The Norrie Disease Foundation Research Strategy 2021

1. Background

Norrie disease (ND) is an ultra-rare, X-linked genetic disorder that affects at least 40 families in the UK and around 500 globally. ND predominantly affects males. Only in very rare cases have females been diagnosed with ND although symptomatic female carriers have been reported.

ND is caused by mutation in the NDP gene, which causes congenital blindness and progressive deafness. The blindness results from the disruption of retinal vascular development causing hypoxia, ischaemia, persistent foetal vasculature and compensatory neovascularization. Hearing appears normal at birth, and boys with ND pass newborn hearing screening. However, nearly all boys go on to develop progressive hearing loss, which usually begins in adolescence. About 30% of patients also have cognitive impairment and peripheral vascular disease.

The Norrie Disease Foundation UK (NDF UK) has established a multidisciplinary scientific and medical advisory board (SMAB) comprising scientists and clinicians to advise on the challenge of identifying treatments to improve the lives of boys affected by ND.

2. The Norrie Disease Foundation's Purposes

- The Norrie Disease Foundation's purposes are to promote the greater understanding of the causes and symptoms of Norrie Disease in all its forms by the promotion of research and to facilitate the sharing and dissemination of the results of such research for the benefit of the general public.

And

- Raising public awareness of the symptoms, needs and related medical conditions of those living with Norrie Disease.

3. The Norrie Disease Foundation's Aims

- The Norrie Disease Foundation's aims are to promote and raise funds for pioneering research towards a better understanding of Norrie Disease with the ultimate aim of finding a treatment for the ND hearing loss.

And

- To provide support to families and strengthen a UK support network through raising awareness of Norrie Disease and patient involvement.

4. Research Priorities

At present, medical interventions cannot save the sight of boys born with ND. After growing up without vision, hearing loss represents the greatest worry for many patients with ND. Therefore, the NDF UK supports and funds research initiatives that are aimed at slowing or preventing hearing loss and thus minimise the dual sensory deprivation that severely restricts the social interactions and independence of adolescents and young men with ND.

The NDF UK and the ND community are committed to raising funds for two main areas of research:

- Clinical research into all aspects of ND.
- Translational scientific research into the causes of hearing loss and the development of therapies that may prevent or restore hearing loss in patients with ND.

5. The Importance of Research into ND Hearing Loss

The NDF UK, guided by the ND community in the UK, considers research into therapies that will allow children with ND to preserve their natural hearing to be the priority area for research into hearing loss. This is because, of all the symptoms caused by ND, hearing loss has the most significant impact on the quality of life and mental health of affected adolescents and men. Loss of hearing limits personal independence in adulthood and causes immeasurable psychological and emotional trauma to individuals and their families.

At present, audiologists recommend the use of hearing aids for boys with ND who are experiencing hearing loss as they provide the child with a more natural sound than cochlear implants. Cochlear implants are an intervention of last resort for boys with ND as the artificial sound created by the implants means that users need to re-learn how to hear, which can be distressing.

6. Priority Research - What We Support

The NDF supports research projects so as to make the maximum impact in establishing treatments for ND and the quality of life of people affected by the condition.

The NDF is committed to supporting laboratory and clinical research focused on:

(i) understanding the genetics of ND and the causes of hearing loss including how and when it occurs, in order to identify the right time for intervention with a potential therapy, and (ii) NDP gene therapy or other approaches to correct the damaging effect of the faulty gene in order to prevent the disease.

The NDF are dedicated and committed to finding a treatment for the ND hearing loss.

7. NDF Fundraising

The NDF fundraise through their partnership with GOSHCC & Sparks, private donors and community fundraising events including taking part in national sporting events eg. the London Marathon and Royal Parks Half marathon.

8. Community Building

The NDF promotes community building through raising awareness of ND at local and national levels; growing and strengthening a Norrie Disease community support network; connecting families with researchers and other stakeholders such as the British Academy of Childhood Disability.

9. Research Updates

- The NDF have commissioned an article with Costello Medical that reviewed the Impact of sight and hearing loss in patients with Norrie disease. This work has been published as an Open Access paper in BMJ Open. It discusses the advantages of Dual Sensory clinics in patient care and was undertaken with clinicians caring for Norrie patients at Great Ormond Street Hospital for Children.

https://bmjpaedsopen.bmj.com/content/bmjpo/4/1/e000781.full.pdf

- The NDF are supporting a clinical study on Understanding the medical features of Norrie disease, at Great Ormond Street Hospital (GOSH). This research is gathering information in a Norrie Disease Patient Registry on how Norrie disease presents in individuals and variation in the symptoms.

- The NDF partnered with GOSH Children's Charity and Sparks in the 2019 National Funding Call for research applications. Applications were peer

reviewed in order to fund the highest quality research most likely to have life-changing benefits to children. A new 3 year project grant has been awarded. The project will evaluate NDP gene replacement, and test its effectiveness in a mouse model of Norrie disease. It will test delivering the gene therapy at different stages of the disease and investigate whether the gene therapy prevents death of the sensory hair cells in the cochlea of the inner ear and hearing loss. It will test whether restoring NDP-induced signalling in vasculature cells prevents hearing loss. These studies will help design NDP viral constructs for clinical Norrie gene therapy. https://www.ucl.ac.uk/child-health/news/2020/feb/gosh-charity-and-sparks-award-over-ps1-million-child- health-research-institute

- The NDF is funding a dedicated NDF PhD Studentship at UCL Great Ormond Street Institute of Child Health on gene therapy for ND investigating delivery of the NDP gene directly to the ear.

- A new study on the onset of cochlea pathology and hearing loss in the mouse model of Norrie disease has been undertaken by members of the NDF SMAB and funded by NewLife and GOSHCC. It has been submitted for Open Access publication and will be freely available.

- The NDF is working towards a US collaboration to move forwards with finding a treatment for the hearing loss.

For more information, please contact uknorriedisease@gmail.com