

**PHENOTYPIC AND GENOTYPIC HETEROGENEITY  
IN FAMILIAL MILROY LYMPHEDEMA**

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*ABSTRACT*

*Familial Milroy lymphedema (ML) is classified as an autosomal dominant disorder characterized by peripheral edema of the lower extremities at birth or in early childhood. The variety of phenotypes are not well described, and the genomic location and functional expression of the gene or genes underlying this and related familial lymphedema syndromes remain largely unknown. In this collaborative study between the University of Arizona and the University of São Paulo, we collected clinical pedigrees on 6 ML families, carried out clinical examination of affected and unaffected individuals, and, in representative affected members of two of the families performed dynamic lymphangioscintigraphy (LAS) of the lower and upper limbs to delineate further the ML lymphangiodysplastic phenotype. To localize the gene for ML, we conducted a genome-wide search in 4 of the families using 387 polymorphic dinucleotide-repeat markers at approximate 10 cM spacing in 54 subjects (affected, unaffected bloodline relatives, and spouses). In all 6 families (86 subjects), we specifically examined the suggested linkage to the vascular endothelial growth factor (VEGF)-C receptor (Flt4) gene localized to the chromosome region 5q34-q35. The findings provide evidence for a spectrum of ML clinical and LAS phenotypes and also suggest ML locus heterogeneity.*