REVIEW

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Genetics of congenital solid tumors

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Abstract

When we discuss the genetics of tumors, we cannot fail to remember that in the second decade of the twentieth century, more precisely in 1914, Theodore Boveri defined for the first time the chromosomal bases of cancer. In the last 30 years, progresses in genetics have only confirmed Boveri's remarkable predictions made more than 80 years ago. Before the cloning of the retinoblastoma 1 (*RB1*) gene, the existence of a genetic component in most, if not all, solid childhood tumors were well known. The existence of familial tumor aggregations has been found much more frequently than researchers expected to find at random. Sometimes, the demonstration of this family predisposition was very difficult, because the survival of children diagnosed as having a certain tumor, up to an age at which reproduction and procreation is possible, was very rare. In recent years, advances in the diagnosis and treatment of these diseases have made it possible for these children to survive until the age when they were able to start their own families, including the ability to procreate. Four distinct groups of so-called cancer genes have been identified: oncogenes, which promote tumor cell proliferation; tumor suppressor genes, which inhibit this growth/proliferation; anti-mutational genes, with a role in deoxyribonucleic acid (DNA) stability; and micro-ribonucleic acid (miRNA) genes, with a role in the posttranscriptional process.

Keywords: solid tumor, cancer genes, oncogenes, suppressor genes.

⊟ Introduction

Cancer is defined as a different group of diseases that have as common denominator the disruption of the mechanisms of proliferation, differentiation, and cell growth. It is among the most common causes of death, being placed, in developed countries, in second place after heart diseases. Different risk factors are involved in the appearance of cancer, such as: environmental factors, age, gender and last, but not least, genetic predisposition. From the end of the twentieth century, it was known that neoplasia is a complex condition caused by genetic and epigenetic changes in multiple genes [1–3].

Extremely rapid advances in genetics, especially after the design of the human genome, the emergence and development of molecular genetics technologies that can analyze the human genome, transcriptome, and proteome of normal and cancer cells and, last, but not least, the sequencing and mapping of the whole human genome has produced a real revolution in the diagnosis and treatment of cancer. Until 2017, a number of 612 genes involved in the pathogenesis of cancer were known.

Aim

The present paper aims to review the main genetic changes that occur in solid tumors of the child.

⊟ Risk factors for the appearance of cancer

Carcinogenesis defines the general process of cancer formation, this process being multistage, involving the accumulation over time of mutations and epigenetic alterations that will produce changes of the genes. In fact, in carcinogenesis there is an imbalance between proliferation and cell death. At adults, environmental factors, and lifestyle (smoking, overeating, sedentary lifestyle, etc.) play a major role in cancer, unlike children where they play an insignificant role.

Genetic factors are incriminated in both the cancerous pathology of the adult and the child. The main genes involved are oncogenes and tumor suppressor genes. In addition to these two main categories of genes, other genes are also discussed, such as: stability (anti-mutational) genes and micro-ribonucleic acid (miRNA) genes. Deoxyribonucleic acid (DNA) alteration is considered, in 70% of cases, the main factor involved in the etiology of cancer. Alterations in DNA consist of changes in its chemical structure, while mutations occur in changes in the DNA sequence, with different subsequent consequences. The genetic predisposition caused by germline mutations is responsible for 30% of cancers (causes hereditary or genetically predisposed cancers).

All these mechanisms (somatic mutations, germinal and epigenetic changes) cause instability of the genome decreasing its ability to remain stable, the occurrence of unrepaired DNA alterations resulting in new somatic mutations and epigenetic alterations.

Oncogenes

Proto-oncogenes are normal genes with a role in regulating cell division (causes cell growth, profiling and inhibits apoptosis). They encode proteins located in various cellular compartments that are expressed at different stages of the cell cycle. As a result of structural or functional changes with overregulation of function ("gain of function"), protooncogenes become oncogenes that cause marked cell proliferation, inhibit cell death, and cause malignant transformation of the carrier cell. The gene product of an oncogene is called an oncoprotein. The mutations that determine the activation of oncogenes are dominant, with "gain of function", practically, for the activation in cancer, another major event is necessary (mutations in other genes) [4].

Oncoproteins are classified, according to their role and location in the cell into seven classes:

(*i*) Cell growth factors: SIS, HST, INT1, and INT2. They encode proteins discharged into the extracellular space. They contribute to malignancy by permanently activating membrane receptors that normally initiate proliferation or differentiation.

(*ii*) Protein kinases, with or without receptor function: ERBB1, KIT. Up to date, 30% of the described oncogenes encode proteins with kinase activity, mostly growth factor receptors. In the absence of specific ligands, these oncoproteins phosphorylate the tyrosine residues that provide, permanently and uncontrolled, intracellular signals, thus triggering unlimited proliferation. Examples: ERBB1 specifies the kinase domain of the epidermal growth factor receptor (EGFR); KIT is the receptor for macrophage growth factor (MGFR).

(*iii*) Receptors without tyrosine kinase activity: the *c-mas* proto-oncogene encodes the angiotensin receptor.

(*iv*) Membrane G proteins. The *ras* proto-oncogene family encodes proteins with a molecular weight of 21 kDa, with the property of binding and hydrolyzing adenosine triphosphate (ATP).

(*v*) Cytoplasmic serine/threonine kinases: the *c-mos* genes regulate the development of normal meiosis, and the *c-raf* genes stimulate mitogenesis.

(*vi*) Cytoplasmic localization regulators: *c-crs* genes that phosphorylate tyrosine.

(*vii*) Transcription factors: more than 20 transcription factors are currently known which consist of two functional domains that produce DNA binding (promoter) and transcriptional activation. We mention the *c-erb A* gene that encodes the erb A protein (thyroid hormone receptor) and the *MYC* gene family (*c-MYC*, *n-MYC* and *l-MYC*).

More than 100 protooncogenes have been identified but only a small fraction of them have been shown to play an important role in the development of cancer [5, 6].

Tumor suppressor genes (antioncogenes)

Tumor suppressor genes (antioncogenes) are genes that in the normal state (without mutations) control the production of proteins that are part of the cell division regulatory system. Through their products, they inhibit cell proliferation and stimulate cell death (apoptosis). Gene mutations, with loss or reduction of function, produce uncontrolled cell proliferation and inefficient apoptosis. Genes have a recessive character at the cellular level; to change the behavior of the cell it is mandatory that both alleles be inactivated [loss of heterozygosity (LOH)]. Loss of tumor suppressor gene function appears to be more significant in tumor production than oncogene activation.

The retinoblastoma protein (pRB1) was the first tumor suppressor gene identified (1986). The p53 protein (also called the "guardian of the genome") has multiple functions: DNA repair, apoptosis, transcription, regularization of the cell cycle. Mutation of the *p53* gene, located on chromosome 17p13.1 is involved in over 50% of cancers (colon, breast, lung, but also leukemia, lymphomas, sarcomas and tumors of the nervous system), increasing the therapeutic interest in the study of this gene in all cancers. Mutations in the *p53* gene may be hereditary, as in Li–Fraumeni syndrome (early onset, multiple tumors, and multiple family cancers), in which there is an increased risk of cancer (choroid plexus carcinoma, leukemia, adrenal, breast, ovary, etc.). Other examples of tumor suppressor genes are: B-cell lymphoma 2 (*BCL-2*) (leukemia/B-cell lymphoma), switch/sucrose non-fermentable (SWI/SNF) is a protein complex with a role in remodeling the chromatin packaging pathway, Von Hippel–Lindau protein (pVHL), adenomatous polyposis coli (APC), cluster of differentiation 95 (CD95) (involved in various neoplasms and diseases of the immune system).

Stability (anti-mutational) genes

Stability (anti-mutational) genes are responsible for the integrity of the genome and the correctness of information transfer. They correct the damage in the DNA due to physical, chemical or biological agents. If both genes are lost (recessive model), the DNA damage cannot be repaired, leading to a large number (of the order of thousands) of stable DNA damage transmissible to offspring.

Regulatory genes (miRNA genes)

Regulatory genes (miRNA genes) are genes that do not code proteins, but sequences of single-stranded non-coding RNA (ncRNA), miRNA, long non-coding RNA (lncRNA), which are involved in the transcriptional or posttranscriptional regulation of gene expression. The miRNA genes act either by blocking the translation of messenger RNA (mRNA) into proteins or by degrading mRNA, thus controlling the cell cycle, aging and cell apoptosis. The lncRNA genes are involved in the control of transcription and post-transcriptional phenomena of mRNA.

Landscaper genes

They have a role in modifying the cellular micro-environment, thus favoring cell proliferation and growth, as they do not have a direct role in malignant transformation. Their role is in controlling the stability of the membrane and the cell matrix, thus controlling

the cell–cell, cell–extracellular matrix interactions, their mutations inducing uncontrolled cell proliferation [7].

Epigenetic changes in cancer

Epigenetic mechanisms do not cause changes in the nucleotide sequence of DNA, but only in the nucleo-protein complex that forms the nuclear chromatin, influencing the spatial or temporal expression of genes. The main epigenetic phenomena are DNA methylation, histone modification (acetylation, methylation) and nucleosome repositioning. These changes play a vital role in normal development, while ensuring the stability of the genome (maintaining the stability and function of centromeres and telomeres). In cancer, epigenetic disorders occur in all cells, thus disrupting the degree of chromatin compaction and gene expression. In this way, oncogenes can be activated, and tumor suppressor genes inactivated, causing mutations and, implicitly, cancer.

