



Next Generation Sequencing Panel for Hereditary Lymphoma

Clinical Features:

Lymphomas are cancers originating from the lymphoid tissues, and can be divided into two broad categories, Hodgkin lymphoma and non-Hodgkin lymphoma, which can be differentiated by their cellular pathology. Hodgkin lymphoma (HL) is characterized by the presence of neoplastic binucleated B-cells called Reed-Steinberg cells [1]. Exposure to Epstein Barr virus is associated with increased risk of HL [1]. In addition, familial HL has also been described, and first degree relatives of a patient with HL having an increased risk of developing the condition [2, 3]. Non-Hodgkin lymphoma (NHL) is a diverse group of more than 50 types of lymphoma that arise from the lymphoid tissues but do not contain Reed-Steinberg cells, each with distinct morphological, cytogenetic, genetic and clinical features [1]. Exposure to Epstein Barr virus and HIV are associated with increased risk of NHL; the contribution of other lifestyle factors and exposures remains unclear. Families with high rates of NHL have also been described, indicating a hereditary component in some cases [1]. In addition, first degree relatives of patients with NHL have a 1.5-3 fold increased risk of developing the condition, again indicating a genetic component to disease susceptibility [1]. Chronic lymphocytic leukemia (CLL) is considered a subtype of NHL. A 3- to 8.5-fold increased risk of CLL among first-degree relatives of probands has been reported [1]. Patients with primary immunodeficiency also have elevated risk to lymphoma [4].

Our Tier 1 Hereditary Lymphoma and Immunodeficiency Panels include sequence analysis of the 11 genes and deletion/duplication analysis of the 8 genes listed below.

Our Tier 2 Hereditary Lymphoma and Immunodeficiency Panels include sequence analysis of the 23 genes and deletion/duplication analysis of the 14 genes listed below.

Tier 1: Hereditary Lymphoma and Immunodeficiency panel

ACD*	CHEK2	KLHDC8B	MLH1
MSH2	MSH6	NPAT	PMS2
POT1*	TERF2IP*	TP53	

Tier 2: Hereditary Lymphoma and Immunodeficiency Panel

ADA	ATM	BRCA1	BRCA2
CARD11	CASP10*	CD27 (TNFRSF7)*	CTLA4*
DOCK8*	FAS (TNFRSF6)	FASLG*	IKZF1*
ITK*	MAGT1*	NBN (NBS1)	NF1
PIK3CD*	PRF1	RECQL3 (BLM)	SH2D1A (SAP)
STXBP2	TNFRSF13B (TACI)	WAS	

*Genes are not included in deletion/duplication analysis.

Cancer/Tumor Susceptibility Syndromes

Gene	Clinical Features
ACD	Guo Y <i>et al.</i> (2014) reported germline mutations of <i>ACD</i> , the gene encoding telomere protein TPP1 in Inherited bone marrow failure [5]. A pathogenic variant in <i>ACD</i> has also been described in a family with chronic lymphocytic leukemia [6]. Hoyeraal-Hreidarsson syndrome can also be caused by a germline mutation in <i>ACD</i> [7].
CHEK2 [OMIM# 604373]	Variants in <i>CHEK2</i> have been associated with a phenotype similar to Li-Fraumeni syndrome [8], which is characterized by increased susceptibility to a number of different cancers including breast cancer, soft-tissue sarcoma, brain tumors, adrenocortical carcinoma and leukemias. Other cancers may also be observed. Ruijs <i>et al</i> (2009) identified four families with a Li-Fraumeni-like phenotype and a heterozygous mutation in <i>CHEK2</i> ; one family included two individuals with Hodgkins lymphoma [9].
MLH1 [OMIM# 120436] MSH2 [OMIM# 609309]	Biallelic mutations in DNA mismatch repair genes <i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> and <i>PMS2</i> are associated with a disorder called constitutional mismatch repair-deficiency syndrome (CMMR-D) [10]. CMMR-D is associated with increased risk of childhood cancers, including hematological malignancies (15%), brain tumors (48%), and gastrointestinal cancers (32%) [11]. The most prevalent hematological

