Genetic Predisposition to Non-Hodgkin Lymphoma

8

Oskar A. Haas and Arndt Borkhardt

Introduction

The two main categories of lymphomas are Hodgkin's disease (HD) and non-Hodgkin lymphomas (NHL). Together they not only comprise the most common malignancies in western countries, but, next to leukemias and brain tumors, also the third largest group of neoplasms in children up to 14 years as well as the largest one in teenagers up to 24 years of age [1–3]. In 0–14-year-old children, NHL is slightly more common than Hodgkin lymphoma, whereas the converse is true for teenagers and young, 15–24-year-old adults. Based on their specific biological, (immuno)phenotypic, and genetic features, the recently updated World Health Organization (WHO) classification guidelines distinguish already a large number of different NHL sub-entities [4], although the literature available for this review is still based on a more crude classification that merely comprises B- or T-cell lymphoblastic lymphoma, follicular (FL), diffuse large B-cell (DLBCL), Burkitt (BL), and anaplastic large cell lymphoma (ALCL), a system that hitherto has also formed the essential basis the prognostic classification and, consequently, the allocation to particular forms of treatment.

In children, lymphomas evolve in a tension field, in which a maturing immune system needs to arrange and familiarize itself with its own body's intrinsic components and, at the same time, also to get accustomed to a multitude of environmental exposures, not least various infectious agents [5]. A flawless genetic make-up of all contributing constituents is thus of crucial importance to guarantee the appropriate assembly of the encoded components and their efficient interaction in functional pathways and the required participation in the proper development of the immune system. Equally, dysfunctional or weakened germline components, be it in the form of major single-gene defects or perhaps likewise vital, but less well-recognized genetic modifiers, can easily interfere with the normal physiological development in this particularly vulnerable stage and tilt the balance, among others, also toward neoplastic transformation. Part of these more or less clearly definable genuine heritable preconditions are also normally inert variants in constituents of a well-adapted immune system, which only become relevant under particular circumstances, for instance, the fortuitous exposure to particular environmental hazards. Such either overstimulating or disruptive conditions are chronic infections, primarily those with Epstein-Barr (EBV), human immunodeficiency (HIV) as well as human papillomaviruses (HPV), chronic inflammations, autoimmune diseases, treatments with certain drugs, and organ transplantations (Fig. 8.1) [5–14].

Considering the above, the identification and characterization of predisposing factors has thus rightfully become the focus of special interest especially also in lymphoma research [15]. The recognition and definition of such disease-associated genetic variants is increasingly required for the management and care of patients not least because it often guides the appropriate choice and adaptation of therapy [16–19]. Even when treated successfully, these patients require further surveillance, because they can develop second or secondary neoplasms. The distinction between de novo or inherited disease-relevant germline mutations is a vital prerequisite for assessing the potential consequences for the patient herself as well as her respective family members and, therefore, also for enabling appropriate counseling [13, 20–22]. Last, but not least, the in-depth individual analysis together with the more general screening for such genetic determiners not only satisfies our scientific curiosity. It also broadens our overall knowledge and understanding of the normal physiological function and pathologic consequences of the

O. A. Haas (✉)
Children's Cancer Research Institute, Vienna, Austria
e-mail: oskar.haas@ccri.at

A. Borkhardt
Department of Pediatric Oncology, Hematology and Clinical Immunology, Medical Faculty, Heinrich Heine University, Düsseldorf, Germany
e-mail: arndt.borkhardt@med.uni-duesseldorf.de

O. Abla, A. Attarbaschi (eds.), *Non-Hodgkin's Lymphoma in Childhood and Adolescence*,
https://doi.org/10.1007/978-3-030-11769-6_8

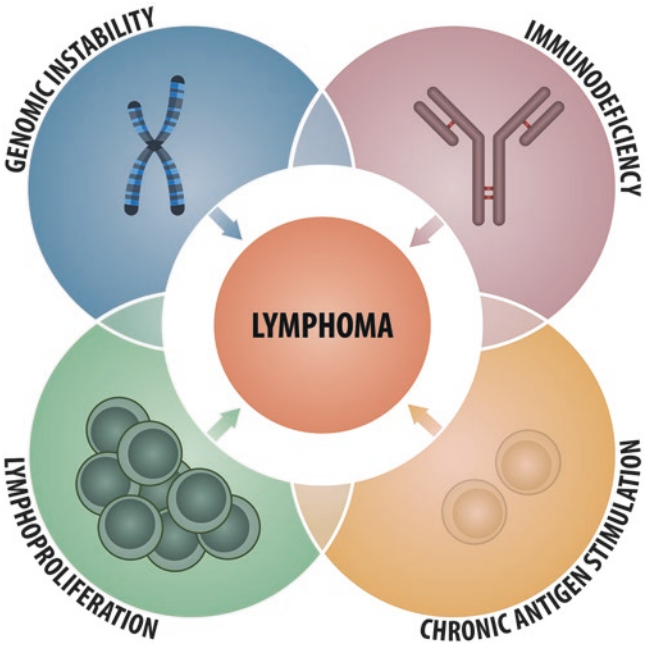

Fig. 8.1 Relevant factors that contribute and participate to lymphoma development in children [5]

respective immune system components and their role in disease mechanisms, which in turn again inevitably enables us to continuously improve and personalize the treatment of the respective patients.

Ascertainment of Genetic Predisposing Factors

There are different tactics one can use to search for and ascertain distinct or more general genetic predisposition factors (Table 8.1) [23]. The special choice of the appropriate mode is primarily a matter of the individual demands and opportunities as well as overall intentions. It can focus on either patient/family-relevant, gene-related, disease-associated or population-based aspects. Whether and when such a predisposing condition is thus suspected and when it becomes apparent depends mainly on the respective screening and verification procedures, which in turn rely on the particular severity and overall consequences of the respective gene defects. In case these generate also obvious physical malformations or other clinical symptoms, such as disturbances of the hematological and/or immune system, they are often known already before lymphoma onset. Conversely, such conditions might only be suspected only once lymphoma is diagnosed. In such scenarios, the careful assessment of medical records and the patient's family history together with his/her physical examination and key laboratory findings will not only help to secure the cause of a preexistent genetic susceptibility but often also provide

Table 8.1 Strategies to ascertain genetic factors that predispose to lymphoma

Based on distinctive or conspicuous clinical features
Ataxia telangiectasia
Nijmegen breakage syndrome
Constitutional mismatch repair syndrome
Primary immunodeficiency syndromes
Other rare DNA repair syndromes
Based on familial predisposition
Twin studies
Familial aggregation
Case-control studies
Cohort studies
Registry-based studies
Based on genetic risk factors
Linkage studies
Genetic association
Candidate genes
Genome-wide association studies (GWAS)
Based on disease
Hodgkin's disease
Non-Hodgkin lymphoma
Diffuse large B-cell lymphoma (DLBCL)
Burkitt lymphoma (BL)
Anaplastic large cell lymphoma (ALCL)

Adapted according to Cerhan and Slager [23]

already those relevant hints, which can ease the identification of the responsible defective gene or at least the category or pathway to which it belongs to [15]. The most relevant indicators comprise dysmorphic features, short stature, various types of cytopenias and immunodeficiencies, specific histopathological lymphoma forms, and/or unproportional treatment toxicities [1, 2, 24–29].

A first global impression about the type and frequency of the various disorders in children and adolescents with NHL can be obtained from information that can be extracted from three large lymphoma trial groups, the "European Intergroup for Childhood NHL (EICNHL)," the "International Berlin-Frankfurt-Münster (i-BFM) Study Group," and the "NHL-Committee of the Italian Association of Pediatric Hematology Oncology (AIEOP)" [1, 2, 30].

Depending on the likelihood that a respective genetic defect is indeed present and directly or indirectly responsible for lymphoma development, the particular conditions can be subdivided into those in which such a connection is undoubtedly established, in which it has not yet been explicitly proven and in which it is either most likely unjustified and/or only an incidental concurrence of two otherwise unrelated events [1, 2]. According to these studies, one can expect that at least 60% of lymphoma cases in children and adolescents occur on the basis of bona fide predisposing genetic germline defects that are even commonly associated with already clinically recognizable syndromes. Compared to that, the group of heterogeneous and hitherto less clear-cut primary immunodefi-

ciency conditions is with up to 15% much smaller, whereas other non-risk syndromes or not unambiguously classifiable conditions make up another 20% and 10%, respectively [2].

Monogenic Disorders

The two main closely intertwined categories of monogenic disorders that not only predispose to lymphoma development but, with a certain propensity also to various other types of malignancies, are the DNA repair deficiency syndromes and inborn errors of immunities that include severe primary (SCID) as well as combined immunodeficiency (CVID) syndromes. Apart from these two groups, the respective lymphoma treatment studies contain also a number of otherwise well-defined genetic syndromes and nongenetic conditions, such as those with merely one or more organ malformations, which seem to be hardly relevant in this context. Given an estimated overall lifetime risk for developing lymphoma of approximately 2%, the frequency of the various disorders and the rarity of their coincidental occurrence, one can expect that this may be an unfortunate pure chance event. Until at least conceptually understandable or proven, any such assumed causal link must therefore remain completely speculative.

Among the noteworthy findings that became apparent in these and other more disease- or condition-specific oriented publications is the unequal distribution of histological subtypes in the different groups. Approximately 85% of patients with ataxia telangiectasia (AT) develop mature B-cell NHLs [5, 30–32], of which diffuse large cell forms (DLBCL) are roughly three times more common than Burkitt lymphoma (BL). Approximately 25% of patients with Nijmegen breakage syndrome (NBS) develop peripheral T-cell lymphoma (PTCL) [17, 28, 30, 33, 34], and approximately 80% of patients with constitutional mismatch repair deficiency (CMMRD) develop T-cell lymphoblastic lymphoma (T-LBL) [26, 35–37]. In contrast, approximately 60% of B-cell lymphoproliferations that take place in patients with primary or secondary immunodeficiencies are oligoclonal and polymorphic [5, 30]. Of note is also the overall inferior prognosis and increased risk of treatment-related toxicity and death in such patients compared to those with sporadic forms of lymphoid malignancies [2].

