Gene therapy for Wilson's disease?

In September 2020, Vertex, a company based in the USA, announced that they were planning to investigate a new approach to treating Wilson's disease using gene therapy. At first, they will study a small group of patients and follow them up over a long time. Vertex indicated that they planned to start in April 2021. Even if all goes as well as possible, it will still be a few years before we know if this treatment is effective. But the fact that they are willing to attempt such an ambitious and expensive study shows they think that gene therapy for patients with Wilson's disease is now a real prospect!

So what does this all mean? What are genes?

We inherit half of our DNA from each parent. The DNA is stored in *every* cell in the body as two non-identical strands. Each of the two strands of DNA contains numerous distinct patterns that determine and control over 20,000 genes that define each one of us. At any one time some of these genes will be silent depending on many things such as age— with different needs in childhood and as adults, events including infections, but also with position in the body. A cell in the skin has different needs from a cell in the liver or brain, for example. Some genes will be active continuously, others intermittently. When a gene within DNA is activated it generates a chemical called RNA. This RNA acts like an architect's plans—to create three dimensional proteins that are specific to the DNA of that individual. Mutations, or changes, in DNA within a cell (not the whole body) occur every day in response to damage and DNA is undergoing continuous repair. These mutations can cause changes to the proteins that the RNA creates. These mutations in response to injury and unchecked can drive diseases such as cancer.

Every one of us carries a small number of mutations in our DNA that arose between conception and birth and ensure each of us is unique. Some mutations have been beneficial; for example the gene that allowed humans to have larger brains than Neanderthals has been identified recently. Other mutations are lethal so the foetus cannot survive. But the great majority of gene mutations are minor and have little effect.

What causes Wilson's Disease?

Genetic diseases are a highly complex area. Some occur because an abnormal protein is produced that causes toxic damage. However others, including Wilson's disease, occur because the mutation in DNA creates RNA that then makes a protein that is missing a small but important component and so cannot function adequately.

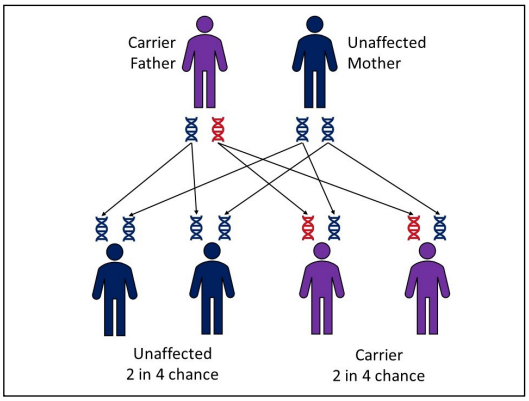
In Wilson's disease the critical gene is ATP7B. This should make a protein in liver cells that helps the body get rid of copper in just the right amount. However, in someone with Wilson's disease, the failure to move copper into the bile duct and then gut (and then down the toilet!) means that copper builds up in many organs and acts as a poison/toxin.

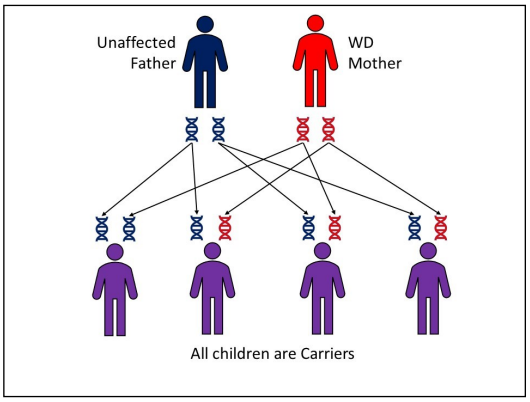
One good ATP7B gene will generate enough capacity to keep copper levels in the body at just the right level. This means that to develop Wilson's disease you need two mutated genes. Estimates for the UK suggest that between 1 person in every 7,500 and 1 in every 30,000 people has two mutated WD genes – i.e. no good ATP7B gene. Over 800 different Wilson's disease related mutations of ATP7B have been found. Some Wilson's disease patients will have *identical* mutations of the ATP7B gene and are known as homozygotes. This is more prevalent in cultures where cousins may marry, but most patients will have inherited *different* mutations from each parent and these patients are known as *compound* heterozygotes.

