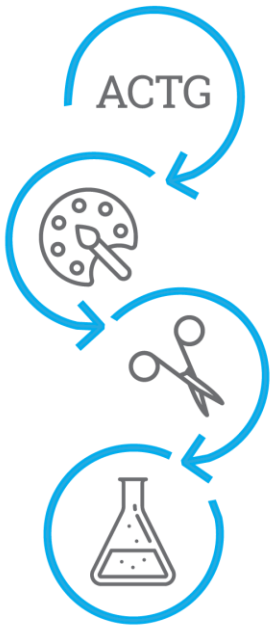

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Genome Wide Association Studies (GWAS)

What it is:

An approach to find novel genetic markers of disease

Genome-Wide Association Studies (GWAS) are a tool that biomedical researchers use to find potential links between genetics and disease. Imagine a disease for which no clear cause is known (for example, Parkinson). Researchers will read parts of the genome that are usually variable across people, and compare these genetic variants in patients and people without the disease. The goal of GWAS is to identify associations between specific genetic variants and the disease. The genetic variants studied are usually single base changes in our DNA, known as single nucleotide polymorphisms *(SNPs.)* GWAS are 'genome-wide' because they look at many SNPs across the whole genome in one go, searching for SNP variants that occur more or less frequently in people with the disease. Finding new genetic associations allows researchers to develop better strategies to prevent, detect, and treat disease.

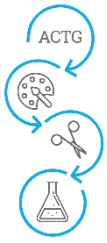
How it works:

Finding possible phenotype-genotype associations

GWAS are particularly useful in finding genetic variations that contribute to complex, multifactorial diseases, such as cancer, diabetes, and mental illnesses. Researchers compare the genomes of a large number of cases and healthy controls. They analyze thousands of SNPs in the two groups, and compare the groups to each other to see if any of the SNPs are more common in disease carriers than in controls. If the odds of having a certain SNP (genetic *variant*) together with the disease are higher, then we say that SNP may be **associated** with the disease.

GWAS typically maps the difference in allele frequencies between the two groups on a display known as a *Manhattan plot.* These plots resemble the Manhattan skyline, with many low-lying points and a few "skyscrapers", indicating a SNP that is associated with the examined disease. The genomic locations of the genetic variation are on the x-axis, and each dot on the graph represents a single SNP (genetic variant). The y-axis represents the probability of a SNP being associated with the disease. The strongest associations between a SNP and a disease will show as the higher points on the graph.

A SNP associated with a disease may not represent the direct genetic cause of the disease. This SNP may just lie in very close proximity to the real genetic cause (genetically *linked*). After identifying this general genomic location, scientists have to look in more detail at its DNA sequence to try and find the exact variant involved in causing the disease.



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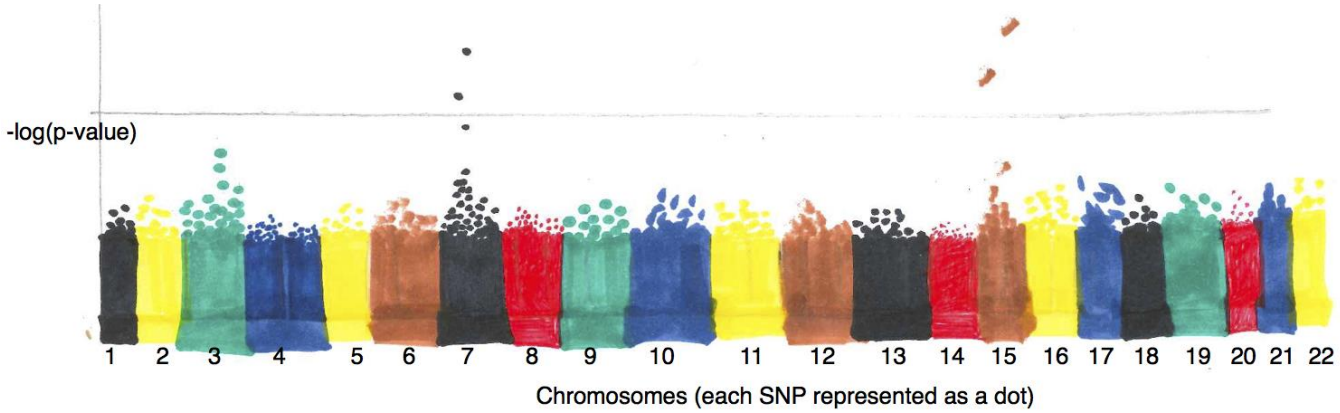

The future:

Learning personal risks and understanding complex diseases

GWAS analysis is now possible because we know the complete sequence of the human genome, revealed by the Human Genome Project in 2003. We also have access to growing databases of genetic variation, through studies such as *HapMap*, completed in 2005. GWAS is made possible by these developments and by new technologies (e.g., SNP chips) that allow researchers to rapidly scan our genomes and study genetic variation.

As these tools develop further and become more accessible, GWAS will be used to investigate more and more complex diseases, such as autoimmune disorders, neuropsychiatric illnesses, and metabolic diseases. GWAS will result in a better understanding of the biology underlying such diseases, which can inform new cures and help develop more personalized treatments for disease. For example, GWAS has identified over 100 genetic loci associated with schizophrenia. While this does not suggest a simple genetic basis for the disease, it does provide many possible starting points for developing new medicines. The search for related drug targets has been ongoing since the first major GWAS for schizophrenia was conducted in 2012.

As whole-genome sequencing becomes faster and cheaper, GWAS may be used to compare genetic variation across the *entire genome*, not just SNPs. Personal genome scans may soon allow us to learn our own genetic risks for many diseases, by revealing multiple variants in a single test. The future of *personalized medicine* relies on knowing all possible genetic associations with a certain disease or syndrome, helping us better prevent and treat disease based on someone's personal risks and drug responses. GWAS is a key tool to understanding more gene-disease relationships, and can help personalized medicine become more effective.

Learn more:

- "Genome-Wide Association Studies." *National Human Genome Research Institute.* https://www.genome.gov/20019523/
- "Genome-wide association studies." *Your Genome, Wellcome Genome Campus* http://www.yourgenome.org/stories/genome-wide-association-studies
- Bust, W, Jason, M "Chapter 11: Genome-Wide Association Studies." *PLoS Computational Biology.* https://www.ncbi.nlm.nih.gov/pcm/articles/PMC3531285/