⬭ Hemangiomas and vascular tumors

Hemangiomas are the most common tumors in childhood, occurring in 3–10% of newborns and infants. Morphologically, they are dysplasia characterized by an abnormal organization of vascular tissue (proliferation of vascular endothelium), causing dense agglomeration of blood vessels (capillaries, veins, arteries, lymph or any combination of them). In the first stage, the hemangiomas undergo a rapid initial proliferation, followed by a stabilization stage, and in most cases involution and regression [8]. There are currently several hypotheses regarding the pathogenesis of hemangiomas. According to Cheung *et al.*, there are two theories that lead to the appearance of hemangiomas: the first refers to the fact that hemangiomas arise from the recrudescence of "sleeping" embryonic angioblasts; the second stipulates that hemangiomas are in fact tumors of neoangiogenesis. After the onset, there are two forms: infantile hemangiomas and congenital hemangiomas. Infantile hemangiomas are the most common, have an onset after birth, proliferate in the first year of life, and then regress. According to Haggstadd *et al.* by the age of 5, about 50% of hemangiomas involve and by the age of 9, about 90% [9]. Congenital hemangiomas begin at birth. Subsequently, some involve fast or slow, while others show no regression [10, 11].

Histologically, infant hemangiomas are glucose transporter 1 (GLUT-1) positive, an erythrocyte-type glucose transporter. Vascular endothelial growth factor (VEGF) appears to have angioproliferative effects. Zang *et al.* demonstrated that there are increased plasma amounts of VEGF-A in patients with infantile hemangiomas during the proliferative phase compared to the infantile involution phase and also compared to the control groups [12]. Congenital hemangiomas, on the other hand, are GLUT-1 negative. Polymorphic mutations of *VEGF* have been found in some studies, particularly in infantile hemangiomas [13].

There are differences between hemangiomas themselves and vascular malformations. Hemangiomas are neoplastic lesions that go with epithelial hypertrophy, while in vascular malformations the epithelial turnover is normal [14, 15].

The literature describes many genetic syndromes that associate hemangiomas in the clinical phenotype, such as: Von Hippel–Lindau (VHL) syndrome and Maffucci syndrome [16]. VHL syndrome is an autosomal dominant disease with a predisposition to both benign and malignant tumors (retinal, cerebellar, hemangioblastoma, renal, pheochromocytoma, pancreas). Genetically, there are mutations in the *VHL* tumor suppressor gene, located on chromosome 3. There are two types of VHL syndrome: type 1 that associates hemangioblastoma, renal cell carcinoma, but not pheochromocytoma. It is associated with large and truncated deletions of the gene leading to loss of protein product or hypofunction. Pheochromocytoma occurs in type 2 and the mutations are nonsense mutations of the *VHL* gene that lead to the formation of a functional, but insufficient protein [17–19]. Maffucci syndrome combines hemangiomatosis and enchondromatosis. Hemangiomas are usually cutaneous or subcutaneous, rarely causing bleeding [20]. Although this syndrome occurs sporadically, certain mutations, associated with the occurrence of enchondromatosis, have been identified [21, 22]. One study found that 77% of patients with Maffucci syndrome had mutations in isocitrate dehydrogenase (*IDH*) in their tumors, especially *IDH1* (98%) and *IDH2* (2%) [23]. These mutations are associated with hyper-methylation and downregulated expression of several genes. Notably, even tumors positive for these mutations demonstrated "intraneoplastic mosaicism", a condition in which there exists a mixture of cells that did and did not express the mutant protein.

⬭ Teratomas

Teratomas are embryonic tumors that are histologically composed of cells from two or all three embryonal structures (ectoderm, mesoderm, and endoderm), with an increased incidence in newborns and children [24]. In 1863, Virchow first described this tumor form, and after 25 years the second case was reported by Horsleng [25]. The most common locations of teratomas are at the sacrococcygeal level (the incidence being one in 27 000 newborns), followed by those in the ovaries/testicles and brain [26].

In most cases, they occur sporadically, family cases being rarely described in the literature. In cases with familial aggregation, transmission was autosomal dominant, with a 50% risk of recurrence in offspring.

There is a direct relationship between aneuploidy and the histological grade of the tumor (immature teratoma). Grade 1 or two immature teratomas are usually diploid in about 90% of cases, aneuploidy being much more common in grade 3, chromosomal abnormalities being present in over 66% of cases [27]. Trisomy for chromosome 3 is the most common trisomy reported in immature ovarian teratomas (in adults). The testicular teratoma was associated with abnormalities of the short arm of chromosome 12 (12p) [28].

Various chromosomal abnormalities were also reported: at chromosome 7 (deletion 7q, associated with partial trisomy 2p); 22; 8p; partial duplication of the long arm of chromosome 1; deletions and mutations in the *hSNF5/INI1* gene. Increased activity of the mutant p53 protein

is associated with an increased risk of malignancy. The variety of cytogenetic patterns described supports the hypothesis that different genetic pathways may lead to the phenotype characteristic of this type of tumor [29].

Other studies have shown the common clonal origin of teratomas and malignancies from testicular germ cells [30]. The defining element of teratomas, which also explains the particular scientific interest given, is represented by the special variety of histopathological changes.

Central nervous system (CNS) teratomas

CNS teratomas are different from those with other locations; they have an increased incidence among children. They are found in about 0.5–1.5% of all brain tumors in children, with an estimated survival rate of 7.8%. In CNS teratomas, chromosomal abnormalities are found with an average of 12.8 (8 with gain of function, 4.8 deletions), those at chromosomes 4 and 5 being the most frequently reported. Mutations in the genes have also been reported: cyclin D1 (*CCND1*) located on chromosome 12 (12p13), *RB1* on chromosome 13 (13q14) and PR/SET domain 14 (*PRDM14*) located on chromosome 8 (8q13), genes that play an important role in the cyclin pathway, cyclin-dependent kinase (CDK)/RB-E2F, cyclins having the role of controlling the progression of cells through the cell cycle by activating CDK enzymes [31]. Interestingly, many pineal region germ cell tumors (GCTs) were found to have multiple copies of the X chromosomes, which may explain the high incidence of GCT in patients with Klinefelter's syndrome.

⊟ Brain tumors

Brain tumors rank second as common childhood tumors. There are mutations that lead to the production of astrocytic infiltrative tumors: molecular studies have identified certain genetic changes that underlie the histopathological differences between these tumors.

Astrocytomas

Astrocytomas are CNS tumors derived from astrocytes. They are classified into two categories: the first category includes astrocytomas with narrow infiltration areas (pilocytic astrocytoma, giant cell subependymal, and infiltration xanthoastrocytoma); the second category includes astrocytomas with diffuse infiltration areas (low-grade infiltrative astrocytoma, anaplastic astrocytoma, and glioblastoma). About two-thirds of low-grade infiltrative astrocytomas (grade 2) had mutations detected in the p53 tumor suppressor gene, with cases of astrocytomas being reported in families with members with Li–Fraumeni syndrome, neurofibromatosis type 1 (NF1), Noonan syndrome.

Pilocytic astrocytomas (PA) are the most common astrocytic tumors of childhood and differ clinically and histopathologically from astrocytomas affecting adults. PA have been reported in 15% of patients with NF1 [32]. The protein encoded by the *NF* gene, neurofibromin, stimulates the intrinsic hydrolysis of guanosine triphosphate (GTP) and acts as a tumor suppressor [33]. Also, Noonan syndrome, which is characterized by germline mutations in the genes of the mitogen-activated protein kinase (MAPK) [protein tyrosine phosphatase non-receptor type 11 (*PTPN11*), SOS Ras/Rac guanine nucleotide exchange factor 1 (*SOS1*), Kirsten rat sarcoma viral oncogene homolog (*KRAS*), neuroblastoma RAS viral oncogene homolog (*NRAS*), Raf-1 proto-oncogene, serine/threonine kinase (*RAF1*), B-Raf proto-oncogene, serine/threonine kinase (*BRAF*), SHOC2 leucine rich repeat scaffold protein (*SHOC2*) and Cbl proto-oncogene (*CBL*)], associate PA, but extremely rarely [34].

There have been numerous studies that have shown changes in the *BRAF* oncogene, which encodes a protein that belongs to the RAS/MAPK signaling pathway that controls important cellular functions (cell growth and division, cell differentiation and migration, apoptosis). At the *BRAF* gene, a 2 Mb duplication occurs at the 7q34 level by fusing the *BRAF* oncogene with the *KIAA1549* gene, resulting in a transforming fusion gene. The N-terminal end of the *KIAA1549* protein replaces the N-terminal regulatory region of *BRAF*, while maintaining the *BRAF* kinase domain, which becomes constitutively activated. This fusion occurs in over 70% of patients with astrocytomas [35, 36]. Although the identification of gene fusion between *KIAA1549* and *BRAF* by whole genome sequencing or RNA sequencing is used as a positive diagnostic marker for brain pathology, there are some studies showing that this fusion is missing in glial astrocytomas including adult oligodendrogliomas where 1p and 19q deletion occurs and the *IDH1* gene mutation [37].

Mutations of the *BRAF* gene without gene fusion have also been mentioned, such as the well-known *V600E* mutation in which valine is replaced by glutamic acid, as well as a series of small insertions that activate *BRAF* signaling [35]. Recent studies have shown mutations in the fibroblast growth factors receptor 1 (*FGFR1*) gene family and in the neurotrophic receptor tyrosine kinase (*NTRK*) gene, where gene fusions occur. At the *FGFR1* level, the mutations were variable.

