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EDITORIAL

CARDIO(BLOOD-LYMPH)VASCULAR GENOMICS: NEED FOR A TERMINOLOGY ADJUSTMENT

In a recent Genomics in Medicine review on Cardiovascular Disease in the *New England Journal of Medicine* (1), consideration was given only to cardio(blood)vascular disease; (lymph)vascular genomics was omitted. This represented an untimely deficiency. Aside from the chromosomal aneuploidies commonly associated with lymphatic anomalies and even fetal demise (2-4), specific genes have now been identified for three monogenic lymphedema-angiodysplasia conditions, and loci have been mapped for several others *(Figure)*. Furthermore, there are close to 40 distinct familial lymphedemas, most OMIM-listed or cross-referenced, affecting the lymphatic segment of the "vasculature." An article by Northup et al in this issue of the Journal presents a syndromic classification of these hereditary lymphedemas along with an atlas of characteristic phenotypic features (5). Mutations have been identified in: endothelial receptor *VEGFR-3* for lymphatic growth factor VEGF-C (6) in a subpopulation of Milroy syndrome of lymphatic *hypo*plasia; winged helix transcription factor *FOXC2* (7) uniformly in hundreds of patients with Lymphedema-distichiasis (LD) syndrome with a *hyper*plastic lymphatic system; and transcription factor *SOX18* (8) in 2 families with autosomal recessive Hypotrichosis-lymphedema-telangiectasia syndrome. Interestingly, the genetically engineered haploinsufficient (+/-) *Foxc2* mouse (9) exhibits a double row of eyelashes and hyperplastic lymphatic phenotype like human LD, and the knockout (-/-) mouse displays aortic arch anomalies and interventricular septal defect (mimicking Tetralogy of Fallot), cleft palate and bony abnormalities spanning the clinical spectrum in severe LD. Clearly, the lymphatic system is an integral, interacting component of the "vasculature" and the "blood-lymph circulatory loop." Moreover, as pointed out in our earlier editorials (10,11) and reviews (12-14) in *Lymphology,* more precise inclusive and exclusive terminology should be used when referring to either the blood- or lymph-containing vessels or both, and the commonly used expression "the vasculature and the lymphatics" should be abandoned altogether since it perpetuates a fundamental misconception. Thus, a "terminology adjustment" is needed to facilitate future discussion of the similarities and differences between the blood vasculature and the lymph vasculature in general and specifically for thoughtful exploration of the genomics of cardiovascular [i.e., cardio(blood-lymph)vascular] disorders.

REFERENCES

1. Nabel, EG: Cardiovascular disease. New Eng. J. Med. 349 (2003), 60-72.
2. Greenlee, R, H Hoyme, M Witte, et al: Developmental disorders of the lymphatic system. Lymphology 26 (1993), 156-168.
3. Witte, MH, R Erickson, FA Reiser, et al: Genetic alterations in lymphedema. Phlebolymphology 16 (1997), 19-25.

