Basics in Genetics

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- 1. Human Genetics: an application
  - A case study of Familial Mediterranean Fever (FMF) patients
- 2. Introduction to human genetics

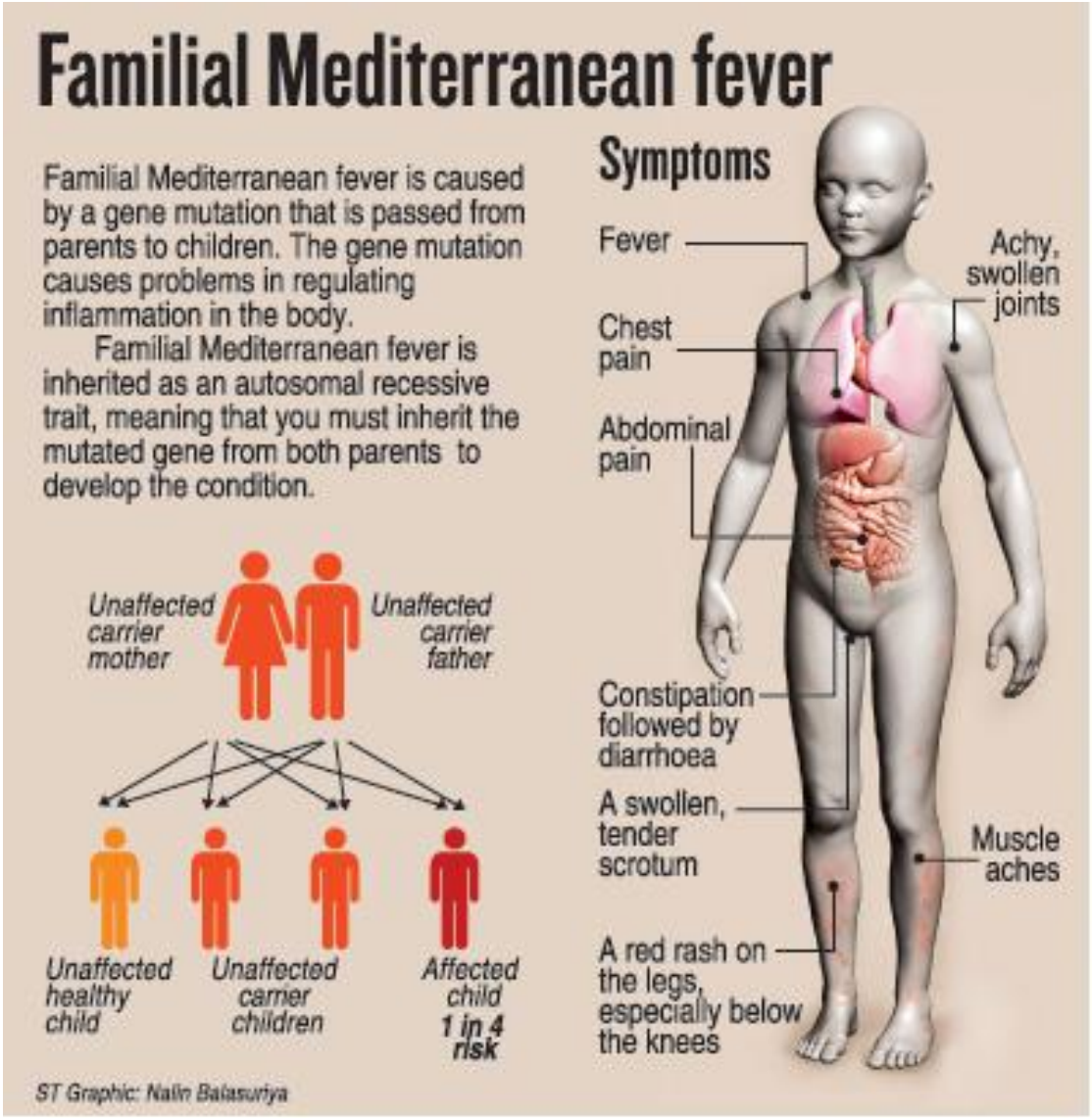
1. Human genetics: an application

- Article: Fukushima Y, Obara K, Hirata H, Sugiyama K, Fukuda T, Takabe K. **Three Japanese patients (mother and two children) with familial Mediterranean fever associated with compound heterozygosity for L110P/E148Q/M694I and an autosomal true dominant inheritance pattern.** Asian Pac J Allergy Immunol. 2013 Dec;31(4):325-9. doi: 10.12932/AP0244.31.4.2013. PubMed PMID: 24383976.