Glioblastomas belong to astrocytomas with diffuse infiltration areas and represent the most frequent and aggressive tumors in adults with an annual incidence of 5.26 per 100 000 inhabitants [38]. The genetic changes that occur most frequently are point mutations in the *IDH1* and *IDH2* genes, which encode isocitrate, these mutations being correlated with the young age of onset and with a favorable prognosis, most glioblastomas being the wild type of *IDH*. Molecular changes also include mutations in the receptor tyrosine kinase (RTK) pathway of the RAS pathway of the *p53* gene [39].

Neuroblastomas

They are neuroendocrine malignancies that develop from neural crest cells and are the most common type of solid extracranial cancer of childhood, with onset up to five years. They usually occur sporadically, but family cases with an incidence of 1–2% are also reported [40, 41].

Only a few familial cases of neuroblatomas in which gene mutations occur have been reported in the literature. Tyrosine kinase receptors (TrkA, TrkB and TrkC) and their ligands, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3),

and Aurora kinase A (AURKA) are involved in the mechanisms of regulation of differentiation, cell proliferation, apoptosis, angiogenesis, and metastasis.

The presence of TrkA (synonymous with NTRK1) in neuroblastoma is a favorable prognostic marker, TrkA receptors stimulating cell differentiation in the presence of NGF ligand. TrkB and BDNF are expressed in aggressive forms of neuroblastoma accompanied by amplification of the *MYCN* oncogene [42]. AURKA pathway signals direct oncogenesis and promote tumorigenesis. If it is low, the *MYCN* expression will decrease and the survival time will increase, but in overexpression, the survival time decreases. AURKA stimulates cell proliferation, cell growth and mediates VEGF angiogenesis. Amplification of the *MYCN* oncogene is an unsatisfactory prognostic factor in neuroblastoma [43].

There have also been identified three non-sense germline mutations (*G1128A*, *R1192P* and *R1275Q*) in the tyrosine kinase domain of the protein encoded by the anaplastic lymphoma kinase (*ALK*) oncogene. In one family case, there were reported two non-germline mutations (*R100L* and *R141G*) located in the similar homeobox 2B (*PHOX2B*) [44].

There have been identified various chromosomal abnormalities, such as:

(*i*) Amplification of the *MYCN* oncogene (located at the level of chromosome 2) is found in 18–38% of primary tumors, as well as in other cell lines of neuroblastomas [45–48]. This is amplified at the 2p24 resident site which is present in many neuroblastoma' cell lines, such as *CHP134*, *KPNYS*, *IMR-5*, *GOTO* and *NB17*, but also in other solid tumors, such as lung carcinoma, adrenal tumors, breast cancer, and esophagus. The amplified segments at the respective chromosomal site show homogeneous staining (hsr).

(*ii*) 1p36 deletion is the most common deletion encountered in neuroblastoma. In this region there is the *KIF1B* gene, which is a tumor suppressor gene, its mutations being identified in several family cases, thus showing that the gene is involved in the appearance and progression of neuroblastoma. Amplification of *MYCN* oncogene together with 1p36 deletion plays an important role in the vascularity of these tumors. There are, also, other genes in this region of chromosome 1, involved in the pathogenesis of neuroblastoma. Abel *et al.* highlighted the DNA fragmentation factor subunit alpha (*DFFA*) gene (1p36) in several cases of Scandinavian neuroblastomas [49].

(*iii*) Chromosome 17 abnormalities have been identified since 1980. Mutual translocation between chromosome 1 and 17 der(1)t(1p; 17q), which results in loss of 1p and gain of 17q terminal (unbalanced translocation), occurs frequently in primary tumor, but also in neuroblastoma cell lines. The baculoviral IAP repeat containing 5 (*BIRC5*) gene located at 17q25.3 is expressed in many cases of primary neurofibroblastomas or in various survivin neuroblast cell lines.

(*iv*) Loss of 11q heterozygosity (at the 11q23.3 locus) is a negative prognostic factor representing neuroblastoma metastasis. This deletion may be accompanied by other deletions: 3p, 4p, 14q and is inversely correlated with *MYCN* oncogene amplification.

We can thus talk about three genetically distinct subgroups of neuroblastomas. According to Brodeur *et al.*, we have the following groups: infants in the early stage and with a very good prognosis whose tumors are triploid, but no 1p deletion is observed and without amplification of the *MYCN* oncogene; children older than one year in stage 3 or 4 disease with diploid or tetraploid tumors, without amplification of *MYCN*, but with 1p loss; older children, with advanced disease, with di- or tetraploid tumors, in which we have both *MYCN* and lipooligosaccharide (*LOS*) amplification of chromosome 1 with a negative prognosis [50].

⚏ Retinoblastoma (RB)

RB represents a rare form of cancer with primary localization in the eye (retina); it is also called retinal glioma. It is the most common ocular tumor of the child representing 6% of all tumors in children with onset in early childhood (up to five years) formed by bialelic activation of a tumor suppressor gene. The incidence is 15 000–20 000 live births [51]. Although the incidence of the disease is relatively constant, there are areas of the Globe where it is higher, especially in underdeveloped areas of the world. This is explained by the fact that in these parts of the world the infection with the human papillomavirus (HPV) is widespread. HPV-infected cells produce an oncogenic protein, which binds to pRB by inactivating it.

RB can be evaluated on a genetic and laterality basis, it can be hereditary or sporadic, unilateral or bilateral. Tumor unilaterality occurs in 60% of cases and bilateral involvement is present in the other 40% of cases. Bilateral forms of RB have familial aggregation as opposed to unilateral ones that occur sporadically.

The molecular changes involved in pathogenesis are complex. The most common are germline or somatic mutations in the *RB1* gene located on the chromosome 13q14.1-q14.2, this being the first tumor suppressor gene identified and expressed in various tissues [52]. It encodes the pRB protein which has multiple roles, the most important being the cell cycle stopping in the G1 phase, but also intervenes in cell differentiation, apoptosis control, chromosomal stability by temporarily stopping the cell cycle. Along with p107 and p130, pRB belongs to a family of proteins that bind to E2F transcription factors, their activity being controlled by phosphorylation. In human cancers, frequent mutations occur in the RB, while p107 and p130 are rarely inactivated [53]. The mutations that occur range from large deletions to non-sense mutations, splicing mutations. Germline mutations occur in 75–80% of cases of bilateral RB and 15–25% in cases of unilateral RB [54]. Another aspect encountered is that in unilateral forms there is a loss of *RB1* function (biliary mutations) in 98% of cases, the remaining 2% having the normal *RB1* gene, but have changes in the *MYCN* oncogene [55].

Epigenetic mechanisms also play an important role in the occurrence of these RBs including DNA methylation, miRNA histone modification, lncRNA, ATP-dependent chromatin remodeling [56, 57].

The *p53* gene also plays a role in the pathogenesis of

RB, being the gene with the most common mutations in human cancer. It controls the cell cycle and causes apoptosis in the retinal cone precursor cells (where the RB cell line originates). It controls the cell cycle and apoptosis in the retinal cone precursor cells, from which the RB cell line originates [58–60].

⌗ Wilms tumor (WT) or nephroblastoma

Nephroblastoma is a malignant embryonic tumor that originates in kidney cells, more precisely from blastemal nephrogenic cells, and often has different differentiation patterns. The incidence is one in 10 000 newborns. The relatively constant incidence of nephroblastomas in all geographical areas suggests that environmental factors do not play a major role in the development of these tumors. There have been variations in racial incidence, with the tumor being more common in the African–American population and less common among Asian children.

Nephroblastoma affects children of both sexes, with no predilection for either sex and with equal frequency in both kidneys. Over 95% of cases occur in children under 10 years of age, although there are presentations in adulthood.

In about 20% of patients, mutations are identified in the *WT1* gene, a gene located on chromosome 11 (11p13) [61, 62]. Approximately 50% of patients with nephroblastoma who have mutations in the *WT1* gene also associated mutations in the catenin-beta 1 (*CTNB1*) gene (encoding the beta-catenin oncoprotein) located at the 3p22 level. The *WTX* gene [also called APC membrane recruitment protein 1 (*AMER1*)] is located at the Xq11.1 level, mutations in this gene occurring in 15% of cases. Both genes encode proteins that stimulate cell growth and division. At the short arm of chromosome 11 are the insulin-like growth factor 2 (*IGF2*) and *H19* genes, both responsible for the appearance of this tumor form (reduced activity of the gene that usually stops cell growth and increased *IGF2* activity that stimulates cell growth causes loss of cell growth control and intensifies growth and cell division) and eventually leads to the appearance of the tumor. In the chromosome 11p15.1, there is a second locus *WT2* (imprinted region) responsible for the appearance of WT. Almost 3% of children with WT have germ epigenetic changes at 11p.15.5.

Chromosomal changes, with genetic material gain on chromosome 1q, are an indicator of a negative prognosis. This cytogenetic change at level 1q is most common in nephroblastoma and is seen in 30% of tumors. At level 16q, in addition to changes at level 1p, there are other tumor suppressor genes [63].