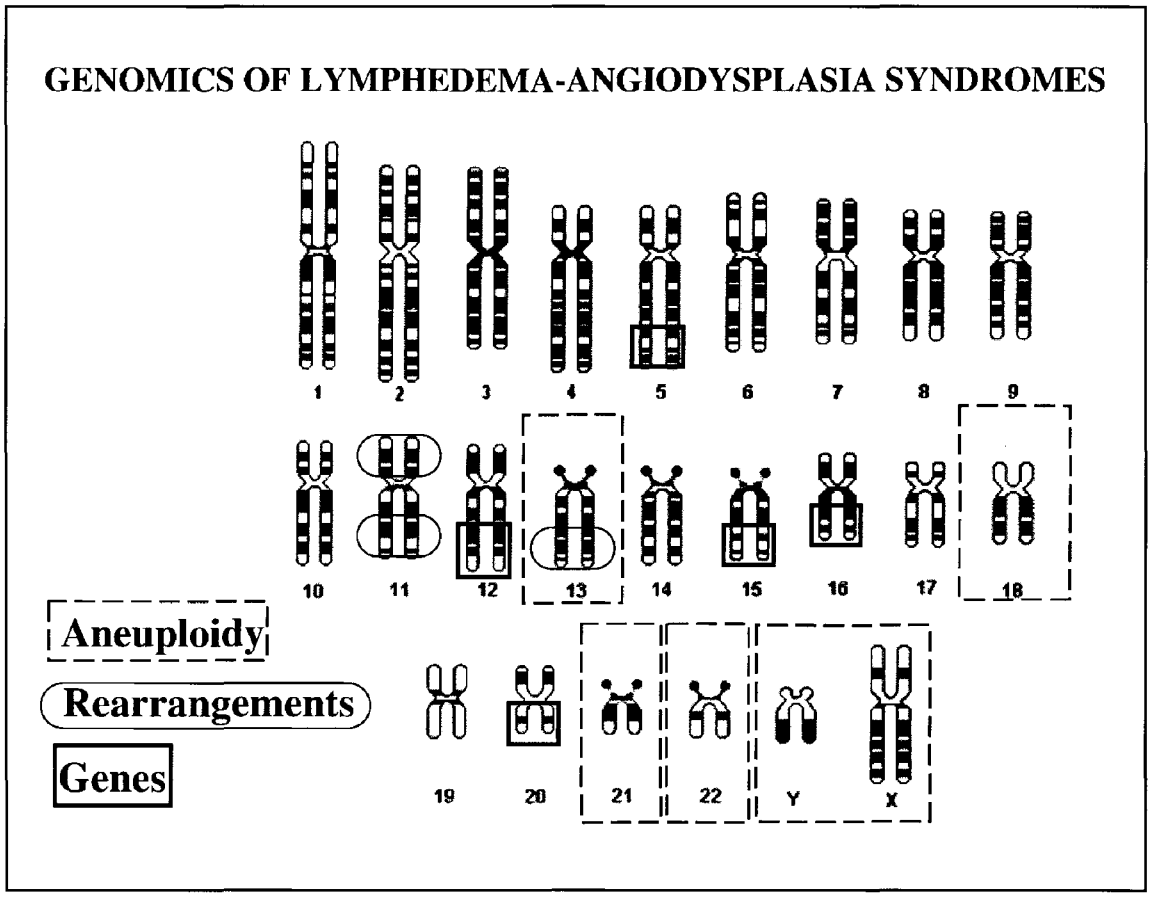

Fig. Genomics of lymphedema-angiodysplasia syndromes displaying mutation of known genes for familial Milroy lymphedema subpopulation (VEGFR-3 at chromosome 5q34-35), lymphedema-distichiasis (FOXC2 at chromosome 16q24), and hypotrichosis-lymphedema-telangiectasia (SOX18 at chromosome 20q13) and linkage locations for Aagenaes syndrome (chromosome 15) and Noonan syndrome (chromosome 12). In addition, aneuploidies and rearrangements involving other chromosomes are associated with additional lymphedema-angiodysplasia syndromes.

4. Witte MH, M Bernas, C Martin, et al: Lymphangiogenesis and lymphangiodysplasias: From molecular to clinical lymphology. In: *The Biology of Lymphangiogenesis.* Wilting J (guest Ed.). Micro. Res. Tech. 55 (2001),122-145.
5. Northup K, MH Witte, CL Witte Syndromic classification of hereditary lymphedema. Lymphology 36 (2003), 162-189.
6. Karkkainen, MJ, RE Ferrell, EC Lawrence, et al: Missense mutations interfere with VEGFR-3 signalling in primary lymphoedema. Nature Genet. 25 (2000), 153-159.
7. Fang, J, SL Dagenais, RP Erickson, et al: Mutations in FOXC2 (MFH-1), a forkhead family transcription factor, are responsible for the hereditary lymphedema-distichiasis syndrome. Am. J. Hum. Genet. 67 (2000), 1382-1388.
8. Irrthum, A, K Devriendt, D Chitayat, et al: Mutations in the transcription factor gene SOX18 underlie recessive and dominant forms of hypotrichosis-lymphedema-telangiectasia. Am. J. Hum. Genet. 72 (2003), 1470-1478.
9. Kriederman, BM, TL Myloyde, MH Witte, et al: Foxc2 haploinsufficient mice are a model for human autosomal dominant lymphedema-distichiasis syndrome. Hum. Mol. Genet. 12 (2003), 1179-1185.

10. Witte, MH: Lymphomas, lymphoids, and lymphologists [Editorial] Lymphology 18 (1985), 143-144.
11. Witte, MH, CL Witte: Lymphangiogenesis and lymphologic syndromes. Lymphology 19 (1986), 21-28.
12. Witte, CL, MH Witte: Contrasting patterns of lymphatic and blood circulatory disorders. Lymphology 20 (1987), 171-178.
13. Witte, MH, CL Witte: Lymphatics and blood vessels, lymphangiogenesis and hemangiogenesis: From cell biology to clinical medicine. Lymphology 20 (1987), 257-266.
14. Witte M, C Witte: On tumor (and other) lymphangiogenesis. [Editorial] Lymphology 30 (1997), 1-2.

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