Introducing Genomics

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Genome

BOOK - GENOME

CHAPTERS - CHROMOSOMES

SENTENCE - GENE

Image: National Society of Genetic Counselors
Your genome

Cells

Chromosomes - DNA

Mitochondrial DNA

genes
Chromosomes

DNA double helix

DNA

Chromosome

46 chromosomes
(2 sets of 23 chromosomes)
DNA double helix is built of nucleotides

Complementary base pairs

3 billion "letters" of DNA
Genes

Recipes for proteins

~22,000 genes
Only 1-2% of the whole genome carries the code for proteins. The protein coding section is called the **exome**.
Gene sequence – human keratin

1 cactcaaggt gtcgagggag ctgttctttg caggaagggc gaaggagttg gcctttgtttt aggggaggag acgaggtccc acaacccct ctgaagggta tataaggagc cccagcgtgc

121 agcctggcct ggtacctcct gccagcatct cttgggtttg ctgagaactc acgggctcca gctacctggc catgaccacc acatttctgc aaaccttcttc ctctacccctt ggagggttgct

241 caaccccagg ggttcccctc ctggcgttggg gagggtctct tgggctgggg aggggagtgg aacgcgaagtt atctcaagctt ctctctctgc acgggcttggt ggggggtgtt ggagggtggc

361 gaggagattc tcggggtttg gctttggcgg tcggctgggg gagctcccccct ggagctctctc gggggttggt ggggggtggc atgggtgtgg ctggctttgt gcggtgtgtc

481 atgggtgctc cctctctgtct tgggagatct gcccagccaa atcttccactg gacaagcagt gctttggggg gggggtgggg cggggggtttt acgaggtggg ctggctttgt gcggtgtgtc

601 tccatactgc gttcaggaag cagaccccct cccagccaga agcgaactac agcagaaact gtaagagctc gcgggagagc cgcagcagtc acgcagagcg ggttggctgt gtcagcttctc

721 tcatcctgga gatggcagat gccccagccct cttcaggctct ccaatctcag aagtatgaga atggagcgcc gttcgaggtc gtcagatgtgg caactttttc ctggctttgt gcggtgtgtc

841 atgcagcagc ctgctgagtgc atgaggtgtc gaaagaagtgc gctgggtttt gcggggtggc atgggtgtgg gcgcacaccc cggggtgggg cggggggtttt acgaggtggg ctggctttgt gcggtgtgtc

961 gcccagcttg tggggttttt gcgggtgggg cggggtgggg gggggtgggg cggggggtttt acgaggtggg ctggctttgt gcggtgtgtc acgcagacac acgcagacac acgcagacac

1081 tctctcctg gggagggggg cagccgagcc gttgggtttt gcggggtggc atgggtgtgg gcgcacaccc cggggtgggg cggggggtttt acgaggtggg ctggctttgt gcggtgtgtc

1201 agtccccactg cagatgagaga ctggggtggc cagcgagcag gcgtgctggct tggggttttt gcggggtggg gggggtgggg cggggggtttt acgaggtggg ctggctttgt gcggtgtgtc

1321 agtcctcagag gcaggaagtc acggggtggg gcggggtggg gggggtgggg cggggggtttt acgaggtggg ctggctttgt gcggtgtgtc acgcagacac acgcagacac acgcagacac

1441 tgtgctgctgg cagcagcttg caggggtttt gcggggtggg gggggtgggg cggggggtttt acgaggtggg ctggctttgt gcggtgtgtc acgcagacac acgcagacac acgcagacac

1561 aagttctctg tgctagcagc ccagggtggg gcggggtggg gggggtgggg cggggggtttt acgaggtggg ctggctttgt gcggtgtgtc acgcagacac acgcagacac acgcagacac

1681 ggttctctgg cactcactctt gggggtttt gcggggtggg gggggtgggg cggggggtttt acgaggtggg ctggctttgt gcggtgtgtc acgcagacac acgcagacac acgcagacac

1801 ctgtttctgt aataaagatct aacttctttttgt gggggtttt gcggggtggg gggggtgggg cggggggtttt acgaggtggg ctggctttgt gcggtgtgtc acgcagacac acgcagacac

1861 coding bases
Proteins are …

The molecules that give us our characteristics
Genes ‘turn on’ and ‘turn off’

Genes are ‘turned on’ to produce protein only when needed
• Different genes are turned on at different times during development
• Different genes are turned on in different cell and tissues
• A gene variant might affect only some cells and tissues

‘Regulator’ genes act as ON-OFF switches
• Variants in the regulators can change how other genes are turned on or off
Genetic variants
Single nucleotide variants

Patient: attgccttgggacctgtccttagtccttt ttaacatgtagcttttatcgatcgtagct
Reference: atttcctttgggatgcctgtcctaagtcctttcttaacatgtagctatcgcatacgtagct
Chromosome variants

- Translocation
- Deletion
- Expansion
Variants can be …

… depending on how they affect the proteins in your cells
Variants can be...

**benign**
- Normal variations in genes - not linked to disease

**variant of uncertain significance (VUS)**
- Not certain whether it is the cause of disease

**pathogenic**
- Some variants cause or increase risk of inherited disease
- Some variants lead to cancer
Variant Curation
Identify and classify variants

- Extract DNA → Sequence the DNA
- Compare patient DNA to reference sequence
- Identify & classify variants
- Clinical action
Testing for genetic variants
Karyotyping

Changes in chromosome number

Examples:
- Down syndrome (trisomy 21)
- Kleinfelter syndrome (XXY)
- Turner syndrome (XO)
Chromosome Microarray

Finds large deletions & duplications within chromosomes

Examples:

- common & unknown chromosome change
- Di George syndrome (deletion)
- Intellectual disability
- Developmental concerns
Single gene test

Identify genetic disease caused by variants in a single gene

Examples:
Cystic fibrosis - CFTR gene
Huntington disease - HTT gene
Haemochromatosis – HFE gene
Gene panel test

Multiple genes known to be associated with a particular type of disorder

Examples:

- Breast cancer susceptibility
  BRCA1, BRCA2 + 12 other genes
- Cardiomyopathy – 62 gene panel

Image: adapted from National Society of Genetic Counselors

Variants in any of these genes cause similar condition
Whole exome sequencing (WES)

Reading 1-2% of the book
Reading the edited sentences
i.e. the protein-coding sections

Diagnosis of:
• Rare
• Complex
• Syndromes
• Previously undiagnosed
Whole genome sequencing (WGS)

Reading the whole book

Diagnosis of:
- Rare
- Complex
- Syndromes
- Previously undiagnosed
GWAS
Genome Wide Association Study

Association between common variants (SNPs) and traits

Examples:
• Common traits – hair colour/type, height
• Complex traits – height, IQ, behaviour
• Ancestry – ethnicity
• Multifactorial conditions – obesity, aging
• Disease risk – diabetes, heart disease
• Response to medication - antidepressants

The NHGRI-EBI GWAS Catalog is a publicly available resource of Genome Wide Association Studies (GWAS) and their results
Source NHGRI-EBI GWAS Catalog
Inheriting genetic characteristics
Germline vs Somatic variants

Germline variants are inherited
- Present in egg or sperm
- Some cause family cancer syndrome

Somatic variants are not inherited
- Occur in body tissues
- May cause cancer
Inheriting the genome
Inheriting the genome
Inheritance patterns

- Dominant
- Recessive
- Sex-linked
- Mitochondrial
New variants – de novo variant
Thank you