Changes in miRNA processing genes (miRNAPG) are present in approximately 20% of WT cases. The most frequently involved are Drosha ribonuclease III (*DROSHA*), *DRCR8*, Dicer 1, ribonuclease III (*DICER1*), and exportin 5 (*XPO5*) genes [64–67]. These genes, through their products, directly control the maturation of miRNA from the initial pre-miRNA transcriber to the final miRNA in the cytoplasm. Germline mutations of miRNAPG involving *DICER1* and DIS3-like 3'–5' exoribonuclease 2 (*DIS3L2*) genes may be encountered. Germline mutations in the *DICER1* gene cause DICER1

syndrome – one allele is inactivated by germline mutation and the other allele has a somatic mutation that affects one of the RNase IIIb metal ion-binding sites (pleuropulmonary blastoma, cystic nephroma, ovarian cancer, thyroid, WT) [68]. Mutations in the *DIS3L2* gene cause Perlman's syndrome (polyhydramnios, macrosomia, bilateral kidney tumors – hamartomas with or without nephroblastomas) [69–71].

Nephroblastoma can occur in various genetic syndromes, but there are also non-syndromic causes. The most common genetic syndromes associated with WT are: WAGR syndrome (WT, aniridia, urogenital system abnormalities and mental retardation), Denys–Drash syndrome (congenital nephropathy, WT, gonadal disgenesia), Frasier syndrome (pseudohermaphroditism, glomerulopathy). All of these syndromes have mutations in the *WT1* gene. Patients with Beckwith–Wiedemann syndrome may develop nephroblastoma through the mechanism of imprinting the *IGF2* and *H19* genes. Other syndromes that associate WT are: Simpson–Golabi–Behmel syndrome (macroglossia, macrosomia, kidney tumors), in which there are mutations in the glypican 3 (*GPC3*) and glypican 4 (*GPC4*) genes, these mutations increasing the risk of nephroblastoma; CLOVES syndrome (congenital lipomas, macrosomia, vascular malformations, epidermal nevi, skeletal abnormalities), in which mutations of the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) gene occur; Sotos syndrome (macrosomia, cerebral gigantism, heart malformations, scoliosis, convulsions, nephroblastoma) with mutations in the nuclear receptor binding SET domain protein 1 (*NSD1*) gene; Bloom syndrome (sensitivity to ultraviolet radiation, WT); Li–Fraumeni syndrome (breast cancer, osteosarcoma, soft tissue cancer, leukemia, kidney cancer, WT, brain cancer); Alagille syndrome (congenital heart malformations, facial dysmorphism, vertebral, renal abnormalities); Bohring–Opitz syndrome (craniofacial dysmorphism, hypertrichosis, severe mental retardation).

Non-syndromic cases of WT are: (*i*) Family forms are found in only 2% of patients, although the number of genes involved is increased. Two genes are involved: *FWT1* (17q12-q21) and *FWT2* (19q13.4). Rarely, germline mutations may occur in the *WT1* gene in which some family members may associate genitourinary malformations. (*ii*) Sporadic aniridia occurs because of mutation in one of the paired box 6 (*PAX6*) copies. About 50% of individuals with sporadic aniridia associate with WT.

⌗ Rhabdomyosarcomas (RMS)

RMS are malignant tumors starting with striated muscles and represent slightly more than 20% of all sarcomatous tumors of the child.

According to the macroscopic and histological aspect, we have three types of RMS: embryonal (ERMS), alveolar (ARMS) and pleomorphic (PRMS). The embryonal form is most common from birth to about 15 years, alveolar between 10–25 years, while pleomorphic RMS predominates in adults and older people and is extremely rare [72]. RMS occurs more frequently in male gender, sex ratio of 1.5:1 [72, 73]. The most common location is in the head and neck (45%), especially orbits (30% of the total RMS in the head), followed by the neck, chest

(40%) and limbs (20–25%). [74]. Due to the complex therapeutic modalities, the survival rate is currently over 70%, five years after diagnosis [75]. If we refer to the severity of clinical manifestations, the embryonal type has a more favorable prognosis (43% at five years) compared to the ARMS type which is the most severe form with increased risk of metastasis (25.9%) and five-year survival rate is up to 29% depending on the type of existing genomic rearrangements (different gene fusions) [76].

The most important histological subtypes in children are ARMS and ERMS, the molecular changes being different in the two types [77].

In ARMS, there is either mutual translocation between chromosomes 2 and 13, t(2; 13)(q35; q14) or between chromosomes 1 and 13, t(1; 13)(q36; q14), in both cases resulting in the fusion of paired box 3 (*PAX3*) genes – forkhead box O1 (*FOXO1*), respectively paired box 7 (*PAX7*) genes – *FOXO*. Following these recombinations, certain transcription factors will initiate the process of tumor genesis encoded proteins by stimulating cell growth and proliferation and stopping terminal differentiation [78].

Different genomic changes occur in the ERMS: mutations with loss of p53 function, activation of the RAS pathway or mutations in the myogenic differentiation 1 (*MYOD1*) gene [79–81]. The mutation of the *MYOD1* gene together with the fusions of the vestigial like family member 2 (*VGLL2*) gene causes the appearance of an aggressive tumor form, sclerosing RMS [82].

Ricker *et al.* described different gene variants associated with ERMS, such as BUB1 mitotic checkpoint serine/threonine kinase B (*BUB1B*), *DICER1*, and *FGFR1*. The *BUB1B* gene mutation has a negative prognosis and leads to other cancers (gastric, breast, prostate) [83]. Decreased expression of *DICER1* correlated with miRNA concentration during organogenesis has an important role in the occurrence of RMS and can occur in both familial and sporadic forms. Shukla *et al.* reported a percentage of 4.9% cases of RMS, in which mutations of the *PI3KCA* gene located on chromosome 3 occur [84].

Among the genetic syndromes that associate this tumor type, we mention Li–Fraumeni syndrome, neurofibromatosis, Beckwith–Wiedemann syndrome and Costello syndrome.

▢ Bone tumors

Bone tumors develop by abnormal growth of cells inside the bone; they can be benign (osteoid osteoma and osteoblastoma) or malignant [osteosarcoma and Ewing's sarcoma (EWS)].

Osteoid osteoma

Osteoid osteoma is a very painful benign bone tumor, usually located at the level of the bone shaft with an incidence of 12%. It can rarely turn into an osteoblastoma. It usually occurs in late childhood and in young adults. Osteoblastoma is a much rarer tumor (3% of benign bone tumors). The sex ratio is 2:1 in favor of males. It is most commonly located in the spine and sacrum. From a morphological point of view, the two tumor types are similar.

Molecular changes are similar in both forms with rearrangements in the Fos proto-oncogene (*FOS*) (AP-1 transcription factor subunit) 87% of cases and *FOSB* 3%, on chromosome 14. Both genes belong to the family of transcription factors FOS (which has a total of four members: FOS, FOSB, FOSL1, and FOSL2), with a role in the differentiation, proliferation, and transformation of osteoblasts. In some cases, *FOS* gene expression has been associated with cellular apoptosis [85].

Among malignant tumors, osteosarcoma and EWS are the most common bone tumors in children.

▢ Osteosarcoma

Osteosarcoma is a severe malignant bone tumor with rapid metastasis and a low prognosis of survival at five years, about 71% [86]. It mainly affects young children and adolescents, the age of onset being 10–15 years, but cases can also occur at younger ages [87]. It has a slightly higher incidence in boys; sex ratio is 1.5: 1.

It is characterized from a molecular point of view by a high degree of genomic instability explained either by the occurrence of the phenomenon of chromothripsis or by the existence of gene mutations with a role in DNA repair. The most common genetic syndromes predisposed to osteosarcoma are: Li–Fraumeni syndrome and RB. Mutations in RecQ-like (RECQL) helicases (important role in DNA repair mechanisms) may occur in: Rothmund–Thomson syndrome (*RECQL4* gene) or there may be syndromes in which germline mutations occur in RECQL helicases: RAPADILINO syndrome, Baller–Gerold syndrome, Werner syndrome and Bloom syndrome [88].

Histologically, there are different types of osteosarcomas, but the most common type is high-grade osteosarcoma. Complex changes occur at the level of chromosomes most often occurring mutual translocations, amplifications, deletions, all these chromosomal abnormalities causing a high degree of genomic instability.

Genomic instability in osteosarcoma is explained by the mechanism of chromothripsis in which thousands of chromosomal ruptures and rearrangements occur in a single or several chromosomes that are then grouped and oriented together in a random, chaotic manner. This phenomenon was first described by Stephens *et al.* showing the presence of chromothripsis in 3% of all cancers and 30% in osteosarcomas [89]. In addition to this phenomenon, many genes are involved in maintaining genomic stability, changes in tumor protein p53 (*TP53*) and *RB1* being the most important in the occurrence of osteosarcoma. The most commonly affected is the *TP53* gene, with genome-wide sequencing studies showing the presence of mutations in this gene in 47–90% of osteosarcoma cases, with translocations in the first intronic region of the *TP53* gene being most commonly observed, followed by mutations of the *RB1* gene [90]. It is known that this gene is involved in blocking the cell cycle in the G1 phase of the cell cycle (it stops the passage in the S phase until the cell is ready). Loss of the function of this gene causes an uncontrolled cell division [91]. Kovac *et al.* showed that in 29–47% of cases of osteosarcoma, somatic mutations can occur at *RB1* level [92].

In addition to mutations in the two genes, there are other genomic changes such as germline and somatic mutations in the ATRX chromatin remodeler (*ATRX*) gene, with 29% of osteosarcoma cases showing somatic

mutations in this helicase with a role in DNA stability [93]. Its mutations also cause alpha-thalassemia X-linked intellectual disability (ATR-X) syndrome, and in some forms of osteosarcomas there are mutations in breast cancer 1 (*BRCA1*) and breast cancer 2 (*BRCA2*) genes [94].

