The Lowe Syndrome Trust

2018 Newsletter

This newsletter is a brief overview of the achievements of this small charity during the past year.

The Lowe Syndrome Trust was founded as a small voluntary charity in June 2000 with an aim to raise funds to support research into Lowe Syndrome and support families and medical professionals.

All research projects, events, a full story about the charity including TV and Radio can be found on www.lowetrust.com

Best wishes

Lorraine Thomas

Founder, Chair & Trustee
The Lowe Syndrome Trust

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Research

The Lowe Syndrome Trust awarded funding to support two new research grants. Manchester University & University of Napoli.


Antonella De Matteis, MD,Professor of BiologyDpt. Molecular Medicine and Medical BiotechnologyUniversity of Napoli Federico II - Medical School £80,000

"We are delighted and honoured to receive this award from the UK Lowe Syndrome Trust. This grant will allow us to continue our studies aimed at the identification of drugs, currently on the market for other purposes, which can counteract Lowe syndrome signs and thus can be "repositioned" and used as therapy for Lowe syndrome. In fact our group, which supported the foundation of AISLO (Associazione Italiana Sindrome di Lowe) 15 years ago and which has contributed important insights into the cellular mechanisms underlying Lowe syndrome during this time, decided few years ago to develop a "repositioning" pharmacological approach for the cure of Lowe syndrome. We have already started this approach at the Telethon Institute of Genetics and Medicine (TIGEM) in Naples, using a high content screening cell-based methodology and we have identified six marketed drugs that are able to correct some of the alterations observed in kidney cells derived from Lowe patients or in cells where OCRL, the gene mutated in Lowe syndrome, has been silenced. With the present project that will be run in collaboration with Prof. Olivier Devuyst (University of Zurich) we will test these drugs on the mouse model of Lowe syndrome developed by Prof. Robert Nussbaum. We believe that the identification of drugs that are able to correct the proteinuria in this model will represent a key step towards the development of a pharmacological treatment of Lowe syndrome". Antonella de Matteis


Professor Martin Lowe, Manchester University £10,000

"I am delighed to receive this award from the Lowe Syndrome Trust. It will allow us to continue our research using the zebrafish model for Lowe Syndrome that we developed using previous funding from the Trust. We have shown that the zebrafish model recapitulates many of the symptoms seen in Lowe Syndrome patients including neurological and renal impairment, allowing us to investigate the underlying mechanisms that lead to these symptoms. Our current work is aimed at using zebrafish to perform a screen to identify drugs that may be used to treat Lowe syndrome. We are making genetically modified strains of zebrafish that allow us to easily and rapidly assess kidney function, which will be used to perform drug screening in a high throughput manner. The current grant provides continuation funding that will allow us to perform the screen itself, which will be carried out using compounds that are already approved for use in humans, meaning that any 'hits' from the screen can be rapidly translated for use in the clinic. We are extremely grateful to the Lowe Syndrome Trust for their ongoing support of our research, which we hope will lead to improved treatments for Lowe patients in the future."

The Lowe Syndrome Trust meets with Director of Research and Evidence Department of Health

Lorraine Thomas, Chair of the Lowe Syndrome Trust and Lowe funded researchers Martin Lowe and Rudiger Woscholski, met with Dr Louise Wood to discuss the charity and how Dr Wood might be able to advise how the charity could seek substantial funding for drug screening using Zebra fish. The meeting was convened in the hope Dr Wood would be able to advise on possible links to help the charity. Pictures Louise Wood, Martin Lowe, Rudiger Woscholski

Lowe syndrome is a genetic disorder that typically leads to kidney failure, which is the major cause of morbidity in Lowe patients. There is currently no effective treatment or cure for this devastating condition. Using funding from the Lowe Syndrome Trust (LST) my laboratory has developed a zebrafish model that faithfully recapitulates the clinical manifestations of Lowe syndrome. Using this model we have identified the underlying mechanisms that lead to the renal impairment seen in Lowe syndrome. The next goal is to exploit the unique power of the zebrafish model to screen for drugs that rescue the renal phenotype, which could then be used in the clinic to treat Lowe syndrome patients. As a first step towards achieving this objective we have generated a zebrafish strain that allows us to monitor kidney function in living animals, which can be exploited to screen for compounds that rescue the renal deficiency of the Lowe model. We would now like to perform a drug screen using the zebrafish renal reporter. The screen will exploit existing libraries of FDA-approved compounds, meaning that any 'hits' identified in the screen will be approved for use in humans, and thus can be repurposed for the treatment of Lowe syndrome and taken directly into the clinic. The renal symptoms of Lowe syndrome are similar to those of several other renal disorders, sharing common pathogenic mechanisms, and moreover, the process defective in the renal tubule of Lowe syndrome is the same as that affected by many nephrotoxic agents including commonly used therapeutics. Hence, the reporter strain we have generated,and any 'hit' compounds we identify in the screen, are likely to have utility beyond Lowe syndrome. They could therefore be exploited to screen for renal function in other diseases and chemically induced kidney damage, as well as treatment of these conditions. It is also worth pointing out that in a separate project, LST funded research has resulted in the development of new rationally designed chemical lead compounds that have the potential to treat Lowe syndrome. These compounds and their derivatives would also be part of the screen. We also have access to human patient cell lines, obtained through LST funding, that could be used to validate 'hits' prior to going into the clinic. We believe the work is at an exciting stage, but unfortunately, due to the intrinsic uncertainty associated with any type of drug screen, it has proven difficult to obtain funding for this project through the Research Councils.

