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New gene discovery provides clue to brain, eye and lymphatic development

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Researchers have found a new gene that, when mutated, can lead to lymphoedema (swollen limbs) as part of a rare disorder that can also cause problems with eye and brain development. This is the fourth lymphoedema-related gene found by the same researchers in three years, and the first linked to the eyes and brain. They say it could lead to better diagnosis and treatment for lymphoedema, an area that has been poorly understood previously.

The new study has linked mutations in the gene KIF11 to Microcephaly-Lymphoedema-Chorioretinal Dyplasia (MLCRD), a very rare condition. Patients with this condition have a small head (microcephaly), lymphoedema (swollen limbs caused by problems with the lymphatic system) and eye problems called chorioretinopathy, which frequently result in night blindness. The lymphatic system is a crucial part of the body which is important for draining fluid and preventing swelling.

The study was led by a group at St George's, University of London and published online in The American Journal of Human Genetics today (26 January). The St George's team worked closely with the Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust and King's College London, Moorfields Eye Hospital, and a group at the Université catholique de Louvain in Belgium.

The team carried out next generation sequencing of the human genome, initially in five patients with MLCRD recruited from the UK's only specialist primary lymphoedema clinic, based at St George's Hospital. A

candidate gene was identified using this new technology, which was then confirmed by traditional sequencing in 24 further patients and their families.

Lead researcher Dr Pia Ostergaard said: “The small head and eye problems associated with MLCRD are present at birth and there are no treatments as yet. These findings will increase our understanding of MLCRD’s genetic cause and may help find a way to prevent it. Microcephaly is rare, but is associated with learning difficulties in children.”

The range and severity of symptoms varies greatly within MLCRD even among people with the same mutation and within the same family. The researchers believe there may be other contributing genetic or environmental factors that determine how people are affected. Further understanding of KIF11 and the protein it encodes, EG5, may shed light on the varying symptoms. EG5 is known to be important for the normal division of cells, but its role in the development of the brain, retina and lymphatic systems is not yet understood.

Dr Ostergaard said: “The really exciting thing here is that, by very careful examination and grouping of the patients in our specialist lymphoedema clinic, we have successfully identified four genes associated with lymphatic development in a very short space of time. This has already led to extensive work looking at the development and function of the lymphatic system, an area that has been overlooked for years and which scientists still know little about.”

Dr Ostergaard said that, in addition to the previous genes identified, this new finding may lead the way to better treatment of lymphoedema. Currently, swelling can be relieved by compression garments, bandaging or massage, but the increasing understanding of the condition should lead to drug treatment in the future.

She added: “The lymphatic system is not just important for draining fluid and preventing swelling. It is vital for the maintenance of the immune system and is linked to the spread of cancer, so continued focus of our research in this area could provide other scientists with the key to understand these other problems.”

More information: *The American Journal of Human Genetics*, 26 January 2012. doi:10.1016/j.ajhg.2011.12.018

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