VIA MEDICA

Genetics and oncology

NOWOTWORY Journal of Oncology
2022, volume 72, number 1, 58–64
DOI: 10.5603/NJO.2022.0007

ISSN 0029–540X, e-ISSN: 2300-2115
www.nowotwory.edu.pl

Phacomatoses, genetic testing for personalisation of clinical management (part 2)

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Von Hippel-Lindau disease and tuberous sclerosis are rare genetic disorders, which belong to the group of phacomatoses. They involve an increased risk of development of multiple cancers, mostly benign ones, which may undergo malignant transformation. Genetic diagnostic including identification of the pathogenic variant of the *VHL* and *TSC1* and *TSC2* genes enables optimisation of patient care and identification of relatives who carry the mutation.

Key words: von Hippel-Lindau disease, VHL, tuberous sclerosis, sclerosis tuberosa complex, *TSC*, phacomatosis

Von Hippel-Lindau disease

Von Hippel-Lindau disease (VHL, OMIM 193300) owes its name to the German ophthalmologist Eugen von Hippel and the Swedish pathologist Arvid Lindau, who, working independently from each other, described in 1904 and 1926 clinical syndromes characterised by the presence of tumours of the retina and the central nervous system [1]. VHL is a genetically determined syndrome, predisposing to development of neoplasms, which is inherited in an autosomal dominant manner with almost full penetration. In about 20% of patients, the mutation occurs *de novo* , but it is passed on by the carrier to their offspring (50% risk of passing the mutation on), and in subsequent generations the course of the disease is more severe, and the symptoms occur earlier, in a process referred to as genetic anticipation [2]. The disease is diagnosed in 1 person per 38–91,000 and the incidence is 1 in 36–45,000 births [1]. The first symptoms appear as early as in the second decade of life, the diagnosis criteria are met in all patients before the age of 70 [1]. If VHL disease is diagnosed, constant patient surveillance is necessary, as it allows early detection of neoplasms and implementation of the optimal therapy. Nevertheless, life expectancy for people with VHL is the shortest among those with other hereditary cancer syndromes [3]. The course of the disease involves development of multiple benign and malignant tumours within the central nervous system (CNS), eye, internal organs, especially kidneys, pancreas, adrenal glands [4].

Hemangioblastomas of the central nervous system are often the first symptom of the disease and occur in 72–75% of patients [1]. They can be located in the cerebellum (*hemangioblastoma cerebelli*), in the medulla oblongata (*hemangioblastoma medullae oblongatae*), and in the spinal cord (*hematoblastoma medullae spinalis*). Depending on their location and size, they lead to a variety of clinical symptoms. The mass effect of intracranial tumours may lead to an increase in intracranial pressure manifested by nausea, vomiting, displacement of brain structures with impaction leading to death. In the case of smaller tumours, there may be focal symptoms, headaches or they may be asymptomatic. Cerebellar location causes balance disturbances, which are also present in the case of the endolymphatic sac tumours (ELST), observed in about 15% of patients with VHL. This tumour is characterised by local

How to cite:
Kofla-Dłubacz A, Stawarski A, Pytrus T, Gil J. ***Phacomatoses, genetic testing for personalisation of clinical management (part 2)*** . *NOWOTWORY J Oncol* 2022; 72: 58–64.

malignancy, and as it increases in size, it destroys the structures of the inner ear and the temporal bone pyramid. It may also infiltrate cranial nerves (facial and vestibulocochlear nerves). As it grows towards the cerebellum, it causes the pontocerebellar angle syndrome. Typical symptoms include complete or partial hearing loss which occurs in 95–100% of patients, tinnitus in 77% of patients, vestibular balance disorders - 62% of patients and facial nerve palsy – 8% of patients [1, 5]. Treatment of CNS hemangioblastomas, as well as ELSTs is mainly surgical and depends on the location, tumour size, as well as possible infiltration of adjacent anatomical structures.

Retinal hemangioblastoma (retinal capillary hemangioma, hemangioblastoma) is observed in 50–60% of patients with VHL [6]. Ophthalmological examination reveals a sharply delineated orange-red lesion, richly vascularized, with intra- and subretinal exudate. The lesions are located in the peridural part or on the periphery of the retina (upper or lower temporal area). In about 25% of patients, permanent loss of vision occurs, and presence of multiple lesions predisposes to formation of further foci [7].

