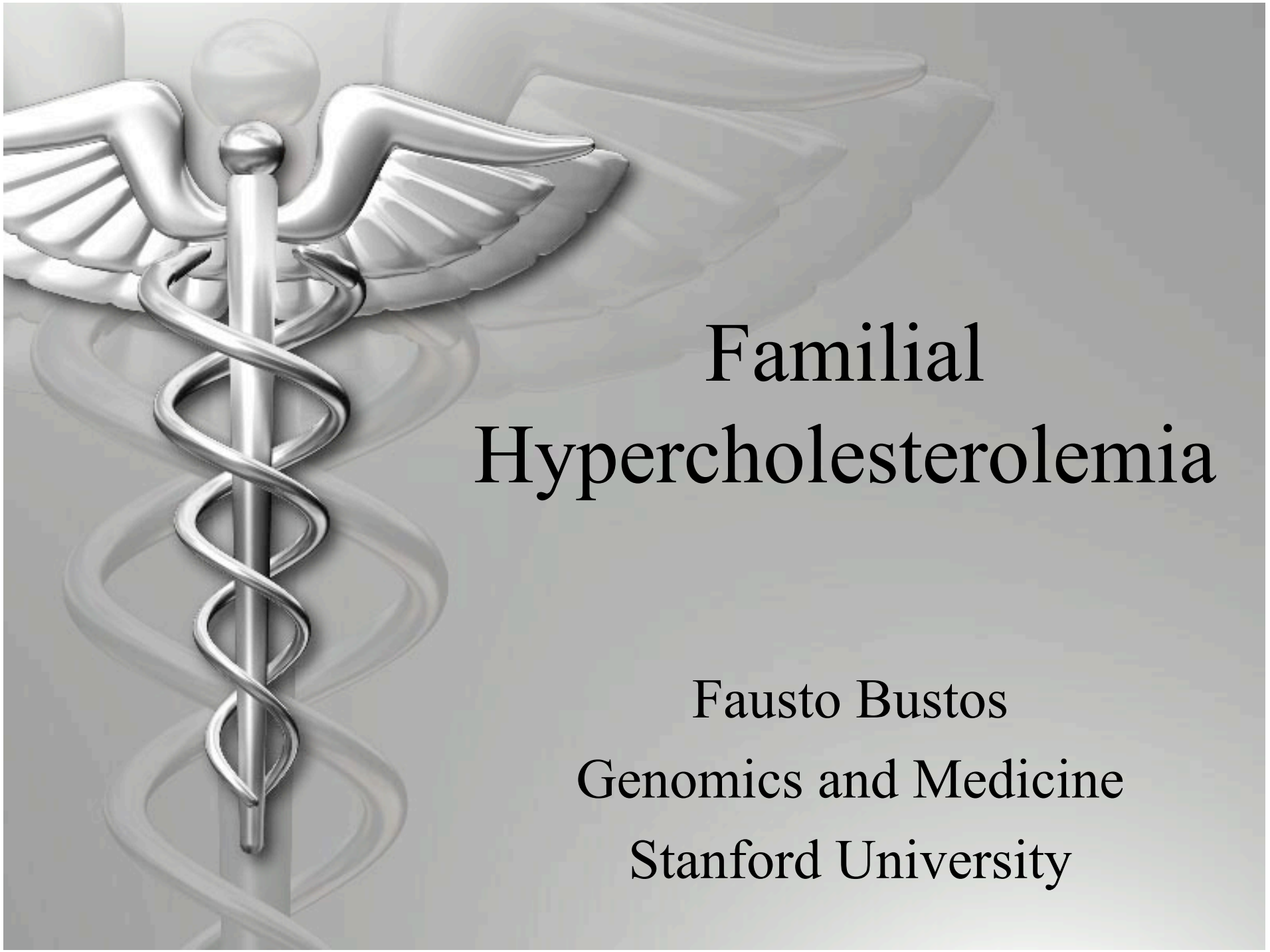

Familial Hypercholesterolemia

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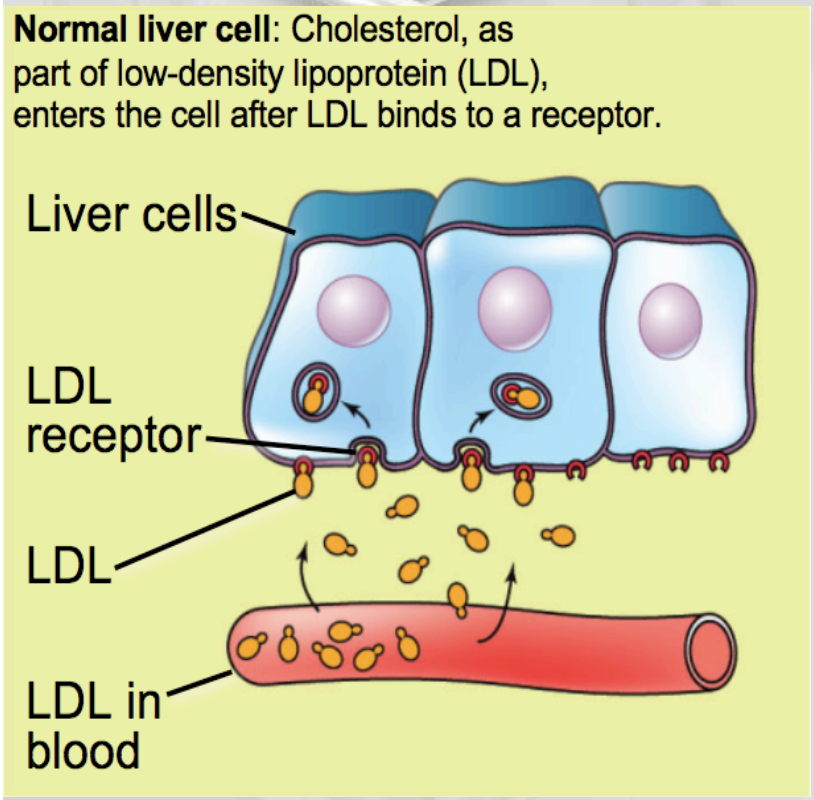
What is Familial Hypercholesterolemia (FH)?