PRESS RELEASE
LOWE SYNDROME FUNDED RESEARCH

Professor Aguilar, Purdue University, USA, who has received continuation research grants from the UK Lowe Syndrome Trust

Lowe Syndrome (LS) is a devastating genetic disease characterized by abnormalities in the eyes, brain and kidneys that unfortunately leads to the premature death of affected children due to renal failure. Despite being described more than 60 years ago, this condition lacks a clear delineation of its mechanism and no specific cure is available. One contributing cause to this slow progress has been the absence of proper disease models for this condition and the inaccessibility of patient cells from the major affected organs.

However, using patient skin fibroblasts the Aguilar lab recently reported the first successful preparation of Lowe syndrome induced Pluripotent Stem Cells (iPSCs) and their reprogramming as renal cells1. This work not only represents a technological advance for the LS research field, but also provided insight as to how the patient's kidney complications develop.

On the one hand, this work constituted the first application of iPSC/reprogramming technology to LS, opening the possibility of *in vitro* generation of cell types difficult to obtain from patients (*e.g.*, brain and kidney) and of more sophisticated disease models such as *in vitro*-generated organoids. Importantly, this study also sets up the basis for future cell replacement therapies.

On the other hand, monitoring the process of *in vitro* kidney cell differentiation provided clues as to how renal deficiency arises in patients. Specifically, Aguilar lab graduate student Wen-Chieh Hsieh and colleagues found that in LS kidney cells the transcription factor Six2 (crucial for renal development) was abnormally retained outside the cell nucleus (Fig. 1) impairing its gene regulatory function. This deficient Six2 activity caused decreased production of the so-called proximal tubular cells which are involved in critical functions of the kidney, such as avoiding the excretion of important serum proteins. Therefore, two important implications arise from these findings:

-*Tubular cells are less readily available within LS kidney cell populations*. This observation supports the hypothesis that LS patients experience kidney developmental abnormalities, particularly affecting tubular cells. Indeed, it is well-known that LS patients display deficient tubular function and tubular atrophy. Further, since Six2 is also involved in craniofacial and eye development as well as in neuro-protection, it is possible that affected function or regulation of this transcription factor contributes to characteristic phenotypes and symptoms of LS in other tissues or organs.

-*Patients would have difficulties to replenish tubular cells following wear or injury*. In fact, there are reports of progressive tubular function loss in LS patients. A body of evidence collected by many groups indicate the existence of kidney-localized progenitor cells able to differentiate into tubular cells when needed to maintain renal functionality. The results presented in this study suggest that the availability of such cell replenishing pool is compromised in LS patients.

Misregulation of a differentiation pathway is a novel LS phenotype that is predicted to have great impact in patients' renal function. Further, this work suggests that developing strategies directed to enhance proper Six2 function or to prevent its retention outside the nucleus constitute viable options to maintain renal function in LS patients.

Reference

1. Hsieh W-C, Ramadesikan S, Fekete D. and Aguilar RC. Kidney-differentiated cells derived from Lowe Syndrome patient's iPSCs show Ciliogenesis defects and Six2 retention at the Golgi complex. *PLOS ONE. 2018 Feb 14;13(2):e0192635. doi: 10.1371/journal.pone.0192635. http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0192635*

This work was supported by the National Institutes of Health and the Lowe Syndrome Trust under Grants 1R01DK109398-01 and BU/CO/2014 to R. C. Aguilar.

