An estimated 1 in 10,000 individuals is affected by a primary lymphatic disorder, or a disorder of lymphatic development (Connell et al., 2010). Many of these disorders have been found to have a genetic component, such as a mutation in the genes that are linked to lymphatic development. These mutations ultimately give rise to lymphatic malformation, resulting in the onset of lymphedema (LE).

LE distichiasis syndrome (LDS) is one example of a primary lymphatic disorder with a known genetic component. LDS is an autosomal dominant disorder (Online Mendelian Inheritance in Man [OMIM], 2011), which means LDS typically appears in every generation of an affected family, and children of affected parents have a 50% chance of inheriting the disease gene. The forkhead box C2 gene, or FOXC2 gene, is the only gene involved in LDS, and mutations in FOXC2 impact the function of its associated protein, also named FOXC2 (Miura et al., 1997). The onset of LDS typically occurs between late childhood and early adolescence, though males tend to be more severely affected than females (Connell et al., 2008; Mansour et al., 2007). Seventy-five percent of all individuals with LDS are symptomatic and usually affected by lymphedema (LE) and distichiasis (double row of eyelashes), for which the condition is named (Connell et al., 2010). LE related to LDS manifests in the lower limbs with characteristically asymmetrical swelling (Connell et al.) and predisposition to cellulitis.

Interestingly, while LE and distichiasis do not occur in every case of LDS, distichiasis occurs more often. Distichiasis occurs in an estimated 94% of individuals (Brice et al., 2002) and results in a “second row” of eyelashes – meaning, additional eyelashes protrude from the inner aspect of the eyelid. The majority of these additional lashes have been found to grow from the surfaces of meibomian glands that normally maintain lubrication of the eye. However, due to alterations in the function of the FOXC2 protein in individuals with distichiasis, affected meibomian glands do not correctly develop, resulting in aberrant eyelash growth. Individuals with distichiasis frequently experience corneal abrasions, conjunctivitis, and light sensitivity, among other ophthalmologic phenomena (Huang et al., 2009; Traboulsi et al., 2002).

Other conditions less frequently associated with LDS include cardiovascular anomalies and venous valve insufficiencies. In one study, congenital cardiac disorders, such as tetralogy of fallot (Finegold et al., 2001), were estimated to impact approximately 7% of all participants, and in another study, venous varicosities affected approximately 50% of all participants (Brice et al., 2002).

Cleft palate has also been implicated in LDS, (Bauhau et al., 2002). These findings reflect profound variations in the manifestation of LDS, necessitating comprehensive clinical assessment in evaluating individuals with this disorder.

Genetic testing for LDS is feasible using gene sequencing techniques that can identify 95% of all LDS-related mutations (Mansour et al., 2007). Treatment options are also available for this condition, including complex decongestive therapy for LE (Rockson, 2008) and plucking and lid splitting surgery for distichiasis (O’Donnell & Collin, 1993). Unfortunately, palliation of symptoms is currently the focus of treatment for LDS, as a cure has not yet been developed for this condition.

However, the molecular biological characteristics of LDS have only come into light within the last decade. The FOXC2 gene was not associated with LDS until identified in 2000 by Fang et al. This gene is known to code, or provide the genetic information, for synthesizing the FOXC2 transcription factor. A transcription factor is a protein important for the activation, and in some instances, inactivation, of different genes. Turning on and off different genes that are potentially important for lymphatic development may be a role of the FOXC2 transcription factor, which is affected by mutations in the FOXC2 gene. Mutations have been found within the FOXC2 gene that are hypothesized to deleteriously impact the function of the FOXC2 protein in its ability to bind to and suppress or induce the activation of different genes, as well as co-regulate the activity of other genes (Berry et al., 2005; Normén et al., 2009). The identification of those genes within the context of LDS and their impact on lymphatic and ocular development will be another major step in primary lymphatic pathophysiology related research.
Although researchers have only begun to understand LDS, continued research in studying the molecular pathways implicated in LDS using animal models will provide opportunities for exploring lymphatic development, with the goal of applying this knowledge to humans. Clinical researchers have also strived to develop guidelines to help differentiate LDS and other primary lymphatic disorders from each other so that appropriate interventions are implemented (Connell et al., 2010). Ongoing research in studying primary lymphatic disorders, such as LDS, also holds the potential to further unravel lymphatic development, growth, and repair so that clinically-relevant applications can be developed for those affected by the many forms of LE and other lymphatic-related conditions.

References