Since we will only superficially portray the most common and prominent representative examples in each of these categories, we refer the interested reader to the many excellent and extensive reviews of individual disease forms that can be found in the scientific literature as well as in several internet resources and compendia, such as "Online Inheritance of Man (https://www.omim.org/)," "Orphanet (www.orpha.net/)," and "Gene Reviews (www.ncbi.nlm.nih.gov/books/NBK1116/)."

Ataxia Telangiectasia

This autosomal recessive disorder has an estimated worldwide prevalence of 1:40.000–1:100.000. It is caused by mutations in the *ATM* gene, whose protein product is a prominent coordinating member of cellular signaling pathways that respond to DNA double-strand breaks as well as to oxidative and other genotoxic stress situations [31, 38]. The clinical consequences of a constitutional ATM-deficient DNA damage response are cerebellar degeneration, telangiectasia, immunodeficiency, cancer susceptibility, and radiation sensitivity (X- and gamma-rays), the latter of which has to be especially accounted for in the medical management of affected patients.

About two-thirds of AT patients suffer from immune system abnormalities, such as reduced T and B cells and low levels of one or more immunoglobulin classes. The lifetime risk to develop cancers is approximately 25%. The most common ones in those less than 20 years of age are lymphomas and leukemias, whereas adults also develop solid tumors including breast, liver, gastric, and esophageal carcinomas [31, 32, 39, 40].

Nijmegen Breakage Syndrome (NBS)

NBS is a similarly well-characterized and clinically recognizable autosomal recessive disorder that is caused by mutations in the *NBN* gene [33]. Although such cases can occasionally be encountered in any part of the world, a specific Slavic origin founder mutation (NM_02485.4:c.657_661del5) makes this mutation particularly common among Central and Eastern European populations. This circumstance facilitates its easy genetic verification especially in these geographic regions. The *NBN* gene encodes a subunit of the Mre11–Rad50–NBN (NMR) DNA double-strand break (DSB) repair complex [41]. Affected children are exceptionally sensitive to ionizing radiation or radiomimetics and share a strong predisposition to develop malignancies of predominantly lymphoid origin and, to a lesser extent, also brain tumors, such as medulloblastoma and glioma. Thus, more than 50% (56/105) of patients in the Polish NBS registry had developed a malignant disease, more than 90% (51/56) of which were lymphomas [28, 34]. Moreover, compared to sporadic lymphomas in children and in individuals with primary or secondary immunodeficiency disorders, they are primarily mature DLBCLs and BL or T-cell LBL/acute leukemias [28]. The estimated lymphoma risk is exceptionally high in NBS patients. Whereas it is increased already 70–250-fold in AT patients, it is increased more than 1.000-fold in NBS patients and therefore without doubt the highest among all the chromosome breakage and immunodeficiency syndromes [28].

The prognosis is generally poor because NBS patients experience an extremely high rate of malignancies and significant treatment-related toxicities as well as infectious complications. Nevertheless, long-term survival can be achieved already in a substantial number of affected children when one accounts for their specific vulnerability during treatment and transplantation, a procedure that will also reestablish their immunity again [17, 34].

Constitutional Mismatch Repair Deficiency (CMMRD)

CMMRD can be caused by mutations in four genes, *MLH1*, *MSH2*, *MSH6*, and *PMS2*, that regulate DNA mismatch repair [25, 42]. The autosomal-dominant Lynch syndrome (LS) results from heterozygous monoallelic germline loss-of-function mutations that predispose to the development of colorectal cancer, endometrial carcinoma, and other malignancies in adults. The distinct autosomal recessive childhood version of CMMRD, on the other hand, is caused by bi-allelic compound heterozygous or homozygous mutations that affect primarily the *PMS2* gene (60%) [25, 26, 35, 37, 43–46]. Affected children develop leukemias and lymphomas, brain (especially glioblastoma) and embryonic type, as well as LS-associated tumors [37]. Their overall prognosis is generally poor, not least because multiple such neoplasms often occur syn- or metachronously [36]. In contrast to AT and NBS patients, those with CMMRD experience no excessive treatment toxicity and the clinical effects of their immunodeficiency remain much subtler. Since one can often find particular physical attributes, i.e., café-au-lait spots, skin hypopigmentation, and pilomatricomas, in these patients that may otherwise also be encountered in other predisposing conditions, such as AT, Fanconi anemia, neurofibromatosis type 1, Li-Fraumeni syndrome, or Peutz-Jeghers syndrome, their differential diagnostic work-up requires clinical expertise and genetic scrutiny. T-cell malignancies in patients with pigment anomalies and consanguine parents are thus a virtually unmistakable indicator for an underlying causative CMMRD. Although several consortia put together helpful criteria and guidelines to support the diagnostic evaluation and surveillance of patients with CMMRD, their clinical utility has not yet been fully evaluated [25, 43–45]. One of the relevant recommendations put forward is that genetic testing in minors at risk is only warranted in case parents opt for surveillance or to exclude CMMRD prior to hematopoietic stem cell donation [42].

So far, 56 patients with CMMRD and hematological malignancies in 48 families are known in the literature, approximately one-third of which had lymphomas or leukemias [35, 45]. Their median age at diagnosis was 6 years (range 0.4–30 years). With 41 cases, lymphomas are the most frequent malignancies; 27 of them were of T- and 10 of B-cell origin (including 2 BL, 2 DLCBL, and 1 post-transplant lymphoproliferative disease). Of special note is not only the high proportion of T-cell lymphomas but especially also their unique and hitherto unexplainable mediastinal predilection. Approximately two-thirds of these patients were homozygotes and one-third compound heterozygotes. 58% of the mutations affected the *PMS2*, 25% the *MSH6*, and 17% each the *MLH1* and *MSH2* gene [35, 44].

Immunodeficiency Syndromes

The recent 2017 update of the "Primary Immunodeficiency Committee" of the "International Union of Immunological Societies" lists and categorizes 344 genetic defects that cause 354 distinct disorders of immunity [47, 48]. Of these, more than 20 are known to predispose to lymphoma (Table 8.2). Since an in-depth review of all these lymphoma-predisposing disorders is beyond the scope of our review, we will only briefly touch some relevant points in three representative examples. The overall sketchy general conclusions one can draw from publications dealing with this subject are that PID patients have a 1.42-fold excess to develop cancer, which is largely due to lymphoma in specific PID populations [49, 50]. The overall risk of individuals with PID to develop a malignant disease is 4–25%, which after infections constitutes their second leading cause of death. With nearly 60% (8.4% HD and 49.6% NHL) lymphoma is the predominant cancer subtype and thus a considerable problem in primary as well as acquired immunodeficiency syndromes [5, 51]. The predominant type of lymphoma is of B-cell origin, of which many of the small cell types are EBV-related [51–55].

Perforinopathies

The recently conceived term "perforinopathies" refers to a related group of perforin-deficient hyperinflammatory disorders with an increased cancer susceptibility, which may either result from rare congenital gene-impairing mono- or bi-allelic mutations or, in less severe forms, also be due to more common hypomorphic alleles [56–58]. Bi-allelic perforin gene (*PRF1*) mutations, in particular, are the cause of the familial hemophagocytic lymphohistiocytosis type 2 (FHL2) [59], a disease that shares some of its typical presenting features with ALCL and accounts for approximately 10–15% of all pediatric NHL [7, 60–63]. Approximately a quarter of these lymphoma patients carry monoallelic *PRF1* mutations but, remarkably, virtually none in *SH2D1A* or *UNC13D*, genes that are implicated in two other forms of FHL [60]. Mutations in *SH2D1A* are best known for causing the X-linked lymphoproliferative disease (XLP), which makes affected male carriers particularly vulnerable to

Table 8.2 Immunodeficiency and DNA repair syndromes that predispose to lymphoma development

OMIM	Condition/syndrome	Gene	Inheritance	Clinical features	Function	Damaging or trigger agent	Lymphoma types	References
208,900	Ataxia telangiectasia	*ATM*	AR	Progressive ataxia, telangiectasia, cellular & humoral ID, increased radiation sensitivity, chromosomal instability, infertility	DSB sensor, activates repair cascade	IR, AA, Bleo	4–five-fold increase in T-cell neoplasms	[17, 31, 32, 39, 91–93]
251,260	Nijmegen breakage syndrome	*NBN*	AR	Microcephaly & growth retardation, dysmorphic face, radiation sensitivity, chromosomal instability, reduced fertility	HR & NHEJ DSB repair, part of NMR complex, replication	IR, AA, Bleo	DLBCL, Burkitt NHL	[17, 28, 30, 33, 34]
126,391	Ligase 1 deficiency	*LIG1*	AR	Growth retardation, radiation & sun sensitivity, recurrent respiratory infections	NHEJ DSB repair, V(D)J recombination	IR, Bleo	T-cell lymphoma, DLBCL	[47]
606,593	Ligase 4 deficiency	*LIG4*	AR	Microcephaly & growth retardation, dysmorphic face, cellular & humoral immunodeficiency	NHEJ DSB repair, V(D)J recombination	IR, Bleo. EBV	EBV-associated lymphoma	[94–96]
210,900	Bloom syndrome	*RECQL3*	AR	Microcephaly & severe growth retardation	Helicase, chromatid separation, suppresses inappropriate HR, part of NMR complex	UV	B- and T-cell NHL, Burkitt	[97]
250,250	Cartilage hair hypoplasia (CHH)	*RMRP*	AR	Chondrodysplasia, immunodeficiency, recurrent infections	RNA component of mitochondrial RNA processing endoribonuclease		NHL	[98, 99]
276,300	Constitutional mismatch repair deficiency syndrome (CMMRD)	*PMS2* (60%), *MSH6, MSH2, MLH1*	AR	"Neurofibromatosis-like": café-au-lait spot and skin hypopigmentation, mild defects of immunoglobulin class switch, agenesis of the corpus callosum, pilomatricomas	DNA mismatch repair		(mediastinal) T-cell NHL	[25, 26, 35–37, 42–46]
603,553	Familial hemophagocytic lymphohistiocytosis (FHL2)	*PRF1*	AR	Hemophagocytic lymphohistiocytosis	Encodes a secreted glycoprotein that permeabilizes target cell membranes	EBV (NK/T-cell NHL)	ALCL, NK/T-cell NHL	[7, 11, 56–58, 60–63, 100, 101]
308,240	X-linked lymphoproliferative disease	*SH2D1A*	XL	Increased susceptibility to EBV infections	Involved in the bidirectional stimulation of T and B cells	EBV	DLBCL, Burkitt	[14, 52, 102–105]
186,973	Lymphoproliferative syndrome 1	*ITK*	AR	Lymphoproliferation	Non-receptor tyrosine kinase, role in T-cell growth, signaling and function	EBV	DLBCL, Burkitt	[52, 106]
615,122	Lymphoproliferative syndrome 2	*CD27*	AR	Lymphoproliferation, hemophagocytosis	Member of the tumor necrosis factor receptor superfamily	EBV	B-cell	[52, 107]