Fundraising

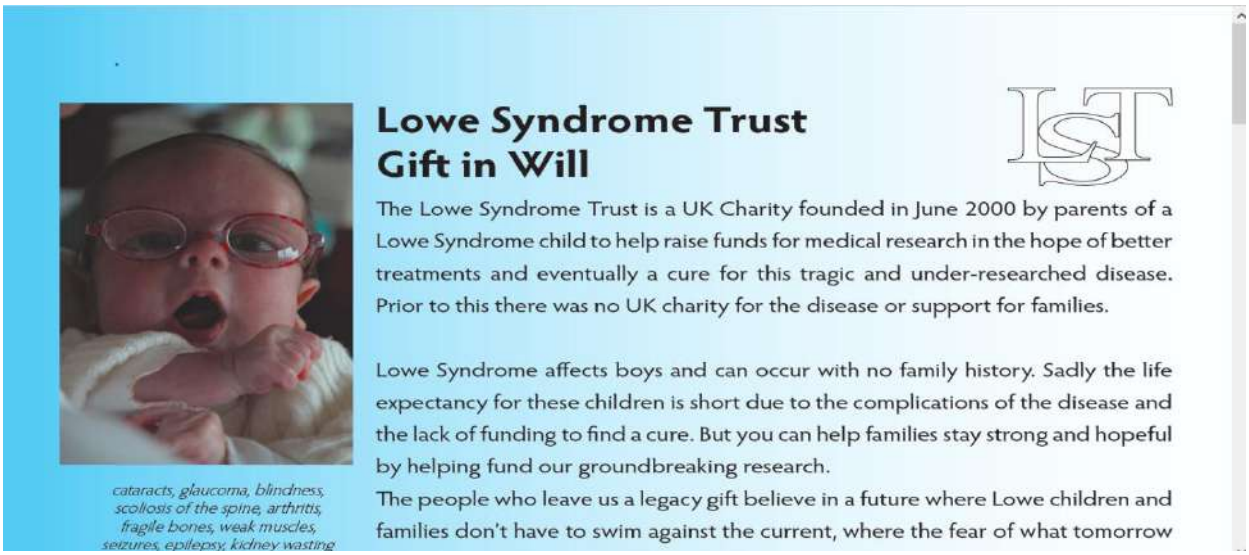
Charitable bookings

Visit a Charitable nominated restaurant and the charity will receive £1 for every diner. Follow the link below to find your restaurant/Lowe Syndrome

Gift to Will

The charity has produced a "Gift to Will" for those wishing to leave a legacy in their Will for Lowe Syndrome research.

Thisform is on www.lowetrust.com or email lowetrust@gmail.com



Jonathan Ross raises £32,000 on UK TV programme "Celebrity Chase"

Jonathan once again has raised money for research into Lowe Syndrome by appearing on a Celebrity game show. Jonathan has been with the charity as a Trustee since it was founded 18 years ago.

Thank you Jonathan – the total amount will be awarded to Manchester University for their continued work into the Lowe syndrome disease.

Lowe Syndrome Platelet letter to families

LOWE SYNDROME PATIENT INFORMATION

I am writing to highlight a problem raised by Joel Lunardi in France which may affect Lowe children. The problem is associated with a defect in Lowe platelets which can be problematic in bleeding especially during certain types of surgery. My son, Oscar, was tested prior to surgery and he was confirmed to have a defect in platelet aggregation and has been recommended to take a drug prior to and after surgery to counteract the platelet problem.

To determine whether your son might be at risk, a PFA100 platelet screening test should be organised at your local hospital. It is quick and easy although about 20mls of blood is taken which might be a little bit of a problem with babies or younger children.

We are interested to find out whether this platelet problem exists with all Lowe children/adults or just some and so your results would be very interesting.

Whilst writing, if you did not complete the LSA survey sent out last year, I would be grateful if you could complete the attached questionnaire. The Trust is also eager to find out whether your son was diagnosed by DNA, Skin Biopsy or clinical diagnosis. If the diagnosis was by DNA, we would be grateful if you could forward a copy of the DNA sequence which can be obtained from your Doctor or Hospital.

Please contact me at any time to discuss in more detail. My email is lowetrust@gmail.com and telephone is 0207 794 8858.

