PgmNr 2683: Primary lymphedema: A novel association with 22q11.2 deletion syndrome.

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BACKGROUND: Lymphedema is an abnormal accumulation of interstitial fluid and fibroadipose tissues. Primary lymphedema (LMP) is congenital, caused by aberrant lymphangiogenesis. Classifications of LMP are based on age at presentation: congenital, precox, tarda. Although most cases are sporadic, LMP may be familial (Hereditary Primary Lymphedema - LMPH) inherited mainly in an autosomal dominant fashion with heterogeneous mutations or in association with chromosomal abnormalities/syndromic diagnoses. **METHODS:** We identified 4 patients (1 male, 3 females) with 22q11.2DS and LMP via our International 22q11.2DS Consortium: 2 congenital; 1 precox; 1 tarda. **RESULTS:** All patients underwent comprehensive clinical, laboratory and imaging assessments to rule out other causes of lymphedema including a negative next generation sequencing panel performed on the infant male with LMP. All patients had *de novo* typical deletions and family histories were negative for lymphedema. Of note, the female patient with congenital LMP developed a nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) in late adolescence and another female with LMP precox had severe pre-eclampsia during pregnancy. **CONCLUSIONS:** We report the novel association of LMP with 22q11.2DS. Importantly, animal models demonstrated *Tbx1* playing a critical role in lymphangiogenesis by reducing *Vegfr3* expression in lymphatic endothelial cells. Moreover, the *VEGFR3* pathway is essential for lymphangiogenesis with mutations identified in LMPH. This is especially notable as *VEGFR3* is also involved in tumor lymphangiogenesis/metastases which may explain the NLPHL in our patient. Finally, severe pre-eclampsia results from abnormal placental angiogenesis in association with mutations in the *VEGF* family of genes, which also may explain the preeclampsia in our patient. Accordingly, our findings provide crucial insight into clinical management, as well as, a window into understanding cellular mechanisms of lymphangiogenesis disorders.