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REVIEW

Hereditary Conditions Associated with Elevated Cancer Risk in Childhood

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Abstract—Widespread use of the next-generation sequencing (NGS) technologies revealed that a significant percentage of tumors in children develop as a part of monogenic hereditary diseases. Predisposition to the development of pediatric neoplasms is characteristic of a wide range of conditions including hereditary tumor syndromes, primary immunodeficiencies, RASopathies, and phakomatoses. The mechanisms of tumor molecular pathogenesis are diverse and include disturbances in signaling cascades, defects in DNA repair, chromatin remodeling, and microRNA processing. Timely diagnosis of tumor-associated syndromes is important for the proper choice of cancer treatment, genetic counseling of families, and development of the surveillance programs. The review describes the spectrum of neoplasms characteristic of the most common syndromes and molecular pathogenesis of these diseases.

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INTRODUCTION

Most tumors arise as a result of accumulation of a critical number of somatic mutations affecting oncogenes and tumor suppressor genes in a single clone of cells. In some cases, high risk of developing neoplasms is inherited from the parents as a Mendelian trait. A number of familial tumor syndromes, i.e., diseases in which tumors are the main and only manifestation, are well known. As a rule, such conditions first appear in adults. Examples include hereditary non-polyposis colorectal cancer (Lynch syndrome), hereditary breast and ovarian cancer, familial medullary thyroid carcinoma, etc. These diseases are well studied; methods for their diagnosis, approaches to treatment, and preventive monitoring have been developed. At the same time, it becomes obvious that the increased risk of neoplasms is also characteristic of a number of hereditary diseases of childhood. The data obtained by high-throughput next-generation sequencing (NGS) indicate that about 10% of tumors in children arise on the background of hereditary defects associated with certain genetic syndromes [1-3].

The spectrum of neoplasms in children differs significantly from that in adults. While the latter have a predominance of solid tumors of epithelial origin, hematological tumors (leukemias and lymphomas), tumors of the brain and spinal cord (medulloblastoma, rhabdoid tumors, gliomas), blastomas (retinoblastoma, nephroblastoma, neuroblastoma) and sarcomas (osteosarcoma, Ewing's sarcoma) are more often diagnosed in childhood [4]. These neoplasms can occur as a part of a wide range of hereditary diseases, including "classic" tumor syndromes, primary immunodeficiencies, phakomatoses, macrosomia syndromes, RASopathies, etc. Other characteristic features of the childhood tumors include a low tumor mutation burden (i.e., a relatively small number of mutations detected in tumor tissue), as well as increased frequency of somatic translocations leading to formation of the fusion proteins with oncogenic properties [5].

Abbreviations: EBV, Epstein–Barr virus; mTOR, mammalian target of rapamycin; MEK, mitogen-activated ERK kinase; PID, primary immunodeficiencies; RNase, ribonuclease; SHH, Sonic Hedgehog.

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Various criteria for identifying children with oncological diseases who need further genetic testing for hereditary mutations have been proposed [6-8]. These include, in particular, detection of the primary multiple tumors, presence in a child of any tumor of the adult type (e.g., colon cancer, ovarian cancer), presence of facial dysmorphism or congenital malformations, developmental delay, growth disturbances, abnormal skin pigmentation, hematological disorders, immunodeficiency, as well as unusually severe toxicity during chemo- and/or radiation therapy. It is also believed that the presence of a tumor of some histological types (atypical teratoid rhabdoid tumor, medulloblastoma, hepatoblastoma, etc.) with high probability points to the hereditary defect [6, 9].