Patients diagnosed with VHL require constant ophthalmic supervision, including fluorescein angiography (AF – distinguishing nutrient arterioles from drainage veins), ultrasound examination (determination of the tumour diameter, visualization of fluid), optical coherence tomography (determination of the subretinal fluid accumulation site). The treatment includes laser photocoagulation, cryotherapy, photodynamic therapy, and techniques of vitroretinal surgery. Pharmacotherapy involves attempts to administer antagonists of vascular endothelial growth factor (VEGF) in the case of posterior pole hemangiomas [1, 7].

Renal cell carcinoma (RRC) occurs in approximately 30% of patients with VHL. It originates from the renal tubular epithelium, histologically most often it is a clear cell carcinoma, differing from the sporadic form by multifocal manifestation and association with renal cysts. It may be bilateral [1, 8]. Clinical symptoms in the form of a palpable tumour mass, pain in the lumbar region and haematuria occur in patients with large tumours (Virchow's triad). Smaller tumours remain asymptomatic and are detected incidentally in screening imaging studies. Occasionally, the so-called paraneoplastic symptoms occur, with hypercalcemia related to the secretion of PTH-like peptide (PThrP), arterial hypertension caused by production of renin by tumour cells or polyglobulia – resulting from release of erythropoietin [9].

The basic diagnostic tools are computed tomography and magnetic resonance imaging. Histological diagnosis is made after harvesting a tumour fragment by kidney biopsy or during nephrectomy, which is one of the basic therapeutic methods in RRC. Surgical treatment for small tumours (smaller than 3 cm) consists in removing the tumour mass with a healthy kidney margin. In advanced stages, pharmacotherapeutic attempts are made to treat the cancer with tyrosine kinase inhibitors that block angiogenesis and mTOR kinases. Interferon alpha immunotherapy is also used.

Pheochromocytoma occurs in approximately 16% of VHL patients [1]. It is a catecholamine-secreting tumour occurring in VHL, usually benign, affecting mainly adrenal glands, often bilateral. It may also be multifocal. As in the sporadic form, the main clinical symptom is arterial hypertension (paroxysmal or permanent), which may be associated with headaches and increased sweating. Other observed symptoms include paroxysmal paling of the skin, a feeling of anxiety, tremors, cardiac arrhythmias in the form of tachycardia, ventricular accessory contractions, atrial fibrillation or additional ventricular beats, which may cause sudden cardiac death or chronic heart disease – cardiomyopathy with development of pulmonary congestion.

Diagnostic includes testing of free catecholamines or their metabolites (vanillylmandelic acid-VMA, methoxycatecholamines) in the 24-hour urine collection. Methoxycatecholamine can also be measured in the serum. Tumour location is determined with computed tomography or magnetic resonance imaging, or occasionally iodine-labelled metaiodobenzylguanidine (MIBG) scintigraphy, which is especially useful for diagnosing small lesions and metastases [1]. Abdominal ultrasound is also used as a screening method to detect *pheochromocytoma*-type tumours.

Treatment of pheochromocytomas involves surgical resection (total or sparing adrenalectomy) after pharmacological pre-treatment, in which blood pressure and heart rate should be normalised. For this purpose, alpha blockers are employed, as the basic drug (phenoxybenzamine) is used for 2 weeks before the planned surgery. Alpha-blocker therapy can be supplemented with beta-blocking drugs, especially in people with concomitant tachycardia. Beta blockers cannot be used as monotherapy [1]. Patients after surgical resection of a pheochromocytoma require constant supervision to enable early detection of the potential tumour recurrence.

Changes in the pancreas are cysts or benign cystic neoplasms (cystadenomas). They occur in a large group of patients with VHL disease – 72% [1]. They may remain asymptomatic or affect the pancreatic and exocrine capacity due to effected pressure. Pancreatic neuroendocrine tumours (PNET) may also occur in the course of VHL.

The multi-organ manifestation of VHL disease and the multitude of possible clinical symptoms associated with it require multidisciplinary supervision and the selection of treatment according to the type of lesions affecting the individual patient. In general, two basic types of the disease can be distinguished: 1, 2, with the latter including a, b, c subtypes [10]. The diagnostic criteria include a clinical analysis of the patient with a diagnosed coexistence of multiple neoplastic lesions [1]. VHL can be diagnosed in the case of detection of:

- at least two haemangioma-type tumours of the central nervous system (central nervous system hemangioblastomas),

- at least one hemangioblastoma of the central nervous system and one of the neoplastic tumours described below,
- at least one of the tumours described below and a mutation typical of VHL or having a first-degree relative diagnosed with VHL.

