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NEXT GENERATION SEQUENCING IS HERE NOW

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ABSTRACT

The availability of massively parallel DNA sequencers has brought the cost of sequencing genes to affordable levels but the cost of analyzing the huge amount of data has not decreased to the same extent. Thus, only analyzing the sequences of the genes relevant to the patient's condition makes the cost manageable. A panel of genes relevant to lymphedematous conditions is described.

Keywords: DNA sequencing, next generation sequencing, lymphedema genes, genome, gene panels, lymphatic malformations

The $1,000 genomic sequence has finally arrived! (But see below for the costs of analyses.) The first complete genomic sequence cost many billions of dollars. A major part was the time and effort to build a "framework" — the structure of chromosomal places and known markers so that the 3 billion, 300 million "letters" of the genome sequence could be placed in relative position. The other major cost was the price of DNA sequencing. Now that the "structure" is established and the cost of sequencing has dropped by 3-4 magnitudes, laboratories with the most modern massively parallel sequencers can do the sequence for this low cost. However, the cost of analyzing 3.3 billion letters of the sequence is multiple times this—more like $10,000). This can be simplified by just sequencing the part of the genome which codes for proteins. This is only about 1.5-2% of the genome. Thus, one can save some money on the sequencing and a lot of money on the analyses. Our diagnostic laboratory provides the sequence of the exons and splice donor and acceptor sites (which would usually cost $1,000 or more per gene, depending on its size and complexity, at other commercial laboratories) of about 50 currently known lymphatic-disorder related genes (see Tables) at the cost of analyzing 2 or 3 of the more commonly studied genes (VEGFR3, *FOXC2, CCEB1,* etc.) at other commercial laboratories (our charge, not covered by insurance at this time, is $2,300). A report of abnormalities would only be issued for the genes in *Table 1*, and some of

TABLE 1
Genes Involved in Lymphatic Abnormalities

Milroy *FLT4*
Lymphedema-distichiasis *FOXC2*
Hennekam lymphangiectasia-lymphedema syndrome *CCBE1*
Meige *GJC2*
Oculodentodigital dysplasia *GJA1*
Hypotrichosis-lymphedema-telangectasia *SOX18*
Choanal atresia *PTPN14*
Milroy-like disease *VEGFC*
Lymphedema-lymphangiectasia *HGF*
Noonan syndrome *PTPN11, SOS1, KRAS, RAF1*
MCMLR *KIF11*
Emberger syndrome *GATA2*
OLEDAID *IKBKG*
Fetal chylothorax *ITGA9*
Costello syndrome HRAS

TABLE 2
Genes Involved in Lymphatic Development in which Mutations May Yet be Found

PROX1
SOX18
NR2F2 (TFCOUPII)
TEK (TIE2)
PDPN (podoplanin)
LYVE1
GJA4 (Connexin 37)
EGR1 (Early growth response 1)
ITGA9 (Integrin alpha 9)
LAMA5 (Laminin alpha 5)
EFNB2 Ephrin B 2
VEGFD
NRP1 (Neuropilin 1)
NRP2
ANGPT1 (Angiopoietin 1)
ANGPT2
FOXC1
LCP2 (SLP-76)
SYK
MIR211 (microRNA 211)
CYP26B1 (cytochrome 26B1)

TABLE 3
Genes involved in Somatic Mosaicism and Peripheral Lymphatic Abnormalites (and which are lethal if inherited, i.e., germ line)

Proteus syndrome *AKT1*
Klippel Trenaunay syndrome *"AGGP1"*
Maffucci syndrome and Ollier disease *IDH1, IDH2*
Sturge Weber syndrome *GNAQ*
Cloves syndrome *P1K3CA*

the genes in *Table 3*, for which causation of the lymphatic condition by the particular gene's mutations is established. The other genes, mostly those in *Table 2*, would be studied for research and not reported. Thus, a research consent needs to be signed.

In addition, somatic (non-germline) mutations in several genes are responsible for non-familial, peripheral lymphatic disorders. These mutations are likely to be present at only small levels in the usual sources of DNA (blood where the DNA is in white blood cells, saliva, or buccal swabs) but higher levels would be found in portions of any surgical biopsy or removed tissue (*Table 3*). If interested in having this sequencing done for research at the cost of $2,300, please contact Robert P. Erickson, MD at 520-626-2314 or Michael Bernas at 520-626-6137 for consent forms to be mailed and, later, for phone consent to be obtained.

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