

Genetic Diagnostic Laboratory
Department of Genetics

LYMPHEDEMA GENETIC TESTING PANEL

Background: This test analyzes genes associated with primary lymphedema and lymphatic malformation syndromes. It includes 43 genes linked to a range of lymphatic malformations, which may occur in isolation or as part of a broader syndrome. Genetic testing can confirm the clinical diagnosis, help define the subtype, and support risk assessment for family members. Pathogenic variants may be germline or somatic. Hereditary forms are often autosomal dominant with variable expression, while somatic variants—frequently mosaic—are better detected in affected tissue than in blood. Submission of affected tissue is strongly recommended to improve diagnostic sensitivity. The cost of testing includes up to two samples. Additional samples may be submitted for an added fee—please contact the lab for details. See Table 2 for a list of genes and associated conditions.

Assay: Targeted capture-based enrichment followed by high-throughput sequencing is performed on the Illumina NextSeq platform to analyze a panel of 43 genes implicated in lymphedema and lymphatic malformation syndromes (see Table 2 for gene list and associated conditions). The panel includes: *ABCC9, ADAMTS3, ALG8, ARAF, BRAF, CBL, CCBE1, CCDC88A, CDC42, CELSR1, EPHB4, FAT4, FLT4, FOXC2, FZD6, GATA2, GJA1, GJC2, HGF, HRAS, ITGA9, KIF11, KRAS, MAP2K1, MAP2K2, MET, MPI, NAGA, NRAS, PIEZO1, PIK3CA, PTEN, PTPN11, PTPN14, RAF1, RASA1, RIT1, SHOC2, SOS1, SOX18, THSD1, VEGFC, and ZNHIT*. 14 SNPs are analyzed to detect 45,X.

Sensitivity: The assay achieves a validated limit of detection of 1% variant allele frequency (VAF) at a minimum read depth of 1,000X. Variants are reported if supported by at least 10 high-quality reads, with balanced representation across both DNA strands. Variants in regions with less than 100x coverage may not be reliably detected and are considered below the assay’s analytical sensitivity threshold. Confirmation of significant variants identified by NGS may be performed by a second NGS run, droplet digital PCR (ddPCR) or Sanger sequencing, depending on the context and sample type.

Clinical Utility: This test can confirm a clinical diagnosis, inform medical management, support prognostic evaluation, and help identify at-risk family members.

Table 1: Testing Options

Name of Test	TAT	Cost	CPT Codes
<p>STAT Request Option: Please note that each test can be ordered STAT (CPT: 99199) this will include results in half (50%) of the below listed TAT and a total cost of +20% of the base cost listed below for the ordered test. This option excludes <i>Expedited</i> and <i>Prenatal</i> test requests.</p> <p>Please call the lab to ensure we are able to accommodate your STAT request.</p>			
Lymphedema NGS Panel <i>UP TO 2 SAMPLES</i>	4-6 weeks	\$3,400	81479
<i>PRENATAL</i> Lymphedema NGS Panel <i>(Prenatal test cost listed includes MCC cost and STAT surcharge)</i>	2-4 weeks	\$4,220	81479, 81265, 99199
FFPE Sample Isolation Surcharge <i>*FFPE samples are not preferred due to DNA quality issues</i>	N/A	\$160	88381

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Table 2: Gene and Disease Information