What is Familial Mediterranean Fever (FMF) like?

- Watch “Ariella's Story - Living with familial Mediterranean fever”
  - https://www.youtube.com/watch?v=KFeqZPPFqvg
- Read an article in the Sunday Times
  - http://www.sundaytimes.lk/150621/plus/little-miracle-154072.html

FMV: symptoms and typical inheritance



http://www.sundaytimes.lk/150621/plus/little-miracle-154072.html

Check List

- 1. What are the phenotypes?
  - What is the disease? What are the symptoms?
- 2. What is the hereditary pattern?
  - Autosomal (dominant/recessive)?
  - X-linked (dominant/recessive)?
- 3. What are the mutations?
  - What is the affected gene?
  - Mutation types and consequences
    - Summarize the types of mutations in general.
      - See http://evolution.berkeley.edu/evolibrary/article/mutations_03
      - and https://ghr.nlm.nih.gov/handbook/mutationsanddisorders/possiblemutations
    - Summarize the consequences of mutation in general.
      - See https://ghr.nlm.nih.gov/handbook/mutationsanddisorders/possiblemutations
    - What are the type and the consequences of the mutations for these patients?
  - Notation of Mutation
    - Which amino acid changed to what?
- 4. What are the treatments for the patients and the results?
  - What are the expected pharmacological effects of the treatments?

2. Introduction to human genetics

- Genetics: scientific study of inherited variation
- Human genetics: the scientific study of inherited human variation
- Understanding human genetic variation for:
  - Better understand ourselves as a species
    - Essentially we are the same: the differences lie among individuals, not among populations.
  - Use this knowledge to improve our health and well-being

Facts about human genome

- About 3 x 10^9 base pairs.
- Any two people have 6x 10^6 (0.1%) base pairs that are different.

What are genetic variations?

- Genetic variations are differences in genetic sequence.
- Variations can be seen at all these levels:
  - In the DNA
  - In the genes
  - In the chromosomes
  - In the proteins
  - In the function of proteins

Types of genetic variation

- Mutations – changes at the level of DNA
- Major deletions, insertions, and genetic rearrangements
- Polymorphisms – differences in individual DNA which are not mutations
  - Single-nucleotide polymorphisms (SNPs)
    - The most common (every 1000 bases or so)
  - Copy number variations
    - Some DNA repeats itself (i.e. AAGAAGAAGAAG) , and
    - There can be variation in the number of repeats.

Consequences of genetic variation

- “Meaningless”: most of the mutations.
- Positive
  - CCR5 mutations: resistance to HIV infection
  - Genetic mutations which cause the disease sickle cell anemia: individuals with sickle cell trait (i.e. carriers of the recessive gene) are less likely to die from the disease malaria
- Diseases
  - Single-gene disorders (e.g. cystic fibrosis and Huntington disease)
  - Preposition to diseases: most of the common diseases
    - Genetic and environmental factors

