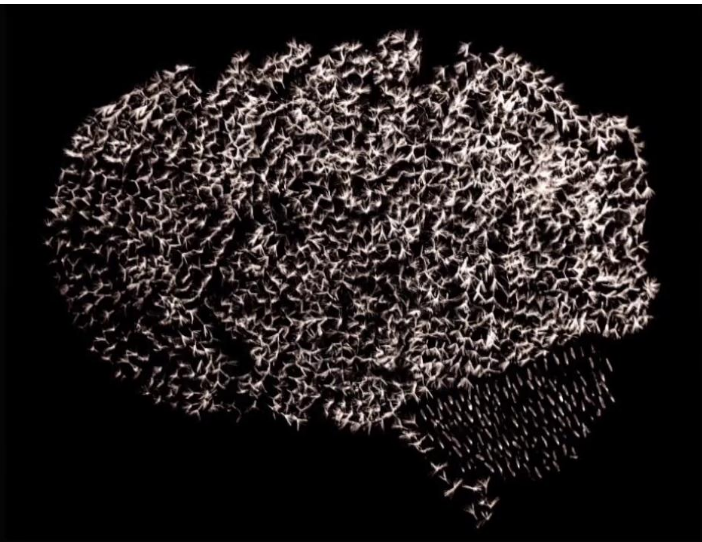
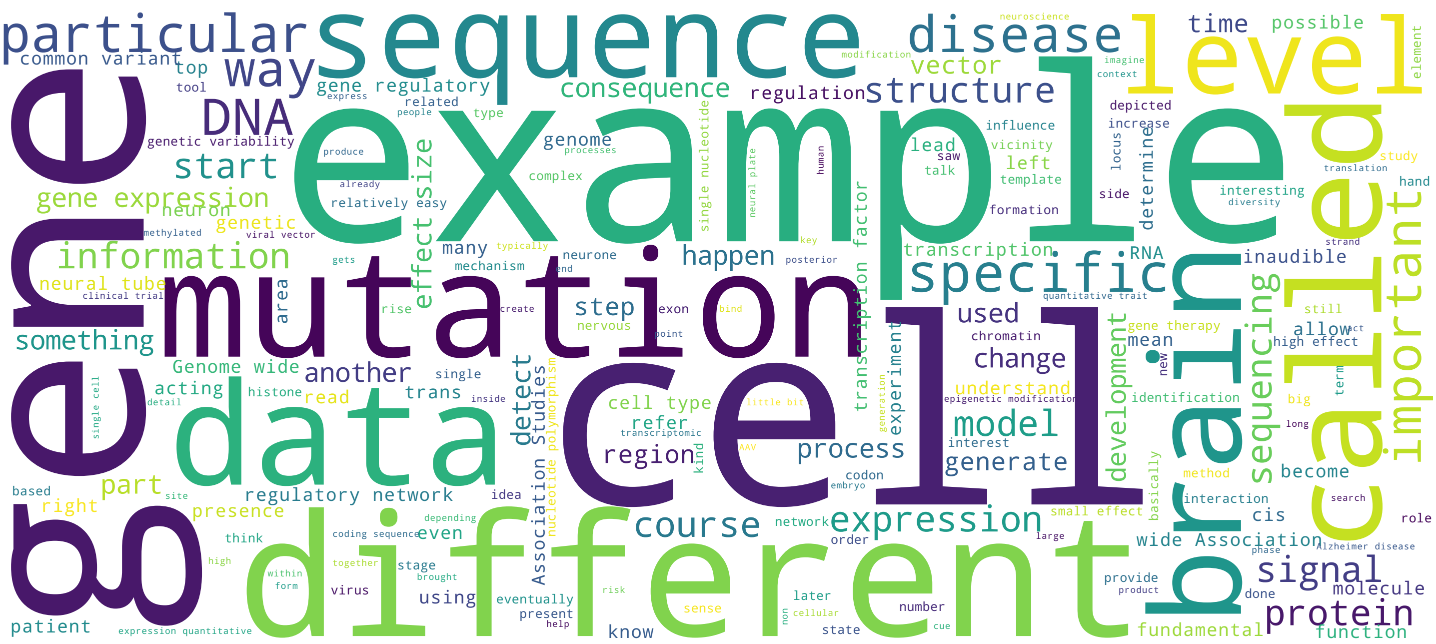