Typical symptoms of VHL included in the diagnostic criteria refer to occurrence of:

- a CNS neuroblastoma (including a diagnosed retinal hemangioblastoma),
- endolymphatic sac tumours,
- renal-cell carcinoma,
- pheochromocytoma, paraganglioma (glomus tumour),
- neuroendocrine tumours and / or multiple pancreatic cysts.

In patients with VHL diagnosis confirmed by a genetic test result, the periodic examinations should include:

- at the age of 0–2 years – annual physical and ophthalmological examination,
- from 2 years of age – MRI of the brain and spinal cord twice a year,
- abdominal ultrasound annually, if cysts or tumours are found – computed tomography (CT) examination every 6 months,
- from 20 years of age – annual CT instead of annual ultrasound,
- from the age of 60 – computed tomography in any year in MRI was not performed; if there are no symptoms, MRI every 3–5 years [11].

Genetic background, diagnosis and genetic counselling

Mutations in the *VHL* suppressor gene constitute the molecular background of von Hippel-Lindau syndrome. The *VHL* gene is located on the short arm of chromosome 3 (locus p25.3, MIM * 608537), it consists of three exons (642 nucleotides) and encodes a highly conserved protein. Gene transcript is present in various cell types in many tissues (both in foetal and postnatal life) [12]. Depending on the point of translation initiation, determined by the presence of two methionine (start) codons, two protein isoforms (pVHL) are formed, one consisting of 213 amino acids ($VHLp_{30}$, cytoplasmic expression) and the other consisting of 160 amino acid residues ($VHLp_{19}$, nuclear expression) [13].

VHL protein acts in complexes with various proteins. First of all, it forms the VBC complex with elongin C and the complex of elongin B with kullin-2 and Rbx (binding through the α domain) [14]. Under physiological conditions (normal oxygen concentration), the VBC complex, of the activity of ubiquitin ligase E3, is responsible for ubiquitination of the alpha subunit of hypoxia-inducible factor 1 (HIF1-α), leading to its proteolysis in the proteasome and consequently inhibiting transcription of hypoxia-induced genes [15]. The domain responsible for binding the substrate to the VBC complex is the β domain of pVHL, which binds HIF1-α via hydroxylated proline residues. Under hypoxic conditions, there is no hydroxylation of HIF1-α proline residues and no binding to pVHL [16]. This results in the accumulation of HIF1-α, and consequently, transcription of genes regulated by the HIF1 protein (HIF1-α and HIF1-β heterodimer) is induced, including genes encoding growth factors such as: vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and transforming growth factor alpha (TGF-α), as well as *EPO* gene encoding erythropoietin. Moreover, the VBC complex also regulates HIF2-α, HIF3-α and atypical protein kinase λ [10, 17, 18].

VHL protein dysfunction results in deregulation in the control of HIF1-α degradation and is associated with a permanently high level of HIF (independent of the oxygen level) which leads to overproduction of VEGF, PDGF and TGF-α. This is the most likely molecular mechanism to explain the excessive abnormal proliferation and angiogenesis in richly vascularized tumours of the VHL spectrum. It has also been shown that the dysfunction of the VBC complex contributes to development of pheochromocytomas as a result of the accumulation of atypical λ protein kinase, which leads to overexpression of the transcription factor B-jun which inhibits apoptosis in nerve crest cells in the adrenal medulla [10, 19].

VHL syndrome is inherited in an autosomal dominant manner and in about 80% of cases the mutation is inherited from one of the parents (Mendelian inheritance, 50% risk of passing the mutation). In the remaining 20% of cases, the mutation occurs *de novo* and in the family there are no people with diagnosed or suspected VHL [13]. Genetic testing is extremely important in terms of developing a preventive care program for the mutation carrier (taking into account the risk of neoplasms from the spectrum of this syndrome) and providing genetic counselling to the entire family. Genetic testing may be targeted to analyse a single gene or a panel of genes associated with phacomatoses, and in the case of an ambiguous phenotype, total or whole genome testing may be considered. The most common types of mutation in the *VHL* gene are missense (approximately 30–60%), intra-gene insertions / deletions, frameshift mutations and splice site mutations, all leading to protein truncation of approximately 20–30%. About 20–40% of the mutations are large deletions, sometimes involving the entire gene [20].