(continued)

Table 8.2 (continued)

OMIM	Condition/syndrome	Gene	Inheritance	Clinical features	Function	Damaging or trigger agent	Lymphoma types	References
602,840	CD70 deficiency	*TNFSF7*	AR	Immunodeficiency	Cytokine binds to CD27 and contributes to T-cell activation	EBV	B-cell	[52, 108, 109]
603,962	*RASGRP1* deficiency	*RASGRP1*	AR	Lymphoproliferation, defective T- and NK-cell function	Encodes a diacylglycerol-regulated guanidine exchange factor	EBV	B-cell	[110]
615,401	Immunodeficiency 8	*CORO1A*	AR	Infections, cognitive impairment	Actin-regulating protein expressed in hematopoietic cells	HPV, EBV	DLBCL	[52, 111, 112]
615,897	Immunodeficiency 24	*CTPS1 & CTPS2*	AR	Lymphoproliferation	Required for synthesis of a precursor of nucleic acids metabolism	Herpes viruses	B-cell	[52, 113, 114]
609,981	Immunodeficiency 54	*MCM4*	AR	Severe growth retardation, microcephaly, decreased numbers of natural killer cells, recurrent viral infections	Essential for initiation of eukaryotic genome replication	Herpes viruses (cytomegaly, EBV)	B-cell	[115]
300,853	XMEN	*MAGT1*	XL	Recurrent & chronic infections, cytopenias, low CD4 T-cell counts	Magnesium transporter	EBV	DLBCL, Burkitt Hodgkin	[52, 116]
301,000	Wiskott-Aldrich syndrome	*WAS*	XL	Thrombocytopenia, neutropenia, eczema, recurrent infections, autoimmunity	Key regulator of actin polymerization in hematopoietic cells	EBV	B-cell	[65, 66]
124,092 146,933 123,889	Interleukin10 (receptor) deficiency	*IL10, IL-10R1, IL-10R2*	AR	Severe chronic intestinal bowel inflammation	Encode IL10 and the two IL10 receptor chains	Immunosuppressive therapy (azathioprine)	DLBCL	[18]
614,868	T-cell deficiency	*STK4*	AR	Lymphoproliferation, progressive loss of T cells, recurrent infections, warts, abscesses, autoimmunity, cardiac malformations	Serine/threonine kinase 4, can phosphorylate myelin basic protein, undergoes autophosphorylation	HPV, herpes viruses	Cardiac T-cell lymphoma	[55, 117]
602,037	*RHOH* deficiency	*RHOH*	AR	HPV infection, molluscum contagiosum, lung granuloma	Member of the RAS superfamily of guanosine triphosphate -metabolizing enzymes	Human papillomavirus	Burkitt	[118]
601,859	Autoimmune proliferative (Canale-smith) syndrome	*FAS, FASLG*	AD	Lymphoproliferation	Apoptosis defect	–	B- & T-cell lymphomas	[6, 7]

AA alkylating agents, *AR* autosomal recessive, *Bleo* Bleomycin, *EBV* Epstein-Barr virus, *HPV* human papillomavirus, *IR* ionizing radiation, *NK* natural killer (cell), *XL* X-linked

Epstein-Barr virus (EBV) infections [64]. One of the severe complications of the accompanying and uncontrollable lymphoproliferations are B-cell lymphomas that develop in a quarter of the respective patients [64]. Noteworthy in this context is also the postulated predisposing role of an otherwise common activity-diminishing *PRF1* gene variant (SNP A91V; rs35947132) in the nasal form of NK/T-cell lymphoma in adults, which is the most frequent EBV-related NK/T-cell malignancy [63].

Wiskott-Aldrich Syndrome (WAS)

This rare X-linked genetic disorder is caused by heterogeneous mutations in the *WAS* gene, which is exclusively expressed in hematopoietic cells [65–68]. So far, approximately 300 different mutations are known, which are scattered over the entire gene. The encoded gene product (WASp) belongs to a family of proteins that relay signals from the cell surface to the actin cytoskeleton [69]. The wide spectrum of clinical symptoms and hematopoietic effects one encounters in this disorder can be clearly attributed to the different types and location of the respective mutations and which are therefore also directly responsible for the severity of the disease. The ensuing problems range from only mild forms of isolated micro-thrombocytopenia or neutropenia to severe forms of eczema, recurrent infections, and autoimmune and neoplastic diseases. The prevalence of malignancy in retrospective studies of patients with severe clinical presentations and an average age of onset of 9.5 years has been estimated to be around 20% and to especially affect those with autoimmune manifestations [65]. The most frequent, often EBV-associated forms of neoplasms are extra-nodal NHLs [65]. One of the postulated mechanisms that apparently facilitate lymphoma development and progression in this disorder is that malfunctioning dendritic, T and NK cells are incapable to keep virally infected or otherwise altered preneoplastic B cells under control and to eliminate them properly [65, 67].

Interleukin (IL)10 and IL-10 Receptor

Interleukin-10 (IL-10) and IL-10 receptor (IL-10R) deficiencies are the first recognized monogenic causes of very early onset severe inflammatory bowel disease [18, 70–72]. This immunoregulatory disorder predisposes to the development of unique monoclonal EBV-negative DLBCL subtypes of germinal center origin that are characterized by a constitutive activation of the NF-kB pathway and a defective local T-cell immune response. Taking into account all 35 reported patients with IL-10 deficiency (5 with IL-10, 11 with IL-10R1, and 19 with IL-10R2), the likelihood to develop lymphoma is estimated to be 36% (5 of 14) at the age of 7 years [72]. These observations clearly indicate that a defective IL-10 pathway is causatively involved in lymphoma development, although one also needs to point out that apparently neither gut inflammation itself nor a distinct pattern of inflammation seems to be the essential causative factor. The increased risk might rather be more connected with the immunosuppressive therapy in the form of azathioprine, which four of the five patients reported by Neven et al. had received [72]. In line with this observation is that thiopurine treatment of inflammatory bowel diseases in adult patients also increases the risk for such lymphoproliferative disorders significantly [73].

Genetic Factors Predisposing to "Sporadic" NHL

Despite the large number of hitherto already identified predisposing monogenic causes, it is clear that even in these instances, the development of lymphoma is a multifactorial process with some probabilistic elements that depend on and involve a liable genetic architecture as well as the participation and interaction of a multitude of other intrinsic (as regards the respective cells, organs, and organism) as well as extrinsic environmental triggers [74]. So far, our understanding of all these lymphoma-initiating and lymphoma-promoting processes primarily derive from such rare monogenic subtypes. However, it is to be expected that the continuous systematic analyses of the rich source of "sporadic" cases, i.e., those in which such a definable genetic component is not (yet) known, will without doubt provide us with a plethora of novel findings and relevant insights. The best evidence that the class of sporadic lymphoma may indeed encompass many more distinct genetic sub-entities is the growing numbers of novel mutations that are still identified especially in rare forms of immunodeficiencies. The notion of a polygenic causation and possible inheritance of such sporadic cases derives, among others, mainly from the observation that lymphoma risk can aggregate in families, albeit without evidence of a clear-cut Mendelian segregation trait. One common interpretation of this phenomenon is that each lymphoma arises in a particular individual based on the combined risk-contributing effects of a large number of otherwise irrelevant modifying genetic variants.

Again, there are multiple ways to assess a familial predisposition and to identify germline susceptibility loci. These include twin, case-control, and registry-based studies for the former and linkage and genetic association studies for the later [23, 75]. Based on a comprehensive overview of such studies, Cerhan et al. reported that in the United States, the estimated overall lifetime risk for developing NHL outside of rare hereditary syndromes is 1 in 48 (2.1%) [23]. The relative risk for first-degree relatives is 1.7-fold elevated, whereas their absolute lifetime risk is 3.6%. The absolute risk is even lower for specific lymphoma subtypes. One noteworthy observation was that there is apparently both commonality and heterogeneity for risk factors by NHL subtype [10].

