The lessons which rare maladies can teach

A rare disease is defined by the European Union as one that affects less than five in 10,000 people. There are between 5,000 and 8,000 distinct rare diseases[1], and five new rare diseases are described in medical literature every week[2]. Each disease affects less than 0.1 per cent of the population. However, taken collectively, one in seven people — 17 per cent — will be affected by a rare disease at some point in their lives. This equates to three million people in the UK, 30 million in Europe and 350 million people worldwide. Indeed, if those three million people in the UK had the same disease, it would be a large public health problem.

The importance of research into rare diseases has been recognised for many years. It was Sir Archibald Garrod — a pioneering doctor and member of the MRC Council — who in 1928 commented:

"The study of nature's experiments is of special value; and many lessons which rare maladies can teach could hardly be learned in other ways"

Sir Archibald Garrod was a pioneer in the field of metabolic diseases and discovered the rare genetic disorder alkaptonuria, which causes bones to turn black and brittle, leading to early joint degeneration. Whereas alkaptonuria affects around 80 people in the UK, it is actually a severe form of osteoarthritis, which in its more common form affects eight million.

It is estimated that the MRC spends around 10 per cent of its translational budget on research into rare diseases[3]. MRC researchers have played a significant role in identifying the genetic basis for many rare inherited diseases and have shown that studying rare diseases can often lead to a better understanding of the mechanisms behind more common conditions.

Sir Archibald Garrod.
One in seven people will be affected by a rare disease at some point in their lives.

Pain

Professor Geoffrey Woods at the Cambridge Institute for Medical Research is a leading researcher in the genetics and molecular mechanisms behind pain sensing. He often studies extremely rare disorders which has given him valuable insights into pain pathways. Read a Q&A article with him on how his identification of a gene mutation causing congenital analgesia — a rare disorder characterised by a total inability to sense pain — may lead to the development of new pain treatments.

Lipodystrophy and diabetes

Studying the rare disorder congenital lipodystrophy has led to the development of improved treatment strategies for patients affected by the condition. It has also offered valuable insights into obesity and insulin resistance, one of the greatest threats to health today and a leading cause of premature death. Congenital lipodystrophy is a genetic disease characterised by a severe lack of adipose — or fat — tissue[4], believed to affect around one in 10 million people worldwide[5]. Because of a lack of functional fat cells, dietary fat and fat made by the body is instead stored in tissues such as muscle and liver. This leads to severe insulin resistance and ultimately diabetes. It can also cause liver and heart disease.

Researchers at the Wellcome Trust-MRC Institute of Metabolic Science have shown that there are significant similarities between the biochemistry of obese individuals and those with congenital lipodystrophy. Studying the latter has offered important insights into the genetics behind normal adipose tissue development and how disruption of normal function can lead to metabolic syndrome — a combination of diabetes, fatty liver and heart disease[6].

Over the past twenty years, various genes associated with congenital lipodystrophy have been identified. That losing the function of these genes leads to lipodystrophy shows that the encoded protein is essential for normal fat tissue development, and likely for human metabolic health.

The metabolic ill health suffered by those without functional fat tissue demonstrates the importance of fat tissue in the maintenance of healthy metabolic function. We now know that in addition to fat storage, adipose tissue serves as a store of energy, acts as a buffer in preventing the rapid post-meal influx of fatty acids from being circulated around the body and plays a role in the synthesis and secretion of hormones.

The link between obesity and diabetes has led to the assumption that an individual's level of insulin resistance rises in parallel to the amount of fat mass. However, those with congenital lipodystrophy develop severe insulin-resistance showing that this cannot necessarily be the case. MRC-funded researchers at the University of Cambridge have therefore proposed that adipose tissue has a limited capacity to increase in mass. It is when an individual reaches their adipose tissue expansion limit that lipid can no longer be stored appropriately in adipose tissue and is deposited elsewhere, leading to insulin resistance[7].

There is a type of lipodystrophy, which, unlike the generalised form that is characterised by a total loss of adipose tissue, results in a more limited loss of tissue. Partial lipodystrophy is often associated with a compensatory increase in the size of other fat depots — where fat deposits are stored. This shows that not all fat depots are equal, and as this form of lipodystrophy still results in insulin resistance, that some are more strongly associated with metabolic health than others. It is the accumulation of fat around the abdominal organs that is associated with obesity-related diseases such as type 2 diabetes and heart disease. And in lipodystrophy, loss of fat tissue is often first seen in the limbs, leading to a compensatory up-regulation of storage of this more 'dangerous' fat.

