoma),
c) skin myxoma,
d) primary pigmented nodular adrenocortical disease,
e) GH-secreting pituitary tumour,
f) psammomatous melanotic schwannoma (PMS),
g) ductal adenoma of the breast,
h) large-cell calcifying Sertoli cell tumour of the testes (LCCST),
i) spotty pigmentation if it is: multiple, present in a characteristic distribution (vermilion border of the lips, conjunctivae, external genitalia), not dependent on exposure to sunlight, and has histology consistent with lentigo rather than ephelide (freckle).

The presence of adrenocortical rest tumours is regarded as corroboratory evidence for the diagnosis [12].

Unfortunately, the name Carney syndrome is used by some to refer to the Carney complex, whereas others use it to refer to Carney triad, which is a completely different disorder.

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Carney triad

Synonym: Carney syndrome
Mode of inheritance: spor/multifact?
OMIM number: 604287
Tumour features:
adrenal adenoma
oesophageal leiomyoma
oesophageal stromal tumour
gastric leiomyosarcoma
gastric stromal sarcoma
paraganglioma, chromaffin (extra-adrenal pheochromocytoma)
pulmonary chondroma
small intestine, stromal tumour of
Tumour features (possible):
exostoses
leiomyosarcoma of the uterus
parathyroid adenoma
renal angiomyolipomas

Comment

The combination of gastric stromal sarcoma, extra-adrenal paraganglioma and pulmonary chondroma is referred to as the Carney triad. Carney reviewed the 79 reported cases [1]. Approximately 85% of Carney triad patients are female. Age of onset ranged from 7 to 48 years (82% diagnosed before age 30); 78% of the reported cases do not present with the complete triad but show only 2 of the 3 features, the paragangliomas being the least frequent component. Although most cases are sporadic, 2 patients have been reported each with a sibling who had one of the tumours of the triad [1]. Gastric stromal sarcomas are usually the presenting tumour. The name (epithelioid) leiomyosarcoma was used in the past to refer to these tumours, but smooth muscle markers have not been identified in all cases; hence the change to 'stromal sarcomas'. The chondromas (diagnosed between 12 and 49 years) are multiple unilateral in 24% and bilateral in 13% of cases and may be recognized more than 15 years earlier and more than 20 years later than the leiomyosarcomas. After surgery for the chondromas, one or more new tumours developed in 56% of patients. The paragangliomas (diagnosed between age 12 to 48 years) are generally catecholamine secreting; they are present in multiple sites in 22% and may undergo malignant change. Silent adrenocortical adenomas were present in 13% of the patients and are considered part of the disorder. Other tumours observed were: oesophageal leiomyoma and stromal tumour, duodenal (multiple) stromal tumours, uterine leiomyosarcoma, bony exostosis, renal angiomyolipoma, parathyroid adenomas, gluteal myoma [1-7].

Unfortunately, the name Carney syndrome is used by some to refer to the Carney triad, whereas others use it to refer to Carney complex (or LAMB or NAME syndrome), which is a completely different disorder.

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Caroli disease

Synonym: Caroli syndrome
Mode of inheritance: AD?/multifact?/AR?
OMIM number: 600643
Tumour features:
intrahepatic cholangiocarcinoma
Non-tumour features:
cystic dilatations of intrahepatic bile ducts

Comment

This disorder is characterized by congenital polycystic dilatation of the intrahepatic bile ducts [1]. It is frequently associated with autosomal recessive polycystic kidney disease and congenital hepatic fibrosis (in the latter case called Caroli syndrome [2]), suggestive of a genetic overlap/allelism. There exists a marked predisposition to the development of cholangitis and liver abscesses. The clinical course can be asymptomatic for the first 5 to 20 years. Cholangiocarcinoma in the intrahepatic cystic lesions has been reported in approximately 7% of cases [3-5].