Familial Predisposition

Although family history is commonly used to identify individuals with a possible heritable predisposition, especially within the pediatric cancer population, it is hardly able to predict such a susceptibility in most patients [76, 77], a problem that has many reasons, in particular incomplete information on family history, small family size, de novo mutations, and incomplete penetrance. Moreover, parents and other first- or second-degree relatives are often still young and cancer may not have developed yet. Notwithstanding all these obstacles, multiple lines of data nevertheless suggest that a family history of lymphoma is indeed associated with an increased risk of lymphoma. Familial risk is elevated for multiple lymphoma subtypes and familial risk does not seem to be confounded by nongenetic risk factors, although there are likely unidentified environmental risk factors and clustering of known (and unknown) such risk factors within families that are difficult to exclude. This suggests that at least some lymphoma subtypes share a genetic etiology. Moreover, genetic factors are also likely to be subtype-specific because a family history of a particular subtype is also most strongly associated with a risk for the same lymphoma subtype.

Twin Studies

The largest twin study that aimed to elucidate a genetic susceptibility to HD comprised altogether 187 dizygotic and 179 monozygotic twins [78]. Compared to background rates, this study found a 100-fold higher risk for a monozygotic twin to also be affected by HD but no excess risk for a dizygotic twin. The relatively young average age at diagnosis of the twins concordant for HD and the relatively short average interval between diagnoses in each pair of twins further corroborate the importance of genetic factors in this context. There was also a 23-fold higher risk of NHL for a patient's monozygotic twin but only a 14-fold higher risk for a patient's dizygotic twin, which indicates that in these instances a shared environment is probably more relevant for their increased NHL susceptibility.

Familial Aggregation

Case-control, cohort, and registry-based studies investigate whether and to which extent an inherited genetic risk to a particular disease, in this instance lymphoma, aggregates within families. Such studies are to a certain extent complicated by the impossibility to reliably separate a shared genetic background from the impact of a shared environment as well as the need to also account for family size.

The largest case-control study available to date was performed by the "International Lymphoma Epidemiology Consortium." This meta-analysis comprised 17.471 NHL cases and 23.096 controls from 20 case control studies and found a 1.8-fold increased risk for patients who had a first-degree blood-related family member with NHL. Albeit less pronounced, this risk was also elevated for those who had a first-degree relative with HD or leukemia [10, 23].

Owing to the fact that only few large cohort studies with a sufficient number and detailed information of familial lymphoma cases are available, the risk for specific NHL subtypes is difficult to assess. A Swedish study that covered 3.5 million people over a 35 years period found a 7.2- and 8.8-fold higher risk in children and young adults to develop HD if a parent or sibling also had HD [79], whereas another study reported a six-fold higher risk for siblings [80]. A cohort study that included 120.000 female teachers in California concluded that a history of lymphoma in a first-degree relative was associated with a 1.7-fold higher risk of B-cell NHL [81].

In the Utah Cancer Registry, which linked population-based family registry with cancer registry data, the risk of NHL was increased 1.7-fold in first-degree relatives of a proband with NHL [82]. The most comprehensive data available on familial aggregation by lymphoma subtypes compared the cancer experience in first-degree relatives of lymphoma patients with that of relatives and matched population controls. First-degree relatives of HD patients had a 3.1-fold increase in risk of HD whereas risk of HD was not associated with a family history of NHL [83]. One striking finding in these studies is the NHL subtype-specific clustering of risk as exemplified by the fact that first-degree relatives of individuals with DLBCL had a 9.8-fold increased risk of also being affected by DLBCL.

Genetic Risk Factors

Linkage studies, which use multi-case families or sib pairs to search for shared regions of inherited alleles among affected individuals in an unbiased manner, were so far little rewarding as regards lymphoma research, a failure that might be due to small sample sizes or the lack of single high-penetrant variants in the investigated cohorts.

Genetic association studies, which rely on high-throughput genotyping of sequence variation in germline DNA became the predominant analytical method in genetic epidemiology. The two major types of association studies are candidate gene and genome wide association studies (GWAS).

Candidate gene studies are mainly driven by the a priori biologic knowledge of lymphoma and lymphoma-associated diseases, such as infectious or autoimmune ones, as well as those which derive from other cancers. Genes of particular interest in this context are those which are involved in immune function, cell cycle/proliferation, apoptosis, DNA repair, and carcinogen metabolism pathways. However, for a variety of reasons, most of these studies had only very limited success in identifying susceptibility loci in adult NHL. The most robust risk association was found between a tumor necrosis factor (*TNF*; rs1800629)/lymphotoxin-alpha (*LTA*; rs909253) haplotype and DLBCL [84], a SNP

(rs3789068) in the proapoptotic *BCL2L11* gene and B-cell NHL, as well as a SNP (rs3132453) in *PRRC2A* in the HLA class III region and B-cell NHL [85].

GWAS uses dense microarrays with several hundred thousand SNPs that are distributed over the entire genome. As all loci are considered equally, such an analytic approach is considered as being hypothesis-free or "agnostic" [23]. To date, such GWAS studies have successfully identified 11 regions that are associated with follicular lymphoma and 6 with DLBCL risk in adults (Table 8.3). The respective common SNPs define loci with a minor allele frequency below 5%, have small effect sizes, and are of largely unknown function. Moreover, so far hardly any of these loci have been also verified in replicate studies.

Table 8.3 GWAS-discovered loci predisposing to follicular and diffuse large B-cell lymphoma in adults of diverse ethnic origin [86]

Chromosomal location	SNP	Nearest gene	References
Follicular lymphoma			
3q28	rs6444305	*LPP*	[119]
6p21.32	rs10484561	*MHC class II*	[120]
6p21.32	rs2647012	*HLA-*	[121]
6p21.32	–	*HLA-DRβ1 Glu*	[119]
6p21.32	rs17203612	*HLA-DRA*	[119]
6p21.33	rs3130437	*HLA-C*	[119]
6p21.33	rs6457327	*C6orf15* et al. *(STG)*	[119]
8q24.21	rs13254990	*PVT1*	[119]
11q23.3	rs4938573	*CXCR5*	[119]
11q24.3	rs4937362	*ETS1*	[119]
18q21.33	rs17749561	*BCL2*	[119]
Diffuse large B-cell lymphoma (DLBCL)			
2p23.3	rs79480871	*NCOA1*	[122]
3q27	rs6773854	*BCL6/LPP*	[123]
6p21.33	rs2523607	*HLA-B*	[122]
6p25.3	rs116446171	*EXOC2*	[122]
8q24.21	rs13255292	*PVT1*	[122]
8q24.21	rs4733601	*PVT1*	[122]

Genetic Testing, Screening, and Counseling Issues

Although all these epidemiologic and "agnostic" mass screening methods for assessing, exploring, and defining genetic risk factors for lymphoma development have certainly their merits, they are hardly of any value for the daily management of individual lymphoma patients. Compared to that, the hitherto pursued approach to search for and verify a genetic cause in particular individuals, which relied primarily on the recognition of associated symptoms and, as such, on the a priori knowledge and alertness of the treating physicians, was still much more rewarding [15, 27, 51]. However, the growing awareness of the high frequency and heterogeneity of such underlying conditions, some of which are also often difficult to recognize and delineate, as well as the continuous improvement of cost-efficient sequencing methods and bioinformatic tools, will definitely lead to a change in the diagnostic evaluation tactic [77, 86]. Given the increasing interest in the role of germline cancer susceptibility in general and in the pediatric setting in particular, it is to be expected that the assessment of lymphoma-associated genetic predisposition factors will soon be performed in a more systematic manner. It is somehow surprising that, to our knowledge, suitable screening programs have not yet been considered or implemented in current lymphoma treatment studies. Given what is known so far and given the high number and variety of such vastly unexplored predisposing immunodeficiencies, it is expected that compared to other cancer and leukemia predisposing conditions such an endeavor must be especially worthwhile in the lymphoma setting. Several pilot projects dealing with other malignancies in children provide some ideas how such programs could be installed [77, 86, 87]. As outlined in Fig. 8.2, there

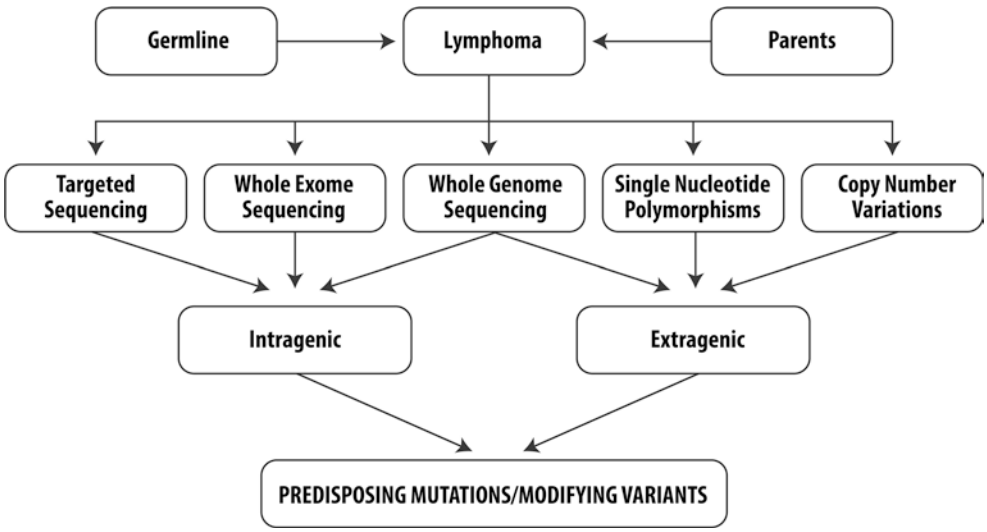

Fig. 8.2 Diagnostic approaches for the genetic assessment of predisposing risk factors in lymphoma patients, whose individual and combined values, advantages, and disadvantages are outlined in the main text