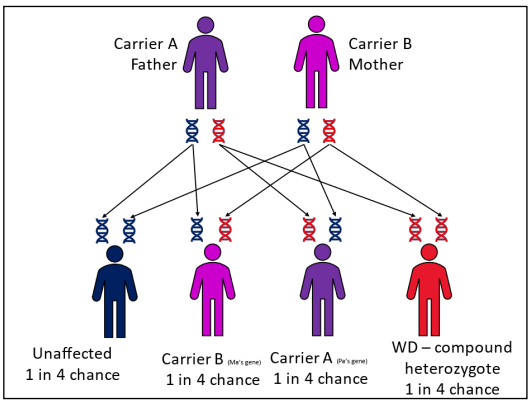
A *simple* heterozygote is someone who carries one mutated gene and one normal gene so is healthy and disease free and these people are referred to as "carriers". They *carry* only one mutated gene so do not have Wilson's disease themselves. There are between 1 in 48 and 1 in 90 such people carrying just one mutated ATP7B gene in the UK. This is important to consider when someone with Wilson's disease is planning to have children; the risk of having a child with two mutated genes is small but real; for someone with Wilson's disease with a partner who just happens to carry one mutated gene each child would have a 50% chance of inheriting two mutated genes. Fortunately, the chance that a partner is a carrier is quite small.

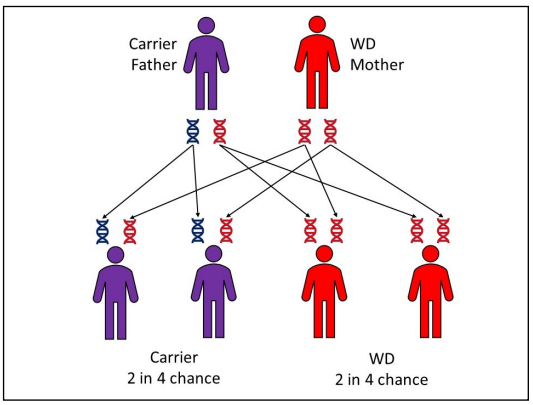
- The gene involved in Wilson's disease is ATP7B
- There are over 800 different Wilson's disease related mutations of ATP7B
- There are between 1:48 and 1:90 WD carriers in the UK i.e. have only one mutated gene
- Wilson's disease patients have inherited two mutated ATP7B genes—one from each parent
- It is suggested that there are between 1:7,500 and 1:30,000 people in the UK with 2 mutated ATP7B genes, i.e. have Wilson's disease
- A simple heterozygote has one mutated ATP7B gene and is known as a carrier
- A homozygote has inherited two identical mutations of the ATP7B gene; one from each parent
- A compound heterozygote has inherited two different mutations of the ATP7B gene; one from each parent.

Charts Showing Inheritance Patterns in People with Mutated ATP7B Genes









Gene Therapy—Approaches and Challenges

A couple of decades ago the first hurdles to gene therapy were getting the 'treatment' into the right place in the body and then finding a way to keep it there—the human cell responds to new genes as if they are viruses and tries to eliminate them.

The first uses for gene therapy have been in the field of stopping genes where mutations produce a toxic protein and after about 25 years of research these have led to life changing developments. However, in Wilson's disease the need is the opposite—we need to introduce a gene that correctly makes a protein to transport copper out of the liver and into the bile duct and then gut.

Also, researchers had to find a way to get the treatment to exactly the place where it was needed in the body—in Wilson's disease this is the liver. Some approaches for the liver link the gene therapy treatment to a protein that the liver can absorb. This has been effective. But more often currently the gene is inserted into an Adenovirus that can get into the liver before releasing the gene correction therapy (in much the same way as the Oxford/AstraZeneca Covid vaccine which is made by inserting the Covid Spike protein into an Adenovirus). Much work has now identified the right type of Adenovirus for efficient delivery of the right gene and sophisticated techniques have been developed to neutralise the Adenovirus itself, without impairing delivery of the gene, so the Adenovirus cannot cause an infection.

There are huge hopes for medicine in general using a technique called CRISPR whereby a specific gene is targeted, the small abnormal area is removed and at the same time the correction is inserted; the early work on CRISPR deservedly won a Nobel prize. But in Wilson's disease there are so many different mutations to correct specifically that this approach may not be very easy to apply across all cases.

Over the past few years modified Adenoviruses have been used to deliver a normal Wilson's gene into mice to correct mouse models of human Wilson's disease. These experiments have gradually been improved so that now the pharmaceutical industry is poised to replicate the process in humans and will use a 'neutered' Adenovirus to deliver the normal version of the Wilson's disease genes into the livers of patients with Wilson's disease.

There are many things that cannot be predicted. No-one knows the answers to the questions: Will it work? Will it have side effects? How long will it last? Will it be good enough to stop conventional treatment and more? No-one knows with certainty because this is, by definition, research. But it is a step with huge potential.

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