Studying patients with lipodystrophy has also highlighted the importance of the *PPARG* gene in fatty acid flux control and therefore insulin action. In a partly MRC-funded study, a patient with a double *PPARG*-mutation was found to have defects in their adipose tissue metabolic flux control, exposing liver

tissue to an unregulated flow of fatty acids, with subsequent effects on insulin sensitivity[8].

Prion disease and Alzheimer's
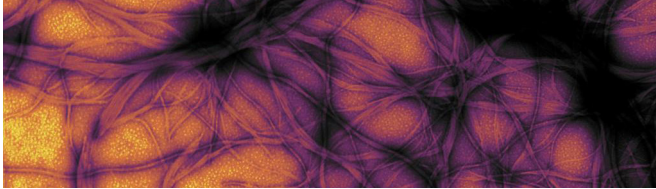
Prion diseases, or transmissible spongiform encephalopathies, are a collection of rare progressive neurodegenerative diseases that affect the brain and nervous system of animals, including humans. Human prion diseases include classic Creutzfeldt–Jakob disease, variant Creutzfeldt–Jakob disease, Gerstmann–Sträussler–Scheinker syndrome, fatal familial insomnia and kuru. It is estimated that around one in a million people are affected each year. There is no cure and the disease is ultimately fatal. Prion diseases are believed to be caused by the aggregated misshapen forms of one of the body's own proteins, the prion protein or PrP in the brain.

It is becoming increasingly acknowledged that other much more common degenerative brain diseases, such as Alzheimer's and Parkinson's disease, also involve the accumulation of abnormal forms of one or more of the body's proteins, resulting in damage to brain cells. As such, prion diseases are used as a model to study these more prevalent diseases. In 2012 researchers at the MRC Toxicology Unit

in Leicester identified for the first time a major pathway leading to brain cell death in prion-diseased mice[9]. The team, led by Professor Giovanna Mallucci, showed that the build-up of misfolded prion protein is seen as a form of cellular stress that is detected by specific cellular sensors. This leads to over-activation of a natural defence mechanism in cells — the part of the 'unfolded protein response' (UPR) that controls protein synthesis —stopping the production of proteins essential for nerve cell survival, which is the key trigger for brain cell death. This pathway is mediated by the kinase PERK. In 2013 the team then demonstrated that oral treatment with a specific inhibitor of PERK stopped the over-activation of UPR and therefore restored protein production, preventing the development of prion disease[10]. This was the case for animals treated both at the preclinical stage and also later in disease when behavioural signs had emerged. The researchers studied mice with prion disease because these mouse models currently provide the best animal representation of human neurodegenerative disorders in which the build-up of misshapen proteins is linked with brain cell death. This process is however likely to be relevant to neurodegenerative diseases more broadly.

Gaucher disease and Parkinson's

Gaucher disease is a rare genetic disorder affecting between one in 40,000 to one in 50,000 people. It is caused by a mutation in the gene GBA coding

for the lysosomal enzyme glucocerebrosidase. Glucocerebroidase breaks down the fatty acid glucosylceramide; when the enzyme is defective, glucosylceramide accumulates in organs such as the spleen, liver, kidneys, lungs and brain and cells, particularly white blood cells. It is characterised by an enlarged liver and spleen, liver malfunction, anaemia, skeletal disorders and severe neurological complications.

Studies of patients with Gaucher disease have recently offered important and unexpected insights into Parkinson's disease. During the past decade, clinicians treating patients with Gaucher disease have noted that several of them had symptoms associated with Parkinson's disease[11]. A later study evaluating a patient with Gaucher disease and Parkinson's disease compared their samples with those from two patients with Parkinson's disease as 'controls'. All three patients had deficient glucocerebrosidase levels. MRC-funded researcher Professor John Hardy has found that in various cohorts of patients with Parkinson's disease, a significant proportion had mutations in the GBA gene[12,13]. These studies and a later larger study have shown that mutations in this gene are a common risk factor for Parkinson's disease.

Aicardi-Goutières syndrome and viral infections
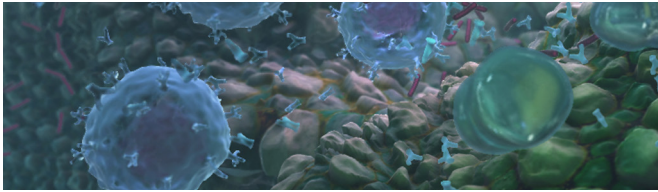
Aicardi-Goutières syndrome (AGS) is a rare genetic disorder that normally affects the brain, immune system and skin. In the first year of life, babies develop severe brain dysfunction and they may have intermittent fevers in the absence of infection and seizures. This phase of AGS leaves behind permanent brain damage that is usually severe. Medical imaging reveals deterioration of white matter in the brain (leukodystrophy). White matter consists of nerve fibers covered by myelin, which is a substance that insulates and protects nerves. Affected individuals also have abnormal deposits of calcium — calcification — in the brain.