are several stepwise possibilities to do so. The most comprehensive one would be of course to sequence and compare DNA samples from the respective lymphoma together with one from the germline as well as the patient's parents. Depending on the infrastructural possibilities as well as cost/benefit calculations, one could perform such analyses either simultaneously or consecutively. The former is certainly more expensive but has the advantage that one can immediately compare the inheritance patterns of any identified abnormal results and thereby assess their validity and relevance in a rapid manner. The latter is probably cheaper because, in principle, one can concentrate only on the comparative confirmation of a smaller number of potentially relevant preselected markers. However, this approach could turn out to be more work- and also more time-consuming to obtain the essential information. Finally, there is also the question what one looks for and what one wants or needs to achieve in such a setting. For simple, clear-cut and easy to resolve diagnostic question, such as verification of a Nijmegen breakage syndrome or carrier screening for already known mutations, simple PCR analyses are clearly sufficient. For any other diagnostic evaluation, we consider targeted screening as the nowadays necessary minimal and also most cost-efficient standard, whereby the respective screening panel should cover at least all those genes that have already been implicated in lymphoma development [88–90]. More extensive sequencing methods that will eventually also aid the discovery of novel variants of potential relevance and interest, include whole exome sequencing (WES), which sooner or later will in any case most likely replace target sequencing, as well as whole genome sequencing (WGS), which has the advantage that it can also identify mutations in the non-coding extragenic part of the genome [86]. Moreover, a hitherto largely unexplored area in the field of lymphoma predisposition research is the conceivable contribution of the multitude of structural and copy number variations in the genome, especially of those which affect lymphoma-relevant gene regions. Although at present, these variants can be best assessed with DNA arrays, it is foreseeable that also this technique will eventually be replaced by whole genome as well as long-range sequencing procedures. With the appropriate bioinformatic support, these tools are not only able to significantly improve and refine these analyses, but at the same time, they will eventually also allow the simultaneously evaluation of associated epigenetic modifications, such as methylation.

Naturally, these remarkable technological advances and foreseeable developments in the diagnosis and research of lymphoma susceptibility also cause a large number of novel legal, ethical, social, and counseling problems, which can only be successfully resolved in a close interdisciplinary collaboration on a national but, even more so, on an international level. The particular topics that eventually need to be regulated comprise the informed consent and assent for minors undergoing testing, the ensuing implications for healthy siblings and parents of our patients, the timing of referral for genetic testing as well as the provision of a continuous educational and counseling support. All these issues are currently already addressed and discussed by a large number of experts from many countries who work together in two large recently established consortia, namely, the EU-funded COST Action "LEukaemia GENe Discovery by data sharing, mining and collaboration (LEGEND)" and the "IBFM Leukemia & Lymphoma Genetic Predisposition Committee."

Acknowledgment The author(s) acknowledge the networking support by the COST Action CA16223 "LEukaemia GENe Discovery by data sharing, mining and collaboration (LEGEND)" as well as the "IBFM Leukemia & Lymphoma Genetic Predisposition Committee." We also thank Fikret Rifatbegovic for help with designing and drawing the figures.

References

1. Arico M, Mussolin L, Carraro E, Buffardi S, Santoro N, D'Angelo P, et al. Non-Hodgkin lymphoma in children with an associated inherited condition: a retrospective analysis of the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP). Pediatr Blood Cancer. 2015;62(10):1782–9. https://doi.org/10.1002/pbc.25565.
2. Attarbaschi A, Carraro E, Abla O, Barzilai-Birenboim S, Bomken S, Brugieres L, et al. Non-Hodgkin lymphoma and pre-existing conditions: spectrum, clinical characteristics and outcome in 213 children and adolescents. Haematologica. 2016;101(12):1581–91. https://doi.org/10.3324/haematol.2016.147116.
3. Vijai J, Wang Z, Berndt SI, Skibola CF, Slager SL, de Sanjose S, et al. A genome-wide association study of marginal zone lymphoma shows association to the HLA region. Nat Commun. 2015;6(1):5751. https://doi.org/10.1038/ncomms6751.
4. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375–90. https://doi.org/10.1182/blood-2016-01-643569.
5. Tran H, Nourse J, Hall S, Green M, Griffiths L, Gandhi MK. Immunodeficiency-associated lymphomas. Blood Rev. 2008;22(5):261–81. https://doi.org/10.1016/j.blre.2008.03.009.
6. Straus SE, Jaffe ES, Puck JM, Dale JK, Elkon KB, Rosen-Wolff A, et al. The development of lymphomas in families with autoimmune lymphoproliferative syndrome with germline Fas mutations and defective lymphocyte apoptosis. Blood. 2001;98(1):194–200.
7. Clementi R, Dagna L, Dianzani U, Dupre L, Dianzani I, Ponzoni M, et al. Inherited perforin and Fas mutations in a patient with autoimmune lymphoproliferative syndrome and lymphoma. N Engl J Med. 2004;351(14):1419–24. https://doi.org/10.1056/NEJMoa041432.
8. Alexander DD, Mink PJ, Adami HO, Chang ET, Cole P, Mandel JS, et al. The non-Hodgkin lymphomas: a review of the epidemiologic literature. Int J Cancer. 2007;120 Suppl 12(S12):1–39. https://doi.org/10.1002/ijc.22719.
9. Cunningham-Rundles C. The many faces of common variable immunodeficiency. Hematology Am Soc Hematol Educ Program. 2012;2012:301–5. https://doi.org/10.1182/asheducation-2012.1.301.
10. Morton LM, Slager SL, Cerhan JR, Wang SS, Vajdic CM, Skibola CF, et al. Etiologic heterogeneity among non-Hodgkin lymphoma subtypes: the InterLymph Non-Hodgkin Lymphoma Subtypes