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Cerebral sarcoma, familial clustering of

Mode of inheritance: multifact?/AR?/AD?
OMIM number: 117600
Tumour features:
brain, sarcoma of the

Comment

Gainer et al. [1] reported four cases of cerebral fibrosarcomas occurring in two families: an affected father (age at diagnosis 73 years) and daughter (at 59 years); and a family with two affected sisters (diagnosed at age 64 and 69 years).

References

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Cerumen type

Mode of inheritance: AD
OMIM number: 117800
Tumour features (possible):
breast cancer
Non-tumour features:
ear wax, wet (as opposed to the dry brittle type)

Comment

Different cerumen types exist [1]. Studies of mainly the Japanese population have demonstrated two types of ear wax inheriting as an autosomal dominant trait: wet, sticky ear wax, or dry, brittle ear wax. A positive association between wet ear wax and breast cancer has been suggested, but data are presently inconclusive [2-5].

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Cervical cancer, familial clustering of

Mode of inheritance: multifact?
Genes: various low penetrant gene mutations have been reported, we do not list them separately here
Tumour features:
cervical cancer
ovarian cancer (i.e. epithelial origin)
Tumour features (possible):
anal cancer
hepatocellular cancer
lung/bronchial cancer
lymphoma, malignant (non-Hodgkin's and/or Hodgkin's)
oral cancer
rectal cancer
skin cancer
urinary bladder cancer

Comment

Familial clustering of cervical cancer has been reported [1-4]. An estimated 15% of patients with this tumour have at least one affected first-degree relative [1]. It has been calculated that having a first-degree relative with cervical cancer is associated with a RR of 3 of developing squamous cell cancer of the cervix, a RR of 10 of developing adenosquamous cancer at this site and no increased risk of developing cervical adenocarcinoma [1]. No other studies have confirmed these detailed findings so far. Data from the Swedish Family-Cancer Database showed a cervical cancer RR of 2.0 for daughters of affected mothers [5]. In a more recent and more detailed analysis the following figures were reported [6]: daughters of mothers with in situ cancer had a RR of 1.7 of developing in situ and RR of again 1.7 of invasive cancer. Daughters of mothers with invasive cervical cancer had a RR of 1.6 of developing in situ cancer and a RR of 2.0 of developing invasive cancer. The following other cancer types in mothers increased the risk for in situ and/or invasive cervical cancer in their daughters: lung, liver, urinary bladder and oral cancer. The following cancer types in daughters increased the risk for in situ and/or invasive cervical cancer in their mothers: lymphoma, ovarian, oral, skin and anorectal cancer.

An analysis of large Mormon families did not show increased risks of cervical cancer in women with an affected sister [7]. However, an excess of cervical cancer was observed in first-degree relatives of patients with early-onset bladder cancer (RR 2.32). A family history of cancer in general was no risk factor for cervical cancer in a Yugoslavian and a Japanese cohort [8, 9]. A study of Finnish patients with borderline ovarian

tumours and their relatives demonstrated a RR of 7.8 for cervical cancer in the mothers of index cases [10]. In a Swedish twin study, the increase in risk of cervical cancer tended to be greater if monozygotic rather than dizygotic twins were affected [11].

Certain HLA haplotypes have been found in association with an increased incidence of cervical cancer or cervical intra-epithelial neoplasia in relation to HPV infections [12-20]. Possibly, some of these HLA types and other genotypes (e.g. P53, GSTT1, GSTM1 [21]) are linked to a less effective immunoresponse to human papilloma virus (HPV) infections, a major risk factor for this tumour [22, 23].

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Chediak-Higashi syndrome

Mode of inheritance: AR
OMIM number: 214500
Genes:
LYST/CHS, mapped to 1q42.1-q42.2
Tumour features:
non-Hodgkin's lymphoma
Tumour features (possible):
ovarian sclerosing stormal tumour
Non-tumour features:
anaemia
immunodeficiency
neutropenia
oculocutaneous albinism

Comment

This disorder (CHS) is characterized by partial oculocutaneous albinism, increased susceptibility to bacterial infections due to impaired natural killer cell activity, and the presence of massive lysosomal

inclusions in all white blood cells and of giant melanosomes in melanocytes. The majority of patients develop a lymphoproliferative disorder during the accelerated phase of the disease, which was demonstrated by Argyle et al. [1] to be a NHL T-cell lymphoma. The patients generally die in early childhood due to recurrent infections, although a late-onset type has been reported. An ovarian sclerosing stormal tumour has been detected in a girl with CHS [2]. The CHS gene has been identified [3].

