Genetics of primary lymphoedema: An update:

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Primary lymphedema can be present at birth, or develop in childhood or later in life. Thus, it may be a developmental disorder and/or due to a dysfunction of lymphatic vessels that develops with time. Since the discovery in 2009 of the first gene mutated in primary congenital lymphedema or Milroy's disease, the *VEGFR3* gene, mutations in numerous genes involved in the initial formation of lymphatic vessels (including valves), in the growth and expansion of the lymphatic system and in associated pathways have been identified in syndromic and non-syndromic forms of PLE. Thus, the current hypothesis is that the majority of cases of PLE has a genetic origin, although a causative mutation can be identified in only about one-third of affected individuals. Overall, three patterns of inheritance are observed, including autosomal dominant (including de novo mutations), autosomal recessive and X-linked. Moreover, penetrance is often less than 100%, making identification of mutations more difficult. Most mutations cause loss-of-function, although some, such as in the genes associated with Noonan syndrome, gain-of-function. Various functional pathways seem to be involved.