In some cases, the tumor subtype is quite clearly associated with certain hereditary diseases: for example, hypodiploid acute lymphoblastic leukemia is characteristic of Li–Fraumeni syndrome [2], and the Sonic Hedgehog (SHH) subtype of medulloblastoma is typical of Gorlin syndrome with *SUFU* mutations [10]. However, most types of tumors are not absolutely syndrome-specific. Thus, one of the most common childhood tumors, Wilms tumor (nephroblastoma), usually occurs sporadically, but can also be part of the clinical manifestations of a number of hereditary diseases [11, 12]. Syndromic forms of Wilms tumor include Beckwith–Wiedemann syndromes, WAGR (Wilms tumor, Aniridia, Genitourinary abnormalities, and mental Retardation), Denis–Drash, Fraser, Perlman, Simpson–Golabi–Behmel syndromes, Fanconi anemia; less commonly, this tumor occurs in the patients with Bloom, DICER1, Li–Fraumeni syndromes, Mulibray nanism, and *PIK3CA*-associated syndromes [12]. In 10% of isolated cases of Wilms' tumor, hereditary mutations in the *REST*, *CHEK1*, *EP300*, *PALB2*, and *ARID1A* genes are detected [13].

CLASSIC TUMOR SYNDROMES

Retinoblastoma is a malignant tumor of the retina that arises from the primitive retinal stem cells or cone progenitors (Table 1). Observation of the patients with this disease allowed Alfred Knudson in 1971 to formulate the so-called "two-hit" hypothesis of tumorigenesis. According to him, two genetic events are required for the development of hereditary retinoblastoma: an inherited mutation of one allele (the first "hit") followed by somatic inactivation of the other allele (the second "hit") during retinal development. This hypothesis was brilliantly confirmed after the discovery of the *RB1* gene in 1986 and demonstration of its biallelic inactivation in the tumor cells [14]. The protein is a negative regulator of the cell cycle with mutations leading to loss of function and uncontrolled cell proliferation [15]. The gene was the first tumor suppressor gene identified and served as an archetypal example of the role of such genes in tumorigenesis.

The Li–Fraumeni syndrome was described over 50 years ago. Over time, classical criteria for the syndrome

Table 1. Classic tumor syndromes

Syndrome	Gene	The main tumor types in children
Li–Fraumeni syndrome	*TP53*	adrenocortical carcinoma; glioblastoma, astrocytoma, ependymoma, choroid plexus carcinoma, supratentorial primitive neuroectodermal tumors; rhabdomyosarcoma, mandibular osteosarcoma, medulloblastoma, hypodiploid acute lymphoblastic leukemia, lymphomas
Hereditary retinoblastoma	*RB1*	retinoblastoma
Gorlin syndrome	*PTCH1*, *SUFU*	medulloblastoma (especially in carriers of SUFU mutations), basal cell carcinomas of the skin
Congenital mismatch repair deficiency syndrome (CMMRD)	*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*	lymphomas, acute lymphoblastic and myeloid leukemias, pilomatrixomas, glioblastoma, astrocytoma, supratentorial primitive neuroectodermal tumors, medulloblastoma, colorectal cancer
Rhabdoid tumor predisposition syndrome	*SMARCB1*, *SMARCA4*	atypical teratoid/rhabdoid tumor of the central nervous system, extracranial malignant rhabdoid tumors (head and neck, paravertebral muscles, liver, bladder, mediastinum, abdominal cavity, pelvis, heart, kidneys); small cell carcinoma of the ovary, hypercalcemic type
DICER1-associated tumor syndrome	*DICER1*	pleuropulmonary blastoma, cystic nephroma; less common: ciliary body medulloepithelioma, nasal chondromesenchymal hamartoma, fetal rhabdomyosarcoma, pituitary blastoma, pineoblastoma, central nervous tissue sarcoma, presacral malignant teratoid tumor

were significantly supplemented: in particular, it turned out that the presence of a positive family history of early cancers or sarcomas is not critical [16]. At the same time, detection of the rare histologic varieties of pediatric tumors is of great diagnostic value (Table 1); the probability of detecting hereditary *TP53* mutations is especially high in the case of adrenocortical carcinomas, choroid plexus carcinomas [17], and anaplastic rhabdomyosarcomas [18]. The p53 protein is the guardian of the genome: in response to DNA damage, it initiates transcription of numerous genes involved in the regulation of the cell cycle, DNA repair, apoptosis, and metabolism. Apparently, up to 1.5% of childhood tumors are associated with germline mutations in *TP53* [3]; at the same time, interpretation of clinical significance of the hereditary variants of this gene is challenging due to the rather high population frequency and varying penetrance [16].

