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Dear Noonan Syndrome Association

Re: Final Report
Title of research project supported: ***Investigating the causes, natural history and complications of lymphatic abnormalities associated with Noonan Syndrome (NS).***

Overall Aim(s) of Research Project:

1. To investigate the cause of primary lymphoedema and chylous reflux in NS
Some patients with Noonan syndrome develop lymphatic problems with swelling of the lower limbs and or genitalia (lymphoedema) and leaking of lymph fluid from the gut or around the lungs. The reason for this is not yet understood.

Since this study started we have completed Magnetic Resonance Lymphangiography for three patients with Noonan syndrome and lymphoedema. We have imaged the lymphatics in the lower limbs, with and without gadolinium and, for two patients, we have attempted to image the central lymphatics (thoracic duct).

In January this year, with the on-going support of the Noonan Syndrome Association, Prof Max Itkin visited us from Philidelphia. He is an interventional radiologist and world leader in imaging the lymphatics. With his help, we successfully did two dynamic MRLs to image the movement of the lymph in the central lymphatics and three intranodal lymphangiograms, using a different contrast (Lipiodol). He helped us set the parameters on the MRI machine and taught our interventional radiologists the technique.

As a consequence of this work, we have successfully secured a large MRC grant (£2 million) over 5 years. One of the branches of this grant is to develop our experience in imaging the lymphatics using MRL and intranodal lymphangiography. These techniques will identify the underlying weakness of the lymphatics and, in some cases with leaking lymphatics, it may be possible to identify and seal the leak.

2. To identify further genetic cause(s) of NS in this cohort
For our genetic investigations, we have done Whole Exome Sequencing (WES) on DNA samples from patients with a Noonan phenotype. We currently have data from 3 parent-offspring trios, 4 affected individuals from one large family and 4 sporadic cases; a total number of 17 cases; 8 of which are index cases/probands (i.e. the first affected individual diagnosed in a family).

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WES data has come off the pipeline and we have started our analysis. Firstly, we screened the data of each proband for the previously identified Noonan syndrome genes. We did not find any previously known genes in our cohort. Most of the probands had been screened on the Noonan gene panel previously, so this result was not a surprise.

We then compared all 8 probands to see if any of them have novel, unreported variants in the same genes. Our investigations showed possible heterogeneity between all 8 probands as none of them are sharing mutations or mutated genes.

We then analysed the 8 probands individual, filtering the data using a model of autosomal dominant inheritance, which is the prevalent model of inheritance in Noonan syndrome. This has allowed the generation of a list of putative causal variants for each proband. For each case, we have focused on novel, unreported rare candidate variants.

We are now in the process of working through this lists of gene variants using Sanger sequencing. We need to verify the variants and see if they co-segregate in the families we have. We have had several BSc and MSc students working on the data generating these candidate gene lists.

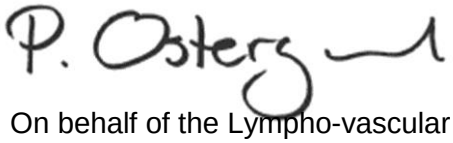
Most recently we have had an MSc student, who has identified a variant in one of the probands, which is involved in the Ras signalling pathway. As many of the Noonan genes are involved in the RAS/MAPK signalling pathway, we are very interested in investigating this gene further.

We have recently been awarded funding from the Swiss National Science Foundation on a large collaborative project with two partners in Switzerland. Through that grant we will be able to recruit a bioinformatician and a post-doctoral research assistant. The samples they will be working on will include the Noonan cases sequenced with the Noonan Syndrome Association funds.

Concluding remark

We would very much like to thank the Noonan Syndrome Association for their support. It is clear that much progress has been made, particularly in the imaging of the lymphatics. This work has helped us to secure two large grants, which will enable us to continue with this work.

Yours sincerely,



On behalf of the Lympho-vascular research group