NEUROSCIENCE RECONSTRUCTED

Genetic variability & diversity: diseases & medicine

Presented by Johannes Gräff



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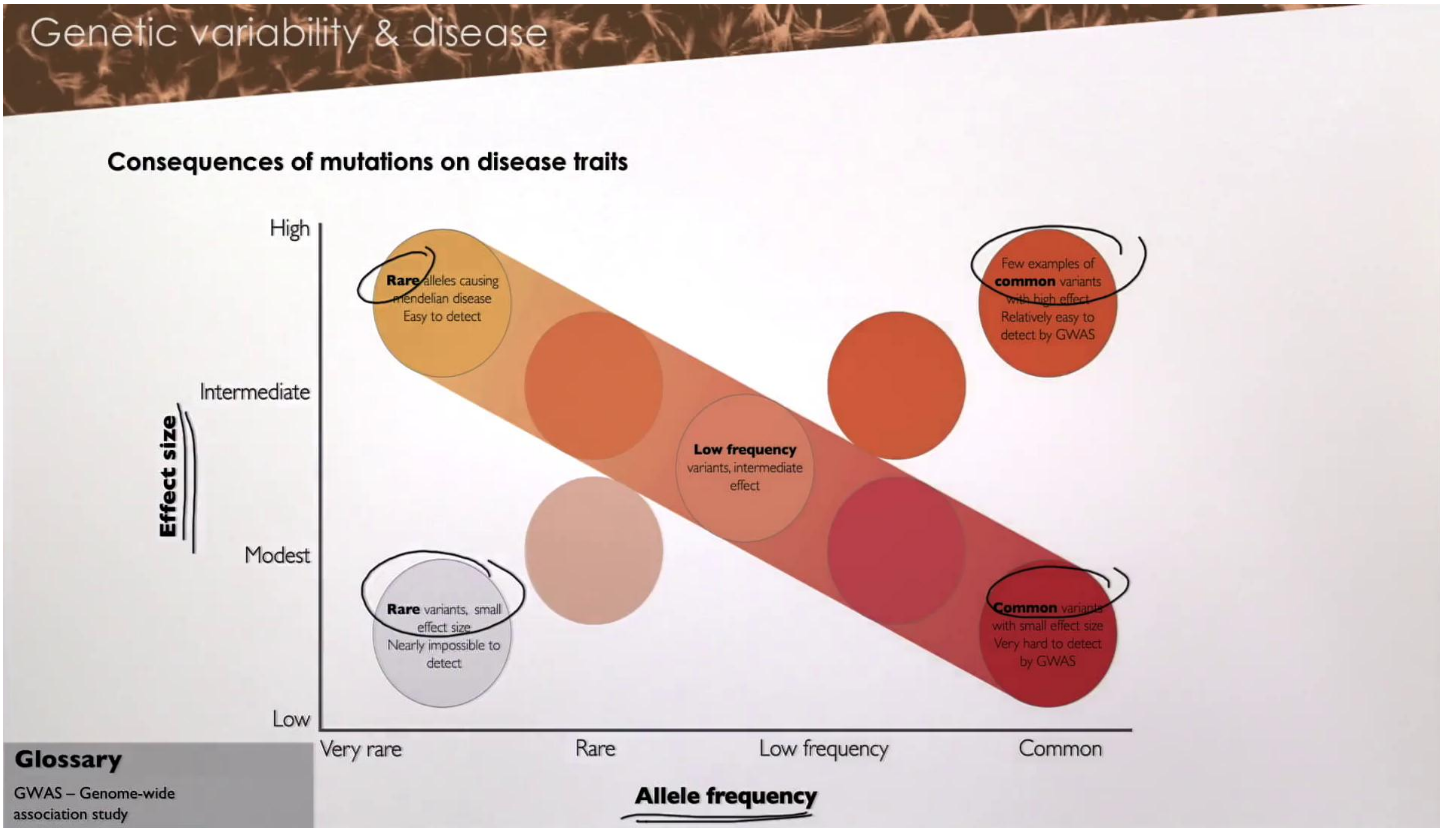