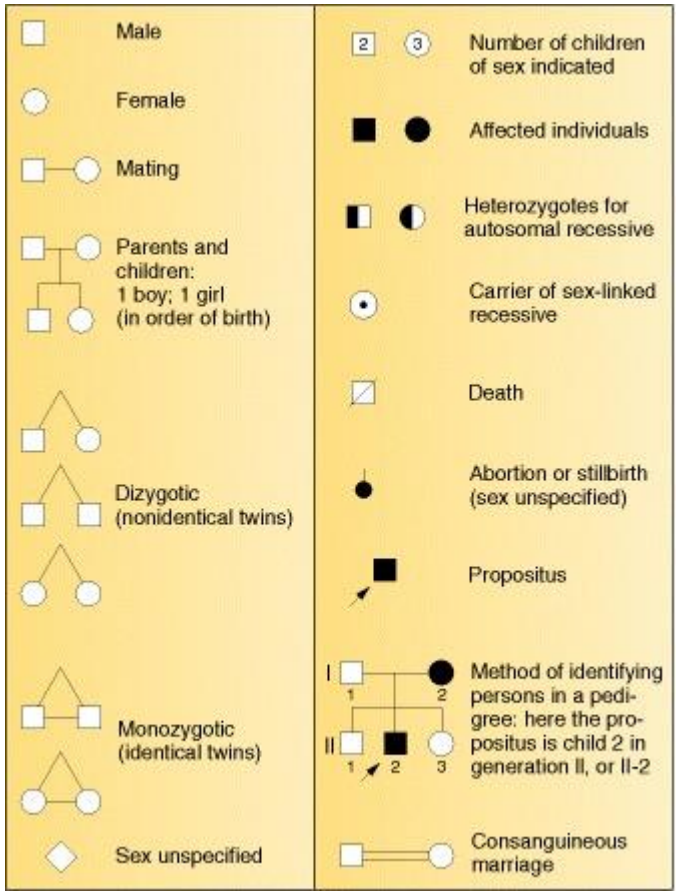
What can we do with genetic variation?

- Awareness of risks: leading to prevention
- Example: Phospholipase A2 (PLA-2) mutation and risk of coronary artery disease
  - This mutation is famous for the tragedy of Sergei Grinkov (1967-1995), Russian pair skater with Ekaterina Gordeeva.

Understanding human genetics

- Pedigree analysis
- Genetic tests

Pedigree analysis

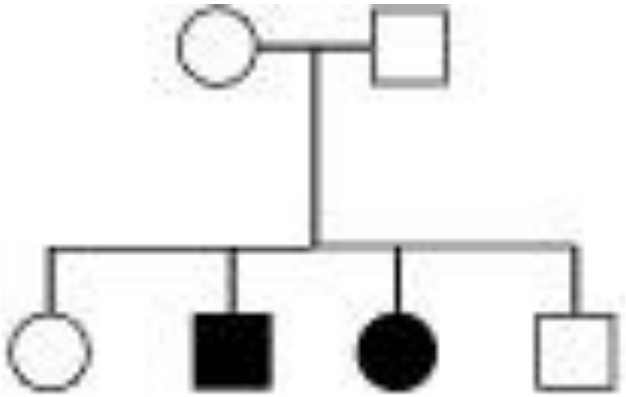


Symbols used in human pedigree analysis. (After W. F. Bodmer and L. L. Cavalli-Sforza, *Genetics, Evolution, and Man.* Copyright © 1976 by W. H. Freeman and Company.)

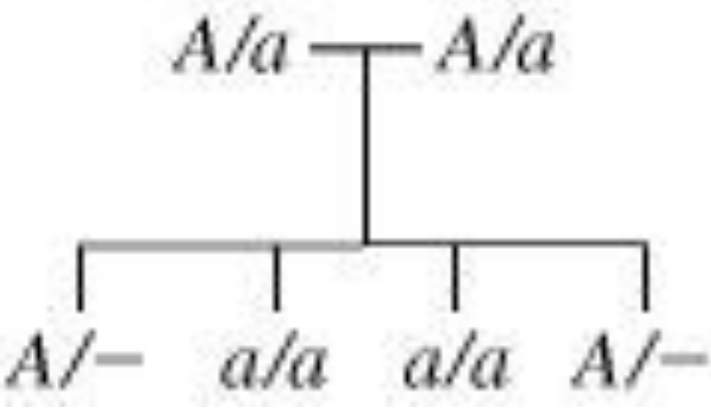
This and the following figures are from "An Introduction to Genetic Analysis. 7th edition."

