Brain Tumors and Syndromes in Children

Fonnet E. Bleeker[1] Saskia M. J. Hopman[2] Johannes H. M. Merks[2] Cora M. Aalfs[1] Raoul C. M. Hennekam[1,3]

[1] Department of Clinical Genetics, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
[2] Department of Paediatric Oncology, Emma Children's Hospital, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
[3] Department of Paediatrics, Emma Children's Hospital, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Address for correspondence Fonnet E. Bleeker, MD, PhD, Department of Clinical Genetics, Room M0-205, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands (e-mail: f.e.bleeker@amc.uva.nl).

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Abstract

(Brain) tumors are usually a disorder of aged individuals. If a brain tumor occurs in a child, there is a possible genetic susceptibility for this. Such genetic susceptibilities often show other signs and symptoms. Therefore, every child with a brain tumor should be carefully evaluated for the presence of a "tumor predisposition syndrome." Here, we provide an overview of the various central nervous system tumors that occur in children with syndromes and of the various syndromes that occur in children with brain tumor. Our aim is to facilitate recognition of syndromes in children with a brain tumor and early diagnosis of brain tumors in children with syndromes. Diagnosing tumor predisposition syndromes in children may have important consequences for prognosis, treatment, and screening for subsequent malignancies and nontumor manifestations. We discuss pitfalls in clinical and molecular diagnoses, and the consequences of diagnosing a hereditary disorder for family members. Our improved knowledge of cancer etiology is increasingly translated into management strategies in syndromes in general and will likely lead in the near future to personalized therapeutic approaches for tumor predisposition syndromes.

Keywords
- infant
- child
- brain tumor
- gene
- genetic
- malformation
- syndrome
- surveillance

Introduction

Genetic and epigenetic changes play an extremely large role in the etiology of cancer.[1] Cancer is usually a disorder of aged individuals and uncommon in children. If cancer occurs in children this suggests an increased susceptibility to develop cancer.[2] Consequently, cancer in children will be frequently caused by a genetic change (mutation) and thus can be inherited. There are numerous examples of cancers occurring within families.[3] Mutations in the same gene can occur both in inherited tumors (germline mutations) and in sporadic tumors (somatic mutations).[4] Well-known examples of this are sporadic basal cell carcinoma and Gorlin syndrome (GS), or sporadic meningioma and neurofibromatosis type 2 (NF2). In patients with inherited mutations of genes that can cause cancer, the inherited mutation itself is not sufficient to cause cancer: cells from such patients need to acquire one or more further mutations (Knudson two-hit theory).[5,6] Not everyone will acquire such a second mutation, so not everyone who inherits a mutation in a cancer gene will indeed develop cancer. In hereditary tumor disorders, patients can develop multiple primary tumors as the second hit can occur independently at different loci. Furthermore, as children with a hereditary predisposition already have the first hit at conception, they are usually younger developing a tumor compared with their sporadic counterparts caused by acquired somatic mutations.[7]

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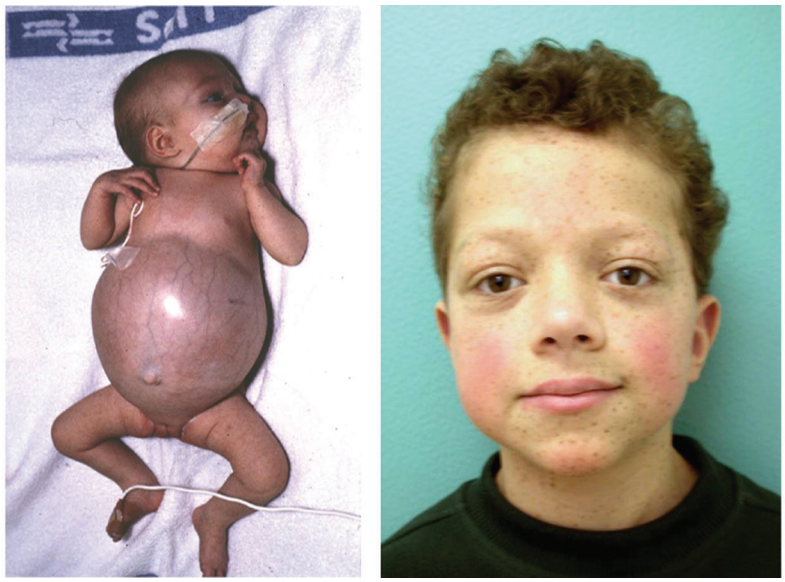

Fig. 1 Child with neuroblastoma and LEOPARD syndrome. Because of the enormous swelling of the belly in the acute stage as a consequence of the neuroblastoma (A), the LEOPARD syndrome was not diagnosed at that time. Only after treatment for the neuroblastoma and recovery, the phenotype became clear and child was diagnosed to have LEOPARD syndrome (B).[12]

Genes and their corresponding proteins have (almost) invariably a dual function, one prenatally and one postnatally: A gene that steers the formation of an organ or body part (developmental gene) during embryogenesis, frequently becomes a gene that is involved in growth regulation after birth.[4] Subsequently, we may expect that a mutated developmental gene causes an unusual phenotype or syndrome prenatally and may go along with an increased risk for the same individual to develop cancer postnatally. Indeed, children with congenital anomalies and syndromes have a higher risk to develop cancer,[8] including tumors of the central nervous system (CNS).[9,10] In addition, children with cancer have more morphological abnormalities,[11] malformations,[12] and more syndromes as well.[13] The recognition of syndromes in children is often problematic as it needs proper examination by a clinical geneticist or a pediatrician skilled in clinical morphology and obtaining a detailed family history to detect this (►**Fig. 1**).[14]

Like other types of cancer, tumors of the CNS usually occur in adults. Only 7% of CNS tumors occur in children.[15] CNS tumors are relatively frequent compared with other types of cancer in children, and comprise approximately 25% of all childhood tumors.[16] Some CNS tumors in children (embryonal CNS tumors as medulloblastoma and ependymoma, and also pilocytic astrocytoma) are linked to factors contributing to brain growth early in (postnatal) life,[17] as these tumors occur less frequent with increasing age.[15] In contrast, during adolescence, the incidence of intracranial germ cell tumors peaks suggesting that puberty itself either initiates or drives their growth.[17] The increased risk for a child with malformations to develop a tumor[8] is reflected in the increased risk for children with CNS malformations to develop CNS tumors.[10] For example, closing defects of the neural tube (including occult spinal dysraphism) are known to have a higher co-occurrence of both intracranial and intraspinal lipoma and teratoma.[18–20] Furthermore, the same pathway seems to be aberrantly activated in different disorders. For example, the SHH-PTCH-GLI pathway is involved in holoprosencephaly, Smith–Lemli–Opitz syndrome, pediatric medulloblastomas and GS (►**Table 1**).[21] Recently, an overview of somatic mosaic mutations in neurodevelopmental and overgrowth syndromes was provided, and some of these genes (or pathways they act in) are also involved in tumor predisposition syndromes.[22]

To our knowledge, no overall analysis has been published on the frequency of CNS tumors in children with a genetic syndrome or the occurrence of syndromes in children with a CNS tumor. Here, we provide a review of the various CNS tumors that occur in children with syndromes and of the syndromes that occur in children with brain tumors. With this, we aim to facilitate recognition of syndromes in children with a brain tumor and early diagnosis of brain tumors in children with syndromes. First, we address from a tumor perspective, which syndromes may be associated with the specific CNS tumor type (►**Table 1**). Next, we concentrate on well-characterized hereditary syndromes that result from germline mutations in high-penetrance genes and predispose to CNS tumor development (►**Table 2**). We do not provide data on brain tumors caused by somatic mutations. Because of limited space we have not aimed to be exhaustive for each syndrome, but have put emphasis on the most frequent (morphologic) manifestations and most prevalent syndromes. We acknowledge that most pediatricians and neurologists may not be familiar with the terminology used in clinical genetics and dysmorphology and have provided short descriptions of the main terms used in ►**Table 3**.

Table 1 Overview of CNS tumors and their associated syndromes

Tumor type	Histology	Syndrome	OMIM	Gene(s) or chromosomal location	Mode of inheritance	Important morphological and clinically relevant manifestations
Glioma	Astrocytoma	Ataxia telangiectasia (Louis–Bar)	208900	*ATM*	AR	Ataxia, chromosome instability/breakage, conjunctival telangiectasia, diffuse increased pigmentation of skin, extrapyramidal disorder, immunoglobulin abnormality, late puberty, lymphomas/leukemias, nasal telangiectasia, premature greying of hair, recurrent infections, short stature (proportionate), speech defect/ dysarthria, telangiectasia of ears, warts/ papillomata.
		Beckwith–Wiedemann (EMG) syndrome	130650	*CDKN1C, NSD1, H19, KCNQ1OT1*	AD	Adrenal tumors (excluding neuroblastoma), auricular pits/fistulas, crease/pits of ear lobule, diastasis recti, enlarged liver, facial hemangiomas, hemihypertrophy, high birth weight (> 90th centile), hypoglycaemia, large kidneys, large spleen, large tongue, omphalocele/ exomphalos, pits of ear helix, posterior helical pits, renal tumors (including Wilms).
		Constitutional mismatch repair deficiency syndrome	276300	*MSH2, MSH6, MLH1, PMS2*	AR	See ►**Table 2**.
		Dysplastic nevus syndrome	155600	*CDKN2/4*	AD	Melanocytic nevi, pancreatic carcinoma, uveal melanoma.
		Familial adenomatous Polyposis	175100	*APC*	AD	See ►**Table 2**.
		Fanconi pancytopenia	227650	*SLX4, FANCA, FANCC, FANCE, FANCF, FANCG, FANCL, FANCD2, FANCM*	AR	Absent or hypoplastic thumbs, agenesis/absent kidney, anaemia/red cell abnormalities, Café-au-lait spots, ectopic/supernumerary kidneys, fusion of vertebra, hypoplastic or absent radii, lymphomas/ leukaemias, mental retardation/developmental delay, microcephaly, platelet abnormalities, polydactyly/bifid thumb, Recurrent infections, short stature (proportionate), small ears/microtia, small penis (including micro), triphalangeal thumb.
		Ishikawa (2000)—chromosome instability syndrome	Not listed	14q11.2	AD	Ataxia, caries, chromosome instability/breakage, mental retardation/developmental delay, myelin abnormality, osteoporosis, short stature, general abnormalities, spasticity/increased tendon reflex.
		L-2-Hydroxyglutaric aciduria	236792	*L2HGDH*	AR	Ataxia, degeneration, myelin abnormality, macrocephaly, mental retardation/developmental delay, seizures/abnormal EEG, spasticity/increased tendon reflex