The consequences of mutations can be devastating. There are multiple examples where mutations can lead to diseases. One example is what is called a monoallelic disease, which would be a rare allele up here that causes a Mendelian disease, and which, by genetic studies, are very easy to detect. One example is the case of Huntington's disease, a neurodegenerative disorder that is caused by a mutation in one single gene. On the other side of the spectrum, we have common variants with very small effect sizes, and those are very difficult to detect by Genome-wide Association Studies. We have a few examples of common variants with a high effect size, and those are relatively easy because of their high effect size to detect by Genome-wide Association Studies. One example of a common variant that is relatively easy to detect by Genome-wide Association Studies is the case of APOE4. APOE4 is a genetic variant that increases the risk to develop Alzheimer's disease, and it is common in a lot of people. Finally, we also have extremely rare variants with a very small effect size, and those by definition are nearly impossible to detect. The consequences of a mutation on a disease trait depend on the one hand on the allele frequency which is depicted down here, and on the effect size which is depicted on the Y-axis over here.

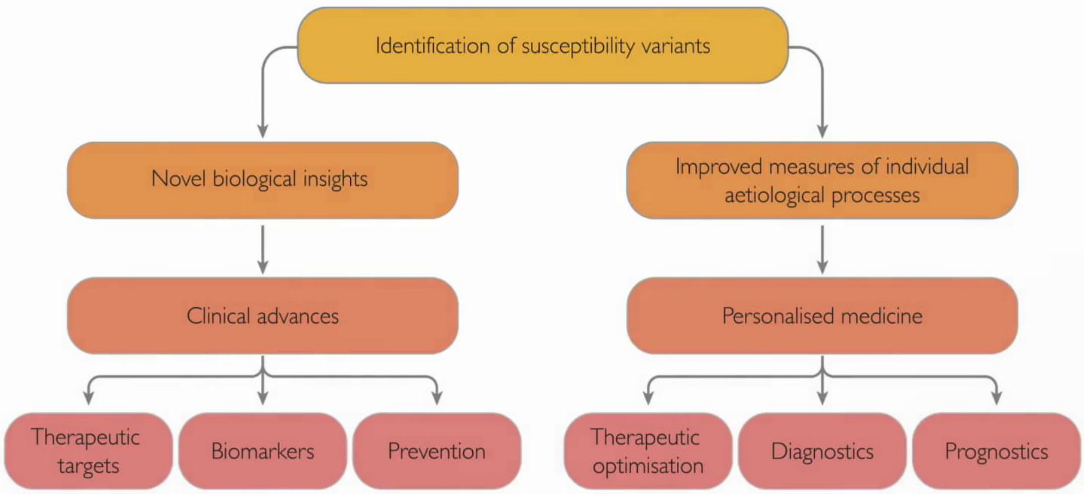
Notes

Summary

0m 05s

Genetic variability & medicine

Utility of genetic variability



Genetic variability is extremely useful for medicine. This is because the identification of susceptibility variance can not only lead to novel biological insights, but also to clinical advances such as the discovery of new therapeutic targets or of novel biomarkers by which a given disease can be more easily, more rapidly detected, which then ultimately leads to a better prevention of the disease. On the other hand, with the identification of susceptibility variants, we can have improved measures of individual etiological processes, which can then lead to improved personalised medicine, thereby leading to therapeutic optimisation, to better diagnostic tools, and ultimately to a better prognosis, even in the presence of a diagnosis of a devastating disease.

Notes

Summary

1m 50s

Genetic variability & other traits

Consequences of mutations on gene expression

- eQTLs (expression quantitative trait locus)

Consequences of mutations on epigenetic mechanisms

- mQTLs (methylation quantitative trait locus)