- A common genetic disorder that can arise from 4 different mutations characterized by high cholesterol levels.
- The most common variant involves the Low-Density Lipoprotein (LDL) receptor gene on Chromosome 9. This form of FH is autosomal dominant, resulting in haploinsufficiency.
- Heterozygous FH is much more common than the homozygous condition, possibly because of premature fetus death, leading to a miscarriage.

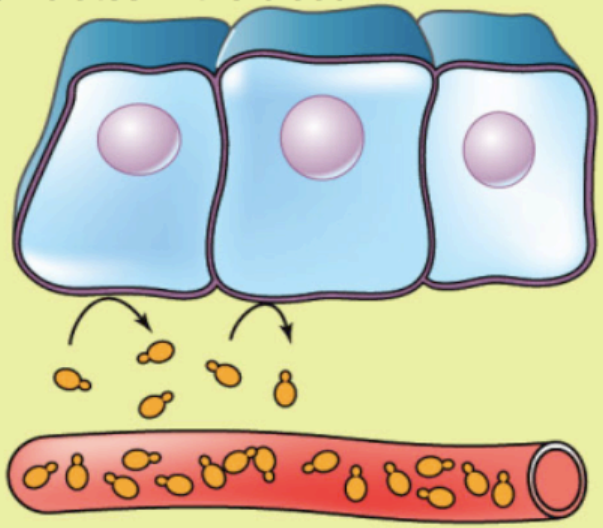
The Normal Phenotype

- Cholesterol travels through the body bound to lipoproteins.
- The low-density lipoproteins are taken up by the liver through endocytosis.
- Cholesterol is thus removed from the bloodstream and it made available for cellular processes.



The Abnormal Phenotype

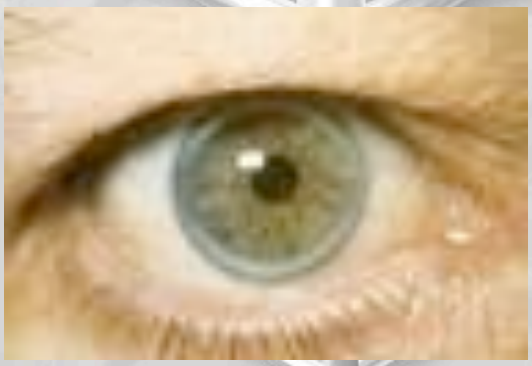
Familial hypercholesterolemia:
Absence of a functional LDL receptor prevents cholesterol from entering the cells, and it accumulates in the blood.



- The LRL receptors are either absent or non-functional, resulting in excess LDL, cholesterol-containing particles in the bloodstream.
- Excess LDL blocks blood flow and resulting in cholesterol deposits throughout the body (xanthomas), heart attacks, strokes, atherosclerosis, & premature cardiovascular disease.

The Classical Diagnosis

- Look for excessive cholesterol residue!



- Externally, look for xanthomas or early arcus (opaque ring near the iris)
- Cholesterol deposits in the aorta, as a sign of cardiovascular disease, can also lead to a diagnosis.
- Measure the lipids as part of a physical/ insurace health screening.
  - LDL levels are typically above the 95% percentile, leading to a diagnosis.

The Classical Treatment

- Liver Transplant
  - Effectively removes the condition, but getting a transplant is difficult and expensive.
- Heart Transplant
  - Useful for a heterozygote in mid-life and a homozygote in early childhood.
- LDL Apheresis (dialysis-like)
  - Removes LDL from the bloodstream, but this expensive treatment must be done every several weeks to prevent cardiovascular disease.
- Statin Therapy
  - These drugs inhibit an enzyme (HMG-CoA-reductase) in the liver, which causes the liver to produce more LDL receptors. This only works for heterozygotes.

Novel Genetic Diagnosis

- Genetic testing can be performed for LDL receptor mutations. If negative, the test can point to other diseases that increase LDL levels.
  - LDL polymorphisms can be found using restriction enzymes through restriction fragment length polymorphism (RFLP's).
- Universal screening has been proposed for this disease as it is relatively common.

Novel Understanding and Gene Therapy

- As the allele involved has pleiotropic effects, gene therapy for FH seeks to repair the hepatocytes.

- In 1994, a woman suffering from FH underwent gene therapy:
  - Herpatocytes were removed and reimplanted after a retrovirus-mediated gene transfer *ex vivo*, thereby restoring the liver cells to normal condition.

Acknowledgments

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