(*Continued*)

Table 1 (*Continued*)

Tumor type	Histology	Syndrome	OMIM	Gene(s) or chromosomal location	Mode of inheritance	Important morphological and clinically relevant manifestations
		Li–Fraumeni syndrome	151623	*TP53*	AD	No morphological abnormalities are reported. For tumor manifestations see ►**Table 2**.
		Lynch syndrome	120435	*MSH6, MMR, MSH6, PMS2*	AD	No morphological abnormalities are reported. For tumor manifestations see ►**Table 2**.
		Maffucci syndrome	166000	*IDH1, IDH2*	Isolated cases	Bowing of bones, calcification (subcutaneous), capillary hemangioma, cavernous hemangioma, enchondromata, hypertrophy of lower limb, hypertrophy of upper limb, intracranial calcification, macrodactyly, multiple fractures, pancreas carcinoma, skeletal cysts.
		Ollier syndrome	166000	*IDH1, IDH2*	Isolated cases	Bowing of bones, calcification (subcutaneous), enchondromata, hypertrophy of lower limb, hypertrophy of upper limb, intracranial calcification, macrodactyly, multiple fractures, pancreas carcinoma, skeletal cysts.
		Melanoma–astrocytoma syndrome	155755	*CDKN2A*	AD	Nevi or lentigines, other tumors of skin.
		Microphthalmos—orbital cyst	Not listed	?	?	Microphthalmia, orbital cyst, phakoma/ pseudoglioma of retina.
		Morning glory syndrome - sphenoeth-moidal encephalocele		?	?	Agenesis/hypoplasia of corpus callosum, Anterior encephalocele/meningocele, bifid nasal tip, cataract, cleft palate, coloboma involving optic nerve, hypertelorism, hypo-pituitarism, hypothyroidism/small/absent thyroid, micro-phthalmia, midline cleft upper lip, optic atrophy.
		Neurofibromatosis type 1	162200	*NF1*	AD	See ►**Table 2**.
		Neurofibromatosis type 2	101000	*NF2*	AD	See ►**Table 2**.
		Nevoid basal cell carci-noma syndrome (Gorlin)	109400	*PTCH1, SUFU*	AD	See ►**Table 2**.
		Noonan syndrome	163950	*PTPN11, KRAS, SOS1, BRAF*	AD	Bleeding diatheses, cardiomyopathy, cryptor-chid testes, cubitus valgus, curly hair, deafness (sensorineural), low-set ears, mental retarda-tion/developmental delay, mitral incompe-tence, nevi or lentigines, edema of feet, pectus abnormalities, posteriorly rotated ears, ptosis of eyelids, pulmonary stenosis, short neck, short stature (proportionate), webbed neck.
		Russell–Silver syndrome	180860	*ICR2, ICR1*	Isolated cases	Asymmetric arms, asymmetric lower limbs, blue sclera, clinodactyly, delayed bone age,

Table 1 (*Continued*)

Tumor type	Histology	Syndrome	OMIM	Gene(s) or chromosomal location	Mode of inheritance	Important morphological and clinically relevant manifestations
						down-turned corners of the mouth, fontanelles (delayed closure/large), low-birth-weight (< 3rd centile), patchy pigment of skin/café-au-lait spots, short stature (prenatal onset), small mandible/micrognathia, thin upper lip, triangular face.
	Astrocytoma (SEGA)	Tuberous sclerosis complex	191100	*TSC1.TSC2*	AD	See ►**Table 2**.
	Glioblastoma	CCMR-D	276300	*MSH6, MMR, MSH6, PMS2*	AR	See ►**Table 2**.
		Fragile X syndrome	300624	*FMR1*	X-linked dominant	Autism/autistic behavior, intellectual disability, joint laxity, macrocephaly, mitral incompetence, large, prominent ears (anteverted), large testes, prominent mandible/prognathism, seizures.
		L-2-Hydroxyglutaric aciduria	236792	*L2HGDH*	AR	See above.
		Li–Fraumeni syndrome	151623	*TP53*	AD	No morphological abnormalities are reported. For tumor manifestations see ►**Table 2**.
		Lynch syndrome	120435	*MSH6, MMR, MSH6, PMS2*	AD	No morphological abnormalities are reported. For tumor manifestations see ►**Table 2**.
		Longman (2001)—peripheral neuropathy; mental retardation	Not listed			Hypotelorism, mental retardation/developmental delay, microstomia/narrow mouth, peripheral neuropathy, Short palpebral fissures, Short philtrum.
		Neurofibromatosis type 1	162200	*NF1*	AD	See ►**Table 2**.
	Glioma (not otherwise specified)	Nijmegen breakage syndrome	251260	*NBS1, MRE11A, RAD50*	AR	Anemia/red cell abnormalities, B-cell deficiency, cafe au lait spots, chromosome instability/breakage, erythema/erythroderma, Immunoglobulin abnormality, large ears, large nose, lissencephaly/pachygyria/polymicrogyria, long philtrum, lymphomas/ leukemias, mental retardation/developmental delay, microcephaly, palpebral fissures slant up, recurrent infections, seizures/abnormal EEG, short stature (proportionate), skin photosensitivity, sloping forehead, small mandible/micrognathia, T-cell deficiency, telangiectasia/angiokeratomata of skin.

(*Continued*)

Table 1 (*Continued*)

Tumor type	Histology	Syndrome	OMIM	Gene(s) or chromosomal location	Mode of inheritance	Important morphological and clinically relevant manifestations
	Oligodendroglioma	CCMR-D	276300	*MSH6, MMR, MSH6, PMS2*	AR	See ►**Table 2**.
		Familial adenomatous polyposis	175100	*APC*	AD	See ►**Table 2**.
		Nevoid basal cell carcinoma syndrome (Gorlin)	109400	*PTCH1, SUFU*		See ►**Table 2**.
		Rubinstein–Taybi syndrome	180849	*CBP, EP300, CREBBP*	AD	Arched eyebrows, broad hallux, broad thumbs, columella below alae nasi, congenital cardiac anomaly (unspecified), convex/beaked profile of nose, dislocated patella, fontanelles, delayed closure/large, frontal upsweep/cowlick, generalized hirsutism/hypertrichosis, glaucoma, hypermetropia, keloids, large nose, long/prominent eyelashes, mental retardation/developmental delay, myopia, narrow palate, palpebral fissures slant down, polydactyly/bifid hallux, posterior helical pits, ptosis of eyelids, short stature (proportionate), small mandible/micrognathia, strabismus/gaze palsy, supernumerary nipples, talon cusp, thick eyebrows.
		Lynch syndrome	120435	*MSH6, MMR, MSH6, PMS2*	AD	No morphological abnormalities are reported. For tumor manifestations see ►**Table 2**.
		Westerhof (1978)—pigmentary anomalies; mental retardation; short stature	154000	?	AD	Mental retardation/developmental delay, Nevi or lentigines, patchy depigmentation of skin, patchy pigment of skin/café-au-lait spots, short stature (proportionate).
Ependymal tumors	Ependymoma	Familial adenomatous Polyposis	175100	*APC*	AD	See ►**Table 2**.
		Nevoid basal cell carci noma syndrome (Gorlin)	109400	*PTCH1, SUFU*	AD	See ►**Table 2**.
		L-2-hydroxyglutaric aciduria	236792	*L2HGDH*	AR	See above
		Leukonychia–sebaceous cysts–renal calculi	Not listed		AD	White nails, sebaceous cysts, pancreatitis, renal stones.
		Neurofibromatosis type 1	162200	*NF1*	AD	See ►**Table 2**.
		Neurofibromatosis type 2	101000	*NF2*	AD	See ►**Table 2**.
		Li–Fraumeni syndrome	151623	*TP53*	AD	No morphological abnormalities are reported. For tumor manifestations see ►**Table 2**.
		Lynch syndrome	120435	*MSH6, MMR, MSH6, PMS2*	AD	No morphological abnormalities are reported. For tumor manifestations see ►**Table 2**.

Table 1 (*Continued*)

Tumor type	Histology	Syndrome	OMIM	Gene(s) or chromosomal location	Mode of inheritance	Important morphological and clinically relevant manifestations
		Multiple endocrine neoplasia type 1	131100	*MEN1*	AD	No morphological abnormalities are reported. Other tumor manifestations include amongst others: adrenal adenoma, adrenocortical cancer, carcinoid, collagenoma of the skin, cutaneous leiomyoma, duodenal gastrinoma, facial angiofibroma, gastrointestinal carcinoid, lipoma, meningioma, pancreatic endocrine tumor, parathyroid adenoma, pituitary adenoma, prolactinoma, thymoma.
		Schinzel–Giedion syndrome	611060	*SETBP1*	AD	Atrial septum defect, coarse facial features, generalized hirsutism/hypertrichosis, hydronephrosis, hypoplastic phalanges, hypospadias, intellectual disability, mid-face hypoplasia (excluding malar region), postaxial polydactyly of fingers, ossification defects of skull, short stature (short limbs).
Choroid plexus tumors	Choroid plexus papilloma	Aicardi syndrome	304050	*Xp22*	XLD	Agenesis/hypoplasia of corpus callosum, aplasia or dysplasia of retina, coloboma involving optic nerve, dandy-walker malformation, fusion of vertebra, hemivertebra, mental retardation/developmental delay, microphthalmia, neuronal migration abnormality/heterotopia, patchy pigment of skin/café-au-lait spots, punched-out lesions of the retina, ribs (general abnormalities), scoliosis, tumors/cysts.
		Costello syndrome	218040	*HRAS*	AD	Cardiomyopathy, coarse facial features, cutis laxa, deep palmar creases, high birth weight, hyperkeratosis, intellectual disability, kinky/curly hair (including pili torti), loose skin in neck, low-set ears, pectus carinatum, pulmonary stenosis, short stature (proportionate), thin/brittle nails, warts/papillomata, uplift of ear lobule.
		Hypomelanosis of Ito	300337	*HMI*	Isolated cases	Asymmetric arms, asymmetric lower limbs, intellectual disability, macrocephaly, microphthalmia, neuronal migration abnormality/heterotopia, patchy depigmentation of skin, patchy pigment of skin/café-au-lait spots.
		Li–Fraumeni syndrome	151623	*TP53*	AD	No morphological abnormalities are reported. For tumor manifestations see ►**Table 2**.
		Pierpont syndrome	602342	?	AD	Abnormal/deep plantar creases, dimple/smooth/absent philtrum, drooping of lower lip, fetal finger pads, intellectual disability, microcephaly, prominent ears, seizures, thin upper lip.