So far, more than 300 pathogenic variants in the *VHL* gene have been identified [17]. Pathogenic variants were found in all three exons. The 167 codon encoding arginine is considered a "mutational hot spot" [21]. The disease is characterised by age-dependent full penetration and variable expression (penetration is assumed to exceed 90% around the age of 65) [13]. Knudson's two-hit hypothesis explains development of VHL. One defective allele is present in all cells (constitutional mutation), and the loss of the second copy (deletion, point mutation, hypermethylation of the promoter sequence) of the gene is a factor that initiates the process of neoplastic transformation [22].

Genotype-phenotype correlations are well studied. Major changes such as whole exon deletion and mutations leading to protein truncation are most often associated with the VHL type 1 phenotype, with retinal and central nervous system haemangiomas, kidney cancer and pancreatic cysts, but no pheochromocytoma. Missense pathogenic changes are associated with type 2 VHL, in which pheochromocytoma is observed. Depending on coexistence of other organ manifestations, type 2 is divided into type 2A (pheochromocytoma, haemangioma, no kidney cancer), 2B (pheochromocytoma, haemangioma, kidney cancer), 2C (pheochromocytoma) [13]. Some researchers suggest also inclusion of 1B type, characterised, like type 1, by no pheochromocytoma and additionally low risk of renal cancer. Type 1B is characteristic of patients who, in addition to the deletion of the *VHL* gene, have a deletion in the *BRK1* gene [13].

Identification of the pathogenic variant of the *VHL* gene allows molecular diagnostics for family members to identify pre-symptomatic carriers of mutation, and then to introduce an appropriate diagnostic and prophylactic surveillance, reducing the need for screening in those who have not inherited the pathogenic variants [23]. Genetic counselling should also take into account the risk of germ cell mosaicism of the parent whose child has a confirmed mutation, if the same change was not found in the parents' examination. Additionally, somatic mosaicism is also possible, signifying that the pathogenic variant is present only in some of the cells of the body. The course of the disease in this case will be milder and if the pathogenic variant is absent in the germ cells, the risk of disease in the offspring is at the level of the population risk of [24].

In Poland, patients with VHL are included in the care program for families of high, hereditary risk of developing malignant neoplasms – Module III – "Prophylaxis and early detection of malignant neoplasms in families with rare hereditary cancer syndromes – retinoblastoma, Von Hippel-Lindau disease (VHL)". The programme guarantees medical procedures concerning identification of patients with VHL based on clinical diagnostic, molecular analysis – genetic testing, and regular patient care including:

- annual medical consultation,
- MRI of the head and spinal cord from the age of 11 (every 1 to 3 years depending on changes present within the CNS),
- abdominal ultrasound (annually)
- abdominal CT (or MRI) (every 2–3 years),
- ophthalmological consultation from the age of 1; fundus examination in the Goldman mirror from the age of 6.

Therefore, it is crucial to identify pre-symptomatic carriers and to introduce screening tests as early as possible. Consequently, it is also justified to perform genetic tests in children from families with the critical mutation to identify the mutation in the *VHL* gene observed in the family. Further, in families with the identified mutation, prenatal and preimplantation tests can be performed, too [21].

Tuberous sclerosis

Tuberous sclerosis (sclerosis tuberosa complex – TSC), also known as Bourneville-Pringle disease, is an autosomal dominant disease with full penetration and variable expression. In about 75% of the cases a TSC mutation arises de novo. The disease is diagnosed in 1 in 10,000 children born, and its frequency in the general population is 1: 6,800–1: 17,300 [25, 26].

Tuberous sclerosis is characterised by formation of hamartomata-type tumours of the skin, central nervous system, kidneys, lungs and heart. The characteristic triad of symptoms includes mental retardation, epilepsy, and Pringle angiofibromas, which appear in early childhood as yellowish-pink papules covering the seborrheic surfaces of the face (nose, medial cheeks, forehead). They occur in almost 90% of patients and their number increases in adolescence. They have an undesirable cosmetic effect, and may spontaneously bleed [26].

Other skin lesions seen in TSC are leaf-shaped discolorations (leaf-shaped leukoderma), often located on the scalp, showing a characteristic discoloured strand of hair growing out of the lesion. "Confetti" stains are observed, too, showing as colourless marks on the extensor surfaces of limbs, shagreen patches in the sacral region of the body or squamous fibromas in the forehead region which occur in about 25% of the patients [27]. Gingival fibromas, similarly to fibromas of the nail folds called Koenen's nodules, appear later, mainly in adults [26].

