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### Investigating the Role of KIF11 in the Lymphatic Function of MCLID Patients

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**Introduction:** Mutations in KIF11 are causative for microcephaly with or without chorioretinopathy, lymphoedema, or intellectual disability (MCLID); a rare autosomal dominant disorder involving a variable spectrum of central nervous system, ocular developmental anomalies and lymphoedema (mostly bilateral in the lower limbs and sometimes restricted to the feet). EG5 (kinesin-5, encoded by KIF11 gene) is a motor protein that participates in various kinds of spindle dynamics during cell mitosis but nothing is known about its specific role in lymphatic endothelial cells (LECs) and how mutations in KIF11 lead to MCLID.

**Methods:** Lymphoscintigraphy by subcutaneous injection of a tracer was used to imaging and assess lymphatic dysfunction in MCLID patients. With KIF11 haploinsufficiency as the likely underlying key disease mechanism in these patients, LECs were treated with Ispinesib to block EG5 function. The effect of EG5 inhibition on LECs was analysed by in-vitro lymphangiogenic assays (e.g. cell proliferation, wound healing).

**Results:** Lymphoscintigraphy revealed the absence of radioactive isotope uptake from the web spaces between the toes, indicating the failure of initial lymphatics to absorb the tracer. LECs treated with Ispinesib, a specific inhibitor of EG5, displayed abnormal, monopolar spindles visualised by  $\alpha$ -tubulin staining. Inhibition of EG5 function with Ispinesib decreased LECs proliferation in an in-vitro cell proliferation assay.

**Conclusions:** The lymphoscintigraphy results and initial functional assays suggest that EG5 clearly has a specific role in LECs. The similarities in the phenotype and lymphoscintigraphy results between Milroy patients (VEGFR3 mutations) and MCLID patients (KIF11 mutations) could suggest a common mechanism for lymphatic dysfunction.