

## EDITORIAL

## LYMPHEDEMA-DISTICHIASIS AND FOXC2 GENE MUTATIONS

Among the delineated inherited forms of lymphedema (Milroy's, Meige's, etc.), lymphedema-distichiasis has been one frequently associated with other congenital anomalies: cardiac defects, cleft palate, vertebral anomalies, and extradural cysts, for instance. Thus, it is not surprising that the gene recently identified as causative of lymphedema-distichiasis is from a class of genes well known for their developmental effects (1). This gene, *FOXC2*, is a member of the forkhead gene family. This is a family of winged-helix transcription factors which has been thoroughly studied in knockout mice. Indeed, mice homozygous for the knockout of *FOXC2* have shown a similar range of birth defects as seen in lymphedema-distichiasis, but in very severe form, causing prenatal lethality. The dominantly inherited lymphedema-distichiasis syndrome is due to hemizyosity, i.e., one instead of two doses of this transcription factor. Thus, it is probable that we are dealing with thresholds for developmental effects influenced by modifying genes. One such candidate modifying gene would be the *FOXC1* gene which has many overlaps in its expression pattern.

The identification of *FOXC2* as causative of lymphedema-distichiasis opens up many avenues for research. It has been said that the heterozygous *FOXC2* knockout is without abnormalities but, of course, subtle abnor-

malities in lymphatic drainage might well have been missed. In addition, we know from the past that genetic modifiers can have great effects in mice as well as in man. Thus, even if the *FOXC2* heterozygous knockout shows no evidence of lymphedema on the original inbred stock, it is quite possible that by crossing it to other inbred strains of mice a lymphatic phenotype will emerge. In addition, it will be of great interest to study the interaction of the *FOXC2* knockout with other knockouts which affect lymphangiogenesis, e.g., vascular growth factor Angiopoietin2 (2).

## REFERENCES

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2. Martin, C., C. Suri, M Witte et al: Imaging documentation of arrested lymphatic development in Angiopoietin2 knockout mice. *FASEB J* 14(2000) A787

**Robert P. Erickson, MD**  
**Department of Pediatrics**  
**University of Arizona Health Sciences Center**  
**PO Box 5073**  
**Tucson, Arizona 85724-5063 USA**  
**Telephone: (520) 626-5483/(520) 626-5175**  
**Fax: (520) 626-7407**  
**E-mail: erickson@peds.arizona.edu**