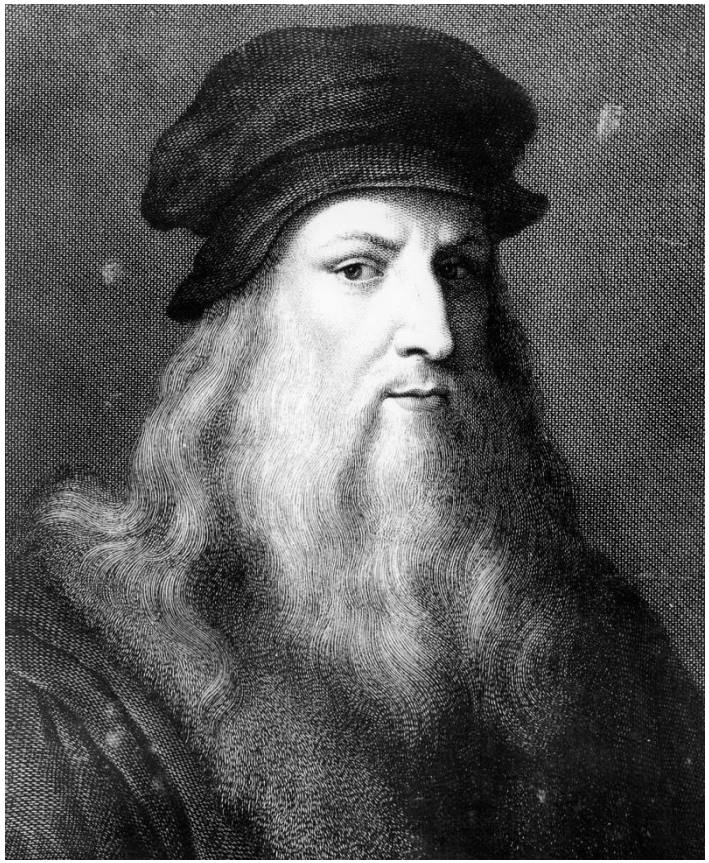
HF Canada
Hypercholestérolémie Familiale

FH Canada
Familial Hypercholesterolemia

Introduction to FH
&
Brief History

Leonardo da Vinci

- 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.



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Ose L. Curr Cardiol Rev. 2008.

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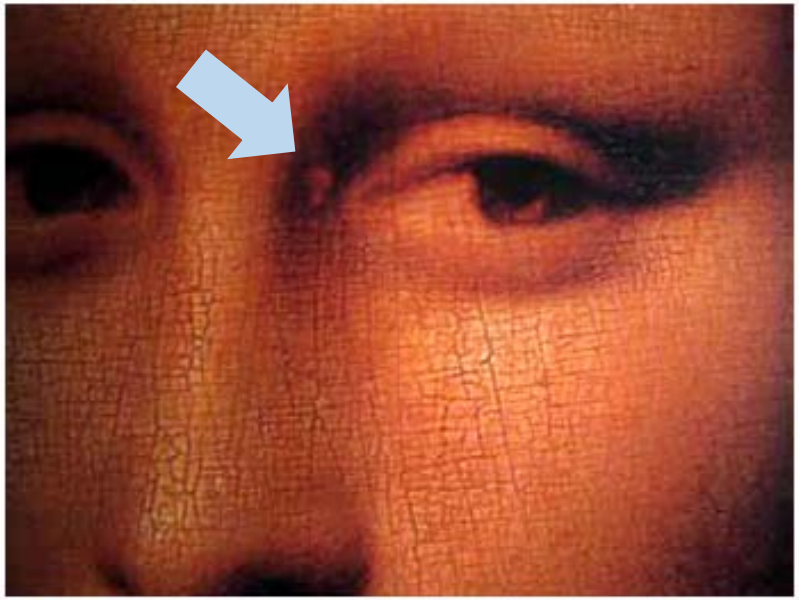
Mona Lisa