(*Continued*)

Table 1 (*Continued*)

Tumor type	Histology	Syndrome	OMIM	Gene(s) or chromosomal location	Mode of inheritance	Important morphological and clinically relevant manifestations
		Von Hippel–Lindau disease	193300	*VHL*	AD	No morphological abnormalities are reported. For tumor manifestations see ►**Table 2**.
	Choroid plexus carcinoma	RTPS	609322	*SMARCB1, SMARCA4*	AD	No morphological abnormalities are reported. For tumor manifestations see ►**Table 2**.
		Li–Fraumeni syndrome	151623	*TP53*	AD	No morphological abnormalities are reported. For tumor manifestations see ►**Table 2**.
Embryonal tumors	Atypical teratoid/rhabdoid tumor	Beckwith–Wiedemann (EMG) syndrome	130650	*CDKN1C, NSD1, H19, KCNQ1OT1*	AD	See above.
		Chromosome 22q13—submicroscopic deletion (Phelan–McDermid syndrome)	606232	*ProSAP2, SHANK3,*	Isolated cases	Agenesis/hypoplasia of corpus callosum, autism/autistic behavior, bulbous nasal tip, cleft palate, constipation, dolichocephaly/scaphocephaly, epicanthic folds, flat face, hypotonia, large ears, long philtrum, long/prominent eyelashes, macrocephaly, macrostomia, mental retardation/developmental delay, prominent ears (anteverted), seizures/abnormal EEG, simple/smooth/absent philtrum, small mandible/micrognathia, speech delay, strabismus/gaze palsy, wide forehead, wide-spaced teeth.
		Distal 22q11.2 deletion syndrome	661867	*22q11.2*	AD	Intellectual disability, hypotonia, high-pitched voice, large ears, laxity, microcephaly, notched/hypoplastic alae nasi, seizures, speech delay, straight eyebrows.
		RTPS	609322	*SMARCB1, SMARCA4*	AD	No morphological abnormalities are reported. For tumor manifestations see ►**Table 2**.
	Ganglioneuroblastoma	Costello syndrome	218040	*HRAS*	AD	See above.
		Li–Fraumeni syndrome	151623	*TP53*	AD	No morphological abnormalities are reported. For tumor manifestations see ►**Table 2**.
	Medulloblastoma	Aicardi syndrome	304050	*Xp22*	XLD	See above.
		Apert syndrome	101200	*FGFR2*	AD	Acrocephaly/turricephaly, brachycephaly, broad thumbs, broad toes, craniosynostosis, flat face, hypoplastic maxilla (excluding malar region), prominent eyes/proptosis, skin syndactyly of fingers, syndactyly of toes.
		Ataxia–telangiectasia (Louis–Bar)	208900	*ATM*	AR	See above.

Table 1 (*Continued*)

Tumor type	Histology	Syndrome	OMIM	Gene(s) or chromosomal location	Mode of inheritance	Important morphological and clinically relevant manifestations
		Bloom syndrome	210900	*RecQ*	AR	Acanthosis nigricans, breast tumors , chromosome instability/breakage, conjunctivitis, erythema/erythroderma, flat malar region, gastrointestinal tumor /polyp/hemangioma, high-pitched voice, hypogonadism, ichthyosis, immunoglobulin abnormality, lymphomas/leukemias, microcephaly, oligodontia, patchy depigmentation of skin, patchy pigment of skin/cafe au lait spots, renal tumors (including Wilms), short stature (prenatal onset), skin photosensitivity, small mandible/micrognathia, telangiectasia.
		Blue rubber bleb nevus syndrome	112200	?	AD	Cavernous hemangioma, gastrointestinal hemangioma, vascular malformations/hemorrhage of brain.
		Branchio-oculo-facial syndrome (hemangiomatous branchial clefts)	113620	*TFAP2A*	AD	Atrophic skin-patchy, auricular pits/fistulas, blocked/absent nasolacrimal duct, branchial cleft/sinus/cysts, cataract, cavernous hemangioma, cleft palate, cleft upper lip (non-midline), coloboma involving optic nerve, coloboma of iris, dimpled or grooved chin, dystopia canthorum (telecanthus), high palate, patchy aplasia/hypoplasia of skin, patchy depigmentation of hair/white forelock, pits of lower lip, premature greying of hair, ptosis of eyelids, short stature, proportionate, telangiectasia/angiokeratomata of skin, wide nasal bridge
		C syndrome	211750	*CD96*	AR	Anteverted nares, beaded/wavy/constrictions of ribs, broad base to nose, contractures (including arthrogryposis), facial haemangiomas, hypoplastic supra-orbital ridges, hypotonia, laxity, long philtrum, low-set ears, macrostomia, mental retardation/developmental delay, metopic ridge, multiple joint dislocation, omphalocele/exomphalos, oral frenula (multiple), palpebral fissures slant up, postaxial polydactyly of fingers, postaxial polydactyly of toes, short neck, short ribs, short stature (short limbs), skin syndactyly of fingers, small ears/microtia, small mandible/micrognathia, syndactyly 2-3 of toes, syndactyly of toes (not 2-3), thick/wide alveolar ridges, ulnar deviation of hand.
		CCMR-D	276300	*MSH6, MMR, MSH6, PMS2*	AR	See ►**Table 2**.

(*Continued*)

Table 1 (*Continued*)

Tumor type	Histology	Syndrome	OMIM	Gene(s) or chromosomal location	Mode of inheritance	Important morphological and clinically relevant manifestations
		Coffin–Siris syndrome	135900	*SMARCA2, SMARCA4, SMARCB1*	AR	Depressed/flat nasal bridge, generalized hirsutism/hypertrichosis, hypoplastic phalanges, intellectual disability, long/prominent eyelashes, prominent upper lip, short philtrum, short stature (proportionate), small/hypoplastic/deep-set nails, sparse hair/alopecia areata, thick eyebrows.
		Cowden—multiple hamartomas	158350	*PTEN*	AD	See ►**Table 2**.
		Curry–Jones syndrome	601707	?	?AR?	Atrophic skin - patchy, broad thumbs, coloboma of iris, craniosynostosis, gastrointestinal tumor/polyp, hydrocephaly/large ventricles (nonspecific), hypotonia, mental retardation/developmental delay, microphthalmia, polydactyly/bifid hallux, polydactyly/bifid thumb, preaxial polydactyly of fingers, preaxial polydactyly of toes, scalp defects, skin syndactyly of fingers, small bowel atresia/absence/obstruction/short.
		Fanconi pancytopenia	227650	*SLX4, FANCA, FANCC, FANCE, FANCF, FANCG, FANCL, FANCD2, FANCM*	AR	See above.
		Familial adenomatous polyposis	175100	*APC*	AD	See above.
		Fragile X syndrome	300624	*FMR1*	X-linked dominant	See above.
		Greig cephalopolysyndactyly syndrome	175700	*GLI3*	AD	Agenesis/hypoplasia of corpus callosum, bifid nails, broad base to nose, broad hallux, broad thumbs, double ureters, hydrocephaly/large ventricles (nonspecific), hypertelorism, macrocephaly, mental retardation/developmental delay, polydactyly/bifid hallux, postaxial polydactyly of fingers, postaxial polydactyly of toes, preaxial polydactyly of fingers, preaxial polydactyly of toes, prominent forehead/frontal bossing, skin syndactyly of fingers, syndactyly of toes (not 2-3), wide nasal bridge.
		Happle–Tinschert syndrome; basaloid follicular hamartoma plus	Not listed	?	?	Abnormally shaped teeth, atrophic skin (patchy), comedones, enamel abnormalities, extra ribs (including cervical), mental retardation/developmental delay, oligodontia, patchy aplasia/hypoplasia of skin, patchy depigmentation of skin, patchy pigment of skin/café-au-lait spots, postaxial polydactyly of toes, scoliosis, skin tumors, small teeth.