EWS is a malignant, aggressive tumor that begins in childhood or in young adults. Although remarkable progress is currently being reported in its treatment, mortality remains high, with death occurring in approximately 40% of patients [95].

In 85% of patients with EWS, reciprocal translocation occurs between chromosomes 11 [where the Fli-1 proto-oncogene, ETS transcription factor (*FLI1*) gene exists] and 22 (where the *EWS* gene exists) t(11, 22)(q24; q12) resulting in an *EWS–FLI1* fusion gene. This abnormality is found in over 85% of diagnosed EWS. Other reciprocal translocations t(21; 22)(q22; q12) were also observed, giving rise to an *EWS–ERG* fusion gene or t(7; 22), t(17; 22) and t(2; 22), and inv(22). In all cases, proteins with abnormal function result in abnormal cell proliferation through continuous activation of insulin-like growth factor 1 (IGF1) [96].

⊟ Conclusions

Congenital solid tumors are heterogeneous containing several cell types, but the initiation and continuous growth usually depend on a single population of neoplastic cells and carry the same genetic or epigenetic abnormality. Genetic risk factors for cancer are incriminated in both adults and children, while environmental factors, incriminated in adults, are insignificant in children. The genetic conditions that can anticipate the neoplasm are diverse and they must be identified as early as possible, in order to monitor them in order to capture, as soon as possible, the neoplastic process. Tumor progression is achieved by certain mutations that activate oncogenes and suppress the activity of tumor suppressor genes. Different combinations of mutations may occur at random in patients with the same form of cancer, so the medical treatment needs to be targeted to that mutation. Thus, the understanding and identification of molecular mechanisms that take place in various forms of neoplasms are the basis for identifying molecules that intervene targeted and customized in the therapy of this extremely complicated disease. The identification and monitoring of these cases involves a multidisciplinary team: pediatrician, geneticist, oncologist, surgeon, chemo- and radiotherapist, psychologist.

Conflict of interests

The authors declare that they have no conflict of interests.

References

[1] Knudson AG Jr. Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci U S A, 1971, 68(4):820–823. https://doi.org/10.1073/pnas.68.4.820 PMID: 5279523 PMCID: PMC389051

[2] Knudson AG Jr, Hethcote HW, Brown BW. Mutation and childhood cancer: a probabilistic model for the incidence of retinoblastoma. Proc Natl Acad Sci U S A, 1975, 72(12): 5116–5120. https://doi.org/10.1073/pnas.72.12.5116 PMID: 1061095 PMCID: PMC388887

[3] Covic M, Ştefănescu D, Sandovici I, Gorduza EV. Genetică medical [Medical genetics]. 3rd edition, Polirom Publishing House, Iaşi, 2017, 550–559 (in Romanian).

[4] Croce CM. Oncogenes and cancer. N Engl J Med, 2009, 358(5):502–511. https://doi.org/10.1056/NEJMra072367 PMID: 18234754

[5] Hunter T. Cooperation between oncogenes. Cell, 1991, 64(2): 249–270. https://doi.org/10.1016/0092-8674(91)90637-e PMID: 1988147

[6] Levine AJ, Broach JR. Oncogenes and cell proliferation. Curr Opin Genet Dev, 1995, 5(1):1–4. https://doi.org/10.1016/s0959-437x(95)90045-4 PMID: 7749316

[7] Berger MF, Mardis ER. The emerging clinical relevance of genomics in cancer medicine. Nat Rev Clin Oncol, 2018, 15(6):353–365. https://doi.org/10.1038/s41571-018-0002-6 PMID: 29599476

[8] Kolbe AB, Merrow AC, Eckel LJ, Kalina P, Ruano R. Congenital hemangioma of the face – value of fetal MRI with prenatal ultrasound. Radiol Case Rep, 2019, 14(11):1443–1446. https://doi.org/10.1016/j.radcr.2019.09.016 PMID: 31695833 PMCID: PMC6823738

[9] Haggstrom AN, Drolet BA, Baselga E, Chamlin SL, Garzon MC, Horii KA, Lucky AW, Mancini AJ, Metry DW, Newell B, Nopper AJ, Frieden IJ. Prospective study of infantile hemangiomas: clinical characteristics predicting complications and treatment. Pediatrics, 2006, 118(3):882–887. https://doi.org/10.1542/peds.2006-0413 PMID: 16950977

[10] Merrow AC, Gupta A, Patel MN, Adams DM. 2014 Revised Classification of vascular lesions from the International Society for the Study of Vascular Anomalies: radiologic-pathologic update. Radiographics, 2016, 36(5):1494–1516. https://doi.org/10.1148/rg.2016150197 PMID: 27517361

[11] Chen TS, Eichenfield LF, Friedlander SF. Infantile hemangiomas: an update on pathogenesis and therapy, Pediatrics, 2013, 131(1):99–108. https://doi.org/10.1542/peds.2012-1128 PMID: 23266916

[12] Zhang L, Lin X, Wang W, Zhuang X, Dong J, Qi Z, Hu Q. Circulating level of vascular endothelial growth factor in differentiating hemangioma from vascular malformation patients. Plast Reconstr Surg, 2005, 116(1):200–204. https://doi.org/10.1097/01.prs.0000170804.80834.5f PMID: 15988268

[13] Boye E, Yu Y, Paranya G, Mulliken JB, Olsen BR, Bischoff J. Clonality and altered behavior of endothelial cells from hemangiomas. J Clin Invest, 2001, 107(6):745–752. https://doi.org/10.1172/JCI11432 PMID: 11254674 PMCID: PMC208946

[14] Mulliken JB, Glowacki J. Classification of pediatric vascular lesions. Plast Reconstr Surg, 1982, 70(1):120–121. PMID: 7089103

[15] Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. Plast Reconstr Surg, 1982, 69(3):412–422. https://doi.org/10.1097/00006534-198203000-00002 PMID: 7063565

[16] Killion E, Mohan K, Lee EI. A review of vascular anomalies: genetics and common syndromes. Semin Plast Surg, 2014, 28(2):64–68. https://doi.org/10.1055/s-0034-1376261 PMID: 20545331 PMCID: PMC4078216

[17] Seshadri MS. Endocrine tumor syndromes and their genetics. Indian J Med Res, 2015, 142(5):630–631. PMCID: PMC4743361

[18] Chen F, Kishida T, Yao M, Hustad T, Glavac D, Dean M, Gnarra JR, Orcutt ML, Duh FM, Glenn G, Green J, Hsia YE, Lamiell J, Li H, Wei MH, Schmidt L, Tory K, Kuzmin I, Stackhouse T, Latif F, Linehan WM, Lerman M, Zbar B. Germline mutations in the von Hippel–Lindau disease tumor suppressor gene: correlations with phenotype. Hum Mutat, 1995, 5(1):66–75. https://doi.org/10.1002/humu.1380050109 PMID: 7728151

[19] Crossey PA, Foster K, Richards FM, Phipps ME, Latif F, Tory K, Jones MH, Bentley E, Kumar R, Lerman MI, Zbar B, Affara NA, Ferguson-Smith MA, Maher ER. Molecular genetic investigations of the mechanism of tumourigenesis in von Hippel–Lindau disease: analysis of allele loss in VHL tumours. Hum Genet, 1994, 93(1):53–58. https://doi.org/10.1007/BF00218913 PMID: 8270255

[20] Kaplan RP, Wang JT, Amron DM, Kaplan L. Maffucci's syndrome: two case reports with a literature review. J Am Acad Dermatol, 1993, 29(5 Pt 2):894–899. https://doi.org/10.1016/0190-9622(93)70265-u PMID: 8408836

[21] Lee NH, Choi EH, Choi WK, Lee SH, Ahn SK. Maffucci's syndrome with oral and intestinal haemangioma. Br J Dermatol, 1999, 140(5):968–969. https://doi.org/10.1046/j.1365-2133.1999.02840.x PMID: 10354047

[22] Halal F, Azouz EM. Generalized enchondromatosis in a boy with only platyspondyly in the father. Am J Med Genet, 1991, 38(4):588–592. https://doi.org/10.1002/ajmg.1320380418 PMID: 2063903

[23] Pansuriya TC, van Eijk R, d'Adamo P, van Ruler MA, Kuijjer ML, Oosting J, Cleton-Jansen AM, van Oosterwijk JG, Verbeke SLJ, Meijer D, van Wezel T, Nord KH, Sangiorgi L, Toker B, Liegl-Atzwanger B, San-Julian M, Sciot R, Limaye N, Kindblom LG, Daugaard S, Godfraind C, Boon LM, Vikkula M, Kurek KC, Szuhai K, French PJ, Bovée JVMG. Somatic mosaic IDH1 and IDH2 mutations are associated with enchondroma and spindle cell hemangioma in Ollier disease and Maffucci syndrome. Nat Genet, 2011, 43(12):1256–1261. https://doi.org/10.1038/ng.1004 PMID: 22057234 PMCID: PMC3427908

[24] Pătraşcu T, Doran H, Guţu D, Pop FI, Prunaiche M, Vereanu I. Teratom sacro-coccigian la adult rezolvat prin abord mixt abdomino-perineal [Sacrococcygeal teratoma in an adult female operated with abdominoperineal approach]. Chirurgia (Bucharest), 2005, 100(2):169–174. PMID:15957460

[25] Saffar H, Khorsand A, Faghih Jouibari M, Tavangar SM. Mature cystic teratoma of spinal cord in a 16-year-old male: a case report. Iran J Pathol, 2020, 15(1):45–47. https://doi.org/10.30699/IJP.2019.89854.1849 PMID: 32095150 PMCID: PMC6995675