MSH6 [OMIM# 600678] PMS2 [OMIM# 600259]	malignancies observed are NHL and acute lymphoblastoid leukemia [10]. The median age of diagnosis for patients who develop lymphoma is 5 years [10]. Patients may also exhibit features typically associated with neurofibromatosis type 1, such as café au lait spots or neurofibromas [10]. Heterozygous mutations in the <i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> and <i>PMS2</i> genes are associated with Lynch syndrome, an autosomal dominant condition with increased risk of a number of different types of malignancies, including colon, endometrial, ovarian and stomach cancer [10].
NF1 [OMIM# 613113]	Mutations in <i>NF1</i> are associated with neurofibromatosis 1 (NF1), an autosomal dominant neurocutaneous disorder associated with increased risk of both benign and malignant tumors [12]. The most common malignancies include gliomas, peripheral nerve sheath tumors, juvenile myelomonocytic leukemia, pheochromocytoma, gastrointestinal stromal tumors, rhabdomyosarcoma, and malignant triton tumors [12]. Patients also have an increased relative risk of childhood NHL of 10 [13].
NPAT [OMIM# 601448]	A heterozygous mutation in NPAT has been described in four cousins who all presented between the ages of 22 and 26 with nodular lymphocyte predominant Hodgkin lymphoma [14].
POT1 [OMIM# 606478]	Germline heterozygous pathogenic variants in <i>POT1</i> have been recently reported in thyroid cancer, breast cancer, renal cell carcinoma, colorectal cancer and familial chronic lymphocytic leukemia [6, 15]. A <i>POT1</i> mutation has been recently reported implicating defective telomere end fill-in and telomere truncations in Coats plus [16].
TERF2IP [OMIM# 605061]	Mutations in <i>TERF2IP</i> have been described in patients with familial melanoma and familial chronic lymphocytic leukemia [6, 17].
TP53 [OMIM# 191170]	Heterozygous mutations in <i>TP53</i> are associated with Li-Fraumeni syndrome (LFS), a cancer susceptibility disorder [18]. The most common cancers associated with LFS are soft tissue sarcomas, osteosarcomas, pre-menopausal breast cancer, brain tumors, adrenocortical carcinomas and leukemias [18]. A number of other cancers, including Hodgkin and non-Hodgkin lymphomas, have also been described in families with LFS [18].

Immunodeficiency and Autoimmune Disorders

Gene	Clinical Features
ADA [OMIM# 102700]	Mutations in the <i>ADA</i> gene are associated with autosomal recessive severe combined immunodeficiency, which is associated with defective T and B cell function [19]. This condition has been associated with a 5% risk of NHL [19, 20].
CASP10 [OMIM# 601762]	Heterozygous germline mutations in <i>CASP10</i> are associated with autoimmune lymphoproliferative syndrome (ALPS). Patients with ALPS frequently present with fulminant Epstein-Barr viral infection, hypogammaglobulinemia, or lymphoma [21].
CD27 (TNFRSF7) [OMIM#186711]	Homozygous or compound heterozygous mutations in <i>CD27</i> are associated with lymphoproliferative syndrome. The phenotype can vary significantly, from asymptomatic borderline-low hypogammaglobulinemia, to a full-blown symptomatic systemic inflammatory response with life-threatening EBV-related complications, including hemophagocytic lymphohistiocytosis, a lymphoproliferative disorder, and malignant lymphoma requiring stem cell transplantation [22, 23]
CTLA4 [OMIM#123890]	Heterozygous germline mutations in <i>CTLA4</i> are associated with ALPS characterized by autoimmune thrombocytopenias and abnormal lymphocytic infiltration of nonlymphoid organs, including the lungs, brain, and gastrointestinal tract, resulting in enteropathy [24].
DOCK8 [OMIM#611432]	Autosomal recessive hyper-IgE recurrent infection syndrome is caused by homozygous or compound heterozygous mutation in the <i>DOCK8</i> gene [25].
FAS (TNFRSF6) [OMIM# 134637]	ALPS type 1A is caused by heterozygous mutations in the <i>FAS</i> gene [26]. The disorder is caused by defective lymphocyte apoptosis and is associated with chronic lymphadenopathy and splenomegaly, and autoimmune cytopenias [26]. ALPS is associated with a 51-fold increased risk of Hodgkin lymphoma, and a 14-fold risk of non-Hodgkin lymphoma. The average of symptom onset is 5 years, and the average age of lymphoma diagnosis is 28 years [26].
FASLG [OMIM#134638]	Heterozygous mutations in <i>FASLG</i> are associated with ALPS type 1B [27].
ITK [OMIM#186973]	Mutations in <i>ITK</i> are associated with an autosomal recessive form of lymphoproliferative syndrome [28, 29].
IKZF1 [OMIM#606023]	A germline <i>IKZF1</i> mutation can cause an autosomal dominant form of common variable immunodeficiency (CVID) that is associated with a striking decrease in B-cell numbers, and is a predisposition to B-cell precursor acute lymphoblastic leukemia, pancytopenia and autoimmune diseases [30, 31].
MAGT1 [OMIM#300715]	Mutations in <i>MAGT1</i> are associated with X-linked immunodeficiency with magnesium defect, Epstein-Barr virus infection and neoplasia [32, 33].
PIK3CD [OMIM#602839]	Heterozygous mutations in <i>PIK3CD</i> are associated with immunodeficiency characterized by onset of recurrent sinopulmonary and other infections in early childhood [34, 35].