https://www.ncbi.nlm.nih.gov/books/NBK21977/

Autosomal recessive

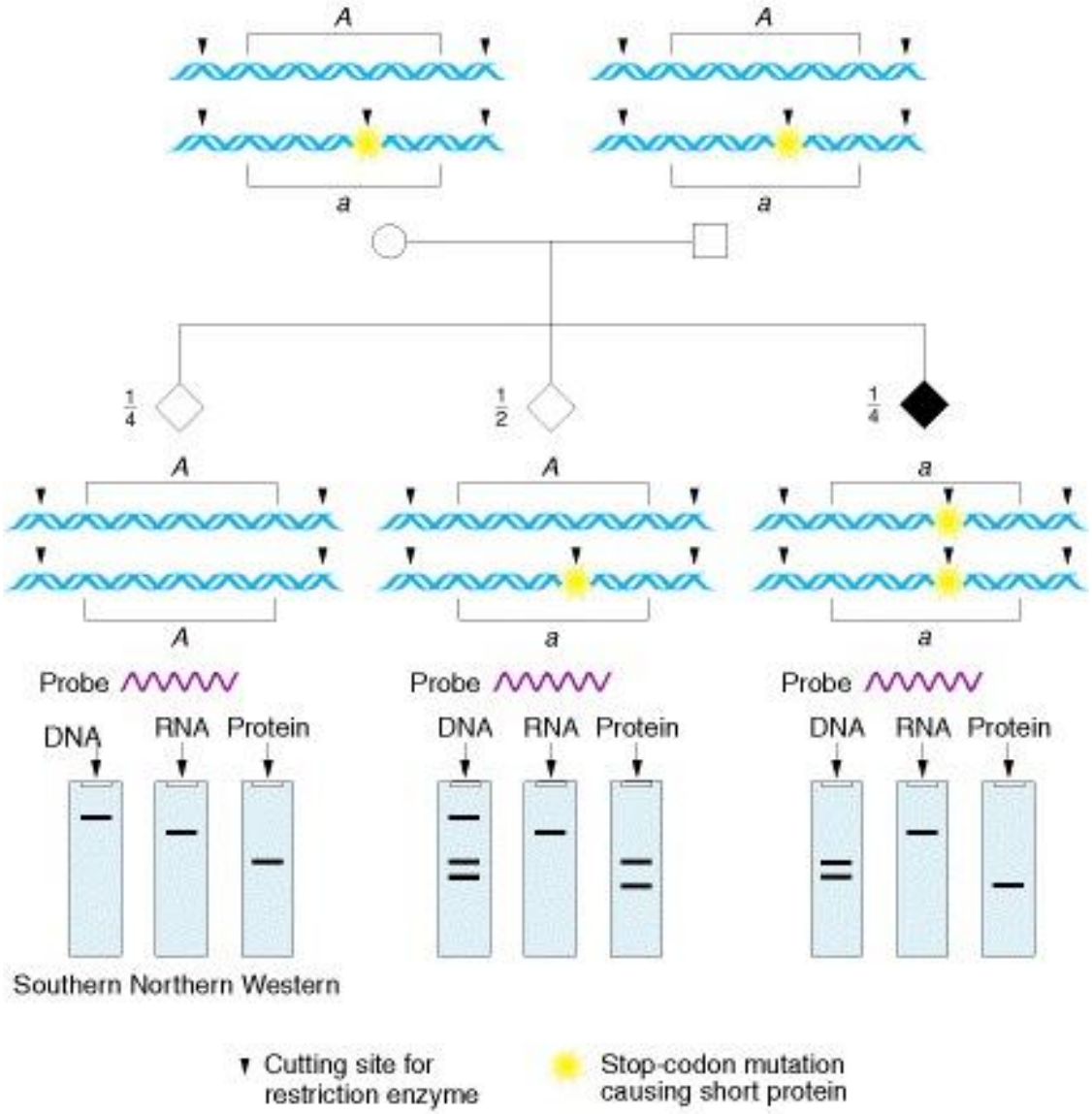


The phenotypes of a family



The genotypes of the family

Genetic tests



The molecular basis of Mendelian inheritance in a pedigree.

Reference

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  - https://www.genome.gov/Pages/Education/Modules/GeneticVariation.pdf
  - An educational material from National Human Genome Research Institute
    - Top page -> Education ->“Genetic Education Resources for Teachers”
- Human Genetics
  - https://www.ncbi.nlm.nih.gov/books/NBK21977/