Project. J Natl Cancer Inst Monogr. 2014;2014(48):130–44. https://doi.org/10.1093/jncimonographs/lgu013.
11. Osinska I, Popko K, Demkow U. Perforin: an important player in immune response. Cent Eur J Immunol. 2014;39(1):109–15. https://doi.org/10.5114/ceji.2014.42135.
12. Skibola CF, Curry JD, Nieters A. Genetic susceptibility to lymphoma. Haematologica. 2007;92(7):960–9.
13. Similuk M, Rao VK, Churpek J, Lenardo M. Predispositions to lymphoma: a practical review for Genetic Counselors. J Genet Couns. 2016;25(6):1157–70. https://doi.org/10.1007/s10897-016-9979-0.
14. Sharapova SO, Fedorova AS, Pashchenko OE, Vahliarskaya SS, Guryanova IE, Migas AA, et al. Novel mutations in SH2D1A gene in X-linked lymphoproliferative syndrome, diagnosed after B-cell non-Hodgkin lymphoma. J Pediatr Hematol Oncol. 2017;39(4):e203–e6. https://doi.org/10.1097/MPH.0000000000000815.
15. Jongmans MC, Loeffen JL, Waanders E, Hoogerbrugge PM, Ligtenberg MJ, Kuiper RP, et al. Recognition of genetic predisposition in pediatric cancer patients: an easy-to-use selection tool. Eur J Med Genet. 2016;59(3):116–25. https://doi.org/10.1016/j.ejmg.2016.01.008.
16. Seidemann K, Tiemann M, Henze G, Sauerbrey A, Muller S, Reiter A. Therapy for non-Hodgkin lymphoma in children with primary immunodeficiency: analysis of 19 patients from the BFM trials. Med Pediatr Oncol. 1999;33(6):536–44.
17. Bienemann K, Burkhardt B, Modlich S, Meyer U, Moricke A, Bienemann K, et al. Promising therapy results for lymphoid malignancies in children with chromosomal breakage syndromes (Ataxia telangiectasia or Nijmegen-breakage syndrome): a retrospective survey. Br J Haematol. 2011;155(4):468–76. https://doi.org/10.1111/j.1365-2141.2011.08863.x.
18. Kotlarz D, Beier R, Murugan D, Diestelhorst J, Jensen O, Boztug K, et al. Loss of interleukin-10 signaling and infantile inflammatory bowel disease: implications for diagnosis and therapy. Gastroenterology. 2012;143(2):347–55. https://doi.org/10.1053/j.gastro.2012.04.045.
19. Chihara D, Nastoupil LJ, Williams JN, Lee P, Koff JL, Flowers CR. New insights into the epidemiology of non-Hodgkin lymphoma and implications for therapy. Expert Rev Anticancer Ther. 2015;15(5):531–44. https://doi.org/10.1586/14737140.2015.1023712.
20. Hampel H, Bennett RL, Buchanan A, Pearlman R, Wiesner GL, Guideline Development Group ACoMGaGPPaGCaNSoGCPGC. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. Genet Med. 2015;17(1):70–87.
21. Wolfe Schneider K, Jasperson K. Unique genetic counseling considerations in the pediatric oncology setting. Curr Genet Med Rep. 2015;3(2):65–73. https://doi.org/10.1007/s40142-015-0064-z.
22. Walsh MF, Chang VY, Kohlmann WK, Scott HS, Cunniff C, Bourdeaut F, et al. Recommendations for childhood cancer screening and surveillance in DNA repair disorders. Clin Cancer Res. 2017;23(11):e23–31. https://doi.org/10.1158/1078-0432.CCR-17-0465.
23. Cerhan JR, Slager SL. Familial predisposition and genetic risk factors for lymphoma. Blood. 2015;126(20):2265–73. https://doi.org/10.1182/blood-2015-04-537498.
24. Desai AV, Perpich M, Godley LA. Clinical assessment and diagnosis of Germline predisposition to hematopoietic malignancies: the University of Chicago Experience. Front Pediatr. 2017;5:252. https://doi.org/10.3389/fped.2017.00252.
25. Bakry D, Aronson M, Durno C, Rimawi H, Farah R, Alharbi QK, et al. Genetic and clinical determinants of constitutional mismatch repair deficiency syndrome: report from the constitutional mismatch repair deficiency consortium. Eur J Cancer. 2014;50(5):987–96. https://doi.org/10.1016/j.ejca.2013.12.005.
26. Ripperger T, Beger C, Rahner N, Sykora KW, Bockmeyer CL, Lehmann U, et al. Constitutional mismatch repair deficiency and childhood leukemia/lymphoma – report on a novel biallelic MSH6 mutation. Haematologica. 2010;95(5):841–4. https://doi.org/10.3324/haematol.2009.015503.
27. Ripperger T, Bielack SS, Borkhardt A, Brecht IB, Burkhardt B, Calaminus G, et al. Childhood cancer predisposition syndromes-a concise review and recommendations by the Cancer Predisposition Working Group of the Society for Pediatric Oncology and Hematology. Am J Med Genet A. 2017;173(4):1017–37. https://doi.org/10.1002/ajmg.a.38142.
28. Gladkowska-Dura M, Dzierzanowska-Fangrat K, Dura WT, van Krieken JH, Chrzanowska KH, van Dongen JJ, et al. Unique morphological spectrum of lymphomas in Nijmegen breakage syndrome (NBS) patients with high frequency of consecutive lymphoma formation. J Pathol. 2008;216(3):337–44. https://doi.org/10.1002/path.2418.
29. Shapiro RS. Malignancies in the setting of primary immunodeficiency: implications for hematologists/oncologists. Am J Hematol. 2011;86(1):48–55. https://doi.org/10.1002/ajh.21903.
30. Seidemann K, Henze G, Beck JD, Sauerbrey A, Kuhl J, Mann G, et al. Non-Hodgkin's lymphoma in pediatric patients with chromosomal breakage syndromes (AT and NBS): experience from the BFM trials. Ann Oncol. 2000;11(Suppl 1):141–5.
31. Rothblum-Oviatt C, Wright J, Lefton-Greif MA, McGrath-Morrow SA, Crawford TO, Lederman HM. Ataxia telangiectasia: a review. Orphanet J Rare Dis. 2016;11(1):159. https://doi.org/10.1186/s13023-016-0543-7.
32. Suarez F, Mahlaoui N, Canioni D, Andriamanga C, Dubois d'Enghien C, Brousse N, et al. Incidence, presentation, and prognosis of malignancies in ataxia-telangiectasia: a report from the French national registry of primary immune deficiencies. J Clin Oncol. 2015;33(2):202–8. https://doi.org/10.1200/JCO.2014.56.5101.
33. Chrzanowska KH, Gregorek H, Dembowska-Baginska B, Kalina MA, Digweed M. Nijmegen breakage syndrome (NBS). Orphanet J Rare Dis. 2012;7(1):13. https://doi.org/10.1186/1750-1172-7-13.
34. Dembowska-Baginska B, Perek D, Brozyna A, Wakulinska A, Olczak-Kowalczyk D, Gladkowska-Dura M, et al. Non-Hodgkin lymphoma (NHL) in children with Nijmegen breakage syndrome (NBS). Pediatr Blood Cancer. 2009;52(2):186–90. https://doi.org/10.1002/pbc.21789.
35. Ripperger T, Schlegelberger B. Acute lymphoblastic leukemia and lymphoma in the context of constitutional mismatch repair deficiency syndrome. Eur J Med Genet. 2016;59(3):133–42. https://doi.org/10.1016/j.ejmg.2015.12.014.
36. Alexander TB, McGee RB, Kaye EC, McCarville MB, Choi JK, Cavender CP, et al. Metachronous T-lymphoblastic lymphoma and Burkitt lymphoma in a child with constitutional mismatch repair deficiency syndrome. Pediatr Blood Cancer. 2016;63(8):1454–6. https://doi.org/10.1002/pbc.25989.
37. Lavoine N, Colas C, Muleris M, Bodo S, Duval A, Entz-Werle N, et al. Constitutional mismatch repair deficiency syndrome: clinical description in a French cohort. J Med Genet. 2015;52(11):770–8. https://doi.org/10.1136/jmedgenet-2015-103299.
38. Tichy A, Vavrova J, Pejchal J, Rezacova M. Ataxia-telangiectasia mutated kinase (ATM) as a central regulator of radiation-induced DNA damage response. Acta Med (Hradec Kralove). 2010;53(1):13–7.
39. Taylor AM, Metcalfe JA, Thick J, Mak YF. Leukemia and lymphoma in ataxia telangiectasia. Blood. 1996;87(2):423–38.
40. van Os NJ, Roeleveld N, Weemaes CM, Jongmans MC, Janssens GO, Taylor AM, et al. Health risks for ataxia-telangiectasia

mutated heterozygotes: a systematic review, meta-analysis and evidence-based guideline. Clin Genet. 2016;90(2):105–17. https://doi.org/10.1111/cge.12710.
41. Schuetz JM, MaCarthur AC, Leach S, Lai AS, Gallagher RP, Connors JM, et al. Genetic variation in the NBS1, MRE11, RAD50 and BLM genes and susceptibility to non-Hodgkin lymphoma. BMC Med Genet. 2009;10:117. https://doi.org/10.1186/1471-2350-10-117.
42. Tabori U, Hansford JR, Achatz MI, Kratz CP, Plon SE, Frebourg T, et al. Clinical management and tumor surveillance recommendations of inherited mismatch repair deficiency in childhood. Clin Cancer Res. 2017;23(11):e32–e7. https://doi.org/10.1158/1078-0432.CCR-17-0574.
43. Durno CA, Sherman PM, Aronson M, Malkin D, Hawkins C, Bakry D, et al. Phenotypic and genotypic characterisation of biallelic mismatch repair deficiency (BMMR-D) syndrome. Eur J Cancer. 2015;51(8):977–83. https://doi.org/10.1016/j.ejca.2015.02.008.
44. Wimmer K, Kratz CP, Vasen HF, Caron O, Colas C, Entz-Werle N, et al. Diagnostic criteria for constitutional mismatch repair deficiency syndrome: suggestions of the European consortium 'care for CMMRD' (C4CMMRD). J Med Genet. 2014;51(6):355–65. https://doi.org/10.1136/jmedgenet-2014-102284.
45. Vasen HF, Ghorbanoghli Z, Bourdeaut F, Cabaret O, Caron O, Duval A, et al. Guidelines for surveillance of individuals with constitutional mismatch repair-deficiency proposed by the European consortium "care for CMMR-D" (C4CMMR-D). J Med Genet. 2014;51(5):283–93. https://doi.org/10.1136/jmedgenet-2013-102238.
46. Wimmer K, Kratz CP. Constitutional mismatch repair-deficiency syndrome. Haematologica. 2010;95(5):699–701. https://doi.org/10.3324/haematol.2009.021626.
47. Picard C, Bobby Gaspar H, Al-Herz W, Bousfiha A, Casanova JL, Chatila T, et al. International Union of Immunological Societies: 2017 Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity. J Clin Immunol. 2018;38(1):96–128. https://doi.org/10.1007/s10875-017-0464-9.
48. Bousfiha A, Jeddane L, Picard C, Ailal F, Bobby Gaspar H, Al-Herz W, et al. The 2017 IUIS phenotypic classification for primary Immunodeficiencies. J Clin Immunol. 2018;38(1):129–43. https://doi.org/10.1007/s10875-017-0465-8.
49. Mayor PC, Eng KH, Singel KL, Abrams SI, Odunsi K, Moysich KB, et al. Cancer in primary immunodeficiency diseases: cancer incidence in the United States Immune Deficiency Network Registry. J Allergy Clin Immunol. 2018;141(3):1028–35. https://doi.org/10.1016/j.jaci.2017.05.024.
50. Verhoeven D, Stoppelenburg AJ, Meyer-Wentrup F, Boes M. Increased risk of hematologic malignancies in primary immunodeficiency disorders: opportunities for immunotherapy. Clin Immunol. 2018;190:22–31. https://doi.org/10.1016/j.clim.2018.02.007.
51. de Jong D, Roemer MG, Chan JK, Goodlad J, Gratzinger D, Chadburn A, et al. B-cell and classical Hodgkin lymphomas associated with immunodeficiency: 2015 SH/EAHP Workshop Report-Part 2. Am J Clin Pathol. 2017;147(2):153–70. https://doi.org/10.1093/ajcp/aqw216.
52. Latour S, Winter S. Inherited Immunodeficiencies with high predisposition to Epstein–Barr virus-driven lymphoproliferative diseases. Front Immunol. 2018;9:1103. https://doi.org/10.3389/fimmu.2018.01103.
53. Arjunaraja S, Angelus P, Su HC, Snow AL. Impaired control of Epstein-Barr virus infection in B-cell expansion with NF-kappaB and T-cell Anergy Disease. Front Immunol. 2018;9:198. https://doi.org/10.3389/fimmu.2018.00198.
54. Worth AJ, Houldcroft CJ, Booth C. Severe Epstein-Barr virus infection in primary immunodeficiency and the normal host. Br J Haematol. 2016;175(4):559–76. https://doi.org/10.1111/bjh.14339.
55. Parvaneh N, Filipovich AH, Borkhardt A. Primary immunodeficiencies predisposed to Epstein-Barr virus-driven haematological diseases. Br J Haematol. 2013;162(5):573–86. https://doi.org/10.1111/bjh.12422.
56. Voskoboinik I, Trapani JA. Perforinopathy: a spectrum of human immune disease caused by defective perforin delivery or function. Front Immunol. 2013;4:441. https://doi.org/10.3389/fimmu.2013.00441.
57. Trapani JA, Thia KY, Andrews M, Davis ID, Gedye C, Parente P, et al. Human perforin mutations and susceptibility to multiple primary cancers. Oncoimmunology. 2013;2(4):e24185. https://doi.org/10.4161/onci.24185.
58. Chaudhry MS, Gilmour KC, House IG, Layton M, Panoskaltsis N, Sohal M, et al. Missense mutations in the perforin (PRF1) gene as a cause of hereditary cancer predisposition. Oncoimmunology. 2016;5(7):e1179415. https://doi.org/10.1080/2162402X.2016.1179415.
59. Cetica V, Sieni E, Pende D, Danesino C, De Fusco C, Locatelli F, et al. Genetic predisposition to hemophagocytic lymphohistiocytosis: report on 500 patients from the Italian registry. J Allergy Clin Immunol. 2016;137(1):188–96 e4. https://doi.org/10.1016/j.jaci.2015.06.048.
60. Ciambotti B, Mussolin L, d'Amore ES, Pillon M, Sieni E, Coniglio ML, et al. Monoallelic mutations of the perforin gene may represent a predisposing factor to childhood anaplastic large cell lymphoma. J Pediatr Hematol Oncol. 2014;36(6):e359–65. https://doi.org/10.1097/MPH.0000000000000073.
61. Clementi R, Locatelli F, Dupre L, Garaventa A, Emmi L, Bregni M, et al. A proportion of patients with lymphoma may harbor mutations of the perforin gene. Blood. 2005;105(11):4424–8. https://doi.org/10.1182/blood-2004-04-1477.
62. Cannella S, Santoro A, Bruno G, Pillon M, Mussolin L, Mangili G, et al. Germline mutations of the perforin gene are a frequent occurrence in childhood anaplastic large cell lymphoma. Cancer. 2007;109(12):2566–71. https://doi.org/10.1002/cncr.22718.
63. Manso R, Rodriguez-Pinilla SM, Lombardia L, Ruiz de Garibay G, Del Mar Lopez M, Requena L, et al. An A91V SNP in the perforin gene is frequently found in NK/T-cell lymphomas. PLoS One. 2014;9(3):e91521. https://doi.org/10.1371/journal.pone.0091521.
64. Panchal N, Booth C, Cannons JL, Schwartzberg PL. X-linked Lymphoproliferative disease type 1: a clinical and molecular perspective. Front Immunol. 2018;9:666. https://doi.org/10.3389/fimmu.2018.00666.
65. Candotti F. Clinical manifestations and pathophysiological mechanisms of the Wiskott-Aldrich syndrome. J Clin Immunol. 2018;38(1):13–27. https://doi.org/10.1007/s10875-017-0453-z.
66. Buchbinder D, Nugent DJ, Fillipovich AH. Wiskott-Aldrich syndrome: diagnosis, current management, and emerging treatments. Appl Clin Genet. 2014;7:55–66. https://doi.org/10.2147/TACG.S58444.
67. Massaad MJ, Ramesh N, Geha RS. Wiskott-Aldrich syndrome: a comprehensive review. Ann N Y Acad Sci. 2013;1285:26–43. https://doi.org/10.1111/nyas.12049.
68. Ochs HD, Filipovich AH, Veys P, Cowan MJ, Kapoor N. Wiskott-Aldrich syndrome: diagnosis, clinical and laboratory manifestations, and treatment. Biol Blood Marrow Transplant. 2009;15(1 Suppl):84–90. https://doi.org/10.1016/j.bbmt.2008.10.007.
69. Blundell MP, Worth A, Bouma G, Thrasher AJ. The Wiskott-Aldrich syndrome: the actin cytoskeleton and immune cell function. Dis Markers. 2010;29(3-4):157–75. https://doi.org/10.3233/DMA-2010-0735.
70. Glocker EO, Kotlarz D, Boztug K, Gertz EM, Schaffer AA, Noyan F, et al. Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. N Engl J Med. 2009;361(21):2033–45. https://doi.org/10.1056/NEJMoa0907206.