SH2D1A (SAP) [OMIM# 300490]	X-linked lymphoproliferative syndrome-1 (XLP1) is caused by mutations in the <i>SH2D1A</i> gene. XLP1 is associated extreme sensitivity to Epstein Barr virus, which leads to severe or fatal infection mononucleosis, acquired hypogammaglobulinemia and a 20% risk of lymphoma [1, 36]. Female carriers are typically asymptomatic [37].
TNFRSF13B (TACI) [OMIM# 604907]	Mutations in <i>TNFRSF13B</i> are one cause of CVID, which is a heterogeneous disorder characterized by impaired production of antibodies after vaccination or antigen exposure, and reduced serum levels of IgG, IgA and IgM [38]. Symptoms can include chronic sinopulmonary infections [38]. First clinical manifestations typically occur in childhood or adolescence [38]. Mellemkjaer <i>et al.</i> (2002), identified 4 cases of NHL out of 176 CVID patients, indicating a 6-fold increase in NHL incidence compared to the general population [39]. Mutations in <i>TNFRSF13B</i> may be inherited in an autosomal dominant or recessive manner, and penetrance is incomplete [38].
WAS [OMIM# 300392]	Wiskott-Aldrich syndrome (WAS) is a rare X-linked immunodeficiency caused by mutations in the <i>WAS</i> gene. Clinical findings may include thrombocytopenia with small platelets, recurrent otitis media, and eczema. The majority of patients are diagnosed in early childhood. The risk of lymphoreticular malignancies such as lymphoma is 13%.

Multisystem Disorders

Gene	Clinical Features
ATM [OMIM# 607585]	Biallelic mutations in <i>ATM</i> are associated with ataxia telangiectasia (A-T), which is characterized by childhood onset progressive cerebellar ataxia, telangiectasias of the conjunctivae, immunodeficiency and increased risk of cancer [40]. The overall lifetime risk of cancer is 30-40%, with 40% of tumors being NHL, and approximately 5% being HL. Other associated cancers include leukemia, gastric cancer, breast cancer and medulloblastoma [40].
NBN (NBS1) [OMIM# 602667]	Mutations in <i>NBN</i> are associated with the rare autosomal recessive disorder Nijmegen breakage syndrome (NBS). Features of NBS include microcephaly, dysmorphic facial features, immunodeficiency, chromosomal instability, and increased cancer susceptibility. In a series of 55 patients, 29% developed lymphoma, which was the most common cancer observed in the cohort [41]. Age of onset ranged from 1-22 years [41]. Biallelic mutations in <i>NBN</i> have also been associated with aplastic anemia [42].
RECQL3 (BLM) [OMIM# 604610]	Mutations in <i>RECQL3</i> are associated with Bloom syndrome, an autosomal recessive disorder characterized by growth deficiency, immunodeficiency, sun-sensitive erythema and cancer susceptibility [43]. The lifetime risk of cancer for Bloom syndrome patients is 20% [44], including a 13% risk of NHL and a 1% risk of HL [1]. Other cancer risks include colorectal, breast, larynx and skin cancers [44].