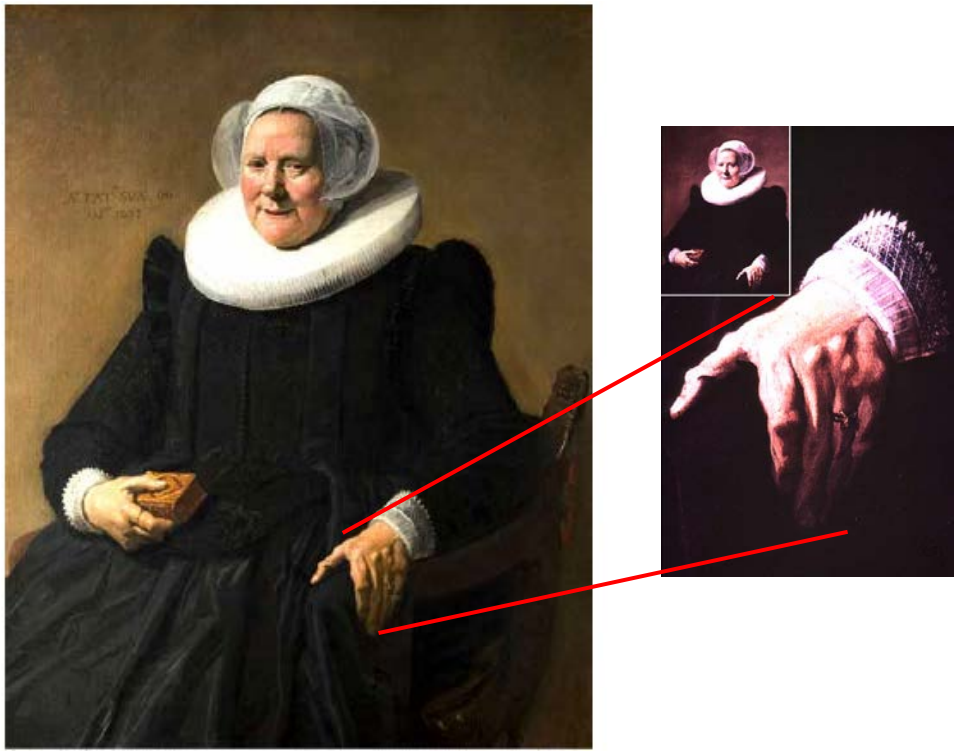
- Possibly the first historic evidence of Familial Hypercholesterolemia (1507).
- Examination of Leonardo da Vinci's masterpiece shows xanthelasmas on her left upper eyelid.



Ose L. Curr Cardiol Rev. 2008.

Portrait of an Elderly Lady

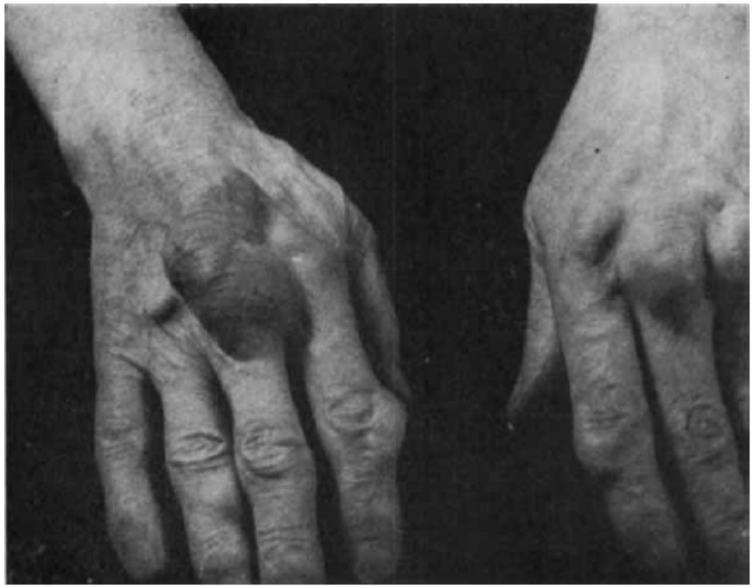
- *The Portrait of an Elderly Lady* painted in 1633 by Frans Hals.
- Strongest evidence of Hypercholesterolemia.
- Tendinous Xanthomas on the left hand.