71. Shouval DS, CL Ebens, R Murchie, K McCann, R Rabah, C Klein, et al. Large B-cell lymphoma in an adolescent patient with Iinterleukin-10 receptor deficiency and history of infantile inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2016;63(1):e15–e17. https://doi.org/10.1097/MPG.0000000000000532.
72. Neven B, Mamessier E, Bruneau J, Kaltenbach S, Kotlarz D, Suarez F, et al. A Mendelian predisposition to B-cell lymphoma caused by IL-10R deficiency. Blood. 2013;122(23):3713–22. https://doi.org/10.1182/blood-2013-06-508267.
73. Kandiel A, Fraser AG, Korelitz BI, Brensinger C, Lewis JD. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. Gut. 2005;54(8):1121–5. https://doi.org/10.1136/gut.2004.049460.
74. Mitchell KJ. What is complex about complex disorders? Genome Biol. 2012;13(1):237. https://doi.org/10.1186/gb-2012-13-1-237.
75. Cerhan JR. Host genetics in follicular lymphoma. Best Pract Res Clin Haematol. 2011;24(2):121–34. https://doi.org/10.1016/j.beha.2011.02.004.
76. Knapke S, Nagarajan R, Correll J, Kent D, Burns K. Hereditary cancer risk assessment in a pediatric oncology follow-up clinic. Pediatr Blood Cancer. 2012;58(1):85–9. https://doi.org/10.1002/pbc.23283.
77. Zhang J, Walsh MF, Wu G, Edmonson MN, Gruber TA, Easton J, et al. Germline mutations in predisposition genes in pediatric cancer. N Engl J Med. 2015;373(24):2336–46. https://doi.org/10.1056/NEJMoa1508054.
78. Mack TM, Cozen W, Shibata DK, Weiss LM, Nathwani BN, Hernandez AM, et al. Concordance for Hodgkin's disease in identical twins suggesting genetic susceptibility to the young-adult form of the disease. N Engl J Med. 1995;332(7):413–8. https://doi.org/10.1056/NEJM199502163320701.
79. Crump C, Sundquist K, Sieh W, Winkleby MA, Sundquist J. Perinatal and family risk factors for Hodgkin lymphoma in childhood through young adulthood. Am J Epidemiol. 2012;176(12):1147–58. https://doi.org/10.1093/aje/kws212.
80. Friedman DL, Kadan-Lottick NS, Whitton J, Mertens AC, Yasui Y, Liu Y, et al. Increased risk of cancer among siblings of long-term childhood cancer survivors: a report from the childhood cancer survivor study. Cancer Epidemiol Biomark Prev. 2005;14(8):1922–7. https://doi.org/10.1158/1055-9965.EPI-05-0066.
81. Lu Y, Sullivan-Halley J, Cozen W, Chang ET, Henderson K, Ma H, et al. Family history of haematopoietic malignancies and non-Hodgkin's lymphoma risk in the California teachers study. Br J Cancer. 2009;100(3):524–6. https://doi.org/10.1038/sj.bjc.6604881.
82. Goldgar DE, Easton DF, Cannon-Albright LA, Skolnick MH. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. J Natl Cancer Inst. 1994;86(21):1600–8. https://doi.org/10.1093/jnci/86.21.1600.
83. Goldin LR, McMaster ML, Ter-Minassian M, Saddlemire S, Harmsen B, Lalonde G, et al. A genome screen of families at high risk for Hodgkin lymphoma: evidence for a susceptibility gene on chromosome 4. J Med Genet. 2005;42(7):595–601. https://doi.org/10.1136/jmg.2004.027433.
84. Skibola CF, Bracci PM, Nieters A, Brooks-Wilson A, de Sanjose S, Hughes AM, et al. Tumor necrosis factor (TNF) and lymphotoxin-alpha (LTA) polymorphisms and risk of non-Hodgkin lymphoma in the InterLymph Consortium. Am J Epidemiol. 2010;171(3):267–76. https://doi.org/10.1093/aje/kwp383.
85. Nieters A, Conde L, Slager SL, Brooks-Wilson A, Morton L, Skibola DR, et al. PRRC2A and BCL2L11 gene variants influence risk of non-Hodgkin lymphoma: results from the InterLymph consortium. Blood. 2012;120(23):4645–8. https://doi.org/10.1182/blood-2012-05-427989.
86. Kuhlen M, Borkhardt A. Cancer susceptibility syndromes in children in the area of broad clinical use of massive parallel sequencing. Eur J Pediatr. 2015;174(8):987–97. https://doi.org/10.1007/s00431-015-2565-x.
87. Kuhlen M, Borkhardt A. Trio sequencing in pediatric cancer and clinical implications. EMBO Mol Med. 2018;10(4):e8641–7. https://doi.org/10.15252/emmm.201708641.
88. Al-Mousa H, Abouelhoda M, Monies DM, Al-Tassan N, Al-Ghonaium A, Al-Saud B, et al. Unbiased targeted next-generation sequencing molecular approach for primary immunodeficiency diseases. J Allergy Clin Immunol. 2016;137(6):1780–7. https://doi.org/10.1016/j.jaci.2015.12.1310.
89. Nijman IJ, van Montfrans JM, Hoogstraat M, Boes ML, van de Corput L, Renner ED, et al. Targeted next-generation sequencing: a novel diagnostic tool for primary immunodeficiencies. J Allergy Clin Immunol. 2014;133(2):529–34. https://doi.org/10.1016/j.jaci.2013.08.032.
90. Stoddard JL, Niemela JE, Fleisher TA, Rosenzweig SD. Targeted NGS: a cost-effective approach to molecular diagnosis of PIDs. Front Immunol. 2014;5(1):531. https://doi.org/10.3389/fimmu.2014.00531.
91. Sandoval C, Swift M. Treatment of lymphoid malignancies in patients with ataxia-telangiectasia. Med Pediatr Oncol. 1998;31(6):491–7.
92. Taylor AM. Ataxia telangiectasia genes and predisposition to leukaemia, lymphoma and breast cancer. Br J Cancer. 1992;66(1):5–9.
93. van Os NJH, Haaxma CA, van der Flier M, Merkus PJFM, van Deuren M, de Groot IJM, et al. Ataxia-telangiectasia: recommendations for multidisciplinary treatment. Dev Med Child Neurol. 2017;59(7):680–9.
94. Ben-Omran TI, Cerosaletti K, Concannon P, Weitzman S, Nezarati MM. A patient with mutations in DNA ligase IV: clinical features and overlap with Nijmegen breakage syndrome. Am J Med Genet A. 2005;137A(3):283–7. https://doi.org/10.1002/ajmg.a.30869.
95. Sharapova SO, Chang EY, Guryanova IE, Proleskovskaya IV, Fedorova AS, Rutskaya EA, et al. Next generation sequencing revealed DNA ligase IV deficiency in a "developmentally normal" patient with massive brain Epstein-Barr virus-positive diffuse large B-cell lymphoma. Clin Immunol. 2016;163:108–10. https://doi.org/10.1016/j.clim.2016.01.002.
96. Altmann T, Gennery AR. DNA ligase IV syndrome; a review. Orphanet J Rare Dis. 2016;11(1):137. https://doi.org/10.1186/s13023-016-0520-1.
97. Cunniff C, Bassetti JA, Ellis NA. Bloom's syndrome: clinical spectrum, molecular pathogenesis, and cancer predisposition. Mol Syndromol. 2017;8(1):4–23. https://doi.org/10.1159/000452082.
98. Kostjukovits S, Klemetti P, Valta H, Martelius T, Notarangelo LD, Seppanen M, et al. Analysis of clinical and immunologic phenotype in a large cohort of children and adults with cartilage-hair hypoplasia. J Allergy Clin Immunol. 2017;140(2):612–4 e5. https://doi.org/10.1016/j.jaci.2017.02.016.
99. Taskinen M, Ranki A, Pukkala E, Jeskanen L, Kaitila I, Makitie O. Extended follow-up of the Finnish cartilage-hair hypoplasia cohort confirms high incidence of non-Hodgkin lymphoma and basal cell carcinoma. Am J Med Genet A. 2008;146A(18):2370–5. https://doi.org/10.1002/ajmg.a.32478.
100. Ding Q, Yang LY. Perforin gene mutations in 77 Chinese patients with lymphomas. World J Emerg Med. 2013;4(2):128–32. https://doi.org/10.5847/wjem.j.1920-8642.2013.02.008.
101. Mehta PA, Davies SM, Kumar A, Devidas M, Lee S, Zamzow T, et al. Perforin polymorphism A91V and susceptibility to B-precursor childhood acute lymphoblastic leukemia: a report from the Children's Oncology Group. Leukemia. 2006;20(9):1539–41. https://doi.org/10.1038/sj.leu.2404299.
102. Koochakzadeh L, Hosseinverdi S, Hedayat M, Farahani F, Tofighi A, Eghbali M, et al. Study of SH2D1A gene mutation in paediatric

