Explainer: What is genetic risk?

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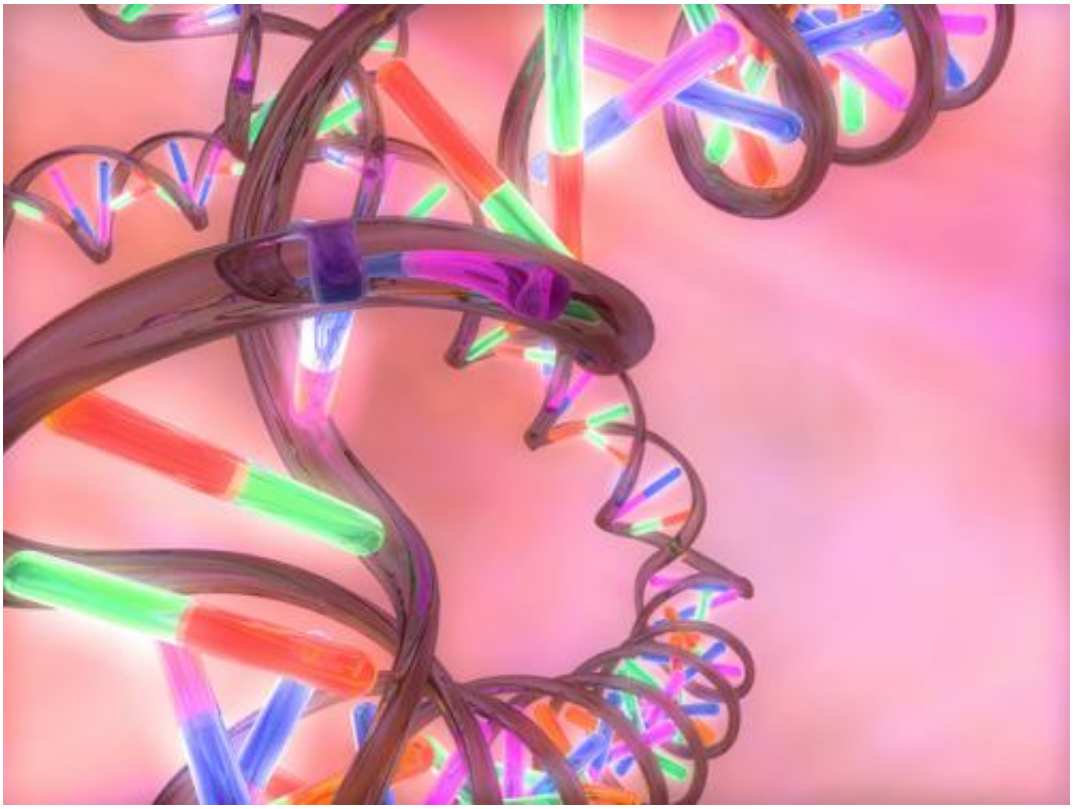

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Genetic risk is the contribution our genes play in the chance we have of developing certain illnesses or diseases. Genes are not the only deciding factor for whether or not we will develop certain diseases and their influence varies depending on the disease. But scientists are increasingly using genetic knowledge to predict the likelihood of developing different illnesses from cystic fibrosis to mental illness.

Genetics explains how individual characteristics are inherited. As a tool, it can identify genes that increase disease risk and is having a major impact on modern medicine. In contrast, our perception of risk is notoriously unreliable, with our appreciation of risk often not matching the likelihood of something actually happening. For example, we generally over-estimate chances of being victim of a crime or winning the lottery. So, how should we best consider genetic risk?

Building blocks

In the 19th century, Gregor Mendel realised that many simple characteristics, such as flower colour in pea plants, have patterns of inheritance where one characteristic is dominant over the other. From this, he deduced that each characteristic derives from the combination of two factors that we now call genes. A dominant gene masks the effects of a recessive gene, and so recessive traits are only seen when an individual inherits genes that are both recessive – this is expected to occur in one in every four offspring.

We call the combination of genes in each individual the genotype, whereas the actual effect of the gene combination is called the phenotype. It is important to remember that however complex the inheritance of phenotype, individual genes are almost always inherited by the genetic rules found by Mendel.

Genetic information is written in the sequence of DNA and stored in the chromosomes of cells. Each cell has two of each chromosome, and almost all genes are present in two copies as predicted by Mendel. Genes are then copied as RNA molecules to make proteins or directly control the cell. DNA mutations change its sequence, and can lead ultimately to variations in phenotypes.

Let's consider a simple case for human disease. Cystic fibrosis is caused

by a specific mutation of the CFTR gene. A mutated CFTR gene is present in 1 in 25 people of European descent, but is usually masked by a dominant, non-mutated gene. The disease phenotype is inherited with Mendelian genetics, so that it occurs much less often than the genes - it only occurs when a child inherits a mutant gene from each parent. This gives a simple genetic test to calculate the chance, or risk, of being born with the disease.

Genetic complexities

The genetic influence on many common illnesses is a lot more complicated. Here, inheritance is often described as "non-Mendelian" because disease phenotypes appear to be inherited with a pattern that is very different from that seen for the mutant CFTR gene. This makes assessment of genetic risk for these conditions more difficult.

Some of the most complex genetics is seen with psychiatric disorders, for example schizophrenia. Having a close relative with schizophrenia increases personal risk by about 10%, and this jumps to more than 50% between identical twins. This points to a significant genetic risk, but the role of environmental factors is also substantial.

Correlating the variation in gene sequences with schizophrenia has begun to uncover gene mutations that are associated with those that increase risk, and in the next few years we will continue to add to the number of these sequences. The situation, however, is very different to the simple genetics of cystic fibrosis, as increased risk of developing schizophrenia results from the combined effect of tens to hundreds of gene mutations each with a small effect.

The involvement of multiple genes (termed polygenic inheritance) has a number of consequences. Rather than the presence or absence of a single gene mutation, risk has to be assessed in terms of a polygenic score. As

some mutant genes may be found in the low risk population – where polygenic score is lower – it is very unlikely that there will be a single genetic test for schizophrenia. Also there is substantial overlap between the genes associated with other psychiatric disorders (like Autism, ADHD, Bipolar Disorder), so there may not be unique schizophrenia genes.

Weighing up the risks

Massive advances in technology now enable us to obtain the sequence of an individual's many tens of thousands of genes. This makes it possible to measure polygenic score, but it is still unclear whether there is sufficient difference on a gene by gene basis to accurately determine risk at the individual level.

An alternative approach is to group genes based on the molecular and physiological processes they control. Diagnostic tests could then be designed to measure irregularities in these intermediate phenotypes – so-called endophenotypes. For patients, this genetic information could be used to select the best therapeutic strategies.

We are now entering a new era, where the results of large-scale DNA sequencing may be combined with other diagnostic indicators to define genetic risk. This can inform an individual's lifestyle choices and if necessary direct personalised medicine to provide the best treatment for a patient's genetic profile.