Table 1 (*Continued*)

Tumor type	Histology	Syndrome	OMIM	Gene(s) or chromosomal location	Mode of inheritance	Important morphological and clinically relevant manifestations
		Muenke syndrome	602849	*FGFR3*	AD	Brachycephaly, broad hallux, broad thumbs, craniosynostosis, macrocephaly, prominent forehead/frontal bossing, ptosis of eyelids, short phalanges, tarsal synostosis.
		Neurofibromatosis type 1	162200	*NF1*	AD	See ►**Table 2**.
		Nevoid basal cell carcinoma syndrome (Gorlin)	109400	*PTCH1, SUFU*	AD	See ►**Table 2**.
		Nijmegen breakage syndrome	251260	*NBS1, MRE11A, RAD50*	AR	See above.
		Noonan syndrome	163950	*PTPN11*	AD	Cardiomyopathy, cryptorchid testes, cubitus valgus, kinky/curly hair (including pili torti), low posterior/trident hairline, nevi or lentigines, edema of feet, pectus carinatum, platelet abnormalities, ptosis of eyelids, pulmonary stenosis, short stature, (proportionate), webbed neck.
		Rubinstein–Taybi syndrome	180849	*CBP, EP300, CREBBP*	AD	See above.
		L-2-Hydroxyglutaric aciduria	236792	*L2HGDH*	AR	See above.
	Medulloblastoma/PNET (not further defined)	Dicer1 syndrome	601200	*DICER1*	AD	No morphological abnormalities are reported. Other tumor manifestations include amongst others: Cystic nephroma, Hamartomatous polyps in small intestine, Ovarian Sertoli–Leydig cell tumor, Pleuropulmonary blastoma, Thyroid hyperplasia/goiter
	(PNET)	Ataxia-telangiectasia (Louis–Bar)	208900	ATM	AR	See above.
		CCMR-D	276300	*MSH6, MMR, MSH6, PMS2*	AR	See ►**Table 2**.
		L-2-Hydroxyglutaric aciduria	236792	*L2HGDH*	AR	See above
Neuronal and mixed neuronalglial tumors	Ganglioglioma	Sotos syndrome (cerebral gigantism)	117550	*NSD1, NFIX1*	Isolated cases	Advanced bone age/large epiphyses, advanced tooth eruption/development, agenesis/ hypoplasia of corpus callosum, coarse facial features, dolichocephaly/scaphocephaly, flat arches of feet, high birth weight (> 90th centile), high palate, hypertelorism, large feet, large hands, laxity, lymphomas/ leukemias, macrocephaly, mental retardation/developmental delay, nystagmus, palpebral fissures slant down, prominent forehead/frontal

(*Continued*)

Table 1 (*Continued*)

Tumor type	Histology	Syndrome	OMIM	Gene(s) or chromosomal location	Mode of inheritance	Important morphological and clinically relevant manifestations
						bossing, prominent mandible/prognathism, renal tumors (including Wilms'), scoliosis, seizures/abnormal EEG, tall stature (proportionate)
		Fragile X syndrome	300624	*FMR1*	X-linked dominant	See above.
Tumors of the meninges	Meningioma	Greig cephalopolysyndactyly syndrome	175700	*GLI3*	AD	Agenesis/hypoplasia of corpus callosum, bifid nails, broad base to nose, broad hallux, broad thumbs, double ureters, hydrocephaly/large ventricles (nonspecific), hypertelorism, macrocephaly, mental retardation/developmental delay, polydactyly/bifid hallux, postaxial polydactyly of fingers, postaxial polydactyly of toes, preaxial polydactyly of fingers, preaxial polydactyly of toes, prominent forehead/frontal bossing, skin syndactyly of fingers, syndactyly of toes (not 2-3), wide nasal bridge.
		Neurofibromatosis type 1	162200	*NF1*	AD	See ►**Table 2**.
		Neurofibromatosis type 2	101000	*NF2*	AD	See ►**Table 2**.
		Nevoid basal cell carcinoma syndrome (Gorlin)	109400	*PTCH1, SUFU*	AD	See ►**Table 2**.
		Nijmegen breakage syndrome	251260	*NBS1, MRE11A, RAD50*	AR	See above.
		Rubinstein–Taybi syndrome	180849	*CBP, EP300, CREBBP*	AD	See above.
		Schwannomatosis	162091	*SMARCB1*	AD	No morphological abnormalities are reported. For tumor manifestations see ►**Table 2**.
		Turner syndrome	Not listed	45, XO	Isolated cases	Aortic incompetence, broad/barrel thorax, cubitus valgus, hypogonadism, hypoplastic/inverted/absent nipples, nevi or lentigines, edema of feet, short stature (general abnormalities), webbed neck.
Other neoplasms related to the meninges	Hemangioblastoma	Von Hippel–Lindau disease	193300	*VHL*	AD	See ►**Table 2**.
Intracranial and intraspinal germ cell tumors	Intracranial and intraspinal embryonal carcinoma	Aicardi syndrome	304050	*Xp22*	XLD	See above.
	Intracranial and intraspinal germinoma	Bachman (1980)—anophthalmia; intracranial germinoma	Not listed	?	?	Anophthalmia, cleft palate, cleft upper lip (nonmidline), hypopituitarism, mental retardation/developmental delay.

Table 1 (*Continued*)

Tumor type	Histology	Syndrome	OMIM	Gene(s) or chromosomal location	Mode of inheritance	Important morphological and clinically relevant manifestations
		Down syndrome	190685	Trisomy 21	Isolated cases	Atrioventricular septal defect, brachycephaly, broad hands, brushfield spots, depressed/flat nasal bridge, duodenal atresia, epicanthic folds, fallot tetralogy, flat face, hypotonia, intellectual disability, large tongue, microcephaly, palpebral fissures slant up, short neck, sandal gap of toes, short stature (prenatal onset), single palmar crease.
		Klinefelter syndrome	Not listed	47, XXY		Abnormal secondary sexual hair, cryptorchid testes, gynecomastia, high-pitched voice, hyper-extensible knees, inguinal hernia, mental retardation/developmental delay, mitral incompetence, oligospermia/azoospermia, pectus excavatum, scoliosis, small penis (including micro), small testes, tall stature (general abnormalities), truncal obesity.
		Peutz–Jeghers syndrome	175200	*STK11*	AD	Breast tumours, café-au-lait spots, colonic tumors, early puberty in females, gastrointestinal polyps, liver cysts/ tumors/angiomas, macules, nasal tumors, nevi or lentigines, oral pigmentation, ovarian cysts/ tumors, pancreatic tumors, testicular tumors, uterine tumors /fibroid.
		Smith–Lemli–Opitz syndrome type I	270400	*DHCR7*	AR	Absent or hypoplastic thumbs, ambiguous/ absent genitalia, anteverted nares, cataract, cholesterol/lipids (abnormal), cleft palate, cryptorchid testes, dandy-walker malformation, hypospadias, hypotonia, long philtrum, megacolon or Hirschsprung syndrome, mental retardation/developmental delay, microcephaly, neuronal migration abnormality/heterotopia, post-axial polydactyly of fingers, prominent lateral palatine ridges, ptosis of eyelids, pyloric stenosis, short thumb, skin photosensitivity, small mandible/micrognathia, syndactyly 2-3 of toes, thick alae nasi.
	Intracranial and intraspinal teratoma	Semerci (2001) — absence of vertebra; renal agenesis; VSD; teratoma	Not listed	?	?	Agenesis/absent kidney, anal atresia/stenosis, congenital hernia of diaphragm, contractures (including arthrogryposis), meningocele/ meningomyelocele, sacral teratoma/ tumor, small bowel atresia/absence/obstruction/short, ventricular septal defect, vertebra, unossified.
Tumors of the sellar region	Craniopharyngioma	Familial adenomatous Polyposis	175100	*APC*	AD	See ►**Table 2**.

(*Continued*)

Table 1 (*Continued*)

Tumor type	Histology	Syndrome	OMIM	Gene(s) or chromosomal location	Mode of inheritance	Important morphological and clinically relevant manifestations
		Nevoid basal cell carcinoma syndrome (Gorlin)	109400	*PTCH1, SUFU*	AD	See ►**Table 2**.
		Russell–Silver syndrome	180860	*ICR2, ICR1*	Isolated cases	See above.
	Pituitary Adenoma	Carney complex	160980	*PRKAR1A*	AD	Abnormal genital pigmentation, acanthosis nigricans, adrenal hyperplasia, breast tumors, café-au-lait spot, capillary hemangioma, cysts, gynecomastia, lobulated tongue (including hamartomata), neurofibromas/schwannomas, nevi or lentigines, nevus of ota, oral pigmentation, osteoporosis, ovarian cysts/ tumors, papules, pituitary tumors, testicular tumors, tumors of the heart.
		McCune–Albright syndrome	174800	*GNAS1*	Isolated cases	Asymmetric face, early puberty in females, early puberty in male, fibrous dysplasia of bones, gynecomastia, patchy pigment of skin/café-au-lait spots, prominent mandible/prognathism, short stature (proportionate)
		Multiple endocrine neoplasia type 1	131100	*MEN1*	AD	No morphological abnormalities are reported. For tumor manifestations see ►**Table 2**.
		Tuberous sclerosis complex	191100	*TSC1, TSC2*	AD	See ►**Table 2**.
Tumors of the pineal region	Pineoblastoma	Dicer1 syndrome	601200	*DICER1*	AD	See above.
Other intracranial and intraspinal neoplasms	Hypothalamic hamartoma	Pallister Hall syndrome	146510	*GLI3*	AD	Agenesis/hypoplasia of corpus callosum, anal atresia, bifid epiglottis, depressed nasal bridge, double ureters, hydrocephaly/large ventricles (nonspecific), hypopituitarism, intellectual disability, macrocephaly, pre-axial polydactyly of toes, polydactyly/bifid hallux, post-axial polydactyly of fingers, post-axial polydactyly of toes, skin syndactyly of fingers, syndactyly of toes (not 2-3), wide nasal bridge.
	Brain tumor, possibly glioma	Biemond IIVSD obesity; polydactyly; iris coloboma	210350	?	AR	Cataract, Coloboma of iris, hydrocephaly/large ventricles (nonspecific), hypospadias, mental retardation/developmental delay, postaxial polydactyly of fingers, preaxial polydactyly of fingers, proximal placement of thumb, short stature (general abnormalities), small penis (including micro), small testes, truncal obesity.

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; ATM, ataxia telangiectasia mutated; CMMR-D, constitutional mismatch repair-deficiency syndrome; CNS, central nervous system; EEG, electroencephalography; EMG, Exomphalos-Macroglossia-Gigantism; OMIM, Online Mendelian Inheritance in Man; PMET, primitive neuroectodermal tumor; RTPS, rhabdoid tumor predisposition syndrome; SEGA, subependymal giant cell astrocytoma; VSD, ventricular septal defect.
Note: Major (morphological) manifestations are listed in alphabetical order.