Gene/ Location	OMIM	Related associated condition(s)
ABCC9 12p12.1	601439	Cantu Syndrome : [#239850]: Congenital hypertrichosis, osteochondrodysplasia, and cardiomegaly. About half of affected individuals are macrosomic and edematous at birth.
ADAMTS3 4q13.3	605011	Hennekam lymphangiectasia-lymphedema syndrome 3 [#618154]: Widespread congenital edema, facial dysmorphism, and protein-losing enteropathy of variable severity
ALG8 11q14.1	608103	CDG, Type 1h [#608104]: A severe congenital disorder of glycosylation (CDG) with most patients having brain involvement, dysmorphology, liver pathology, GI symptoms, and skin findings including edema.
ARAF X911.3	311010	Single case reports ; patients reported with angioimmunoblastic lymphadenopathy with dysproteinemia.
BRAF 7q34	164757	Cardiofaciocutaneous syndrome [#115150] and Noonan syndrome [#613706]: These conditions have many overlapping features including congenital anomalies that affect the heart, face, and stature. Either condition may present with lymphedema.
CBL 11q23.3	165360	Noonan syndrome-like disorder w/ or w/o juvenile myelomonocytic leukemia [#613563]: Developmental disorder resembling Noonan Syndrome, including possible lymphedema/ abnormalities of the lymphatic system.
CCBE1 18q21.32	612753	Hennekam lymphangiectasia-lymphedema syndrome 1 [#235510]: Generalized lymphatic dysplasia affecting various organs, including the intestinal tract, pericardium, and limbs. May also present with dysmorphism and cognitive impairment
CCDC88A 2p16.1	609736	Progressive encephalopathy w/ edema, hypsarrhythmia, and optic atrophy-like syndrome [#617507]: Reported in a single family with a homozygous variant in CCDC88A. 3 children presented with severe encephalopathy, progressive microcephaly, hypotonia, and persistent edema present from birth on the face, hands, and feet. These children also had cognitive and motor delays and subtle dysmorphic features.
CDC42 1p36.12	116952	Takenouchi-Kosaki Syndrome [#616737]: A congenital developmental disorder presenting with dysmorphism, ID, and cardiac, GI, hematologic, and/or lymphatic defects, including lymphedema. Presentation in variable, with more mild patients resembling Noonan Syndrome patients.
CELSR1 22q13.31	604523	A variant reported in this gene associated with non-syndromic, lower extremity lymphedema [PMID: 268055770].
EPHB4 7q22.1	600011	Lymphatic malformation syndrome 7 [#617300]: Variable lymphatic malformations, ranging from adult varicose veins to severe nonimmune lymphatic-related hydrops fetalis.

FAT4 4q28.1	612411	Hennekam lymphangiectasia-lymphedema syndrome 2 [#616006]: Generalized lymphatic dysplasia affecting various organs, including the intestinal tract, pericardium, and limbs. May also present with dysmorphism and cognitive impairment
FLT4 5q35.3	136352	Lymphatic malformation syndrome 1 [#153100]: Primary lymphedema with possible nail and skin changes such as nail dysplasia or papillomatosis. Congenital heart defects [#618780]
FOXC2 16q24.1	602402	Lymphedema-distichiasis syndrome [#153400]: Lymphedema of the limbs and double rows of eyelashes with possible cardiac defects, varicose veins, ptosis, cleft palate, spinal extradural cysts, and photophobia.
FZD6 8q22.3	603409	Nail disorder, nonsyndromic congenital, 1 [#161050]: Characterized by excessive longitudinal striations and numerous superficial pits on the nails. A pathology study of these patients found mild to moderate lymphocytic infiltrate in the superficial dermis of the proximal nail fold and matrix.
GATA2 3q21.3	137295	Emberger syndrome [#614038]: A chronic condition characterized by swelling of the extremities due to altered lymphatic flow, associated with myelodysplasia. May also present with deafness.
GJA1 6q22.31	121014	Oculodentodigital dysplasia [#164200]: Characteristic facial features with teeth that are typically small and carious and complete syndactyly of the fourth and fifth fingers. Presentation may include lymphedema and neurologic abnormalities.
GJC2 1q42.13	608803	Lymphatic malformation syndrome 3 [#613480]: Variable lymphedema with possible nail and skin changes such as nail dysplasia or papillomatosis.
HGF 7q21.11	142409	Candidate gene for primary lymphedema [PMID: 18564920].
HRAS 11p15.5	190020	Costello syndrome [#218040]: Condition of multiple congenital anomalies with coarse facies, short stature, distinctive hands, severe feeding difficulties, and possible lymphedema.
ITGA9 3p22.2	603963	Lymphedema-distichiasis syndrome [PMID: 19686679].
KIF11 10q23.33	148760	Microcephaly, lymphedema, chorioretinopathy dysplasia syndrome [#152950]: A variable spectrum of central nervous system and ocular anomalies, microcephaly with characteristic facies, and congenital lymphedema which, when present, is typically confined to the feet.
KRAS 12p12.1	190070	Noonan syndrome [#609942]: A variable condition characterized by dysmorphic facial features, cardiac abnormalities, and short stature, among other features. Many babies are born with edema, commonly at the back of the hands and top of feet, and many individuals develop lymphedema of the legs in their teenage years. Lymphatic system malformations in utero may lead to polyhydramnios, lymphedema of fetal tissue, or total hydrops fetalis.

