Disease-defying research

Dr Reetta Hinttala, a molecular biologist from the University of Oulu, Finland, has been working with Northern Finnish populations to discover new causes of neuromuscular mitochondrial diseases.

How did your interest in mitochondrial diseases develop, and how has your background fed this interest?

I became interested in mitochondria because these cell organelles are unique – they have their own genome and are vital to the cell in many ways. My PhD thesis was about mitochondrial complex I deficiencies in paediatric patients, and during this time I became passionate about mitochondrial research. That was also the time when I was able to establish a collaborative network with the colleagues with whom I’m currently working. For me, the close relationship between basic and medical science has been highly motivating; the combination of finding something new in basic science and the ability to help the patients and their families is the driving force of my work.

Does the genetic and clinical variability of mitochondrial diseases make them a particularly difficult disease group to study? How can these difficulties be overcome?

Yes, the fact that mitochondrial proteins are either nuclear or mitochondrially encoded makes identification of the genetic origin of the disease more difficult. There are also other specific features that influence the severity of the disease. The mitochondrial genome is inherited maternally and there are several copies of it within each organelle, creating a phenomena called heteroplasmy, where mutated mitochondrial genomes exist together with wild type genomes. The ratio varies between tissues and this creates variable clinical symptoms within patients depending on the mutation load and the energy the specific tissues need. To identify the genetic cause of such a heterogeneous disease, we need to focus our studies on the correct tissue, understand the family history of the patient and work very closely with clinicians in order to focus on the most likely causative pathways and genes.

Why does your research focus specifically on patients in Northern Finland?

The research project is led together with a paediatrician, Adjunct Professor Johanna Uusimaa, who has also specialised in paediatric neurology. Uusimaa and our clinical research collaborators meet the patients and their families at the Oulu University Hospital, which is the northernmost of the five university hospitals in Finland. In 1990, Professor Heikki Rantala initiated the collection of muscle biopsy samples from children with undefined encephalomyopathies/myopathies and our research group has since gathered numerous additional cohorts of patients for the study: children with undefined encephalomyopathies, severe multiple organ diseases, neurometabolic diseases, neuromuscular diseases and genetic epilepsies. In our previous prospective and retrospective studies, we attained a cohort of 276 children from Northern Finland with a biochemical, histological or clinical diagnosis of neurometabolic or neuromuscular disease, including patients with mitochondrial respiratory chain deficiencies and patients with biochemically verified neurometabolic diseases with unknown genetic aetiology.

One of the strengths of our research project is based on our patient population in Northern Finland, which is genetically unique. The clustering of rare, recessive genetic diseases is due partly to the founder effect and partly to the Finnish population’s isolation which arises from geographical, linguistic and cultural reasons.

An additional interesting point is that old Church files in Finland contain detailed information on our population dating back to the 16th Century. This information can be utilised to define the segregation of identified novel mutations in different family lineages to determine whether they originate from a single ancestor or are caused by multiple separate occasions.

What other proteins are you characterising? Why is it necessary to characterise genetic items other than mitochondrial complex subunits in these diseases?

It has become obvious that in some of our cases, mitochondrial respiratory chain deficiencies are actually the secondary phenomenon caused by defects in other cellular pathways. This has led us to study factors involved in cellular signalling, mRNA transport and the cytoskeleton.

Can you describe the role collaboration has played in this investigation?

We are working closely with several research groups at the University of Oulu, and we also have a good national collaboration network. Our international collaborators are mainly in Europe and Canada. The laboratories involved are among the most distinguished in their field of research. Our team is also part of two networks called the Mitochondrial Clinical & Research Network (MCRN) and the MITO-Network, the latter of which bring together young mitochondrial scientists from Scandinavia and the Baltics.

Are there triumphs you have experienced in your research of which you are particularly proud?

I always feel that we have succeeded when we are able to solve the genetic cause of a disease in a patient. As a researcher, I feel amazing when I find something completely new, something that nobody has characterised before.
Expanding the aetiology of mitochondrial disorders

Scientists at the Department of Pediatrics at the University of Oulu, Finland, are working on identifying disease-causing factors behind mitochondrial disorders. Their work focuses on neuromuscular disorders, primarily multi-syndromic diseases of childhood.

Mitochondria are the organelles found within almost all eukaryotic cells that take in nutrients and generate adenosine triphosphate (ATP), the chemical which provides energy for cells. This process is thought to account for 90 per cent of the total energy required for the body to sustain life and support growth. Mitochondria are also involved in numerous other cellular functions such as signalling, differentiation and mitochondrial fatty acid synthesis, and they support the maintenance of the cell cycle, from growth to death.

Diverse diseases

As mitochondria are so critical to cell function and can be found in almost all eukaryotic cells, mitochondrial dysfunction contributes towards a variety of seemingly disparate disorders. The term ‘mitochondrial disease’ refers to this group of disorders that are caused by either mutations in mitochondrial DNA or genetic mutations in nuclear DNA. These disorders – though sharing a common cause – manifest themselves in extremely different ways. They typically affect tissues that are highly dependent on energy, such as the brain, heart and muscles. The central nervous system is also commonly affected. They are often inherited, and represent the most common group of inborn errors, affecting every 1 in 5,000 births worldwide.