Ose L. Curr Cardiol Rev. 2008.

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



Müller C. Angina pectoris in hereditary xanthomatosis. Arch Intern Med. 1939;64:675–700.

Ose L. Curr Cardiol Rev. 2008.

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 *Penicillum citrinum.*
- Mevastatin

https://en.wikipedia.org/wiki/Akira_Endo_(biochemist)#/media/File:Jp_endo.jpg

Ose L. Curr Cardiol Rev. 2008.

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.

Michael S. Brown

Joseph L. Goldstein

https://www.nobelprize.org/nobel_prizes/medicine/laureates/1985/

Ose L. Curr Cardiol Rev. 2008.

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Discovery of apoB

- 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.

Dr. Scott Grundy

PCSK9: A Canadian Discovery

Mutations in *PCSK9* cause autosomal dominant hypercholesterolemia

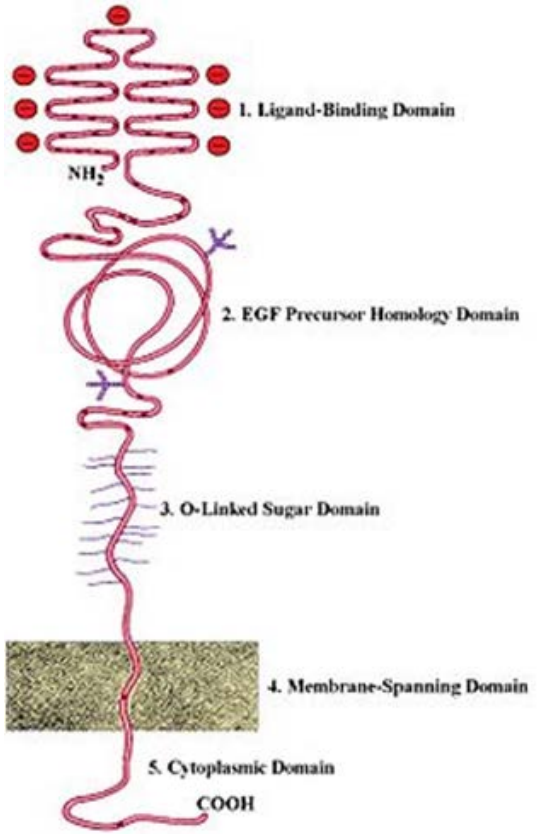
Marianne Abifadel[1,2], Mathilde Varret[1], Jean-Pierre Rabès[1,3], Delphine Allard[1], Khadija Ouguerram[4], Martine Devillers[1], Corinne Cruaud[5], Suzanne Benjannet[6], Louise Wickham[6], Danièle Erlich[1], Aurélie Derré[1], Ludovic Villéger[1], Michel Farnier[7], Isabel Beucler[8], Eric Bruckert[9], Jean Chambaz[10], Bernard Chanu[11], Jean-Michel Lecerf[12], Gerald Luc[12], Philippe Moulin[13], Jean Weissenbach[5], Annick Prat[6], Michel Krempf[4], Claudine Junien[1,3], Nabil G Seidah[6] & Catherine Boileau[1,3]

Nature Genetics **34**, 154 - 156 (2003)