The Gorlin syndrome is caused by the hereditary mutations in the Patched1 (*PTCH1*) and Suppressor of fused (*SUFU*) genes associated with the SHH-mediated signaling cascade. The *PTCH1* product is the receptor for SHH; binding of these molecules leads to the change in activity of Smo (smoothened). Normally, PTCH1 is a Smo repressor; in the case of mutation, a signaling complex consisting of Gli-1 (glioma-associated oncogene) and SUFU is activated. In tumors, loss of heterozygosity for the normal allele of *SUFU* and *PTCH1* and activation of SHH signaling, leading, in particular, to inhibition of apoptosis, has been demonstrated [19].

Vast majority of the hereditary tumor syndromes have an autosomal dominant mode of inheritance. A few exceptions include constitutional mismatch repair deficiency (CMMRD) syndrome. It is known that the heterozygous mutations in the mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) cause colon and endometrial carcinomas in the structure of Lynch syndrome [20]. Biallelic lesions of these genes are much less common and are associated with the development of a wide range of tumors (primarily hematological and brain neoplasms) with a very early onset. Patients with café-au-lait spots on the skin, Lisch nodules on the iris, and neurofibromas make this disease similar to the type 1 neurofibromatosis. There is a certain association between the genotype and phenotype: for example, hematological tumors occur more often in children with *MLH1* and *MSH2* defects than in those with *MSH6* and *PMS2* mutations, while the latter are more likely to develop brain neoplasms [21].

The syndrome of predisposition to rhabdoid tumors is associated with mutations in the subunits of ATP-dependent chromatin-remodeling complex SWI/SNF (BAF) involved in cell differentiation and maintenance of stem cell pluripotency [22]. Obviously, the development of neoplasms is not associated with violation of the stability of the genome, since the rhabdoid tumors are characterized by an unusually low tumor mutation burden [23]. Considering that this complex interacts with the promoters of a huge number of genes, the mechanism of tumor formation is apparently not associated with any single signaling cascade, but rather is caused by epigenetic disturbances in transcriptional regulation [24].

The *DICER1* gene associated with the wide range of benign and malignant childhood tumors plays an important role in protein translation. Its product is RNase (ribonuclease) III, which is required for microRNA (miRNA) production by cutting the pre-miRNA or double-stranded RNA. In turn, miRNAs, interacting with messenger RNAs (mRNAs), are involved in the regulation of expression of more than 30% of all protein-coding genes [25]. Most tumors arising in the structure of this syndrome result from combination of the hereditary loss-of-function mutation and acquired somatic missense mutation in one of the five "hot spots" of the RNase IIIb RNase domain [26]. In the patients with pleuropulmonary blastoma and other tumors, mosaicism in missense mutations in the same "hot spots" has also been described, and it is associated with more severe course of the disease, early onset, and formation of multiple primary tumors [27].

PRIMARY IMMUNODEFICIENCIES

Primary immunodeficiencies (PID) or inborn errors of immunity (IEI) are an extremely heterogeneous group of genetic defects of the immune system, leading to the increased incidence of infectious, oncological, and autoimmune complications [28, 29]. Up to 25% of children with primary immunodeficiencies suffer from malignant neoplasms [30]; moreover, cancer is the second leading cause of death in the PID patients after infections [31]. Often, development of a tumor is one of the first clinical manifestations of immunodeficiency. Approximately 60-70% of tumors that occur on the background of PID are represented by lymphomas and leukemias [32].

The risk of tumor development varies greatly depending on the specific form of PID [29]. High oncological risk is typical for the patients with impaired humoral (common variable immune deficiency, X-linked agammaglobulinemia) or cellular immunity (severe combined immune deficiency, X-linked lymphoproliferative syndrome, Wiskott–Aldrich syndrome), as well as with DNA repair defects. In most PID patients with tumor manifestations, the function of B-lymphocytes is impaired to varying degrees, while the T-cell function may be completely or partially intact. Existing data demonstrate that the patients with primary defects of antibody formation, as a rule, have the greatest number of functional capabilities necessary for the process of tumorigenesis (hallmarks of cancer) [33].