Kidney symptoms

Angiomyolipoma is a hamartoma- type tumour which occurs in 80% of the patients. It is a benign neoplasm, however, as it enlarges, it may cause spontaneous haemorrhage into the kidney capsule (Wunderlich's syndrome) or its failure, resulting in increased mortality among patients [26]. Negative prognosis is also associated with presence of the renal clear cell carcinoma. Its incidence is higher in TSC patients as compared to the general population. Mutations in the *TSC2* gene increase the risk of polycystic kidney disease in people with TSC [28].

Neurological symptoms

Epilepsy diagnosed in early childhood, often infancy, is a characteristic symptom of TSC which occurs in 79–90% of patients [26]. Behavioural disorders from the autism spectrum, ADHD, and mental retardation are also observed – in about 40% of patients [29]. Some of these disorders are related to structural changes in the brain resulting from formation of hamartoma-type cortical-subcortical tumours subependymal heterotopic / periventricular nodules. Subependymal periventricular nodules may become a starting point for a malignant tumour referred to as a subependymal giant cell astrocytoma which grows in lateral ventricles of the brain and may lead to Monro foramen obstruction, ventricular enlargement, hydrocephalus and death. Diagnosis is based on brain imaging including computed tomography and magnetic resonance imaging,

which also shows white matter heterotypes (white matter linear migration lines) occurring in 20–30% of the patients [30].

Pulmonary symptoms

Lymphangioleiomyomatosis is one of the symptoms of pulmonary TSC, and is caused by the proliferation of smooth muscle cells around the bronchi and small vessels resulting in pulmonary remodelling and cyst formation. The patients' symptoms include cough, dyspnoea and haemoptysis. Lymphangioleiomyomatosis occurs mainly in adult women [25]. In patients with TSC, multifocal micronodular hyperplasia of pneumocytes may also occur, visible in imaging as small nodules [31].

Cardiac symptoms

Rhabdomyomata are lesions which may undergo spontaneous involution. They occur in the youngest children and mostly disappear in the preschool period. In some patients, however, they may lead to cardiac arrhythmias and sometimes to heart failure [32].

Ocular symptoms

Ocular changes occurring in the course of TSC are hamartomatous nodules of the retina, which, despite their multifocal manifestation, do not deteriorate vision in most cases. They are divided into flat lesions, mulberry lesions and mixed type (transitional lesions) [33].

The multiplicity of clinical symptoms and the diverse expression may pose diagnostic difficulties. The currently applicable criteria, which were proposed in 2021 at the Washington conference [34], are helpful in establishing the diagnosis as well as the further treatment of the patient.

The criteria listed below (two major or one major and two minor ones) are required for the diagnosis of the disease.

Major criteria:

- discoloration patches (>3 patches >5 mm in diameter),
- facial angiofibromas (>3) or frontal squamous fibroids (angiofibromas) (>3) or fibrous cephalic plaque,
- periungual fibromas, non-traumatic (ungula fibromas) (>2),
- shagreen patches,
- multiple retinal hamartomas,
- cortical brain tumours (cortical dysplasia),
- subependymal nodules of the brain,
- subependymal giant cell astrocytoma,
- rhabdomyomata of the heart,
- lymphangioleiomyomatosis,
- angiomyolipoma [2].

Minor criteria:

- confetti-type skin lesions,
- multiple dental enamel pits (>3),
- intraoral fibromas (>2),
- retinal achromic patches,
- multiple renal cysts,
- nonrenal hamartomas.

Genetic background, diagnosis and genetic counselling

The genetic background of tuberous sclerosis is constituted by pathogenic variants in the tumour suppressor genes *TSC1* or *TSC2*. The *TSC1* gene is located on the long arm of chromosome 9 (locus q34.13), the longest transcript of the gene consists of 23 exons (the first two are non-coding, and exons 5 and 12 are alternatively spliced), it encodes the hamartin protein. The *TSC2* gene is located on the short arm of chromosome 16 (locus p13.3), the longest transcript consists of 42 exons (non-coding exon 1 and alternatively spliced exons 25 and 31), it encodes tuberin [35]. Hamartin and tuberin form a complex in which hamartin is responsible for stabilisation through the super-helical domain "coiled-coil", additionally interacting with other proteins, while tuberin performs, among others, the function of a GTPase activating protein (GAP) for the small G Rheb protein which regulates / inhibits mTORC1 (mTOR kinase complex 1, mammalian target of rapamycin kinase), controlling protein translation, cell growth and proliferation. The activity of the hamartin-tuberin complex is inhibited by the protein kinases Akt and p38 MAPK [36].