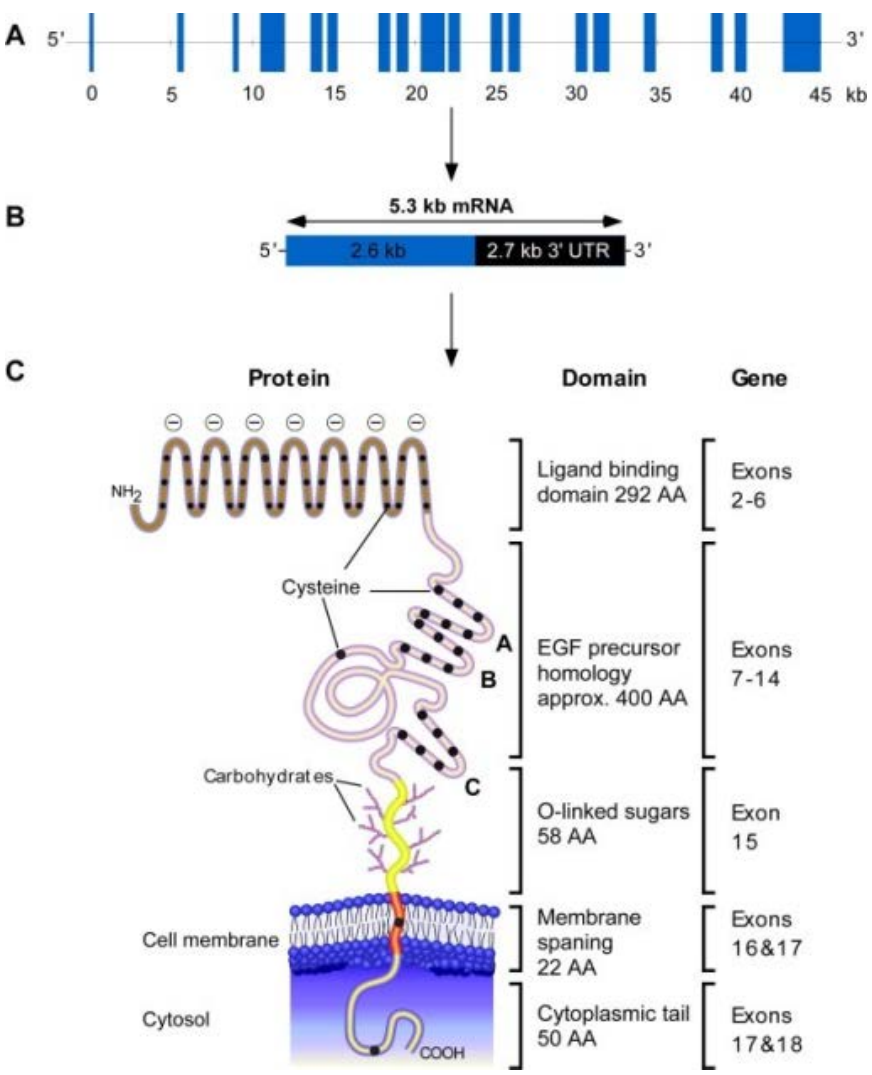
Dr. Nabil Seidah IRCM

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



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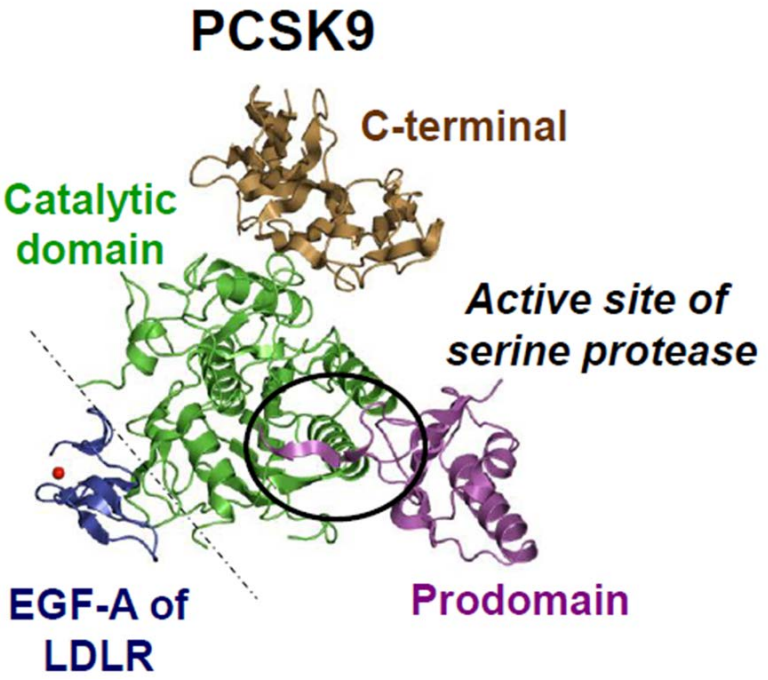
Familial defective ApoB-100

- 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
- PSCK9 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.