Despite unquestionable contribution of the compromised cancer immunosurveillance to the tumor development, the internal causes of oncological predisposition in the PID patients are not universal. These include

various disturbances in the processes of differentiation, apoptosis, signaling interactions, metabolism and reorganization of the cytoskeleton of immune cells, as well as mechanisms responsible for chromosomal stability, telomere maintenance, and DNA repair [34, 35].

In addition, an important role is played by the disruption of protection against viruses. In particular, the Epstein–Barr virus (EBV) is involved in pathogenesis of a number of lymphoproliferative diseases, hematological tumors, and some carcinomas [36]. EBV has an increased affinity for B-lymphocytes, which explains predominance of the B-cell EBV-associated lymphomas. The Epstein–Barr virus triggers excessive proliferation of the antibody-producing B cells, followed by induction of the cellular immune response associated with cytotoxic T cells. Absence of the normal cytotoxic response leads to the EBV-mediated B cell proliferation. For example, in the X-linked lymphoproliferative syndrome, defect in the signaling lymphocyte-activating molecule (SLAM)-associated SAP protein results in severe impairment of the cytotoxic lymphocyte function, while the healthy EBV carriers are usually asymptomatic. Another form of the lymphoproliferative syndrome is associated with the hereditary defect in the *XIAP* gene. The product of this gene inhibits caspases, preventing cell apoptosis; dysfunction leads to the immune imbalance and chronic inflammation, mainly due to hyperexpansion of the virus-specific T-lymphocytes in response to EBV infection [37].

The Wiskott–Aldrich syndrome refers to the combined immunodeficiencies and is associated with mutations in the *WAS* gene. The product of this gene is involved in reorganization of the actin cytoskeleton, which is necessary for formation of immunological synapses, ensuring cytotoxicity of the natural killers (NK), chemotaxis, and chemokinesis [38].

An increased risk of tumor development in the case of DNA double-strand break repair defects is associated with the decrease in effectiveness of immune surveillance due to defects in the development of T- and B-cells, decrease in the diversity of the clonal repertoire, impaired proliferation of lymphocytes, transformation of B-cells, as well as their immortalization under the influence of EBV [39]. Direct induction of point mutations, translocations, and chromothripsis is also possible [40], which disrupts stability of the genome and increases likelihood of the malignant transformation.

Many PID types are associated with disruption of the important processes affecting T- and B-lymphocytes including V(D)J recombination, antibody class switching, and somatic hypermutation [41]. These events, involving endogenous generation and subsequent repair of the DNA double-strand breaks, are critical for normal development and maturation of the immune system.

In particular, V(D)J recombination is initiated by binding of RAG1 and RAG2 molecules to the signal sequences flanking the V, D, and J regions. The DNA double-strand breaks are formed with the ends stabilized by hairpin structures [42]. After phosphorylation by the catalytic subunit of the DNA–protein kinase complex (DNA–PKc), the Artemis protein, encoded by the *DCLRE1C* gene and having endonuclease activity, is involved in hairpin elimination [43]. Mutations that cause loss of the RAG1/2 or DCLRE1C function, interfering with normal development of T- and B-lymphocytes, are the cause of severe combined immunodeficiencies. Double-strand breaks are eliminated due to involvement of the proteins participating in non-homologous end-joining of DNA ends (Non-Homologous End-Joining, NHEJ), defects in some of the molecules involved in these processes (Artemis, DNA-PKcs, LIG4, Cernunnos) are also associated with some PID types.

Syndromes with chromosomal instability, primarily associated with recognition of the DNA double-strand breaks, deserve special attention [44]. The patients with ataxia–telangiectasia have the highest risk of neoplasms (Table 2): tumors are observed in 25% of the patients [45]. The *ATM* gene product serves as a sensor in recognition of the DNA double-strand breaks; mutations lead to the decrease in ability to activate the cell cycle checkpoints in response to exposure to ionizing radiation [46]. Leukemias and lymphomas are especially common; the risk of these diseases is tens and even hundreds of times higher than the population risk [47]. Unfortunately, prognosis for the development of tumors is usually very poor: while the average 5-year life expectancy in children with Hodgkin's lymphoma exceeds 90%, the average survival of patients with ataxia–telangiectasia is about 3 months, regardless of the presence or absence of treatment [47, 48].