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Cheilitis glandularis

Mode of inheritance: multifact?/AD?
OMIM number: 118330
Tumour features:
lip, squamous cell cancer of the
Non-tumour features:
lips, hypertrophy of the labial mucous glands

Comment

This disorder is characterized by chronic inflammation of the labial salivary glands, resulting in swelling, eversion and hypersecretion of the affected lips (usually the lower lip) [1]. Swerlick and Cooper [2] stated that the condition is not related to hyperplasia of the labial salivary glands, but rather is the result of an unusual reaction in response to chronic irritation of the lips. A high incidence of lower lip squamous cell cancer (in whites) is found in this disorder [3]. Possibly lip eversion causes a higher sensibility/exposure to carcinogens (rather than cheilitis glandularis itself being a precancerous condition [4]) [5]. Familial cases have been reported [5, 6].

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Chemodectoma, intra-abdominal, with cutaneous angiolipomas

Mode of inheritance: AR?/AD?/multifact?
OMIM number: 118350
Tumour features:
cutaneous angiolipomas
paraganglioma, nonchromaffin (including glomus tumour/chemodectoma)

Comment

Lee et al. [1] reported a Maori family in which a 37-year-old man presented with multiple malignant chemodectomas (para-aortic extending to the liver, and tumours in the duodenum, pancreas, lungs and skull). He also had multiple subcutaneous angiolipomas of the limbs and abdominal wall. Two brothers had died before the age of 45, cause unknown. One of them was reported to have had multiple skin tumours. Another, 40-year-old brother had similar skin tumours and presented with a malignant chemodectoma involving one of the kidneys and metastases in bones and lungs.

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Cherubism

Synonym: familial benign giant-cell tumour of the jaw, familial multilocular cystic disease
Mode of inheritance: AD
OMIM number: 118400
Genes:
SH3BP2, mapped to 4p16.3
Tumour features (possible):
gingival fibroma
osteosarcoma
Non-tumour features:
dental abnormalities
jaw cysts associated with multinucleated giant cells

lower face swelling
rib cysts associated with multinucleated giant cells

Comment

This benign self-limiting disorder is characterized by swelling of the lower face, associated with multiple cystic changes in the jaw and anterior end of ribs. Biopsies of these skeletal lesions show multinucleated giant cells. Onset is around the 3rd-4th year of life and it progresses until the late teens [1-3]. Some cases may behave very aggressively [4-6]. Mangion et al. reported the occurrence of an osteosarcoma in the irradiated jaw of one of their patients [7].

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CHIME syndrome

Mode of inheritance: AR
OMIM number: 280000
Tumour features (possible):
leukaemia, acute lymphoblastic (ALL)
Non-tumour features:
brachiocephaly
cerebral atrophy
cleft palate
deafness, conductive
eye, coloboma of the
heart, congenital defect
helices, overfolding
high birth weight
hypertelorism
ichthyosiform rash
mental deficiency
nasal bridge, broad
palmoplantar hyperkeratosis
philtrum, short
seizures
Non-tumour features (possible):
polythelia (supernumerary nipples)

Comment

This is a very rare disorder characterized by colobomas of the eye, congenital heart defects, migratory ichthyosiform rash of the skin, mental retardation and ear defects (overfolding helices and conductive deafness) (CHIME). Epilepsy, neonatal macrosomia and craniofacial dysmorphisms are additional features. Schnur et al. [1] reported a girl with this disorder who developed acute lymphoblastic leukaemia.

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