This phenotypically and genetically heterogeneous group of diseases generally manifest as multisystem disorders, often having a fatal outcome. Moreover, this heterogeneity makes their aetiology – the origin and causes of disease – very difficult to decipher, let alone understand. In recent years, technologies such as exome sequencing (a technique for sequencing all the protein-coding areas of the gene found in a genome) and high-throughput gene panels (a technology that enables low cost parallel sequencing) have enabled faster and more accurate diagnostics. However, there is still no consistent means of diagnosis, and treatments are currently alleviative, aimed at improving symptoms and slowing the progression of disease.

Mitochondrial myopathies

Mitochondrial myopathies, a group of neuromuscular diseases, comprise a large proportion of all mitochondrial disorders. The prognosis for these diseases, which usually manifest before 20 years of age, ranges in severity from progressive weakness to death, and the majority of patients die within a few years of the first clinical manifestation. Symptoms include muscle weakness, heart failure or rhythm disturbances, deafness, blindness and seizures. Currently, about 60 per cent of the causes of these diseases are identified using exome sequencing and courses of treatment only provide vitamin supplements to mitigate symptoms.

Researchers at the University of Oulu, Finland, have been working with Northern Finnish populations to expand understanding of the aetiology behind these neuromuscular diseases, focusing specifically on the multi-syndromic diseases of childhood that are caused by mitochondrial dysfunction. The people of Northern Finland have remained a largely

Destroying disease

Dr Reetta Hinttala intends to use her scientific abilities and interests to solve the genetic puzzles underlying:

Mitochondrial diseases – every person with a mitochondrial disease presents differently; however, each individual has cells that are unable to produce enough energy to function. The commonest parts of the body affected are those that have the highest energy demands; brain, muscle, liver, heart and kidney.

Mitochondrial myopathies – this is the name given to a mitochondrial disease that causes prominent muscular problems. Muscular and neurological problems including muscle weakness, exercise intolerance, hearing loss, trouble with balance and coordination, seizures and learning deficits are common features of mitochondrial myopathies.
Researchers at the University of Oulu, Finland, have been working with Northern Finnish populations to expand understanding of the aetiology behind these neuromuscular diseases and contributed greatly to the current understanding of mitochondrial disease. They are now expanding their findings to develop a greater understanding of the genes that cause neuromuscular diseases.

The exome sequencing of 30 Finnish patient samples has revealed several novel genes that are potentially responsible for the development of mitochondrial respiratory chain deficiency. In some cases, however, these deficiencies have turned out to be a symptom of problems in other cellular pathways. Following on from prior research, the scientists are currently undertaking a project that looks into the effect of imbalanced cellular signalling pathways on severe multi-organ disorders in childhood. They are now including factors involved in mRNA transport and cytoskeleton function in their study.

MOVING FORWARD

The researchers at the university have already succeeded in identifying novel disease-causing genes through the use of whole exome sequencing. In addition, they are now aiming to push this technology further and attempt to identify the remaining unknown factors that cause neuromuscular diseases. As their work progresses, they will incorporate new developments in whole genome sequencing that will allow them to continue building a more complete picture of the aetiology of mitochondrial diseases.

Hinttala is confident that the work of her team will have a positive impact upon future clinical practice: “The final goal of our project is focused on prevention and improved diagnostics of diseases related to brain development and degeneration. Thus, we aim to influence prenatal diagnostics, genetic counselling of the families, treatment options and long-term prognosis which will have a valuable impact on individuals, from infants to elderly people.”

isolated population, and as such are genetically unique. This quality makes them an ideal group to study.

Dr Reetta Hinttala, the Academy of Finland Research Fellow at the Department of Pediatrics and Adolescence in the University of Oulu, is the Principle Investigator of the project in a research group led together with Adjunct Professor Johanna Uusimaa. “We are aiming to identify novel disease-causing genes behind those multi-syndromic diseases, to verify the functional mechanisms of these genes and, most importantly, to help the families of the patients and other families with the same disease,” she states.

Johanna Uusimaa, a paediatric neurologist at the Department of Pediatrics and Adolescence, the University of Oulu, is responsible for the clinical evaluation of patients, communicating with the families of patients and ensuring that all tests are ethically approved. Uusimaa and clinical researchers meet patients and their families at the Oulu University Hospital, the northernmost university-central hospital in Finland. Here, they have acquired a paediatric patient cohort who all have a severe multi-organ disorder with an unknown aetiology.

The researchers at the University are driven by the goal of providing new information on disease-causing factors in children with severe multi-organ disorders; by tracing their genealogy they plan to establish new targets for genetic analysis. As well as identifying new mechanisms behind the disorders, the results of their research will contribute in the clinical field, facilitating prenatal diagnosis, providing a basis for genetic counselling of the families involved and also providing a knowledge base for approaches to treatment.

CURRENT PROJECT

Hinttala and the team have undertaken several research endeavours so far, all of which have produced positive results

OBJECTIVES

The aim of the project is to identify novel disease-causing factors behind severe neuromuscular diseases of childhood and to verify their functional mechanisms.

KEY INTERNATIONAL COLLABORATORS

Professor Eric Shoubridge; Professor Jacek Majewski, McGill University, Montreal, Canada

Professor Bert van den Heuvel; Assistant Professor Richard Rodenburg, Radboud University Medical Center, Nijmegen, the Netherlands

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