The Bloom syndrome (Table 2) is associated with biallelic mutations in the *BLM* gene, which encodes a protein of 1417 amino acids and belongs to the RecQ DNA helicase subfamily. The BLM protein plays an important role in maintaining genome stability by being a DNA damage sensor and recruiting other repair proteins to the site of the defect [49]. The BLM helicase ensures accuracy of homologous recombination by destroying Holliday junctions and thus preventing crossover between the sister chromatids [50]. In addition, it controls regression of the stopped replication fork [51]. Participation of BLM in maintaining the structure of telomeres has been described [52]. Impaired helicase function leads to the high level of homologous recombination of chromosomes. This is manifested as an increase in the non-sister chromatid exchange, elevation in the number of quadriradial configurations in the lymphocyte culture, and appearance of the chromosomal breaks and rearrangements, which can be detected during cytogenetic studies. Breast carcinomas associated with the BLM defect do not show loss of heterozygosity (LOH) of the *BLM* locus, which suggests development of the tumors by the mechanism of haploinsufficiency [53, 54].

Table 2. Primary immunodeficiencies

Disease	Genes	Main symptoms	The main tumor types in children
Severe combined immune deficiency (SCID)	*IL2RG*, *JAK3*, *ADA*, *IL7RA*, *RAG1*, *RAG2*, *DCLRE1C/Artemis*, *NHEJ1/Cernunnos*, *ZAP70*	severe infections of the respiratory and digestive tract; candidiasis, chronic diarrhea, poor growth; opportunistic infections	Non-Hodgkin's and Hodgkin's lymphomas, EBV-associated lymphoma, Burkitt's lymphoma, leukemias, multiple leiomyomas of the kidneys and lungs
Wiscott–Aldrich syndrome	*WAS*	bleeding diathesis, eczema, recurrent bacterial and viral infections; microthrombocytopenia	B-cell lymphoma, leukemia, astrocytoma, Kaposi's sarcoma, leiomyomas
X-linked lymphoproliferative syndrome	*SH2D1A, XIAP*	severe course of EBV – and other viral infections; hemophagocytic lymphohistiocytosis	Hodgkin's and non-Hodgkin's lymphomas
Ataxia–telangiectasia	*ATM*	progressive ataxia, dysarthria, oculomotor apraxia, choreoathetosis; skin and conjunctiva telangiectasias; frequent infections	lymphomas, leukemias
Bloom syndrome	*BLM*	pre- and postnatal growth delay, deficiency of subcutaneous fat, sun-induced facial and skin erythema; infections of the middle ear and respiratory tract	acute lymphoblastic and myeloblastic leukemias, lymphomas, Wilms tumor, medulloblastoma
Nijmegen syndrome	*NBN*	microcephaly, intrauterine growth retardation, short stature, developmental delay; recurrent respiratory infections	lymphomas (mainly B-cell), acute lymphoblastic and myeloid leukemia; brain tumors (medulloblastoma, glioma), rhabdomyosarcoma
Fanconi anemia	more than 20 *FANC* genes	short stature, microcephaly, skin pigmentation, skeletal malformations of the upper and lower extremities, genitourinary tract anomalies, pancytopenia	acute myeloid and lymphoblastic leukemia

The patients with Nijmegen breakage syndrome have a characteristic phenotype (short stature, "bird-like" face, microcephaly) and have severe impairment of humoral and cellular immunity [55]. The nibrin protein (NBN/NBS1) is a part of the MRE11-RAD50-NBS1 (MRN) complex, which plays an important role in response to the main types of cellular stress: DNA damage in the form of double-strand breaks, arrest of replication forks, telomere dysfunction, and viral invasion [56]. It is noteworthy that almost all the patients with Nijmegen syndrome are homozygous for the *NBN* c.657_661del allele, which occurs with high frequency in Eastern Europe, including Russia [57, 58]. Somatic loss of the normal allele seems to be uncharacteristic of the tumors developing in the carriers of *NBN/NBS1* mutations [54, 59].