In 2006 Professor Andrew Jackson at the MRC Human Genetics Unit, in collaboration with scientists at the University of Leeds, identified loss of function mutations in four genes: *TREX1*, *RNASEH2B*, *RNASEH2C* and *RNASEH2A* that cause the disease[14]. These genes code for nuclease enzymes, which break up molecules of DNA and RNA. Mutations in the genes result in absent or dysfunctional nuclease enzymes causing the accumulation of unrequired DNA and RNA. These superfluous molecules are seen as viral invaders by the body's cells, and the immune system responds accordingly, triggering the symptoms of the disease.

This was the first time that the role of nucleases had been linked to the immune response. The researchers suggested that the genes themselves may also be implicated in the body's immune response, which will help to identify more effective treatments for viral infections and autoimmune diseases.

TREX1 mutations have actually been found in up to two per cent of patients with systematic lupus erythematosus, an autoimmune disorder that can affect any part of the body, and most often harms the heart, joints, skin, lungs blood vessels, liver, kidneys and nervous system. This represents one of the highest disease risks recorded for a single susceptibility gene in the condition[15].

Respiratory infections

In 2013 researchers at the University of Cambridge in collaboration with the MRC's Laboratory of Molecular Biology (LMB) discovered a rare genetic immune disease that predisposes the patient to severe respiratory infections and lung disease[16].

They have identified a genetic mutation that increases the activity of an enzyme called Phosphoinositide 3-Kinase δ (PI3Kδ), which is found in immune cells and regulates their function. A constantly activated PI3Kδ impairs the work of the immune cells, preventing them from responding effectively to infection.

The researchers believe that the newly identified disease — Activated PI3Kδ Syndrome (APDS) — may be responsive to Idelalisib, a drug currently undergoing clinical trials for the treatment of leukaemia, as it was shown to inhibit the mutant enzyme.

The researchers hope to identify abnormalities in this, and related, signalling pathways that may contribute to susceptibility to respiratory infections — the commonest diseases to affect mankind — in the wider population.
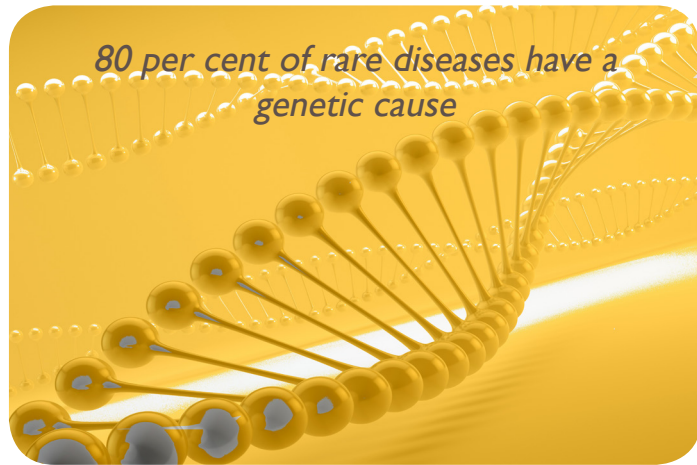
Cancer

MRC researchers have also advanced understanding of the molecular basis for cancer from studying rare diseases.

Tuberous sclerosis is a rare genetic disorder that causes non-malignant tumours to grow in the brain and on other vital organs such as the kidneys, heart, eyes, lungs, and skin. A combination of symptoms may include seizures, intellectual disability, developmental delay, behavioural problems, skin abnormalities, lung and kidney disease. It is estimated to affect between 10 and 16 per 100,000 people.

The disease is caused by mutations in the tumour-suppressant genes Tuberous Sclerosis 1 and 2 (*TSC1* and *TSC2*) encoding the proteins hamartin and

tuberin[17,18], identified by a group including MRC researcher Professor Julian Sampson at Cardiff University. Mutations in the gene *TSC1* has since been implicated in the cause of bladder cancer[19].

> *80 per cent of rare diseases have a genetic cause*

End notes

[1] http://www.eurocat-network.eu/aboutus/eurarediseasespolicy

[2] http://www.raredisease.org.uk

[3] 2011/12 figure reported to the RDUK report Funding Support for Rare Disease Research. http://www.raredisease.org.uk/documents/RDUK-Research-Funding-Report.pdf

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