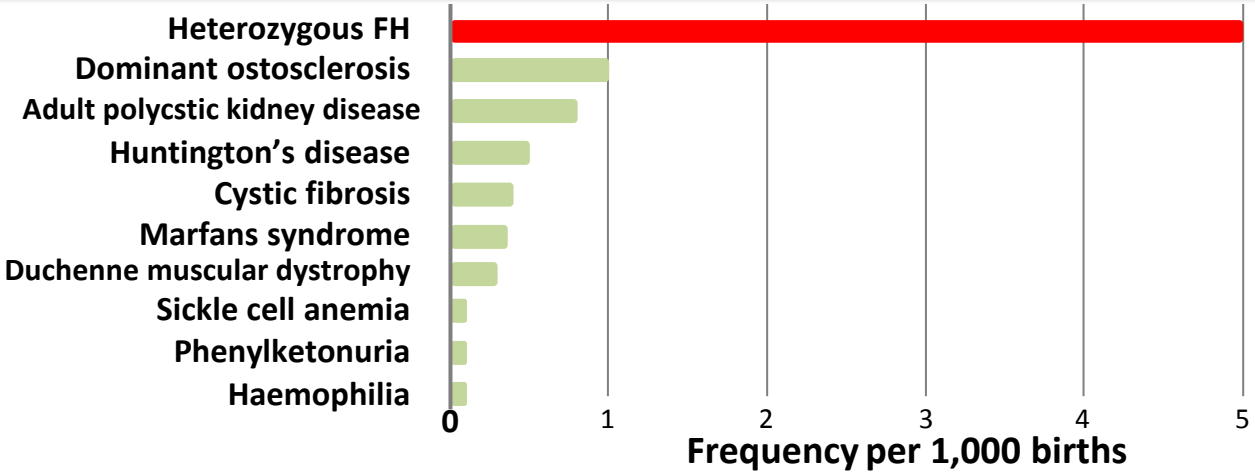
Familial Hypercholesterolemia (FH)

- 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].

1. Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: Consensus Statement of the European Atherosclerosis Society. Eur Heart J. 2013;34(45):3478-90.
2. Goldberg AC, Hopkins PN, Toth PP, et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011;5(3):133-140.
3. Awan Z, Alrasadi K, Francis GA, et al. Vascular calcifications in homozygote familial hypercholesterolemia. Arterioscler Thromb Vasc Biol 2008; 28(4): 777-85.
4. Alrasadi K, Alwaili K, Awan Z, et al. Aortic calcifications in familial hypercholesterolemia: potential role of the low-density lipoprotein receptor gene. Am Heart J 2009; 157(1): 170-6.
5. Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. Science 1986; 232(4746): 34-47.
6. Hobbs HH, Russell DW, Brown MS, Goldstein JL. The LDL receptor locus in familial hypercholesterolemia: mutational analysis of a membrane protein. Annual review of genetics 1990; 24: 133-70.
7. Humphries SE, Whittall RA, Hubbart CS, et al. Genetic causes of familial hypercholesterolaemia in patients in the UK: relation to plasma lipid levels and coronary heart disease risk. Journal of medical genetics 2006; 43(12): 943-9.
8. Tosi I, Toledo-Leiva P, Neuwirth C, et al. Genetic defects causing familial hypercholesterolaemia: identification of deletions and duplications in the LDL-receptor gene and summary of all mutations found in patients attending the Hammersmith Hospital Lipid Clinic. Atherosclerosis 2007; 194(1): 102-11.

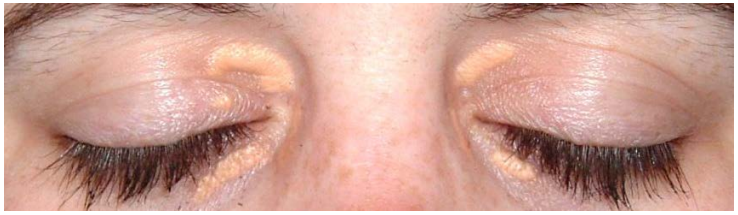
Familial Hypercholesterolemia

FH is One of the Most Common of Inherited Diseases

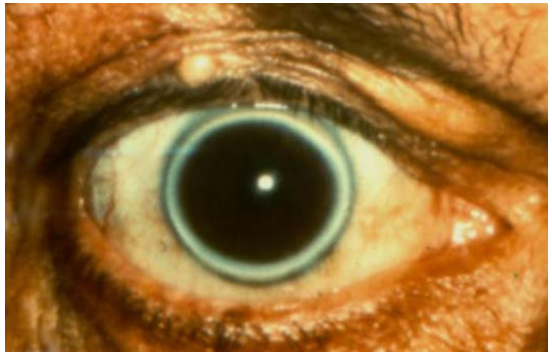


Nordestgaard B G et al. Eur Heart J 2013;34:3478-3490

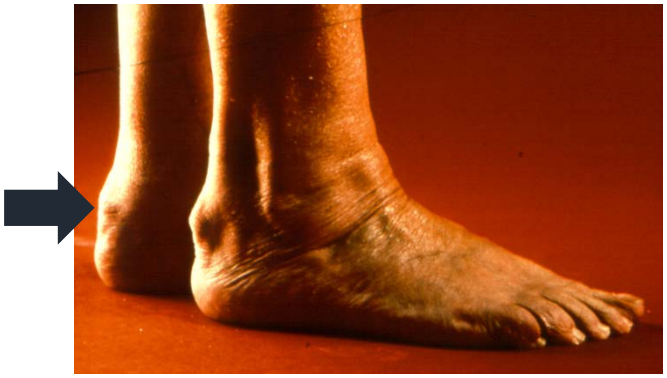
Clinical manifestations



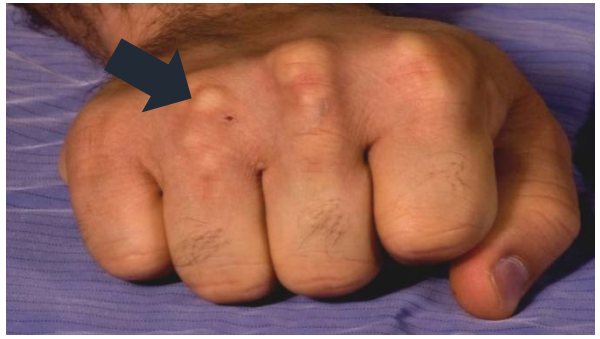
Bilateral xanthelasma



Arcus Cornae



Xanthomas within the Achilles tendons



Xanthoma within extensor tendon of the hand

Genest J, Hegele RA, Bergeron J, Brophy J, Carpentier A, Couture P, et al. Canadian Cardiovascular Society position statement on familial hypercholesterolemia. The Canadian journal of cardiology. 2014;30(12):1471-81.

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].

1. Benn M, Watts GF, Tybjærg-Hansen A, Nordestgaard BG. Mutations causative of familial hypercholesterolaemia: screening of 98 098 individuals from the Copenhagen General Population Study estimated a prevalence of 1 in 217. Eur Heart J. 2016;37:1384-94.
2. de Ferranti SD, Rodday AM, Mendelson MM, et al. Prevalence of Familial Hypercholesterolemia in the 1999 to 2012 United States National Health and Nutrition Examination Surveys (NHANES). Circulation. 2016 ;133:1067-72.
3. Talmud PJ, Shah S, Whittall R, et al. Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolaemia: a case-control study. Lancet 2013; 381(9874): 1293-301.

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