Patients with the Fanconi anemia have a variety of clinical manifestations, including short stature, skin spots, microcephaly, anomalies of the upper and lower extremities, and pancytopenia. High frequency of hematological and solid tumors is characteristic for those patients with acute myeloid leukemia being the most common [60]. The disease has very high genetic heterogeneity. More than 20 genes responsible for the development of Fanconi anemia have been described; vast majority of the cases are inherited in an autosomal recessive manner. Function of the Fanconi anemia proteins is associated with the repair of interstrand DNA cross-links that prevent replication, as well as with regulation of the cell cycle checkpoints and remodeling of replication forks in response to cellular stress [61]. Thus, disruption

of these molecules leads to genome instability and promotes tumorigenesis.

It is noteworthy that the biallelic damage to the *ATM*, *NBN*, *BLM*, *FANC* genes is the direct cause of childhood genetic diseases combining infectious and tumor manifestations, while heterozygotes (carriers of mutations) are characterized by the increased risk of some solid tumors with late onset [62-65].

RASOPATHIES

RASopathies are a group of diseases associated with hyperactivation of the components of RAS/MAPK signaling cascade, which plays a key role in the cell growth, proliferation, differentiation, and apoptosis. RASopathies include autosomal dominant Noonan, Costello, cardiofaciocutaneous, and CBL syndromes, characterized by proportional short stature and specific facial dysmorphisms (Table 3).

Increased oncological risk is by no means characteristic of all the diseases of this group. Up to 10% of the patients with Noonan syndrome suffer from a transient myeloproliferative disease in their childhood. In most cases, the condition resolves spontaneously, but some patients progress to juvenile myelomonocytic leukemia (JMML). Transition to leukemia is typical for the patients with *PTPN11* and *KRAS* mutations, but not for those with defects in other genes [66]. The *PTPN11* gene encodes the non-receptor tyrosine phosphatase SHP2. *PTPN11* defects are the most common cause of Noonan syndrome; mutations, as a rule, lead to permanent activation of the catalytic PTP domain of SHP2, enhancing activity of the RAS/MAPK signaling cascade [67]. The *KRAS* mutations lead to activation of the same signaling cascade in two ways, either through reduced intrinsic or GAP-dependent GTPases activity or through changes in the affinity of guanine nucleotides for the RAS protein [68].

RASopathy also includes such common disease as type 1 neurofibromatosis associated with mutations in the *NF1* gene. The product of this gene, neurofibromin, is a negative regulator of RAS; dysfunction leads to the reduced GTPase activity of the protein and, consequently, to the excessive activity of the GTP-bound proteins of RAS family [69].

SYNDROMES WITH MACROSOMIA

The Beckwith–Wiedemann syndrome is characterized by macrosomia, hemihyperplasia, macroglossia, and abdominal wall defects (Table 4). The most common cause of this syndrome is a disturbance of imprinting of the chromosome region 11p15.5; rarer are *CDKN1C* mutations affecting the maternal allele [70]. The patients are more than 600 times more likely to have nephroblastoma (Wilms tumor); also, they suffer from hepatoblastoma, and, less often, neuroblastoma, embryonic rhabdomyosarcoma, and tumors of the adrenal cortex [71].