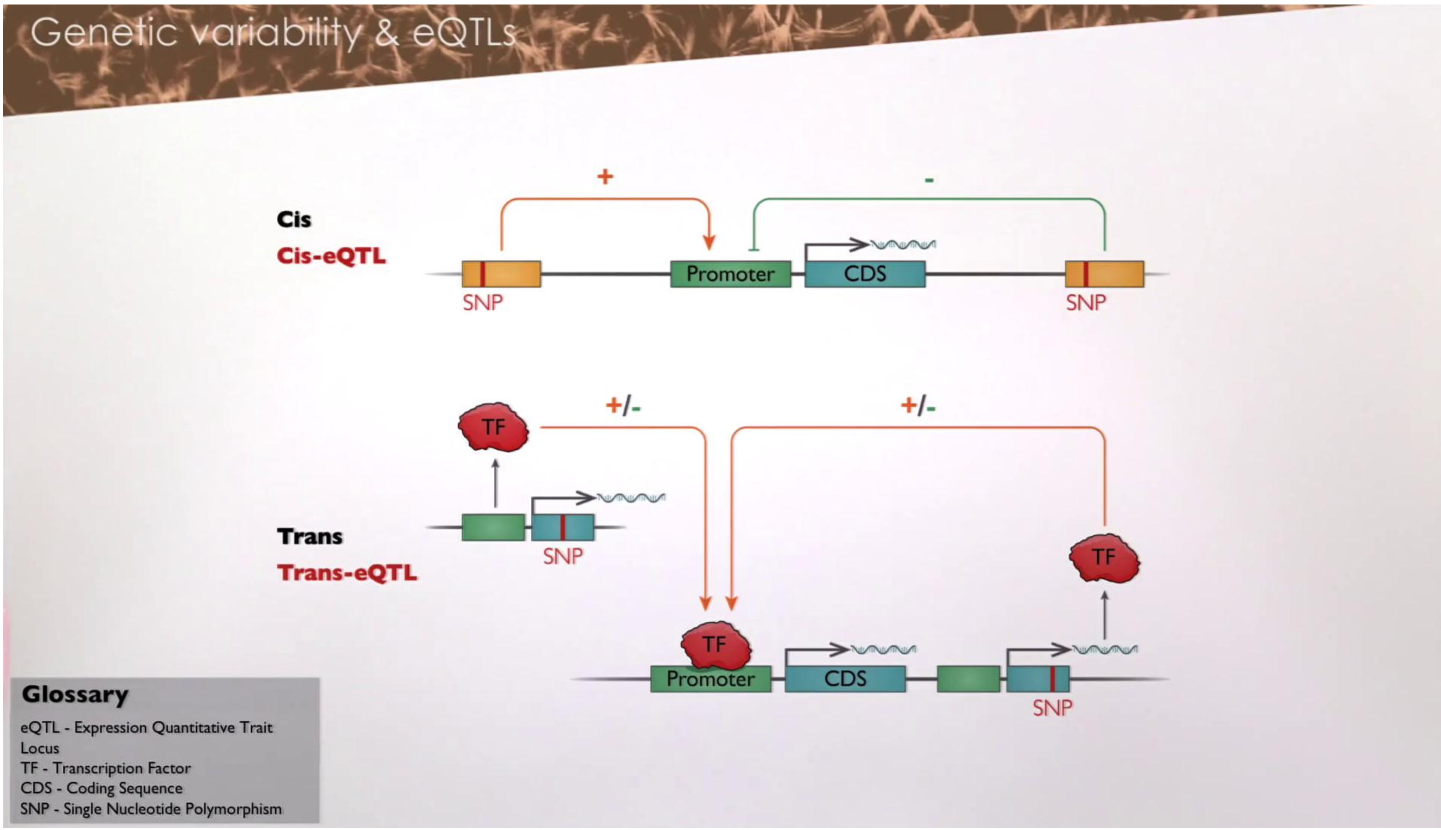
can act in *cis* or in *trans*

A disease outcome is only one of the possible consequences of genetic variability. If we look inside a given cell, these consequences can be manyfold. For examples, we can have consequences of mutations at the level of gene expression, in which case we refer to these changes as expression quantitative trait loci, meaning that a given locus will change its expression in the presence of a mutation. Furthermore, the consequences of mutations can also affect epigenetic mechanisms. For example, we can have a given locus that is methylated or not, depending on the presence of a mutation in the sequence nearby. It is important to realise that mutations can act in cis or in trans.

Notes

Summary

2m 47s



What do we mean by acting in cis or in trans? Acting in cis means that a given mutation depicted here on the left or here on the right will influence the trait of a gene that is in the vicinity of the mutation. In this case, on the left, we have a mutation that positively influences the expression of the coding sequence of this gene here in the middle, whereas on the right, we have a mutation that negatively influences this expression. But the key point to remember when something is acting in cis is that it happens in the vicinity of the trait of interest. In contrast, when we refer to something as acting in trans, in this case, an expression quantitative trait locus that is influenced by something in trans, we either refer to an effect that is brought about by a single nucleotide polymorphism situated on a different chromosome, hence it is acting in trans, it is far away, or we refer to a single nucleotide polymorphism that is situated on the same chromosome but multiple hundreds of kilobases away. Together, both cis and trans effects of mutations, of base substitutions, co-influence the functioning of gene regulatory networks.

Notes

Summary

3m 43s