RESEARCH PERSPECTIVE

Genetics of Childhood Lymphedema-Angiodysplasia Syndromes

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For more than 100 years, physicians have recognized that some forms of lymphedema, particularly those manifesting early in childhood, are hereditary1-3. Advances in lymphatic imaging (oil contrast lymphography) in the middle of the last century further classified the varied clinical manifestations (clinical phenotypes) and contrasting lymphatic and lymph node abnormalities (lymphatic phenotypes) of some affected individuals and families thereby defining specific syndromes as well as modes of inheritance (autosomal dominant, recessive, sex-linked)4. It was not, however, until the late 1990's with the advent of widespread genomic screening and advanced DNA techniques that actual linkage of specific gene mutations with several forms of familial lymphedema took place.

The first disorder elucidated was autosomal dominantly inherited Milroy lymphedema, which generally presents at birth with lower limb lymphedema associated with lymphatic truncal hypoplasia or aplasia (lymphatic undergrowth). Linkage in a subpopulation of Milroy patients was pinpointed to the distal short arm of chromosome 5 (5-7) and subsequently to the gene for VEGFR-3 (the receptor for Vascular Endothelial Growth Factor-C, the so-called Lymphatic Growth Factor), in which multiple mutations have since been documented8,9. While 5q35.3 linkage was described in all five families studies in one report7, only a subset of families exhibited linkage in two other reports6,6 indicating possible genetic differences in the group designated as Milroy syndrome10. The second lymphan giogenesis/lymphedema gene, discovered in 2000 is FOXC2 on chromosome 1611. FOXC2 is a “master gene” transcription factor and mutations in the gene underlie autosomal dominant lymphedema-distichiasis (LD) syndrome, in which lower limb lymphedema typically appears at puberty and occurs in combination with distichiasis (a double row of eyelashes), and often other eye abnormalities as well as various congenital anomalies such as cardiovascular defects and cleft palate12-14. Lymphography in LD patients shows a hyperplastic (overgrowth) lymphatic system with increased number of lymphatic channels and lymph nodes, interestingly mimicked in genetically engineered Foxc2 deficient mice, which also exhibit distichiasis. In addition, the rare hypotrichosis (hair loss)-lymphedema-telangiectasia (spiderly blood vessels) syndrome, is thought to be due to mutations in the gene for the transcription factor SOX18 on chromosome 2015 and lymphedema associated with cholestasis (bile duct obstruction) (Aagenaes syndrome), maps to chromosome 1516. Furthermore, there remain ~40 additional familial syndromes where lymphedema is a distinctive feature accompanied by various constellations of other clinical findings (particularly head, eye, ear, and neck, cardiovascular, gastrointestinal, pulmonary, neurological, urogenital, and musculoskeletal abnormalities)17,18, in which neither the chromosome nor specific linkages or gene mutations have yet been identified. Chromosomal aneuploidies (unequal chromosome number- either extra or deficient), the most common of which are Down syndromes11 and Turner (XO) syndrome, and chromosomal rearrangements underlie still other lymphedema syndromes often associated with fetal demise, the genetic mechanisms for which have yet to be elucidated19.

Current genetic investigation follows two different directional pathways. In the first - “forward genetics” - the search begins with a known gene or growth factor of interest and proceeds to delineate the effect on development and phenotype, typically through the use of transgenic mice in which the growth factor is overexpressed, underexpressed, or deleted. The opposite approach - “reverse genetics” - begins with a group of affected patients or family pedigrees and works backwards to identify the gene(s) responsible through linkage studies focused on genetic similarities among affected individuals and differences from unaffected individuals. Of paramount importance to either approach is a correct, precise definition of the affected phenotype, i.e. the spectrum of clinical presentations of the altered (mutated) gene(s). The assignment of individuals to unaffected or carrier status and the consideration of age of onset or patterns of lymphedema distribution and lymphatic/lymph node involvement remain imprecise or even incorrect in pedigree analyses and may only be revealed by an “accident” of localized injury or...
infection-precipitated overt lymphedema. Accurate delineation of lymphatic system structure and function (lymphatic fluid transport, lymph reflux, lymphatic vessel size, number, and distribution patterns, nodal defects, etc.) is absolutely necessary to complement the fine molecular determination required in genomic analysis. In collaboration with the Translational Genomics Research Institute (TGen) of Phoenix, we are now employing higher resolution technologies for still finer mapping of genetic sequences in our lymphedema families under study by using single nucleotide polymorphisms (SNPs) (found approximately every thousand bases along the human genome). This technology is likely to identify lymphedema causing genes more rapidly.

Accordingly, our Comprehensive Lymphedema-Angiodysplasia Center, developed with the guidance of the late surgeon-lymphologist Charles Witte, focuses on a multidisciplinary team approach to the child and/or family with lymphedema - establishing the diagnosis, identifying the associated clinical features, delineating the specific lymphatic system abnormalities, providing individualized multimodal non-operative and operative management as well as genetic counseling. Concomitant basic and clinical research is an important overarching theme. As gene discovery proceeds at a rapid pace, new molecular-based therapies will gradually emerge on the horizon. The active collaboration of molecular and clinical lymphologists with multidisciplinary specialists and patient advocacy organizations like the NLN is more than ever needed for safe and effective translation of research from “bench to bedside to community”, i.e. from “mice to men” (women, and children) with aim to fulfill the promise of a better tomorrow for those afflicted with lymphedema and other lymphatic disorders.

References: