Introduction to FH & Brief History
• Amongst many other projects, Leonardo da Vinci (1452-1519) spent a portion of his time investigating atherosclerosis.

• His findings allowed him to conclude that the obstruction of vessels was not caused by a thickening of blood, but rather a change in structure of the blood vessels.

• Possibly the first historic evidence of Familial Hypercholesterolemia (1507).
• Examination of Leonardo da Vinci’s masterpiece shows xanthelasmas on her left upper eyelid.

• The Portrait of an Elderly Lady painted in 1633 by Frans Hals.
• Strongest evidence of Hypercholesterolemia.
• Tendinous Xanthomas on the left hand.
Dr. Carl Müller

- In the late 1930’s, a Norwegian Doctor by the name of Carl Müller described the clinical condition presently known as hypercholesterolemia.
- He described patients with tuberous xanthomas and angina.
- He studied 17 families in which 68 of 76 members showed signs of heart disease.
- He proposed that this disorder was hereditary with an autosomal dominant characteristic.
- Noted that these patients had Cholesterol levels between 4-15mmol/L


Dr. Khachadurian

• In the mid 1960’s Dr. Khachadurian analyzed several Lebanese families with hypercholesterolemia and categorized the results into 3 categories:
  • Homozygous Hypercholesterolemia
  • Heterozygous (Dominant) Hypercholesterolemia (ADH)
  • Heterozygous (Recessive) Hypercholesterolemia (ARH)

Fellin R et al. Gene. 2015
Akira Endo

• In 1971, Akira Endo started researching for a way to inhibit HMG-CoA reductase, the rate-limiting enzyme in the biosynthesis of cholesterol.

• He discovered active compounds in a strain of *Penicillium citrinum*.

• Mevastatin


https://en.wikipedia.org/wiki/Akira_Endo_(biochemist)
Brown & Goldstein

• Discovered that the cellular uptake of LDL requires the LDL-r receptors.

• If missing, the LDL levels in the plasma raise to 20-25mmol/L.

• Discovered that mutations in the LDL-r gene cause hypercholesterolemia

• These mutations have a dominant quality, which explains their hereditary characteristic

• Awarded the Nobel prize in Physiology and Medicine in 1985.


Dr. Scott Grundy and his student Gloria Vega discovered a second gene mutation that affects plasma cholesterol levels.

Apolipoprotein B found on the membrane of the LDL particle.
Mutations in PCSK9 cause autosomal dominant hypercholesterolemia

Marianne Abifadel1,2, Mathilde Varret1, Jean-Pierre Rabès1,3, Delphine Allard1, Khadija Ouguerram4, Martine Devillers1, Corinne Cruaud5, Suzanne Benjannet6, Louise Wickham6, Danièle Erlich1, Aurélie Derré1, Ludovic Villéger1, Michel Farnier7, Isabel Beucler8, Eric Bruckert9, Jean Chambaz10, Bernard Chanu11, Jean-Michel Lecerf12, Gerald Luc12, Philippe Moulin13, Jean Weissenbach5, Annick Prat6, Michel Krempf4, Claudine Junien1,3, Nabil G Seidah6 & Catherine Boileau1,3

Nature Genetics 34, 154 - 156 (2003)
LDL-R

- OMIM: #606945
- Low Density Lipoprotein Receptors
- >1800 mutations
- Mutations in this gene disrupt the receptor's ability to remove low-density lipoproteins from the blood.
- LDL-C particles accumulate in the blood and cause atherosclerosis.
**LDL-R GENE**

Familial defective ApoB-100

- OMIM: #107730
- Apolipoprotein B-100
- At least 4 mutations (near residue 3500)
- Mutations in the ApoB-100 gene change the shape and length of the ApoB found on the LDL particles.
- The ApoB becomes harder to recognize for the LDL-R of the peripheral cells.
- Causes an increase in plasma cholesterol.
Gain-of-function PCSK9

- OMIM: #607786
- Proprotein Convertase Subtilisin/Kexin type 9
- PCSK9 controls the number of LDL-R receptors on the cell membrane.
- A gain of function mutation will cause a decrease of LDL-R on the cell membrane resulting in more LDL left in the blood.
Familial Hypercholesterolemia (FH)

- Familial hypercholesterolemia (FH) is a genetic lipoprotein disorder characterized by elevated LDL-C levels, tendon xanthomas and a **10-20 fold increased risk of CHD**\(^1,2\). Early diagnosis and treatment can normalize life expectancy.

- At least 5 genes are known to cause an autosomal dominant FH phenotype: the **LDLR** and **APOB** account for the majority of cases; **PCSK9**, **APOE** and **STAP1** genes are rare.

- Several other genes, including LDL-R adaptor protein (**LDLRAP1**) and lysosomal acid lipase (**LIPA**) cause a recessive form of FH\(^3-8\).

---

Familial Hypercholesterolemia

FH is One of the Most Common of Inherited Diseases

- Heterozygous FH
- Dominant osteosclerosis
- Adult polycystic kidney disease
- Huntington’s disease
- Cystic fibrosis
- Marfan’s syndrome
- Duchenne muscular dystrophy
- Sickle cell anemia
- Phenylketonuria
- Haemophilia

Frequency per 1,000 births

Nordestgaard B G et al. Eur Heart J 2013;34:3478-3490
Clinical manifestations

Bilateral xanthelasma

Arcus Cornae

Xanthomas within the Achilles tendons

Xanthoma within extensor tendon of the hand

Prevalence of FH

- The prevalence for the rest of Canada was conservatively estimated at 1:500 until two recent publications reported a prevalence of FH of 1:217 and 1:250 in Denmark and USA respectively\(^1\)-\(^2\).

- Applied to Canada, a prevalence of 1:250 would give an estimate of FH subjects of **approximately 143,000**, and this estimate may be low as recent data from the UK also suggests that up to 20% of FH cases are due to the cumulative effect of mutations in genes affecting LDL-C\(^3\).

FH Registries

• There are well-developed FH Registries in:
  • Netherlands
  • United Kingdom
  • Spain
  • France
  • USA

• The aim of the FH Canada registry is to improve the detection and management of individuals and families with FH in Canada. Rare diseases of lipoprotein metabolism are also included (SMASH initiative)
Available treatments