Pathogenesis of the tumors is associated with the arrest of cell maturation in the specific cell populations during certain periods of embryonic development, i.e., with interruption of the normal nephrogenesis. Depending on the stage when the disorder occurred, nephroblastoma will contain different proportions of blastematous, epithelial, and stromal components. The highest risk of developing the Wilms tumor is characteristic of the variant of Beckwith–Wiedemann syndrome caused by hypermethylation of the imprinting center 1 (IC1) or uniparental disomy 11p15.5. As a result, expression of the insulin-like growth factor IGF2 is enhanced, followed by hyperactivation of the signaling cascade that promotes cell growth and proliferation [72]. At the same

Table 3. Syndromes with macrosomia (overgrowth syndromes)

Disease	Genes	Main symptoms	The main tumor types in children
Beckwith–Wiedemann syndrome	11p15.5 locus (loss of imprinting, deletions and duplications); *CDKN1C* (mutations)	macrosomia, hemihyperplasia, macroglossia, omphalocele, visceromegaly, neonatal hypoglycemia	Wilms tumor, hepatoblastoma, less often – embryonic rhabdomyosarcoma and adrenocortical carcinoma
Simpson–Golabi–Behmel syndrome	*GPC3*, *GPC4*	macrosomia, abdominal wall defects, macroglossia, facial dysmorphia, mental retardation, congenital heart disease	Wilms tumor, hepatoblastoma, hepatocellular carcinoma
Perlman syndrome	*DIS3L2*	polyhydramnios, postnatal ascites; neonatal macrosomia, hemihyperplasia, facial dysmorphia, macrocephaly, hyperinsulinism	Wilms tumor

Table 4. RASopathies

Disease	Genes	Main symptoms	The main tumor types in children
Noonan syndrome	*PTPN11*, *SOS1*, *RAF1*, *RIT1*, *KRAS*, *NRAS*, *BRAF*, *MAP2K1*, *RRAS*, *RASA2*, *A2ML1*, *SOS2*, *LZTR1*	short stature, congenital heart defects, facial dysmorphism, cardiomyopathy	juvenile myelomonocytic leukemia (JMML), acute lymphoblastic leukemia, dysembryoplastic neuroepithelial tumor, neuroblastoma, rhabdomyosarcoma
Costello syndrome	*HRAS*	facial dysmorphism, developmental delay, cardiomyopathy, papillomas	embryonic rhabdomyosarcoma, neuroblastoma, bladder cancer
CBL-syndrome	*CBL*	Noonan-like phenotype	juvenile myelomonocytic leukemia (JMML)
Neurofibromatosis type 1	*NF1*	multiple café-au-lait spots on the skin, freckles in the armpits and groin, neurofibromas, Lisch nodules	optic nerve gliomas, peripheral nerve tumors (neurofibromas, malignant peripheral nerve sheath tumors), pheochromocytoma, gastrointestinal stromal tumors, juvenile myelomonocytic leukemia (JMML), osteosarcoma, rhabdomyoma

Table 5. Phakomatoses

Disease	Genes	Main symptoms	The main tumor types in children
Tuberous sclerosis	*TSC1*, *TSC2*	hypopigmented skin macules, facial angiofibromas, developmental delay, epilepsy	subependymal giant cell astrocytoma (SEGA), cardiac rhabdomyomas
Neurofibromatosis type 2	*NF2*	a few skin café-au-lait spots, vestibular schwannomas (pathognomonic sign)	schwannomas, meningiomas, ependymomas, gliomas

time, oncological risk in the patients with the Beckwith–Wiedemann syndrome associated with the loss of methylation of the imprinting center 2 (IC2) is significantly lower [73].

The X-linked Simpson–Golabi–Behmel syndrome is in many respects similar to the Beckwith–Wiedemann syndrome. Specific manifestations include hypertelorism, coarse facial features, and mental retardation. Pathogenesis is based on the defect in biosynthesis of the heparan sulfate proteoglycans on the cell surface. Functional role of the glypican-3 (product of the *GPC3* gene) as a negative regulator of IGF2 and FGF2 expression has been shown [74]. The patients have the highest risk of Wilms tumor, but cases of other tumors (hepatoblastoma, hepatocellular carcinoma) have also been described [75].

Much less common is the Perlman syndrome, an autosomal recessive disorder associated with the *DIS3L2* mutations. The product of this gene is a component of the exosome complex and, having the 3'-5' exoribonuclease activity, regulates RNA processing and degradation [76]. The disease is characterized by very high perinatal mortality, and among the survivors, there is a high risk of Wilms tumor [77].