[26] Yoon HM, Byeon SJ, Hwang JY, Kim JR, Jung AY, Lee JS, Yoon HK, Cho YA. Sacrococcygeal teratomas in newborns: a comprehensive review for the radiologists. Acta Radiol, 2018, 59(2):236–246. https://doi.org/10.1007/02841851177 10680 PMID: 28530139

[27] Piazza MJ, Urbanetz AA. Germ cell tumors in dysgenetic gonads. Clinics (Sao Paulo), 2019, 74:e408. https://doi.org/10.6061/clinics/2019/e408 PMID: 31721911 PMCID: PMC6827326

[28] Semjén D, Bíró K, Kapitány E, Kálmán E, Tornóczky T, Kajtár B. Histology, 12p status, and IMP3 expression separate subtypes in testicular teratomas. Virchows Arch, 2020, 477(1):103–110. https://doi.org/10.1007/s00428-020-02771-2 PMID: 32144540 PMCID: PMC7320034

[29] Wharton SB, Wardle C, Ironside JW, Wallace WH, Royds JA, Hammond DW. Comparative genomic hybridization and pathological findings in atypical teratoid/rhabdoid tumour of the central nervous system. Neuropathol Appl Neurobiol, 2003, 29(3):254–261. https://doi.org/10.1046/j.1365-2990.2003.00451.x PMID: 12787322

[30] Kernek KM, Ulbright TM, Zhang S, Billings SD, Cummings OW, Henley JD, Michael H, Brunelli M, Martignoni G, Foster RS, Eble JN, Cheng L. Identical allelic losses in mature teratoma and other histologic components of malignant mixed germ cell tumors of the testis. Am J Pathol, 2003, 163(6):2477–2484. https://doi.org/10.1016/S0002-9440(10)63602-4 PMID: 14633619 PMCID: PMC1892383

[31] McCarthy RP, Zhang S, Bostwick DG, Qian J, Eble JN, Wang M, Lin H, Cheng L. Molecular genetic evidence for different clonal origins of epithelial and stromal components of phyllodes tumor of the prostate. Am J Pathol, 2004, 165(4):1395–1400. https://doi.org/10.1016/S0002-9440(10)63397-4 PMID:15466403 PMCID: PMC1618623

[32] Collins VP, Jones DTW, Giannini C. Pilocytic astrocytoma: pathology, molecular mechanisms and markers. Acta Neuropathol, 2015, 129(6):775–788. https://doi.org/10.1007/s0040 1-015-1410-7 PMID: 25792358 PMCID: PMC4436848

[33] Jurcă MC, Bembea M, Kozma K, Şandor MI, Negrean RA, Dobjanschi L, Cuc EA, Petcheşi CD, Jurcă AD. Empty sella associated with growth hormone deficiency and polydactyly. Rom J Morphol Embryol, 2018, 59(1):381–384. PMID: 29940653

[34] Fryssira H, Leventopoulos G, Psoni S, Kitsiou-Tzeli S, Stavrianeas N, Kanavakis E. Tumor development in three patients with Noonan syndrome. Eur J Pediatr, 2008, 167(9):1025–1031. https://doi.org/10.1007/s00431-007-0636-3 PMID: 18057963

[35] Forshew T, Tatevossian RG, Lawson AR, Ma J, Neale G, Ogunkolade BW, Jones TA, Aarum J, Dalton J, Bailey S, Chaplin T, Carter RL, Gajjar A, Broniscer A, Young BD, Ellison DW, Sheer D. Activation of the ERK/MAPK pathway: a signature genetic defect in posterior fossa pilocytic astrocytomas. J Pathol, 2009, 218(2):172–181. https://doi.org/10.1002/path.2558 PMID: 19373855

[36] Jones DTW, Kocialkowski S, Liu L, Pearson DM, Bäcklund LM, Ichimura K, Collins VP. Tandem duplication producing a novel oncogenic BRAF fusion gene defines the majority of pilocytic astrocytomas. Cancer Res, 2008, 68(21):8673–8677. https://doi.org/10.1158/0008-5472.CAN-08-2097 PMID: 18974108 PMCID: PMC2577184

[37] Badiali M, Gleize V, Paris S, Moi L, Elhouadani S, Arcella A, Morace R, Antonelli M, Buttarelli FR, Figarella-Branger D, Kim YH, Ohgaki H, Mokhtari K, Sanson M, Giangaspero F. KIAA1549–BRAF fusions and IDH mutations can coexist in diffuse gliomas of adults. Brain Pathol, 2012, 22(6):841–847. https://doi.org/10.1111/j.1750-3639.2012.00603.x PMID: 22591444

[38] Omuro A, DeAngelis LM. Glioblastoma and other malignant gliomas: a clinical review. JAMA, 2013, 310(17):1842–1850. https://doi.org/10.1001/jama.2013.280319 PMID: 24193082

[39] Wirsching HG, Galanis E, Weller M. Glioblastoma. Handb Clin Neurol, 2016, 134:381–397. https://doi.org/10.1016/B9 78-0-12-802997-8.00023-2 PMID: 26948367

[40] Aygun N. Biological and genetic features of neuroblastoma and their clinical importance. Curr Pediatr Rev, 2018, 14(2):73–90. https://doi.org/10.2174/1573396314666180129101627 PMID: 29380702

[41] Malis J. Clinical presentation of neuroblastoma. In: Shimada H (ed). Neuroblastoma. IntechOpen Ltd., London, 2013, 3–12. https://doi.org/10.5772/55921

[42] Zhu Y, Li Y, Haraguchi S, Yu M, Ohira M, Ozaki T, Nakagawa A, Ushijima T, Isogai E, Koseki H, Nakamura Y, Kong C, Mehlen P, Arakawa H, Nakagawara A. Dependence receptor UNC5D mediates nerve growth factor depletion-induced neuroblastoma regression. J Clin Invest, 2013, 123(7):2935–2947. https://doi.org/10.1172/JCI65988 PMID: 23778138 PMCID: PMC3696554

[43] Seeger RC, Brodeur GM, Sather H, Dalton A, Siegel SE, Wong KY, Hammond D. Association of multiple copies of the N-myc oncogene with rapid progression of neuroblastomas. N Engl J Med, 1985, 313(18):1111–1116. https://doi.org/10.1056/NEJM198510313131802 PMID: 4047115

[44] Mossé YP, Laudenslager M, Longo L, Cole KA, Wood A, Attiyeh EF, Laquaglia MJ, Sennett R, Lynch JE, Perri P, Laureys G, Speleman F, Kim C, Hou C, Hakonarson H, Torkamani A, Schork NJ, Brodeur GM, Tonini GP, Rappaport E, Devoto M, Maris JM. Identification of ALK as a major familial neuroblastoma predisposition gene. Nature, 2008, 455(7215):930–935. https://doi.org/10.1038/nature07261 PMID: 18724359 PMCID: PMC2672043

[45] Brodeur GM, Seeger RC, Schwab M, Varmus HE, Bishop JM. Amplification of N-myc in untreated human neuroblastomas correlates with advanced disease stage. Science, 1984, 224(4653):1121–1124. https://doi.org/10.1126/science.6719 137 PMID: 6719137

[46] Schwab M, Alitalo K, Klempnauer KH, Varmus HE, Bishop JM, Gilbert F, Brodeur G, Goldstein M, Trent J. Amplified DNA with limited homology to myc cellular oncogene is shared by human neuroblastoma cell lines and a neuroblastoma tumour. Nature, 1983, 305(5931):245–248. https://doi.org/10.1038/305245a0 PMID: 6888561

[47] Altungoz O, Aygun N, Tumer S, Ozer E, Olgun N, Sakizli M. Correlation of modified Shimada classification with MYCN and 1p36 status detected by fluorescence in situ hybridization in neuroblastoma. Cancer Genet Cytogenet, 2007, 172(2):113–119. https://doi.org/10.1016/j.cancergencyto.2006.10.005 PMID: 17213019

[48] Bartram CR, Berthold F. Amplification and expression of the N-myc gene in neuroblastoma. Eur J Pediatr, 1987, 146(2):162–165. https://doi.org/10.1007/BF02343225 PMID: 3569354

[49] Abel F, Sjöberg RM, Ejeskär K, Krona C, Martinsson T. Analyses of apoptotic regulators CASP9 and DFFA at 1p36.2, reveal rare allele variants in human neuroblastoma tumours. Br J Cancer, 2002, 86(4):596–604. https://doi.org/10.1038/sj.bjc.6600111 PMID: 11870543 PMCID: PMC2375272

[50] Brodeur GM, Maris JM, Yamashiro DJ, Hogarty MD, White PS. Biology and genetics of human neuroblastomas. J Pediatr Hematol Oncol, 1997, 19(2):93–101. https://doi.org/10.1097/00043426-199703000-00001 PMID: 9149737

[51] Kivelä T. The epidemiological challenge of the most frequent eye cancer: retinoblastoma, an issue of birth and death. Br J Ophthalmol, 2009, 93(9):1129–1131. https://doi.org/10.1136/bjo.2008.150292 PMID: 19704035

[52] Lan X, Xu W, Tang X, Ye H, Song X, Lin L, Ren X, Yu G, Zhang H, Wu S. Spectrum of *RB1* germline mutations and clinical features in unrelated Chinese patients with retinoblastoma. Front Genet, 2020, 11:142. https://doi.org/10.3389/fgene.2020.00142 PMID: 32218800 PMCID: PMC7080181