Dysfunction of the hamartin-tuberin complex contributes to the lack of control over many signalling pathways, including the mTOR pathway, leading to its constant activity, thus leading to uncontrolled cell division and proliferation, and further to development of benign hamartoma-type tumours in many organs [37].

So far, about 650 pathogenic variants present in *TSC1* have been identified, the most common changes leading to protein truncation. The changes are scattered throughout the gene and no "hot spots" were found with the exception of exon 15, where several repetitive mutations were noted. Missense variants are rare and occur mainly at the N-terminus coding of the protein, thus contributing to its destabilisation [38]. About 1,900 pathogenic variants are known in the *TSC2* gene. They are distributed throughout the gene and over 30% of them are located in exons 32 to 41, encoding the carboxylic domain containing important functional domains including GAP [39].

No correlation was found between the type of mutation in *TSC1* and the phenotype, moreover, those patients have a less severe disease course compared to patients with mutations in *TSC2*. Women with found mutations in the carboxyl domain of the *TSC2* gene (exons 40 and 41) are more likely to develop lymphangioleiomyomatosis [40]. In addition, TSC patients with polycystic kidney disease have a higher risk of a more severe course of the disease if pathogenic variants of the *TSC2* gene are present. If the *TSC2* gene is deleted, the *PKD1* (polycystin 1) gene is also deleted (3' ends of these genes overlap) causing a contiguous gene syndrome [41]. Interestingly, there are also reports of people / families with mutations in *TSC2*, who had a milder course of the disease, either mildly symptomatic or asymptomatic [42, 43].

Tuberous sclerosis is inherited in an autosomal dominant manner with a significant predominance of disease cases with *de novo* mutations. It is estimated that about 70% of patients have no family history of an affected person, while the remaining 30% are family cases [35]. Mutations in the *TSC1* gene are almost twice as frequent in hereditary cases as compared to the sporadic form. Penetration of the *TSC1* and *TSC2* mutations is complete, while expression of disease is variable [42]. Symptoms of the disease occur in people in whom the second copy of the gene is silenced due to changes in the DNA sequence (mutations) or epigenetic changes – in line with Knudson's two-hit theory [35].

Identification of the pathogenic change is necessary for prophylactic treatment that is optimal for the patient and genetic counselling for the patient's family. The risk of a carrier passing a critical change over to their offspring is 50%. Currently, genetic testing involves analyses of the sequences of both key genes and searching of deletion / duplication. The method that allows quick sequence analysis is next generation sequencing (NGS), while for deletion / duplication analysis, recommended methods include those based on e.g. MLPA (multiplex ligation-depend probe amplification) and FISH (fluorescent in situ hybridization) as well as aCGH (array comparative genomic hybridization) [35, 39]. In cases of uncertain clinical diagnosis, application of a test based on a selected panel of genes (differential diagnosis) may be considered. About 70% of the mutations are found in the *TSC2* gene and further 25% in the *TSC1* gene. Finding no pathogenic variant in a patient with a clinical diagnosis is often associated with presence of mosaicism. Therefore, examination of the patient's other tissues should be considered. Moreover, germline mosaicism is also possible in healthy parents (without the mutation) who have an affected child [35]. In the case of identification of a germinal mutation, it is also possible to perform prenatal and preimplantation tests [39].

Conclusions

Von Hippel-Lindau disease and tuberous sclerosis belong to the group of phacomatoses, genetically determined diseases predisposing to development of multiple neoplasms. Due to the similarity of skin lesions associated with the discussed disorders, it is necessary to differentiate them from neurofibromatosis 1 and 2 and schwannomatosis. Early detection and, consequently, placing patients under multidisciplinary supervision improves the prognosis, enabling implementation of cancer treatment in the early stages of the disease. The constantly expanding genetic knowledge makes it possible to better understand the molecular aspect of both diseases, which will probably allow introduction of personalised treatment in the future, which will significantly increase the patients' quality of life.

Conflict of interest: none declared

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Received: 7 Jun 2021
Accepted: 18 October 2021

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