The circulatory (blood) system is comprised of two separate components: the venous system which returns blood to the heart, so that it can pass through the lungs to get oxygen, and the arterial system which delivers this oxygenated blood to the tissues. The heart serves as a pump to move the blood through the body. The lymphatic system, however, works on a one-way principle, the purpose of which is to drain lymphatic fluids from the tissues, where it collects, and return that fluid to the bloodstream. Muscles serve as the “pumps” and one-way valves prevent fluid from flowing backward in the system.

Lymphatic fluid, also called lymph, consists of four components: protein, water, dead cells and toxins, and some fats. Certain fats in our diet can only be absorbed by the lymphatic vessels of the intestines. Approximately half of the total protein found in the blood and two liters of water escape from the bloodstream into the tissues each day and are returned to the bloodstream through the lymph. The lymph nodes filter this fluid to remove dead cells, bacteria, and toxins from the tissues, before the remaining fluid is returned to the venous system.

When the lymphatic system is unable to remove some of this lymph fluid, it collects in the tissues such as the feet or legs, resulting in swelling. This swelling, known as lymphedema, can be either primary or secondary. Primary lymphedema is caused by inherited abnormalities of the lymphatic system, such as underdevelopment of the lymphatic vessels, while secondary lymphedema results from a lymphatic system that has been damaged or blocked by some environmental cause such as surgery, injury, or infection. Although secondary lymphedema is far more common than primary, knowledge of the genetic mechanisms that cause primary lymphedema will lead to a better understanding of the function of the lymphatics, easier and more accurate diagnosis of the condition, and new ideas for treatment of both primary and secondary lymphedema.

As many people with lymphedema know all too well, this condition has been poorly understood and largely ignored by both researchers and clinicians until relatively recently. Except for a few isolated studies in the latter half of the 1900’s, there has been little new information about lymphedema until the past few years. Recently, however, we have witnessed an explosion of research and new information on this disease. Primary lymphedema has been estimated to occur in about one in six thousand people, more often in females than in males, and age of onset tends to be similar within families. Primary lymphedema can be present from birth (congenital lymphedema or Milroy’s Disease), symptoms can begin at the time of puberty (lymphedema praecox or Meige’s Disease), or onset can occur in adulthood (lymphedema tarda). Primary lymphedema can be sporadic, meaning that no other family members develop the disease, or its dominant inheritance through the generations can be easily observed. Primary lymphedema occasionally occurs in association with other traits, such as distichiasis (an extra row of eyelashes) or yellow nails.

Because of the complexity of the lymphatic system, it is widely accepted that there are many genes involved in its development. Changes (mutations) in any one of these genes could theoretically cause primary lymphedema. Genetic heterogeneity is the term used to describe this situation in which different genes can cause the same or a similar condition. Although different genes may cause lymphedema in different families, only one of these genes is responsible for the lymphedema in any particular family.

The first step in the identification of these genes is a process called linkage analysis. Linkage analysis, or linkage studies, is a method in which the genetic material or DNA is compared between family members with and
without lymphedema. Differences between these two groups within a family can help pinpoint the chromosomal location of the gene causing the lymphedema in that particular family. The larger the family, the more information that family provides about the location of a gene. Because there are many genes that can cause lymphedema, different families may help point researchers toward different genes.

By using this method of linkage analysis, we were able to determine the location of the first lymphedema gene on chromosome 5 in families with congenital lymphedema (Milroy’s Disease). Ultimately, we were able to identify the particular gene responsible, and in 1998 we reported lymphedema-causing mutations in the vascular endothelial growth factor receptor 3 or VEGFR-3 gene (previously referred to as FLT4). This finding was confirmed by several other research groups. VEGFR-3 belongs to a family of growth factors and growth factor receptors which are known to be involved in the formation of lymphatic vessels during a baby’s development. We have observed several lymphedema-causing mutations in the VEGFR-3 gene in different families. These mutations prevent this receptor from responding to the messages it receives from certain growth factors that signal development of lymphatic vessels, resulting in an underdevelopment (hypoplasia) of these vessels. To date, we have identified VEGFR-3 mutations in four families with congenital lymphedema or Milroy’s Disease and additional mutations have been reported by other research groups.

There are over one hundred families participating in the Lymphedema Family Study, for which a mutation in VEGFR-3 has not been identified. Although we continue to search in these families for additional mutations in this gene, we have identified some families, in which this gene is not responsible for their lymphedema. Currently, we are studying these families to determine the location of other primary lymphedema genes. Because there are many genes thought to be involved in the development of the lymphatic system, we expect that many additional genes which are responsible for congenital primary lymphedema as well as lymphedema of later onset (praecox and tarda) will ultimately be identified. For example, the location of a gene on chromosome 16 for lymphedema and extra eyelashes (distichiasis) has already been reported, though the gene itself has not yet been identified.

A genetic test for lymphedema is not yet available and, in most cases, specific genetic information is not available for individuals or family members participating in the Lymphedema Family Study. However, as genes and mutations are identified and proven to be responsible for causing lymphedema in specific families, family members will be contacted.

Although there have been significant advances in the research of lymphedema in the last few years, there is still much work to be done. Researchers from across the globe came together in May to set the research agenda for lymphedema and related disorders. Hopefully, the collaborations established there will help this research move forward at an even faster pace than we have seen in the last few years. The ultimate hope is that advances in understanding the genetic basis of lymphedema will help provide a definitive diagnosis and allow earlier treatment to minimize long-term complications sometimes associated with this condition. Therapeutic implications of this knowledge about the genetics of the lymphatic system include the potential for drugs that modify the activity of the receptors and growth factors involved in maintaining a healthy lymphatic system. Like the regrowth of blood vessels that has recently been reported in the news, the same potential exists for regrowth of underdeveloped or damaged lymphatic vessels.

Identification of other lymphedema genes will be dependent on large families with this condition. Therefore, advances in understanding underlying causes of lymphedema are critically dependent on the voluntary participation of individuals and families in research. We continue to recruit families in which two or more individuals are affected with lymphedema. If you have questions or if you and your family are interested in participating, please contact us at 412-624-4657 or genetics@pitt.edu for more information or look up our web page at www.pitt.edu/~genetics/lymph.
REFERENCES