[53] Burkhart DL, Sage J. Cellular mechanisms of tumour suppression by the retinoblastoma gene. Nat Rev Cancer, 2008, 8(9):671–682. https://doi.org/10.1038/nrc2399 PMID: 18650841 PMCID: PMC6996492

[54] Parma D, Ferrer M, Luce L, Giliberto F, Szijan I. *RB1* gene mutations in Argentine retinoblastoma patients. Implications for genetic counseling. PLoS One, 2017, 12(12):e0189736. https://doi.org/10.1371/journal.pone.0189736 PMID: 29261756 PMCID: PMC5738096

[55] Soliman SE, Racher H, Zhang C, MacDonald H, Gallie BL. Genetics and molecular diagnostics in retinoblastoma – an update. Asia Pac J Ophthalmol (Phila), 2017, 6(2):197–207. https://doi.org/10.22608/APO.201711 PMID: 28399338

[56] Wilting RH, Dannenberg JH. Epigenetic mechanisms in tumorigenesis, tumor cell heterogeneity and drug resistance. Drug Resist Updat, 2012, 15(1–2):21–38. https://doi.org/10.1016/j.drup.2012.01.008 PMID: 22356866

[57] Reis AHO, Vargas FR, Lemos B. More epigenetic hits than meets the eye: microRNAs and genes associated with the tumorigenesis of retinoblastoma. Front Genet, 2012, 3:284. https://doi.org/10.3389/fgene.2012.00284 PMID: 23233862 PMCID: PMC3516829

[58] Barnoud T, Parris JLD, Murphy ME. Common genetic variants in the *TP53* pathway and their impact on cancer. J Mol Cell Biol, 2019, 11(7):578–585. https://doi.org/10.1093/jmcb/mjz052 PMID: 31152665 PMCID: PMC6736421

[59] Xu XL, Fang Y, Lee TC, Forrest D, Gregory-Evans C, Almeida D, Liu A, Jhanwar SC, Abramson DH, Cobrinik D. Retinoblastoma has properties of a cone precursor tumor and depends upon cone-specific MDM2 signaling. Cell, 2009, 137(6):1018–1031. https://doi.org/10.1016/j.cell.2009.03.051 PMID: 19524506 PMCID: PMC5659855

[60] Mraz CE, Mureşan M, Micle O, Vicaş L, Pallag A, Coltău M, Puşcaş I. Effects of vitamin D on carbonic anhydrase activity experimental research *in vitro* and *in vivo*. Farmacia, 2012, 60(2):264–271. https://farmaciajournal.com/wp-content/uploads/2012-02-art.12.mraz-264-271.pdf

[61] Call KM, Glaser T, Ito CY, Buckler AJ, Pelletier J, Haber DA, Rose EA, Kral A, Yeger H, Lewis WH, Jones C, Housman DE. Isolation and characterization of a zinc finger polypeptide gene at the human chromosome 11 Wilms' tumor locus. Cell, 1990, 60(3):509–520. https://doi.org/10.1016/0092-8674(90)90601-a PMID: 2154335

[62] Huff V. Wilms tumor genetics. Am J Med Genet, 1998, 79(4):260–267. https://doi.org/10.1002/(sici)1096-8628(19981002)79:4<260::aid-ajmg6>3.0.co;2-q PMID: 9781905

[63] Grundy PE, Breslow NE, Li S, Perlman E, Beckwith JB, Ritchey ML, Shamberger RC, Haase GM, D'Angio GJ, Donaldson M, Coppes MJ, Malogolowkin M, Shearer P, Thomas PRM, Macklis R, Tomlinson G, Huff V, Green DM; National Wilms Tumor Study Group. Loss of heterozygosity for chromosomes 1p and 16q is an adverse prognostic factor in favorable-histology Wilms tumor: a report from the National Wilms Tumor Study Group. J Clin Oncol, 2005, 23(29):7312–7321. https://doi.org/10.1200/JCO.2005.01.2799 PMID: 16129848

[64] Walz AL, Ooms A, Gadd S, Gerhard DS, Smith MA, Guidry Auvil JM, Meerzaman D, Chen QR, Hsu CH, Yan C, Nguyen C, Hu Y, Bowlby R, Brooks D, Ma Y, Mungall AJ, Moore RA, Schein J, Marra MA, Huff V, Dome JS, Chi YY, Mullighan CG, Ma J, Wheeler DA, Hampton OA, Jafari N, Ross N, Gastier-Foster JM, Perlman EJ. Recurrent *DGCR8*, *DROSHA*, and *SIX* homeodomain mutations in favorable histology Wilms tumors. Cancer Cell, 2015, 27(2):286–297. https://doi.org/10.1016/j.ccell.2015.01.003 PMID: 25670082 PMCID: PMC4800737

[65] Wegert J, Ishaque N, Vardapour R, Geörg C, Gu Z, Bieg M, Ziegler B, Bausenwein S, Nourkami N, Ludwig N, Keller A, Grimm C, Kneitz S, Williams RD, Chagtai T, Pritchard-Jones K, van Sluis P, Volckmann R, Koster J, Versteeg R,

Acha T, O'Sullivan MJ, Bode PK, Niggli F, Tytgat GA, van Tinteren H, van den Heuvel-Eibrink MM, Meese E, Vokuhl C, Leuschner I, Graf N, Eils R, Pfister SM, Kool M, Gessler M. Mutations in the *SIX1/2* pathway and the *DROSHA/DGCR8* miRNA microprocessor complex underlie high-risk blastemal type Wilms tumors. Cancer Cell, 2015, 27(2):298–311. https://doi.org/10.1016/j.ccell.2015.01.002 PMID: 25670083

[66] Rakheja D, Chen KS, Liu Y, Shukla AA, Schmid V, Chang TC, Khokhar S, Wickiser JE, Karandikar NJ, Malter JS, Mendell JT, Amatruda JF. Somatic mutations in *DROSHA* and *DICER1* impair microRNA biogenesis through distinct mechanisms in Wilms tumours. Nat Commun, 2014, 2:4802. https://doi.org/10.1038/ncomms5802 PMID: 25190313 PMCID: PMC4159681

[67] Torrezan GT, Ferreira EN, Nakahata AM, Barros BDF, Castro MTM, Correa BR, Krepischi ACV, Olivieri EHR, Cunha IW, Tabori U, Grundy PE, Costa CML, de Camargo B, Galante PAF, Carraro DM. Recurrent somatic mutation in *DROSHA* induces microRNA profile changes in Wilms tumour. Nat Commun, 2014, 5:4039. https://doi.org/10.1038/ncomms5039 PMID: 24909261 PMCID: PMC4062040

[68] Foulkes WD, Priest JR, Duchaine TF. *DICER1*: mutations, microRNAs and mechanisms. Nat Rev Cancer, 2014, 14(10):662–672. https://doi.org/10.1038/nrc3802 PMID: 25176334

[69] Palculict TB, Ruteshouser EC, Fan Y, Wang W, Strong L, Huff V. Identification of germline *DICER1* mutations and loss of heterozygosity in familial Wilms tumour. J Med Genet, 2016, 53(6):385–388. https://doi.org/10.1136/jmedgenet-2015-103311 PMID: 26566882 PMCID: PMC4866907

[70] Wu MK, Sabbaghian N, Xu B, Addidou-Kalucki S, Bernard C, Zou D, Reeve AE, Eccles MR, Cole C, Choong CS, Charles A, Tan TY, Iglesias DM, Goodyer PR, Foulkes WD. Biallelic *DICER1* mutations occur in Wilms tumours. J Pathol, 2013, 230(2):154–164. https://doi.org/10.1002/path.4196 PMID: 23620094

[71] Jurcă AD, Kozma K, Ioana M, Streaţă I, Petcheşi CD, Bembea M, Jurcă MC, Cuc EA, Vesa CM, Buhaş CL. Morphological and genetic abnormalities in a Jacobsen syndrome. Rom J Morphol Embryol, 2017, 58(4):1531–1534. PMID: 29556653

[72] Amer KM, Thomson JE, Congiusta D, Dobitsch A, Chaudhry A, Li M, Chaudhry A, Bozzo A, Siracuse B, Aytekin MN, Ghert M, Beebe KS. Epidemiology, incidence, and survival of rhabdomyosarcoma subtypes: SEER and ICES database analysis. J Orthop Res, 2019, 37(10):2226–2230. https://doi.org/10.1002/jor.24387 PMID: 31161653

[73] Ruymann FB, Grovas AC. Progress in the diagnosis and treatment of rhabdomyosarcoma and related soft tissue sarcomas. Cancer Invest, 2000, 18(3):223–241. https://doi.org/10.3109/07357900009031827 PMID: 10754991

[74] Morales RL, Álvarez A, Esguerra J, Prada Avella MC, Rojas F. Primary conjunctival rhabdomyosarcoma in a pediatric patient. Cureus, 2019, 11(12):e6310. https://doi.org/10.7759/cureus.6310 PMID: 31938602 PMCID: PMC6944172

[75] Dasgupta R, Fuchs J, Rodeberg D. Rhabdomyosarcoma. Semin Pediatr Surg, 2016, 25(5):276–283. https://doi.org/10.1053/j.sempedsurg.2016.09.011 PMID: 27955730