Table 2 Major CNS tumor predisposition syndromes

						Neurological manifestations		Nonneurological manifestations			
Syndrome	Incidence	Gene(s)	Locus	Inheritance	% de novo	CNS manifestations	PNS involvement	Other tumors	Skin	Eye	Other manifestations
NF1	1:2500–1:3000	*NF1*	17q11.2	AD	50	Optic pathway glioma	Neurofibroma	Pheochromocytoma	Café-au-lait spots	Lisch nodules	Pseudarthrosis
						(Pilocytic) astrocytoma	Malignant peripheral nerve sheeth tumor	Leukemias	Axillary freckling	Neurofibroma	Scoliosis, kyphosis
						Unidentified bright objects		Breast carcinoma	Neurofibroma	Optic atrophy	Hemihypertrophy of one limb
						Macrocephaly		Subungal glomus tumors	Pruritus	Ptosis	
						Intellectual disability		GIST			
						Seizures					
NF2	1:33,000–1:40,000	*NF2*	22q12	AD	50	Meningioma	(Vestibular) schwannoma		Café-au-lait spots	Cataract	Deafness, sensorineural
						Ependymoma (spinal localization)	Neuropathy (mono or poly)		Pedunculated skin lesions /skin tags	Strabismus	
						Pilocytic or diffuse astrocytoma				Amblyopia	
										Retinal hamartoma	
										Opticus meningioma	
Schwannomatosis	Not known (rare)	*SMARCB1*	22q12	AD	5	Meningioma	Schwannoma (but not vestibular localization)	Uni/bilateral renal malignant rhabdoid tumors			
RTPS	Not known (rare)	*SMARCB1*	22q12	AD	5	Atypical teratoid/rhabdoid tumor	Schwannoma (but not vestibular localization)	Uni/bilateral renal malignant rhabdoid tumors			
VHL	1:36,000	*VHL*	3p25	AD	20	Hemangioblastoma		(Bilateral) clear-cell renal cell carcinoma		Retinal hemangioblastoma	Cysts of kidney, pancreas, epididymus and broad ligament
								Pheochromocytoma			
								Neuroendocrine tumor			
								Endolymphatic sac tumors			
TSC	1:5800	*TSC1*	9p34	AD	66	Subependymal giant cell astrocytoma		Cardiac rhabdomyoma	Cutaneous angiofibroma	Retinal nodular hamartoma	Cysts of kidney and lung
		TSC2	16p13			Cortical tubers		Hamartomatous rectal polyps	Shagreen patch	Retinal achromic patch	Lymphangiomyomatosis
						Subependymal Nodule		Renal angiomyolipoma	Hypomelanotic macule		Bone cysts
						Intellectual disability		Renal cell carcinoma	(Peri)ungal fibroma		Gingival fibromas
						Seizures			“Confetti” skin lesions		

(*Continued*)

Table 2 (*Continued*)

						Neurological manifestations		Nonneurological manifestations			
Syndrome	Incidence	Gene(s)	Locus	Inheritance	% de novo	CNS manifestations	PNS involvement	Other tumors	Skin	Eye	Other manifestations
LFS	1:5,000–1:20,000	*TP53*	17p13	AD	7–20	Glioma	Malignant triton tumor	Premenopausal breast carcinoma			
						Choroid plexus tumors		Sarcoma of bone and soft tissue			
						Medulloblastoma		Adrenocortical carcinoma			
						Primary neuroecto-dermal tumor		Leukemias			
CS	1:250.000	*PTEN*	10q23	AD	50–90	Dysplastic ganglio-cytoma of cerebellum		Thyroid carcinoma	Trichilemmoma		Benign thyroid disease
						Macrocephaly		Benign and malignant breast tumors	Fibroma		Fibrocystic disease of the breast
						Meningioma		Endometrial carcinoma			Hamartomatous polyps of the colon
						Medulloblastoma		Renal cell carcinoma			Genitourinary malformation
						Astrocytoma					Lipomas
						Intellectual disability					Fibromas
											Uterine fibroids
FAP	1:10,000	*APC*	5q21	AD	20–25	Medulloblastoma		Colorectal polyps and carcinoma	Epidermoid cysts	Congenital hypertro-phy of retinal pigment epithelium	
						Glioma		Osteoma			
						Craniopharyngioma		Desmoid tumor			
						Meningioma		Hepatoblastoma			
								Ampulla of Vater carcinoma			
LS or HNPCC	1:660–1:2000	*MLH1*	3p21	AD	Rare	Glioma		Colorectal adenoma and carcinoma	Sebaceous skin neoplasms		
		MSH2	2p16			Ganglioma		Endometrial carcinoma			
		MSH6	2p21			Meningioma		Gastric carcinoma			
		PMS2	7p22			Hemangioblastoma		Ovarian carcinoma			
		EPCAM	2p21					Urinary tract carcinoma			
								Small bowel carcinoma			
								Pancreas and hepato-biliary tract carcinoma			

Table 2 (*Continued*)

						Neurological manifestations		Nonneurological manifestations			
Syndrome	Incidence	Gene(s)	Locus	Inheritance	% de novo	CNS manifestations	PNS involvement	Other tumors	Skin	Eye	Other manifestations
CMMR-D	46 families reported in 2008	See LS	See LS	AR	Unknown (likely rare)	Medulloblastoma	Neurofibroma (rare)	Colorectal adenoma and carcinoma	Café-au-lait spots	Lisch nodules	
						Glioma		Hematological malignancies	Axillary freckling (rare)		
GS or NBCCS	1:57.000	*PTCH1*	9q31	AD	20–30	Medulloblastoma		Ovarian fibroma	Basal cell carcinomas	Cataract	Jaw keratocysts
		SUFU	10q24			Meningioma		Cardiac fibroma	Palmar and plantar pits	Coloboma of iris, choroid, and optic nerve	Vertebral/rib anomalies
						Macrocephaly		Ameloblastoma	Facial milia	Pigmentary retinal changes	Cleft lip/palate
						Intracranial calcifications (falx; tentorium; diaphragma sellae)		Rhabdomyomas			Preaxial or postaxial polydactyly
								Lymphoma			Lymphoma-mesenteric or pleural cysts

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CMMR-D, constitutional mismatch repair-deficiency syndrome; CNS, central nervous system; CS, Cowden syndrome; FAP, familial adenomatous polyposis; GIST, gastrointestinal stromal tumors; GS, Gorlin syndrome; HNPCC, hereditary nonpolyposis colorectal cancer; NBCCS, naevoid basal cell carcinoma syndrome; NF1, neurofibromatosis type 1; NF2, neurofibromatosis type 2; LFS, Li–Fraumeni syndrome; LS, Lynch syndrome; PNS, peripheral nervous system; VHL, Von Hippel–Lindau disease; TSC, tuberous sclerosis.

Methodology

We used four sources to obtain data for the overview: the Winter–Baraitser Dysmorphology Database (WBDD)[23]; the book *Gorlin's Syndromes of the Head and Neck*[8]; the *WHO Classification of Tumours of the Central Nervous System*[24]; and literature searches using PubMed. A detailed description of the methodology to obtain the data from the first two sources is available elsewhere.[25] In short, search terms derived from the diagnostic groups of the *International Classification of Childhood Cancer*[26] were checked in all syndromes from the WBDD and the Gorlin text. This search was focused on syndromes with morphological abnormalities in which malignant brain tumors occur in infants and/or children. This overview was supplemented with syndromes with either benign CNS tumors (e.g., meningioma) and/or tumor predisposition syndromes without unusual morphology (e.g., Li–Fraumeni Syndrome [LFS]). Data for this was derived from the *WHO Classification of Tumours of the Central Nervous System*,[24] Familial Cancer Database (http://www.facd.info), Gene Reviews (http://www.ncbi.nlm.nih.gov/books/NBK1116/), and directed searches for each of the CNS tumor types in this overview in PubMed (http://www.ncbi.nlm.nih.gov/pubmed). The CNS tumor types are named according to the *WHO Classification of Tumours of the Central Nervous System*.[24] To decrease the number of citations, we do not refer to original references but to the above main sources.

All syndromes resulting from our searches, in which at least once a CNS tumor was reported, have been included in this overview. In infrequent entities, it may remain uncertain whether the co-occurrence of a tumor is explainable by chance or has a true causal relation. Therefore, the present overview (►**Table 1**) may contain overestimations of associations between CNS tumors and syndromes. We have accepted this as in our opinion it is preferable to report all known possible associations instead of exclusion of true but presently uncertain associations.

In ►**Table 1**, only major (morphologic) manifestations are reported. Therefore, other manifestations that may be seen in children do not exclude the presence of either one of the mentioned syndromes.

Results

General

►**Table 1** contains all major brain tumor types occurring in children and the various syndromes that have been reported to be associated with these tumors. ►**Table 2** contains a short overview of all major tumor predisposition syndromes. The most frequent entities with a high chance to develop a brain tumor are summarized in ►**Table 2**. We provide short descriptions restricted to major presentations and co-occurring brain tumor of each of the entities below.

Neurofibromatosis Type 1

The first clinical suspicion of NF1 (Recklinghausen disease) should be raised when in an infant or child multiple café-au-lait spots are noticed. NF1 may not be obvious immediately:

Table 3 Genetic vocabulary

Genetic vocabulary
• Names of genes: These are derived from HGNC (http://www.genenames.org/) and are listed in capitals and italics to indicate their human origin (gene names in animal models are in small letters and italics). • Names of proteins: These may be similar to the gene which encodes for it, but can also be completely different (examples: the gene *NF1* encodes for the protein Neurofibromin; the gene *NF2* encodes for the protein Merlin). A protein name of human origin starts with a capital (protein names in animal models are without a capital). • Names of syndromes: These may be related to the name of the gene causing it, but can also be completely different (examples: mutations in *NF1* cause NF1; mutations in *TP53* cause LFS). • Syndrome: A pattern of anomalies, at least one of which is morphologic, known or thought to be causally (etiologically) related.[91] • Tumor predisposition syndrome: A syndrome in which a germline mutation leads to increased susceptibility (typically $>$ 5%) to develop a syndrome-related tumor. • Genotype: The primary DNA sequence, either overall or at a specific locus, of an individual or of the organ(s), tissue(s), or cell(s) of that individual. The genotype includes both the nuclear and mitochondrial DNA sequence, and is the counterpart of the phenotype.[91] • Phenotype: All morphologic and functional attributes of an individual, or of the organs, tissues, or cells of that individual.[91] • Penetrance: The proportion of genotypes that actually show the expected phenotype. Penetrance is frequently an age-dependent phenomenon, so individuals with a particular genotype can gradually develop (part of) the expected phenotype over time (example: in NF1 children are usually born with some café-au-lait spots but may develop more in time, and later during life also freckling, Lisch nodules, and neurofibromas may become evident). • Expressivity: The severity of the phenotype (examples: NF1 can show in a child all manifestations, but can be detected in its parent only by careful directed searches for café-au-lait spots and freckling, which can be present only in a very limited way). • Germline mutation: A mutation that occurs in all cells of the body including the germ cells. Therefore, the mutation is hereditary and can be passed on to offspring. • Somatic mutation: A mutation that occurs in any cell of the body except germ cells (example: a cell that acquires somatic mutations during life and undergoes malignant transformation to form a sporadic tumor). Therefore, the mutation is not hereditary and cannot be passed on to offspring. • De novo mutation: A germline mutation that has arisen in an individual and is not inherited from either parent. The chance for the parents to have another affected child is not increased, except in case of gonadal mosaicism. The affected child can transmit the abnormal gene to its own offspring (example: *NF2* mutations arise de novo in 50%, therefore only half of the NF2 patients can have a positive family history for NF2). • Mosaicism: A mutated gene is not present in all tissues of an individual, but only in (part of) the its cells (example: $\sim$ 30% of NF2 patients mutations are not detected in the blood as a result of somatic mosaicism, but only in an affected body part). • Gonadal mosaicism: A mutated gene is not present in all tissues of an individual, but only in (part of) the egg cells or sperm cells. The individual himself/herself does not show the phenotype and the mutated gene is not found in its blood, but can be passed on to offspring who will then have the mutated gene in all body cells and show the phenotype. If gonadal mosaicism is present, this can be passed on to more than a single child, so there is a recurrence risk for sibs of the affected child. Typically this recurrence risk is around 1% but in some entities it can be much higher (example: 6% in TSC). • Microdeletion syndrome: Genetic disorder caused by a deletion of a segment of chromosome (example: both NF1 and NF2 may be caused a deletion of a segment of a chromosome including the *NF1* or *NF2* gene). • Next-generation sequencing: A high-throughput method of sequencing, allowing sequencing the complete genome or large regions of the genome in a short period of time for acceptable costs. • Whole-exome sequencing: The sequencing of only the coding regions (exons) of the total genome of an individual and not the noncoding regions within the genes (introns) and between genes. All exons together are $\sim$ 1.5% of the total genome.

Abbreviations: HGNC, HUGO Gene Nomenclature Committee; LFS, Li–Fraumeni syndrome; NF1, neurofibromatosis type 1; NF2, neurofibromatosis type 2; TSC, tuberous sclerosis complex.

axillary or inguinal freckling appears during the first 5 years of age. Iris hamartoma (Lisch nodules) generally appear just after and are found only if specifically looked for at ophthalmological examination. Cutaneous neurofibromas are seen in most patients starting in puberty.[27] *NF1* mutations are highly penetrant, but expression is extremely variable. Approximately 15% of patients with NF1 develop a CNS tumor. Particularly, optic nerve astrocytoma is common, which only requires treatment if symptoms develop or progression occurs. Other gliomas seen in NF1 are pilocytic and diffuse astrocytomas (preferential localizations pons and cerebellum) and rarely glioblastoma. At T2-weighted magnetic resonance images (MRI) unidentified bright objects (UBO), previously wrongly tagged as hamartomas, can be noted in over 50% of NF1 patients. They are seemingly innocent and disappear with age. Neurofibromas are generally treated surgically if causing pain by nerve compression or for cosmetic reasons. Diffuse plexiform neurofibromas are generally hidden internally in close vicinity of organs, and can be difficult to detect and treat. Approximately 10% of NF1 patients develop malignant peripheral nerve sheath tumors (MPNST). Radical surgical resection is the mainstay of treatment of MPNST and adjuvant chemotherapy and/or radiotherapy should be considered. A limited (32%) 5-year overall survival in the context of NF1 is seen.[28,29] Also other, non-nervous system associated tumors and osseous and vascular

abnormalities occur more often in NF1 patients. In NF1 patients, exposure to diagnostic and therapeutic radiation should be minimized to avoid the risk of radiation-induced malignancies. With an extreme clinical variability even within families, the genotype-phenotype correlation is complex in NF1. A few correlations have been identified thus far. A more severe phenotype occurs in NF1 patients who have a microdeletion (5–10% of patients) due to a loss of approximately 1.5 Mb at 17q including the *NF1* gene, whereas a milder phenotype is observed in NF1 patients with a common 3bp in frame deletion in exon 17. Other genotype–phenotype correlations have been described for spinal neurofibromatosis, optic pathway gliomas, and Watson syndrome. The life expectancy of individuals with NF1 is about 8 years lower compared with the general population.[30]

A NF1-Noonan syndrome phenotype occurs in approximately 12% of individuals with NF1 and is caused by *NF1* mutations. Affected individuals have a phenotype that combines NF1 and Noonan syndrome including ocular hypertelorism, down-slanting palpebral fissures, low-set ears, webbed neck, and pulmonic stenosis.

Neurofibromatosis Type 2

The hallmark of NF2 is (bilateral) vestibular schwannoma, which typically present with hearing disabilities, tinnitus, and balance dysfunction in patients by their third decades. NF2 is generally considered an adult-onset disease, however, in childhood skin features (schwannomas and café-au-lait spots) and ocular findings (cataract, strabismus, and amblyopia) may be evident but remain often unrecognized.[31,32] Dermatological and ophthalmological manifestations can sometimes resemble NF1.[33,34] Furthermore in children, palsy due to mononeuropathy is an increasingly recognized finding. As most patients (50–75%) develop (often multiple) meningioma, any childhood meningioma should be considered as a possible early sign of NF2. Two-third of NF2 patients develop spinal tumors, both with extramedullary (schwannoma and less frequent meningioma) and intramedullary (ependymoma and rarely pilocytic or diffuse astrocytoma) localization. Penetrance is almost 100%. Truncating mutations have been associated with earlier onset and more NF2-associated tumors.[34] Furthermore, when NF2 presents in children, the phenotype is usually more severe because of symptoms of meningioma.[35] With earlier diagnosis and novel therapeutic strategies such as cochlear and brain stem implants, life expectancy and quality of life has improved considerably. Still, many NF2 patients have a limited survival (15 years after initial diagnosis).

Rhabdoid Tumor Predisposition Syndrome and Schwannomatosis

In early childhood, RTPS is characterized by an increased risk for developing malignant rhabdoid tumors (MRTs). MRTs may be localized in the kidney, extra renal but intra-abdominally or in the CNS. CNS-localized MRTs are called atypical teratoid/rhabdoid tumors (AT/RTs), which are highly malignant and have a limited survival, despite aggressive multimodality therapy (surgery, irradiation, and chemotherapy). AT/RTs generally present before the age of 3 years, an age at which radiation therapy is relatively contraindicated because of an increased vulnerability to long-term neurocognitive deficits.[36] Penetrance is highly variable.[13] In children with an AT/RT in which no *SMARCB1* mutation is found, germline mutations in *SMARCA4* may be considered.[37] In families with RTPS, choroid plexus carcinoma (CPC), infratentorial medulloblastoma and supratentorial primitive neuroectodermal tumors (PNETs) have been reported as well.[38] However, it is possible that these cases because of similar histologies have been misdiagnosed and may in fact represent AT/RTs with a prominent epithelial component, as was afterward shown for the medulloblastoma reported in that study.[39]

SMARCB1 germline mutations are also found in 40 to 50% of families with schwannomatosis (previously referred to as NF3).[40,41] The main distinction with NF2 is that schwannoma in RTPS are generally not localized at the nervus vestibularis.[41,42] At adult age, sometimes meningioma, preferentially located at the falx, may be seen.[43] At this moment, only three families have been described with a combined phenotype of both RTPS and schwannoma. This suggests that the combined phenotype is rare. However, if RTPS patients survive, they may suffer at adult age from schwannoma.[41] A genotype–phenotype correlation likely explains why not in all schwannomatosis families the risk for MRT is increased.[13] Germline mutations in *SMARCB1* and related genes have been found to cause Coffin–Siris syndrome,[44] but until now no individual with a molecularly confirmed syndrome diagnosis has developed an AT/RT malignancy.[45]

von Hippel–Lindau Disease

von Hippel–Lindau Disease (VHL) disease is characterized by hemangioblastomas of the CNS and retina, pheochromocytoma, renal cysts and clear cell carcinoma, and other visceral cysts. Penetrance of VHL is close to 100%. At the age of 65 years, most patients have VHL-related manifestations. However, the manifestations and severity are highly variable both within and between families. Although hemangioblastomas typically occur in young adults, the occurrence of a hemangioblastoma in a child or adolescent should point to VHL as multiple hemangioblastomas are likely to develop.[46] Most VHL patients have multiple hemangioblastomas, which are localized in the brain stem, spinal cord, and nerve roots, compared with sporadic hemangioblastomas which are generally localized in the cerebellum. Hemangioblastomas are frequently accompanied by cysts which can cause symptoms because of their rapid growth. To avoid cysts to recur, complete surgical removal of the hemangioblastomas is essential, and gamma knife treatment is not sufficient. On the basis of genotype, four different VHL phenotypes have been suggested to predict the likelihood to develop pheochromocytoma or renal cell carcinoma. Median life expectancy is significantly lower in VHL patients,[30] as approximately 70% of individuals with VHL develop renal cell carcinoma which is the major cause of death.