patients with B-cell lymphoma. Allergol Immunopathol (Madr). 2015;43(6):568–70. https://doi.org/10.1016/j.aller.2015.01.007.
103. Tangye SG. XLP: clinical features and molecular etiology due to mutations in SH2D1A encoding SAP. J Clin Immunol. 2014;34(7):772–9. https://doi.org/10.1007/s10875-014-0083-7.
104. Booth C, Gilmour KC, Veys P, Gennery AR, Slatter MA, Chapel H, et al. X-linked lymphoproliferative disease due to SAP/SH2D1A deficiency: a multicenter study on the manifestations, management and outcome of the disease. Blood. 2011;117(1):53–62. https://doi.org/10.1182/blood-2010-06-284935.
105. Arico M, Imashuku S, Clementi R, Hibi S, Teramura T, Danesino C, et al. Hemophagocytic lymphohistiocytosis due to germline mutations in SH2D1A, the X-linked lymphoproliferative disease gene. Blood. 2001;97(4):1131–3.
106. Linka RM, Risse SL, Bienemann K, Werner M, Linka Y, Krux F, et al. Loss-of-function mutations within the IL-2 inducible kinase ITK in patients with EBV-associated lymphoproliferative diseases. Leukemia. 2012;26(5):963–71. https://doi.org/10.1038/leu.2011.371.
107. Salzer E, Daschkey S, Choo S, Gombert M, Santos-Valente E, Ginzel S, et al. Combined immunodeficiency with life-threatening EBV-associated lymphoproliferative disorder in patients lacking functional CD27. Haematologica. 2013;98(3):473–8. https://doi.org/10.3324/haematol.2012.068791.
108. Abolhassani H, Edwards ES, Ikinciogullari A, Jing H, Borte S, Buggert M, et al. Combined immunodeficiency and Epstein-Barr virus-induced B cell malignancy in humans with inherited CD70 deficiency. J Exp Med. 2017;214(1):91–106. https://doi.org/10.1084/jem.20160849.
109. Izawa K, Martin E, Soudais C, Bruneau J, Boutboul D, Rodriguez R, et al. Inherited CD70 deficiency in humans reveals a critical role for the CD70-CD27 pathway in immunity to Epstein-Barr virus infection. J Exp Med. 2017;214(1):73–89. https://doi.org/10.1084/jem.20160784.
110. Winter S, Martin E, Boutboul D, Lenoir C, Boudjemaa S, Petit A, et al. Loss of RASGRP1 in humans impairs T-cell expansion leading to Epstein-Barr virus susceptibility. EMBO Mol Med. 2018;10(2):188–99. https://doi.org/10.15252/emmm.201708292.
111. Stray-Pedersen A, Jouanguy E, Crequer A, Bertuch AA, Brown BS, Jhangiani SN, et al. Compound heterozygous CORO1A mutations in siblings with a mucocutaneous-immunodeficiency syndrome of epidermodysplasia verruciformis-HPV, molluscum contagiosum and granulomatous tuberculoid leprosy. J Clin Immunol. 2014;34(7):871–90. https://doi.org/10.1007/s10875-014-0074-8.
112. Moshous D, Martin E, Carpentier W, Lim A, Callebaut I, Canioni D, et al. Whole-exome sequencing identifies Coronin-1A deficiency in 3 siblings with immunodeficiency and EBV-associated B-cell lymphoproliferation. J Allergy Clin Immunol. 2013;131(6):1594–603. https://doi.org/10.1016/j.jaci.2013.01.042.
113. Martin E, Palmic N, Sanquer S, Lenoir C, Hauck F, Mongellaz C, et al. CTP synthase 1 deficiency in humans reveals its central role in lymphocyte proliferation. Nature. 2014;510(7504):288–92. https://doi.org/10.1038/nature13386.
114. Verzegnassi F, Valencic E, Kiren V, Giurici N, Bianco AM, Marcuzzi A, et al. The challenge of next generation sequencing in a boy with severe mononucleosis and EBV-related lymphoma. J Pediatr Hematol Oncol. 2018;40(5):e323–6. https://doi.org/10.1097/MPH.0000000000001004.
115. Gineau L, Cognet C, Kara N, Lach FP, Dunne J, Veturi U, et al. Partial MCM4 deficiency in patients with growth retardation, adrenal insufficiency, and natural killer cell deficiency. J Clin Invest. 2012;122(3):821–32. https://doi.org/10.1172/JCI61014.
116. Li FY, Chaigne-Delalande B, Su H, Uzel G, Matthews H, Lenardo MJ. XMEN disease: a new primary immunodeficiency affecting Mg2+ regulation of immunity against Epstein-Barr virus. Blood. 2014;123(14):2148–52. https://doi.org/10.1182/blood-2013-11-538686.
117. Sherkat R, Sabri MR, Dehghan B, Bigdelian H, Reisi N, Afsharmoghadam N, et al. EBV lymphoproliferative-associated disease and primary cardiac T-cell lymphoma in a STK4 deficient patient: a case report. Medicine (Baltimore). 2017;96(48):e8852. https://doi.org/10.1097/MD.0000000000008852.
118. Crequer A, Troeger A, Patin E, Ma CS, Picard C, Pedergnana V, et al. Human RHOH deficiency causes T cell defects and susceptibility to EV-HPV infections. J Clin Invest. 2012;122(9):3239–47. https://doi.org/10.1172/JCI62949.
119. Skibola CF, Berndt SI, Vijai J, Conde L, Wang Z, Yeager M, et al. Genome-wide association study identifies five susceptibility loci for follicular lymphoma outside the HLA region. Am J Hum Genet. 2014;95(4):462–71. https://doi.org/10.1016/j.ajhg.2014.09.004.
120. Conde L, Halperin E, Akers NK, Brown KM, Smedby KE, Rothman N, et al. Genome-wide association study of follicular lymphoma identifies a risk locus at 6p21.32. Nat Genet. 2010;42(8):661–4. https://doi.org/10.1038/ng.626.
121. Smedby KE, Foo JN, Skibola CF, Darabi H, Conde L, Hjalgrim H, et al. GWAS of follicular lymphoma reveals allelic heterogeneity at 6p21.32 and suggests shared genetic susceptibility with diffuse large B-cell lymphoma. PLoS Genet. 2011;7(4):e1001378. https://doi.org/10.1371/journal.pgen.1001378.
122. Cerhan JR, Berndt SI, Vijai J, Ghesquieres H, McKay J, Wang SS, et al. Genome-wide association study identifies multiple susceptibility loci for diffuse large B cell lymphoma. Nat Genet. 2014;46(11):1233–8. https://doi.org/10.1038/ng.3105.
123. Tan DE, Foo JN, Bei JX, Chang J, Peng R, Zheng X, et al. Genome-wide association study of B cell non-Hodgkin lymphoma identifies 3q27 as a susceptibility locus in the Chinese population. Nat Genet. 2013;45(7):804–7. https://doi.org/10.1038/ng.2666.