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MAP2K1 15q22.31	176872	Cardiofaciocutaneous syndrome 3 [#615279]: Congenital anomaly syndrome that affect the heart, face, and stature and affected individuals may present with lymphedema.
MAP2K2 19p13.3	601263	Cardiofaciocutaneous syndrome 4 [#615280]: Congenital anomaly syndrome that affect the heart, face, and stature and affected individuals may present with lymphedema.
MET 7q31.2	164860	Primary lymphedema [PMID: 18564920].
MPI 15q24.1	154550	CDG, Type 1b [#602579]: A congenital disorder of glycosylation (CDG) with the predominant symptoms being chronic diarrhea with failure to thrive and protein-losing enteropathy with coagulopathy. Hepatic fibrosis and intestinal lymphangiectasias are seen in some affected individuals.
NAGA 22q13.2	104170	Kanzaki disease [#609242], Schindler disease, types I and III [#609241]: A rare clinically heterogenous group of lysosomal storage disorders caused by a deficiency of Alpha-N-acetylgalactosaminidase (NAGA) with case reports of symptoms including lymphedema.
NRAS 1p13.2	164790	Noonan syndrome [#613224]: See KRAS for description. RAS-Associated autoimmune leukoproliferative disorder [#614470]: Characterized by lymphadenopathy, splenomegaly, and variable autoimmune anomalies.
PIEZO1 16q24.3	611184	Lymphatic malformation syndrome 6 [#616843]: Generalized lymphatic dysplasia with uniform, widespread edema and systemic involvement such as intestinal and pulmonary lymphangiectasias and pleural and cardiac effusions. There is a high incidence of nonimmune hydrops fetalis. Dehydrated hereditary stomatocytosis 1 w/ or w/out pseudohyperkalemia &/or perinatal edema [#194380]: A hemolytic anemia condition that may present with perinatal edema.
PIK3CA 3q26.32	171834	CLAPO syndrome [#613089]: Capillary malformation of the lower lip, lymphatic malformation of face and neck, asymmetry of face and limbs, and partial or generalized overgrowth. CLOVES syndrome ³ [#612918]: Congenital lipomatous overgrowth, vascular malformations, epidermal nevi and spinal/skeletal anomalies. May include lymphatic malformations.
PTEN 10q23.31	601728	Macrocephaly Autism Syndrome [#605309]: Macrocephaly with delayed psychomotor development resulting in autistic behavior or intellectual disability. Affected individuals may have recurrent infections due to abnormal T- and B- cell function. Case reports with lymphadenopathy have been published.
PTPN11 12q24.13	176876	Noonan syndrome [#163950]: See KRAS for description. LEOPARD syndrome [#151100]: Lentigenes, Electrocardiographic anomalies, Ocular hypertelorism, Pulmonary stenosis, Abnormal genitalia, Retardation of growth, and sensorineural Deafness. Also called Noonan syndrome with multiple lentigenes.

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PTPN14 1q32	603155	Choanal atresia and lymphedema [#613611]: Patients with homozygous variants have been reported with choanal atresia and lymphedema.
RAF1 3p25.2	164760	Noonan syndrome [#611553]: See KRAS for description. LEOPARD syndrome [#611554]: Lentiginos, Electrocardiographic anomalies, Ocular hypertelorism, Pulmonary stenosis, Abnormal genitalia, Retardation of growth, and sensorineural Deafness. Also called "Noonan syndrome with multiple lentiginos".
RASA1 5q14.3	139150	Capillary Malformation-Arteriovenous Malformation 1³ (#608354): Atypical capillary malformations including arteriovenous malformations and fistulas. Associated with lymphedema [PMID: 23650393].
RIT1 1q22	609591	Noonan syndrome [#609591]: See KRAS for description.
SHOC2 10q25.2	602775	Noonan syndrome-like with loose anagen hair 1 [#607721]: Features similar to Noonan Syndrome, with characteristic easily plucked, sparse, thin, slow-growing hair. Affected individuals have been reported with perinatal edema
SOS1 2p22.1	182530	Noonan syndrome [#610733]: See KRAS for description.
SOX18 20q13.33	601618	Hypertrichosis-lymphedema-telangiectasia syndrome [#607823]: Characterized by these features, typically presenting at birth or in early childhood. These features are typically progressive. Hypertrichosis-lymphedema-telangiectasia-renal defect syndrome [#137940]: Characterized by these features, typically presenting at birth or in early childhood. These features are typically progressive.
THSD1 13q14.3	616821	Associated with lymphedema [PMID: 26036949].
VEGFC 4q34.3	601528	Lymphatic malformation syndrome 4 [#615907]: Primary lymphedema with possible nail and skin changes such as nail dysplasia or papillomatosis.
ZNHIT3 17q12	604500	PEHO syndrome [#260565]: Progressive encephalopathy with edema, hypersarhythmia, and optic atrophy.