Tuberous Sclerosis Complex

Patients with tuberous sclerosis complex (TSC) develop multiple hamartomas, mainly in the brain (70%), heart (30%) and

eyes (50%), and renal (60%) and skin abnormalities (nearly 100%). At birth, hypomelanotic macules, sometimes only visible with a Wood lamp, may be present. Before the age of 15 years most children with TSC have manifestations.[47] Epilepsy (up to 80%), intellectual disability (40%), and behavioral problems due to cortical tubers, subependymal hamartomatous nodules and intracranial calcifications are frequently seen. Penetrance is thought to be 100%. TSC exhibits extreme variability in clinical findings both among and within families. The severe end of the spectrum is represented by the classic triad consists of seizures, intellectual disability, and angiofibroma. Patients with *TSC1* mutations are usually less severely affected than patients with *TSC2* mutations, and females tend to have milder disease than males. In 10 to 15% of individuals with TSC, usually within the first two decades of life, a subependymal giant cell astrocytoma (SEGA) may be detected. SEGA is a benign, slowly growing tumor, typically arising unilateral or bilateral in the wall of the lateral ventricles, and virtually pathognomonic of TSC.[48] Treatment of enlarging SEGAs may consist of mammalian target of rapamycin (mTOR) inhibitors; if size causes life-threatening neurologic symptoms neurosurgery is unambiguously indicated.

Li–Fraumeni Syndrome

LFS is characterized by multiple primary tumors in children and young adults. The predominant tumors are brain tumors, bone and soft tissue sarcomas, breast, and adrenocortical tumors. Half of LFS-associated malignancies are estimated to occur before the age of 30 years. Individuals with LFS are at increased risk of developing various types of generally highly malignant brain tumors (astrocytomas, glioblastomas, medulloblastomas, CPC). The median age of onset for brain tumors is 16 years, suggesting that more than half of LFS-associated brain tumors occur in children younger than 18 years. The risk for brain tumors has been reported to be increased if the *TP53* mutation lies in the DNA-binding loop that contacts the minor groove of DNA. Children with a CPC, who typically present at young age ($\leq$ 3 years), are at high risk to harbor a *TP53* germline mutation, even in the absence of a positive family history, due to de novo mutations.[49,50] In a recent report, *TP53* germline mutations were also found children with medulloblastoma of the sonic hedgehog subtype (SHH-MB) with chromothripsis.[51] In SHH-MB, typically presenting between 5 and 18 years of age, 12% of *TP53* germline mutations were identified.[52] Overall, LFS is known to give a high lifetime risk for a range of tumors: 93% in woman and 75% in men, with an estimated 30 to 40% risk for cancer in childhood and adolescence.[53] In LFS affected family members, the risk to develop a second or third malignancy was estimated to be 15 and 4%, respectively. For 30 childhood cancer survivors, these risks were considerably higher (57 and 38%). Various genotype–phenotype correlations have been reported. Because of the high risk to develop (multiple) malignant tumors, overall survival is limited. Preliminary studies have shown positive aspects of early diagnosis and surveillance in LFS patients for overall survival.[53] In LFS patients, exposure to diagnostic and therapeutic radiation should be minimized to avoid the risk of radiation-induced malignancies.

Gorlin Syndrome

Individuals with GS (nevoid basal cell carcinoma syndrome) have congenital abnormalities such as bifid or fused ribs or wedge-shaped vertebra ($>$ 50%), often macrocephaly ($>$ 50% above $>$ 97th percentile), sometimes cleft lip and/or palate (5%) and polydactyly (5%). Jaw keratocysts develop around their teens; sporadic reports of ameloblastoma arising in these are known. Generally, basal cell carcinoma of the skin are seen starting in adolescence or early adulthood, unless prior exposure to radiotherapy. Palmar and plantar pits can be seen in most patients (►**Fig. 2A**). Approximately 5% of GS patients present during their first years of life with a medulloblastoma. These medulloblastomas have desmoplastic histology with an expression pattern indicating activation of the sonic hedgehog signaling pathway and have a more favorable prognosis compared with their sporadic counterparts. Treatment of medulloblastoma exists of surgical resection, (intrathecal) chemotherapy and irradiation in indicated cases (e.g., metastatic cases or residual disease after surgery).[54] It has been suggested that young children presenting with medulloblastoma of nodular or desmoplastic histology need to be assessed for GS.[54,55] In *PTCH1*-negative children younger than the age of 3 years with a desmoplastic/nodular medulloblastoma, with and without other manifestations fitting GS, germline mutations in suppressor of fused homolog (*SUFU*) have been identified. Nontumor CNS manifestations include

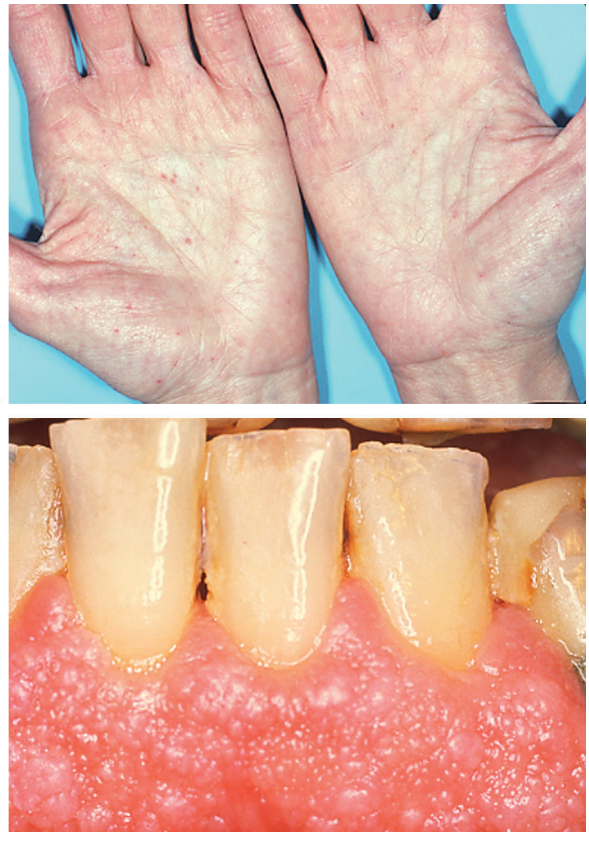

Fig. 2 Various nonneurological signs that can be seen at regular outpatient contacts in children (and/or their parents) with tumor predisposition syndromes causing brain tumors. Palmar pits as can be seen in Gorlin syndrome (A), and mucosal lesions at the gingiva in Cowden syndrome (B).

calcification of the falx cerebri or tentorium cerebellum, present in 90% of individuals by the age of 20 years. Meningioma are also reported to occur with an increased frequency in GS patients, furthermore, incidental cases of astrocytomas, oligodendroglioma, and craniopharyngioma have been reported. Penetrance is probably 100%, and expression is highly variable also within a single family. Except for an increased chance for intellectual disability in individuals with a microdeletion that include *PTCH1*, no genotype–phenotype correlations have been recognized. Patients with GS generally have a good prognostic outcome with (near) normal life expectancy.[30]

Cowden Syndrome

Cowden syndrome (CS) is one of the clinical manifestations of the phosphatase and tensin homolog (*PTEN*) hamartoma tumor syndromes and is characterized by multiple hamartomas and a high risk for benign and malignant tumors of predominantly the thyroid, breast, and endometrium. Patients with CS usually present by their 20s when mucocutaneous manifestations (►**Fig. 2B**) have been developed. Dysplastic gangliocytoma of cerebellum, also known as Lhermitte–Duclos disease (LDD), is the pathognomonic CNS manifestation of CS. LDD is a rare benign hamartomatous overgrowth composed of dysplastic ganglion cells in the cerebellum and usually arises at adult age, but affected children do occur. Sporadically occurring meningioma, medulloblastoma, gangliocytoma, and glioblastoma have been reported at adult age in patients with CS. Additional cerebral manifestations of CS include macrocephaly in 20 to 70% of cases (often skull circumferences are three standard deviation or more above the mean), hydrocephalus, intellectual disability, autism, and seizures. In children diagnosed with CS, neurodevelopmental evaluation is generally useful. An age-dependent penetrance has been observed, becoming complete in the late fourth decade. Because of the variable and often subtle external manifestations of CS, many individuals remain undiagnosed.[56] Both the presence of a germline mutation (in 85% of patients who fulfil the diagnostic criteria of CS a mutation is identified) and the location of the mutation are associated with severity of disease. Because of the risk to develop (multiple) malignant (extra-CNS) tumors survival is limited.

Turcot Syndrome

Turcot syndrome is characterized by the co-occurrence of a primary brain tumor and (multiple) colorectal adenoma(s) or carcinoma.[57] This association was described as possible result from two germline defects: mismatch-repair gene mutations or *APC* mutations. The pathology of the CNS tumor may help distinguish between the underlying genetic cause. Medulloblastoma are generally associated with *APC* mutations, whereas glioblastoma are usually associated with mismatch repair gene mutations.[58] It is important to note that in the original consanguineous family described by Turcot et al,[57] one child developed at 15 years multiple polyps with two adenocarcinoma and a spinal medulloblastoma and his sister had multiple polyps at 13 years and developed a glioblastoma at the of age 21 years. We think that this family suffered from constitutional mismatch repair-deficiency syndrome (CCMR-D) and that the term Turcot syndrome should be revised. Thus far, however, the term Turcot syndrome is being used for the co-occurrence of a primary brain tumor and (multiple) colorectal adenoma(s) or carcinoma. Of note, the association of brain tumors and colon cancer also may occur in LFS, but in this context the term Turcot syndrome is generally not used.

Lynch syndrome

Lynch syndrome (LS; previously known as hereditary non-polyposis colorectal cancer) predisposes to colorectal cancer and other tumor types (as endometrial, gastric, ovarian, urinary tract, small bowel, pancreas, breast, and sebaceous skin neoplasias). Also brain tumors are associated with LS.[58,59] Glioma, predominantly glioblastoma, but also ependymoma, high grade astrocytoma and oligodendroglioma, and incidental cases of ganglioma, meningioma, and hemangioblastoma are described in LS.[60,61] LS is quite common (3–5% of colorectal cancer cases are caused by LS), but a CNS tumor as primary manifestation, especially in children, has not been reported.[61] In adolescents with LS glioblastoma are sporadically described, this may be due to an unidentified constitutional mismatch repair-deficiency syndrome (CMMR-D).