[76] Rudzinski ER, Anderson JR, Chi YY, Gastier-Foster JM, Astbury C, Barr FG, Skapek SX, Hawkins DS, Weigel BJ, Pappo A, Meyer WH, Arnold MA, Teot LA, Parham DM. Histology, fusion status, and outcome in metastatic rhabdomyosarcoma: a report from the Children's Oncology Group. Pediatr Blood Cancer, 2017, 64(12):e26645. https://doi.org/10.1002/pbc.26645 PMID: 28521080 PMCID: PMC5647228

[77] Ricker CA, Crawford K, Matlock K, Lathara M, Seguin B, Rudzinski ER, Berlow NE, Keller C. Defining an embryonal rhabdomyosarcoma endotype. Cold Spring Harb Mol Case Stud. 2020, 6(2):a005066. https://doi.org/10.1101/mcs.a005066 PMID: 32238403 PMCID: PMC7133750

[78] Barr FG, Nauta LE, Davis RJ, Schäfer BW, Nycum LM, Biegel JA. *In vivo* amplification of the *PAX3-FKHR* and *PAX7-FKHR* fusion genes in alveolar rhabdomyosarcoma. Hum Mol Genet, 1996, 5(1):15–21. https://doi.org/10.1093/hmg/5.1.15 PMID: 8789435

[79] Taylor AC, Shu L, Danks MK, Poquette CA, Shetty S, Thayer MJ, Houghton PJ, Harris LC. *P53* mutation and *MDM2* amplification frequency in pediatric rhabdomyosarcoma tumors and cell lines. Med Pediatr Oncol, 2000, 35(2):96–

103. https://doi.org/10.1002/1096-911x(200008)35:2<96::aid-mpo2>3.0.co;2-z PMID: 10918230

[80] Stratton MR, Fisher C, Gusterson BA, Cooper CS. Detection of point mutations in *N-ras* and *K-ras* genes of human embryonal rhabdomyosarcomas using oligonucleotide probes and the polymerase chain reaction. Cancer Res, 1989, 49(22): 6324–6327. PMID: 2680062

[81] Kohsaka S, Shukla N, Ameur N, Ito T, Ng CK, Wang L, Lim D, Marchetti A, Viale A, Pirun M, Socci ND, Qin LX, Sciot R, Bridge J, Singer S, Meyers P, Wexler LH, Barr FG, Dogan S, Fletcher JA, Reis-Filho JS, Ladanyi M. A recurrent neomorphic mutation in *MYOD1* defines a clinically aggressive subset of embryonal rhabdomyosarcoma associated with PI3K-AKT pathway mutations. Nat Genet, 2014, 46(6):595–600. https://doi.org/10.1038/ng.2969 PMID: 24793135 PMCID: PMC4231202

[82] Mentzel T, Kuhnen C. Spindle cell rhabdomyosarcoma in adults: clinicopathological and immunohistochemical analysis of seven new cases. Virchows Arch, 2006, 449(5):554–560. https://doi.org/10.1007/s00428-006-0284-4 PMID: 17013628

[83] Fu X, Chen G, Cai ZD, Wang C, Liu ZZ, Lin ZY, Wu YD, Liang YX, Han ZD, Liu JC, Zhong WD. Overexpression of *BUB1B* contributes to progression of prostate cancer and predicts poor outcome in patients with prostate cancer. Onco Targets Ther, 2016, 9:2211–2220. https://doi.org/10.2147/OTT.S101994 PMID: 27143916 PMCID: PMC4844448

[84] Shukla N, Ameur N, Yilmaz I, Nafa K, Lau CY, Marchetti A, Borsu L, Barr FG, Ladanyi M. Oncogene mutation profiling of Fpediatric solid tumors reveals significant subsets of embryonal rhabdomyosarcoma and neuroblastoma with mutated genes in growth signaling pathways. Clin Cancer Res, 2012, 18(3): 748–757. https://doi.org/10.1158/1078-0432.CCR-11-2056 PMID: 22142829 PMCID: PMC3271129

[85] Lam SW, Cleven AHG, Kroon HM, Briaire-de Bruijn IH, Szuhai K, Bovée JVMG. Utility of FOS as diagnostic marker for osteoid osteoma and osteoblastoma. Virchows Arch, 2020, 476(3):455–463. https://doi.org/10.1007/s00428-019-02684-9 PMID: 31768625 PMCID: PMC7085481

[86] Smeland S, Bielack SS, Whelan J, Bernstein M, Hogendoorn P, Krailo MD, Gorlick R, Janeway KA, Ingleby FC, Anninga J, Antal I, Arndt C, Brown KLB, Butterfass-Bahloul T, Calaminus G, Capra M, Dhooge C, Eriksson M, Flanagan AM, Friedel G, Gebhardt MC, Gelderblom H, Goldsby R, Grier HE, Grimer R, Hawkins DS, Hecker-Nolting S, Sundby Hall K, Isakoff MS, Jovic G, Kühne T, Kager L, von Kalle T, Kabickova E, Lang S, Lau CC, Leavey PJ, Lessnick SL, Mascarenhas L, Mayer-Steinacker R, Meyers PA, Nagarajan R, Randall RL, Reichardt P, Renard M, Rechnitzer C, Schwartz CL, Strauss S, Teot L, Timmermann B, Sydes MR, Marina N. Survival and prognosis with osteosarcoma: outcomes in more than 2000 patients in the EURAMOS-1 (European and American Osteosarcoma Study) cohort. Eur J Cancer, 2019, 109:36–50. https://doi.org/10.1016/j.ejca.2018.11.027 PMID: 30685685 PMCID: PMC6506906

[87] Kansara M, Teng MW, Smyth MJ, Thomas DM. Translational biology of osteosarcoma. Nat Rev Cancer, 2014, 14(11): 722–735. https://doi.org/10.1038/nrc3838 PMID: 25319867

[88] Hameed M, Mandelker D. Tumor syndromes predisposing to osteosarcoma. Adv Anat Pathol, 2018, 25(4):217–222. https://doi.org/10.1097/PAP.0000000000000190 PMID: 29668499 PMCID: PMC6688172

[89] Stephens PJ, Greenman CD, Fu B, Yang F, Bignell GR, Mudie LJ, Pleasance ED, Lau KW, Beare D, Stebbings LA, McLaren S, Lin ML, McBride DJ, Varela I, Nik-Zainal S, Leroy C, Jia M, Menzies A, Butler AP, Teague JW, Quail MA, Burton J, Swerdlow H, Carter NP, Morsberger LA, Iacobuzio-Donahue C, Follows GA, Green AR, Flanagan AM, Stratton MR, Futreal PA, Campbell PJ. Massive genomic rearrangement acquired in a single catastrophic event during cancer development. Cell, 2011, 144(1):27–40. https://doi.org/10.1016/j.cell.2010.11.055 PMID: 21215367 PMCID: PMC3065307

[90] Macintyre G, Ylstra B, Brenton JD. Sequencing structural variants in cancer for precision therapeutics. Trends Genet, 2016, 32(9):530–542. https://doi.org/10.1016/j.tig.2016.07.002 PMID: 27478068

[91] Franceschini N, Lam SW, Cleton-Jansen AM, Bovée JVMG. What's new in bone forming tumours of the skeleton? Virchows Arch, 2020, 476(1):147–157. https://doi.org/10.1007/s00428-019-02683-w PMID: 31741049 PMCID: PMC6969005

[92] Kovac M, Blattmann C, Ribi S, Smida J, Mueller NS, Engert F, Castro-Giner F, Weischenfeldt J, Kovacova M, Krieg A, Andreou D, Tunn PU, Dürr HR, Rechl H, Schaser KD, Melcher I, Burdach S, Kulozik A, Specht K, Heinimann K, Fulda S, Bielack S, Jundt G, Tomlinson I, Korbel JO, Nathrath M, Baumhoer D. Exome sequencing of osteosarcoma reveals mutation signatures reminiscent of BRCA deficiency. Nat Commun, 2015, 6:8940. https://doi.org/10.1038/ncomms9940 PMID: 26632267 PMCID: PMC4686819

[93] Chen X, Bahrami A, Pappo A, Easton J, Dalton J, Hedlund E, Ellison D, Shurtleff S, Wu G, Wei L, Parker M, Rusch M, Nagahawatte P, Wu J, Mao S, Boggs K, Mulder H, Yergeau D, Lu C, Ding L, Edmonson M, Qu C, Wang J, Li Y, Navid F, Daw NC, Mardis ER, Wilson RK, Downing JR, Zhang J, Dyer MA; St. Jude Children's Research Hospital–Washington University Pediatric Cancer Genome Project. Recurrent somatic structural variations contribute to tumorigenesis in pediatric osteosarcoma. Cell Rep, 2014, 7(1):104–112. https://doi.org/10.1016/j.celrep.2014.03.003 PMID: 24703847 PMCID: PMC4096827

[94] Bembea M, Patocs A, Kozma K, Jurca C, Skrypnyk C. Y-chromosome STR haplotype diversity in three ethnically isolated population from North-Western Romania. Forensic Sci Int Genet, 2011, 5(3):e99–e100. https://doi.org/10.1016/j.fsigen.2010.12.004 PMID: 21269904

[95] Lézot F, Corre I, Morice S, Rédini F, Verrecchia F. SHH signaling pathway drives pediatric bone sarcoma progression. Cells, 2020, 9(3):536. https://doi.org/10.3390/cells9030536 PMID: 32110934 PMCID: PMC7140443

[96] Sbaraglia M, Righi A, Gambarotti M, Dei Tos AP. Ewing sarcoma and Ewing-like tumors. Virchows Arch, 2020, 476(1): 109–119. https://doi.org/10.1007/s00428-019-02720-8 PMID: 31802230

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