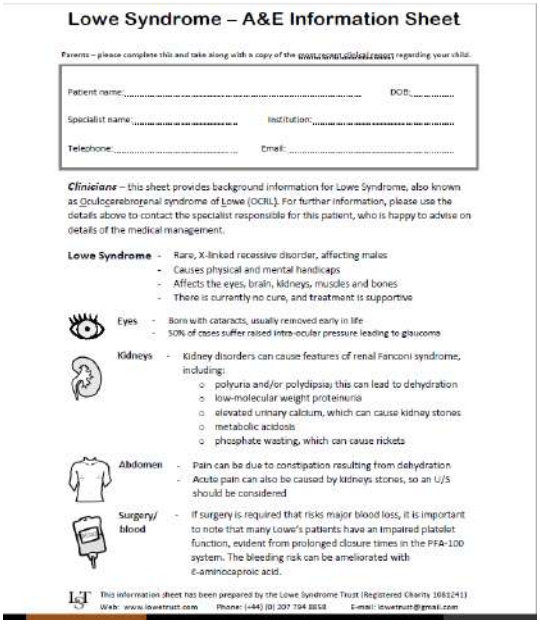
Best wishes

Yours sincerely

Lorraine Thomas
Trustee
The Lowe Syndrome Trust
www.lowetrust.com

Lowe letter about Lowe blood platelet disorder

Lowe Syndrome UK A&E leaflet



Lowe Syndrome – A&E Information Sheet

Parents – please complete this and take along with a copy of the most recent clinical report regarding your child.

Patient name:..... DOB:.....
Specialist name:..... Institution:.....
Telephone:..... Email:.....

Clinicians – this sheet provides background information for Lowe Syndrome, also known as Oculocerebrorenal syndrome of Lowe (OCRL). For further information, please use the details above to contact the specialist responsible for this patient, who is happy to advise on details of the medical management.

Lowe Syndrome - Rare, X-linked recessive disorder, affecting males
- Causes physical and mental handicaps
- Affects the eyes, brain, kidneys, muscles and bones
- There is currently no cure, and treatment is supportive

Eyes - Born with cataracts, usually removed early in life
- 50% of cases suffer raised intra-ocular pressure leading to glaucoma

Kidneys - Kidney disorders can cause features of renal Fanconi syndrome, including:
- polyuria and/or polydipsia; this can lead to dehydration
- low-molecular weight proteinuria
- elevated urinary calcium, which can cause kidney stones
- metabolic acidosis
- phosphate wasting, which can cause rickets

Abdomen - Pain can be due to constipation resulting from dehydration
- Acute pain can also be caused by kidneys stones, so an U/S should be considered

Surgery/ blood - If surgery is required that risks major blood loss, it is important to note that many Lowe's patients have an impaired platelet function, evident from prolonged closure times in the PFA-100 system. The bleeding risk can be ameliorated with ε-aminocaproic acid.

This information sheet has been prepared by the Lowe Syndrome Trust (Registered Charity 1081241)
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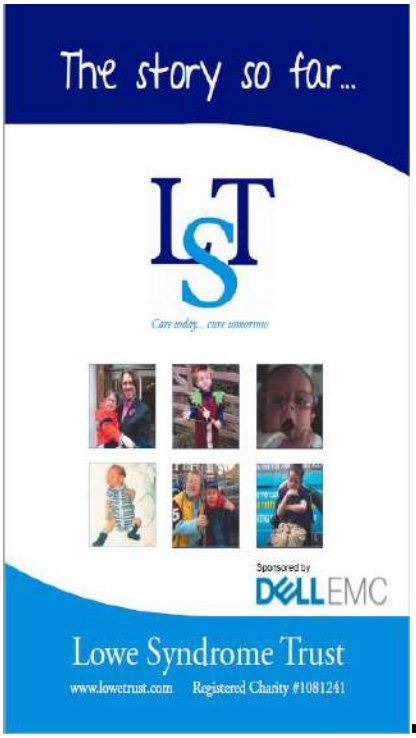
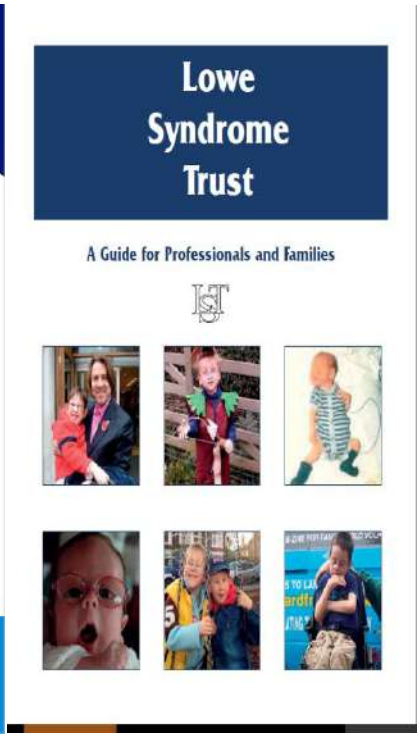
Lowe Acccident & Emergency sheet for all patients





Facebook

The Lowe Syndrome Trust has a FB page with updates and video/magazine articles.

Search under lowe trust

Thank you to all those of you that have supported the charity by donations or organising events to fund Lowe Syndrome Research. I would also like too thank the Lowe Syndrome Trustees, Scientific Advisory Board and Patrons.