Constitutional Mismatch Repair-Deficiency Syndrome

CMMR-D is caused by mutations of both alleles of one of the four mismatch repair genes. This causes a more severe phenotype with tumors at young age. Children resemble the NF1 phenotype with café-au-lait spots. A minority also have freckling, Lisch nodule, or neurofibroma, although generally no other NF1 features have been seen.[62] Children develop various tumors, predominantly hematological malignancies, brain tumors, and colorectal carcinoma around the age of 10 years. Other LS-associated and not LS-associated tumors are reported in CMMR-D (reviewed in Wimmer and Etzler[62]). The risk to develop a second malignancy is high.[62,63] Brain tumors observed at a mean age of 8 years are glioma, predominantly glioblastoma, medulloblastoma, and supratentorial PNET.[62] Pedigree analysis and sometimes parental consanguinity may point to autosomal recessive inheritance; however, with low penetrant mutations negative family histories for LS are common.[64]

Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) patients generally have a colorectum carpeted by hundreds to thousands of polyps, which without treatment will lead to colorectal carcinomas. Polyps are usually first detected in adolescence. However, in rare cases the first manifestation of FAP is a medulloblastoma in childhood. Children presenting with medulloblastomas having no evidence of polyps is of poor prognosis.[65] Extracolonic (non)neoplastic manifestations as osteoma, hepatoblastomas, ampulla of vater carcinomas, desmoid tumors, and epidermoid cysts are also associated with *APC* germline mutations[66] and are known as Gardner syndrome.[67] Efforts are being made to further delineate the observed genotype–phenotype correlation thus far. Several cases of craniopharyngioma in the cerebellopontine angle[68] and also meningioma[69,70] were reported in Gardner

syndrome. Gliomas have been incidentally reported as well, however, this may be erroneous because of confusion in Turcot syndrome. The life-expectancy in FAP patients has significantly increased in the past decennia because of preventive surgical options and ameliorated screening.

Discussion

In 5 to10% of children with cancer an underlying genetic syndrome has been suggested.[12,71,72] The development of new molecular techniques and more stringent diagnostic efforts may well cause a further increase of this percentage. This article demonstrates that also in children with brain tumors a significant number of syndromes can be diagnosed, with wide-spread consequences. Merks et al and Méhes[12,73] have recommended that all children diagnosed with a tumor should be assessed by a clinical geneticist or a pediatrician skilled in clinical morphology.

In some cases, the tumor type itself pinpoints to an underlying syndrome. An example is a child with a CPC, who has a high likelihood to have a germline mutation in *TP53* causing LFS even in the absence of a family history suggestive of LFS. Another example is formed by dysplastic gangliocytoma of cerebellum (LDD) which is a pathognomic CNS manifestation of CS. In other cases, various morphological abnormalities may pinpoint to recognizable syndromes.[11,12,14] Several CNS tumor predisposition syndromes (such as GS, NF1, NF2, TSC, and VHL) have dermatological manifestations, which can be expected due to their joint embryological origin and are referred to as neurocutaneous syndromes or phakomatoses.[71] Consultation of a dermatologist may be helpful in diagnosing such entities. Absence of skin anomalies does not exclude every phakomatosis completely however, and further studies may still be indicated. The same holds for various other anomalies in tumor predisposing syndromes: it is uncommon that a manifestation is an absolute prerequisite for an entity, and absence does not exclude the entity with certainty. Referral to a clinical geneticist, who is also specialized in obtaining detailed family histories and combines seemingly unrelated data from patients and family members, needs to be considered.[71] An example is the combination of medulloblastoma in a child and young age onset breast cancer and sarcoma in family members, which fulfils LFS criteria.

Once a clinical diagnosis is made or suspected, DNA diagnostics is generally subsequently performed to confirm this. Interpretation of molecular results, particularly of unclassified variants which may be identified in DNA diagnostics, can be difficult. The absence of a likely pathogenic variant in a gene which fits very well the clinical phenotype should not immediately lead to the rejection of the gene as the cause and asks for further analyses. We have also learned that we cannot always rely on investigating DNA derived from lymphocytes in the blood: sometimes a mutation is detectable only in other (tumor) tissues (mosaicism). Well-known examples are Proteus syndrome[74] and Cornelia de Lange syndrome,[75] but it has also been described in segmental NF1[76] and NF2.[77] Evaluation of results of recently developed techniques such as next-generation sequencing, especially whole-exome sequencing, asks for a careful interplay between molecular geneticist, bioinformatician and clinician. Whole-exome sequencing is used in diagnostics for well-known entities for which the causative gene was not identified.[51,78,79] Whole-exome sequencing may also be considered in families with a phenotype in which regular clinical and molecular diagnostics have failed to find the cause. A commonly used strategy is checking genes acting in the same pathway(s) as the genes known to cause such phenotypes. An example can be a patient with a phenotype that resembles CS but who has no detectable *PTEN* mutation. Whole-exome sequencing in such patients has learned that germline mutations in *PIK3CA* and *AKT1*, both belonging to the PTEN/PI3K/AKT pathway can be found.[74] Undoubtedly, further genes acting in this pathway will be found in other, clinically similar patients. The present molecular techniques allow for much more rapid detection of causative genes in rare entities and indeed the number of genes known to cause syndromes is growing enormously. It has led to the understanding that deletions of tumor suppressor genes can cause tumor predisposition phenotypes in the same way as mutations in these genes can do. We also understand now that clinically different entities can be caused by mutations in the same gene. For example, both Turcot and Gardner syndromes can be seen as tails of the FAP spectrum caused by *APC* mutations. In addition, mutations in *SMARCB1* are not only known to be responsible for RTPS and schwannomatosis, but also play a role in other diseases including Coffin–Siris syndrome (CSS).[44] In CSS no increased risk of schwannomas or MRTs has been noticed; however, a medulloblastoma in a child with CSS that was not molecularly confirmed has been described (►**Table 1**).[80]

Diagnosing tumor predisposition syndromes in children has several important consequences.[71] First, syndrome-associated malignancies may have a different prognosis and require specific treatments. Elevated risks for developing secondary malignancies after treatment of the primary tumor may influence the choice of chemotherapy or radiation. Optic nerve gliomas may serve as an example. If treatment is required, optic nerve gliomas are generally treated with radiotherapy, but in the context of NF1, radiotherapy, should be avoided.[81] In several other tumor predisposition syndromes (NF2, LFS, and GS) irradiation should be avoided as well, especially in childhood, as this may induce, accelerate, or transform tumors in children with an inactive tumor suppressor gene. Furthermore, increased intrinsic radiosensitivity and chemosensitivity to standard treatment can be seen in syndromes as Nijmegen breakage syndrome and ataxia telangiectasia (►**Table 1**), in which DNA repair genes are nonfunctional. In such entities, standard treatments need to be adjusted, otherwise severe unexpected, potentially fatal, toxicity may be observed.[82] Second, some tumor predisposition syndromes require screening for subsequent malignancies. The mere knowledge of the presence of any of the tumor predisposition syndromes listed in ►**Table 2** in a child will elicit increased vigilance to warning signs that may reflect an underlying malignancy. If radioimaging is indicated as part of

Table 4 Take-home messages

Take-home messages
• Genetic factors play a significant role in the etiology of brain tumors in children. • Every child who develops a brain tumor should be evaluated for signs and symptoms pointing to a syndrome with more widespread consequences and by taking a detailed family history. • A significant number of syndromes are associated with an increased risk to develop a brain tumor as a child. • Counselling patients with syndromes should also include information about (possible) liabilities to develop tumors and other syndrome manifestations both in the patients and their family members. • Screening recommendations are available only for the most prevalent tumor predisposition syndromes; screening should be determined on an individual basis after multidisciplinary consultation and taking data on the patient and family into account.

surveillance, MRI imaging is recommended instead of computed tomographic scanning due to the risk for radiation-induced malignancies in most tumor predisposition syndromes. Third, the other, nontumor manifestations of the syndrome may require surveillance or even preventive measurements as well. As example, NF1 individuals should be regularly checked for the development of hypertension due to a higher risk of vascular abnormalities. Finally, tumor predisposition syndromes are hereditary disorders, and siblings, parents, and other family members may be affected as well. Most tumor predisposition syndromes follow an autosomal dominant pattern of inheritance and have recurrence risks of 50% for offspring of an affected individual. If the germline mutation is not de novo, there is a recurrence risk of 50% for all other first degree family members. These family members should be informed about their increased risks to develop cancer, and preventive (screening) options. Prenatal diagnostics and preimplantation diagnostics are options to consider in order not to pass the tumor predisposition syndrome on to offspring. Genetic testing can bring along ethical issues,[83] insecurities on prognosis and quality of life, and patients and their relatives may be hesitant to get tested. Genetic counselling may help them to make the right choices for them in these ethical dilemmas.

A large amount of tumors has been sequenced in the search for therapeutic targets[84] and more studies will probably follow. In those studies, many somatic "driver" mutations are described; however, germline mutations are hardly reported and not generally checked for in research basis.[85] Our ameliorated knowledge of the etiology of cancer is increasingly translated into management strategies in tumor predisposition syndromes.[53] Textbooks (such as *Management of Genetic Syndromes* by Cassidy and Allanson)[86] and sites (such as Orphanet, http://www.orpha.net/consor/cgi-bin/home.php) are available that describe the general care for individuals with one of the various syndromes described above. Small molecule inhibitors, that act against a particular function of a protein causing tumors, have been developed and are being tested, also in tumor predisposition syndromes.[87] For example, a range of small molecule inhibitors are tested in clinical trials to inhibit growth of neurofibroma and vestibular schwannoma in individuals with NF1[88] and NF2, respectively.[89] In TSC, loss of function mutations in *TSC1*/*TSC2*, encoding for the proteins hamartin and tuberin, disrupt the complex of these two proteins and activate mTOR signaling. Indeed, mTOR inhibitors have shown to induce partial regression of SEGA in TSC.[90] It is conceivable that in the near future, such strategies are not only based on this knowledge but also on the specific mutation(s) found in an individual, and that personalized therapy will become possible for tumor predisposition syndromes, also in children (►**Table 4**).

Conflicts of Interest
There are no conflicts of interest to be reported.

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