Other disorders

Gene	Clinical Features
BRCA1 [OMIM#113705]	Germline mutations in <i>BRCA1</i> increase the risks of breast or ovary cancer and all other cancers including Hodgkin's and non-Hodgkin's lymphoma[45, 46]
BRCA2 [OMIM#600185]	Germline mutations in <i>BRCA2</i> increase the risks of breast or ovary cancer and all other cancers including Hodgkin's and non-Hodgkin's lymphoma[45, 46]
CARD11 [OMIM# 607210]	Recurrent somatic mutations in the <i>CARD11</i> gene have previously been identified in tumor samples from diffuse large B-cell lymphoma [47, 48]. A heterozygous germline missense mutation in <i>CARD11</i> has also been described in a family with hereditary polyclonal B cell lymphocytosis and splenomegaly [49]. B cell lymphocytosis is a condition that resembles chronic lymphocytic leukemia, and can be difficult to clinically distinguish from lymphoma.
KLHDC8B [OMIM# 613169]	Salipante <i>et al</i> (2009) identified a family with multiple individuals with HL, where disease segregated with a chromosomal translocation that disrupted the <i>KLHDC8B</i> gene [50]. In three other families with HL a variant in the 5' untranslated region of the <i>KLHDC8B</i> gene was found to segregate with the disease phenotype [50].
PRF1 [OMIM# 170280]	Biallelic mutations in <i>PRF1</i> are associated with familial hemophagocytic lymphohistiocytosis-2 (FHL2), a life-threatening disorder caused by uncontrolled proliferation of CD25+ T-cells and activation of macrophages that phagocytose blood cells [51]. Symptoms can include fever, hepatosplenomegaly, cytopenias, hypertriglyceridemia, and hypofibrinogenemia [51]. Onset is typically in infancy, however late onset cases have also been described [52]. Clementi <i>et al</i> (2005) identified biallelic <i>PRF1</i> mutations in 4 out of 29 patients with HL or NHL who also had clinical features of hemophagocytic lymphohistiocytosis [53]. In addition, 4 patients had a heterozygous mutation in the <i>PRF1</i> gene.
STXBP2 [OMIM# 601717]	Biallelic <i>STXBP2</i> mutations have been described in patients with familial hemophagocytic lymphohistiocytosis-5 (FHL5), a genetic disorder of lymphocyte cytotoxicity that typically presents within the first two years of life [54]. Atypical cases with later onset in adulthood have also been described [54]. Associated complications of hemophagocytic lymphohistiocytosis (HLH) can include immunodeficiency, granulomatous lung or liver disease, encephalitis or lymphoma. Rohr <i>et al</i> described one individual with biallelic <i>STXBP2</i> mutations who presented with Hodgkin lymphoma at age 6 years, 2 years prior to first onset of HLH [54].

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp. Deletion/duplication analysis of the panel genes is performed by oligonucleotide array-CGH. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

Tier 1: Hereditary Lymphoma and Immunodeficiency Panel (sequence analysis of 11 genes and deletion/duplication analysis of 8 genes)

Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: \$3300
CPT codes: 81479
Turn-around time: 4-6 weeks

Note: We cannot bill insurance for this test.

Tier 2: Hereditary Lymphoma and Immunodeficiency Panel (sequence analysis of 23 genes and deletion/duplication analysis of 14 genes)

Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: \$2000
CPT codes: 81479
Turn-around time: 4-6 weeks

Note: We cannot bill insurance for this test.

Results:

Results, along with an interpretive report, are faxed to the referring physician as soon as they are completed. One report will be issued for the entire Inherited Bone Marrow Sequencing Panel. All abnormal results are reported by telephone or email.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

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