PHAKOMATOSES

Phakomatoses (from the Greek "phakos" – spot) or neurocutaneous dermatoses represent a group of diseases involving derivatives of the embryonic ectoderm, usually affecting skin and central nervous system (Table 5).

Tuberous sclerosis is a fairly common genetic disease characterized by the development of hamartomas of various organs (brain, kidneys, skin, heart, retina, lungs) and has an autosomal dominant mode of inheritance. The tuberous sclerosis genes, *TSC1* and *TSC2*, are classic tumor suppressors. The hamartin protein (product of the *TSC1* gene) in complex with tuberin (product of the *TSC2* gene) are negative regulators of the mTOR-mediated signal transduction pathway that plays a critical role in regulating cell growth, size, shape, and

proliferation. Mutations lead to the increase in activity of the mTORC1 complex, which, in turn, enhances protein translation, accelerates cell growth, enhances nucleotide synthesis, and reduces autophagy [78]. Observations obtained in relation to the tumors arising in the structure of tuberous sclerosis indicate that their pathogenesis fits into the "2-hit model" of carcinogenesis. In addition to the hereditary defect of the *TSC1* or *TSC2* genes, there is a deletion of the second intact allele in some somatic cells, which leads to formation of a tumor (hamartoma) of the corresponding organ [79, 80].

Neurofibromatosis type 2 is characterized by the development of bilateral vestibular schwannomas; few café-au-lait spots are observed on the skin of the patients. Pathogenesis is based on mutations in the *NF2* gene encoding the merlin protein, which is involved in stabilization of cytoskeleton by inhibiting the PI3K/Akt, Raf/MEK/ERK, and mTOR signaling cascades [81]. Although the mechanism of tumor development is not entirely clear, the phenomenon of loss of heterozygosity at the *NF2* locus has been demonstrated for the vestibular schwannomas and meningiomas [82].

TREATMENT

Knowledge of the molecular pathogenesis of childhood tumors is important in relation to several practical aspects. In particular, treatment of some neoplasms can be accompanied by the extremely pronounced toxicity or insensitivity to the treatment [4]. In addition, the ongoing drug or radiation therapy can induce development of the secondary tumors. This phenomenon has been described in the Li–Fraumeni syndrome [17, 83], retinoblastoma [84], and type 1 neurofibromatosis [85]. In the treatment of patients with DNA repair defects, such as Bloom's syndrome, ataxia–telangiectasia, Fanconi's anemia, Nijmegen's syndrome, the reduced dosage of chemotherapy and exclusion of radiation therapy are recommended [86, 87]. Treatment of the tumors arising in the PID patients requires control of infections, such as pneumonia caused by *Pneumocystis jirovecii* [88].

In some cases, it has been possible to develop drugs targeting the key signaling pathways. Prominent examples are the MEK inhibitor selumetinib, used in the patients with neurofibromatosis type I [69], or everolimus, an mTOR inhibitor successfully applied in the treatment of tuberous sclerosis [89] and RASopathy [90].

Screening strategies for the tumor syndromes in children are being developed [91]. These measures are considered necessary if the chance of developing a childhood tumor exceeds 5% [92]. The results of observation of children with the Li–Fraumeni syndrome and Beckwith–Wiedemann syndrome demonstrate that early detection of the tumors leads to a significant improvement in overall survival [93, 94].

CONCLUSION

The study of tumors arising in the structure of hereditary syndromes makes it possible to expand the existing ideas about the causes of childhood neoplasms. Timely detection of the carriage of germinal mutations increases likelihood of early or even presymptomatic diagnosis, makes it possible to assess the risk of getting the disease in the relatives of the patients, and also stimulates development of the targeted therapy. A detailed description of the "molecular portraits" of tumors provides hope for the discovery of new prognostic and predictive markers contributing to personalization of the treatment. At the same time low tumor mutation burden generally characteristic of the childhood tumors indicates the need for a more meticulous study of the disturbances in epigenetic regulation processes, such as histone and CpG island methylation. Obviously, the prospects for studying pediatric neoplasms are associated with integration of the data obtained using genomic, transcriptomic, and epigenomic approaches.

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