Improving management through genetic testing for Familial Hypercholesterolaemia (FH)

This e-learning programme has been developed with a panel of FH experts, approved by the International Atherosclerosis Society (IAS) and endorsed by the European Association of Preventive Cardiology (EAPC).

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EAPC
European Association of Preventive Cardiology
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Improving management through genetic testing for Familial Hypercholesterolaemia (FH)

General Introduction

On completion of this e-learning you will have an understanding of:

- Key aspects of genetic testing in Familial Hypercholesterolaemia (FH)
- How and why to test
- How to interpret results
- How to treat patients with FH
- How to use cascade screening to identify related individuals at risk.

At the end of this e-learning you will be able to take an assessment quiz in order to test how much you have learnt and earn your EBAC CME credit or 1 ECMEC®.

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Expert Panel

Name: Alain Carrié, MD, PhD

Position: Professor of Biochemistry and Molecular Biology at the Pierre and Marie Curie School of Medicine, coordinator of the Center of Molecular Genetics at University Hospital Pitié Salpêtrière, Paris, France

Institution: University Hospital Pitié Salpêtrière, Paris, France

Relevant experience:

Medical Doctor specialising in molecular genetics recruited to Pitié Salpêtrière Hospital in 2001. Since then, he has implemented the genetic testing of Familial Hypercholesterolemia (FH).

Member of the ClinGen FH Expert Panel dedicated to the annotation of the potential pathogenicity of molecular variants associated with FH.

Scheme organiser of the FH External Quality Assessment provided by the European Molecular Genetics Quality Network.

EBAC Disclosure of Interests Score: 2

For more information on the EBAC score please go to http://www.ebac-cme.org/

Expert Panel

Name: Eric Bruckert, MD

Position: Director of the Endocrinology and Prevention of Cardiovascular Disease Department

Institution: University Hospital Pitié Salpêtrière, Paris, France

Relevant experience:

Medical Doctor and University Professor

Past President of the French Society of Atherosclerosis

Member and/or co-chair of EAS consensus statement on heterozygous Familial Hypercholesterolemia (2012), homozygous hypercholesterolemia (2015) statin intolerance (2014) Familial Hypercholesterolemia in children (2015) and Fasting / non-fasting blood samples (2016).

EBAC Disclosure of Interests Score: 3

For more information on the EBAC score please go to http://www.ebac-cme.org/

Expert Panel

Name: Christine Eng, MD

Position: Professor of Department of Molecular and Human Genetics at Baylor College of Medicine and Chief Medical Officer and Chief Quality Officer of Baylor Miraca Genetics Laboratories

Institution: Baylor College of Medicine

Relevant Experience:

A paediatrician and medical geneticist, Dr Eng joined Baylor in 2000. She has been recognized for contributions to the implementation of genomics in clinical practice.

Senior author of articles in the NEJM and JAMA regarding exome sequencing and is principal investigator of the Genomic Sequencing Core for the NIH Undiagnosed Diseases Network.

Received a BA from Yale University and an MD from Tulane University School of Medicine.

EBAC Disclosure of Interests Score: 2

For more information on the EBAC score please go to http://www.ebac-cme.org/

Expert Panel

Name: Christie M. Ballantyne, MD

Position: Professor, Department of Medicine; Chief, Section of Cardiology; Chief, Section of Cardiovascular Research; Baylor College of Medicine
Director, Center for Cardiovascular Disease Prevention; Houston Methodist Hospital DeBakey Heart & Vascular Center

Institution: Baylor College of Medicine

Relevant experience:

An expert in the area of cholesterol, statins and heart disease prevention. His research interest in the prevention of heart disease has led him to become an established investigator for the American Heart Association. Additionally, he has several National Institute of Health (NIH) grants to study leukocyte-endothelial adhesion molecules and novel markers for atherosclerosis.

Previous accomplishments include honoured as Fellow of the American Association for the Advancement of Science, the American College of Cardiology and the American College of Physicians.

In 2014, Thomson Reuters recognised Christie as one of *"The World's Most Influential Scientific Minds".*

Over 600 publications in the area of atherosclerosis, lipids and inflammation. Christie also serves as an Editorial Director for www.lipidsonline.org as well as Associate Editor for *Circulation* and *The Journal of Cardiovascular Risk*.

EBAC Disclosure of Interests Score: 4

For more information on the EBAC score please go to http://www.ebac-cme.org/

Genetic origins of FH

Introduction

The following section includes key background information on Familial Hypercholesterolaemia (FH), including epidemiology, impact, pathophysiology and current rates of diagnosis

By the end of this section you should:

- Know the prevalence and impact of FH
- Understand how FH impacts on long-term cardiovascular (CV) outcomes
- Appreciate the role of LDL-R, PCSK9 and ApoB in lipid metabolism and FH pathophysiology

FH is common and shortens lives due to lifelong elevation of LDL-C

- FH is a common genetic cause of premature coronary heart disease.[1] It causes lifelong elevation of plasma low-density lipoprotein cholesterol (LDL-C) levels
- FH can be[2–4]:
  - homozygous (**hoFH**) – 1 in 300,000–1,000,000 births
  - or heterozygous (**heFH**) – 1 in 200–500 births
- Patients with **hoFH** usually live for less than 20 years if left untreated[4]
- Increased intima media thickness has been shown to be associated with ageing and elevated CV risk. **heFH** patients aged 40 years have the same intima media thickness as 80 year-old control patients[4]

This training will focus on **heFH** unless otherwise stated

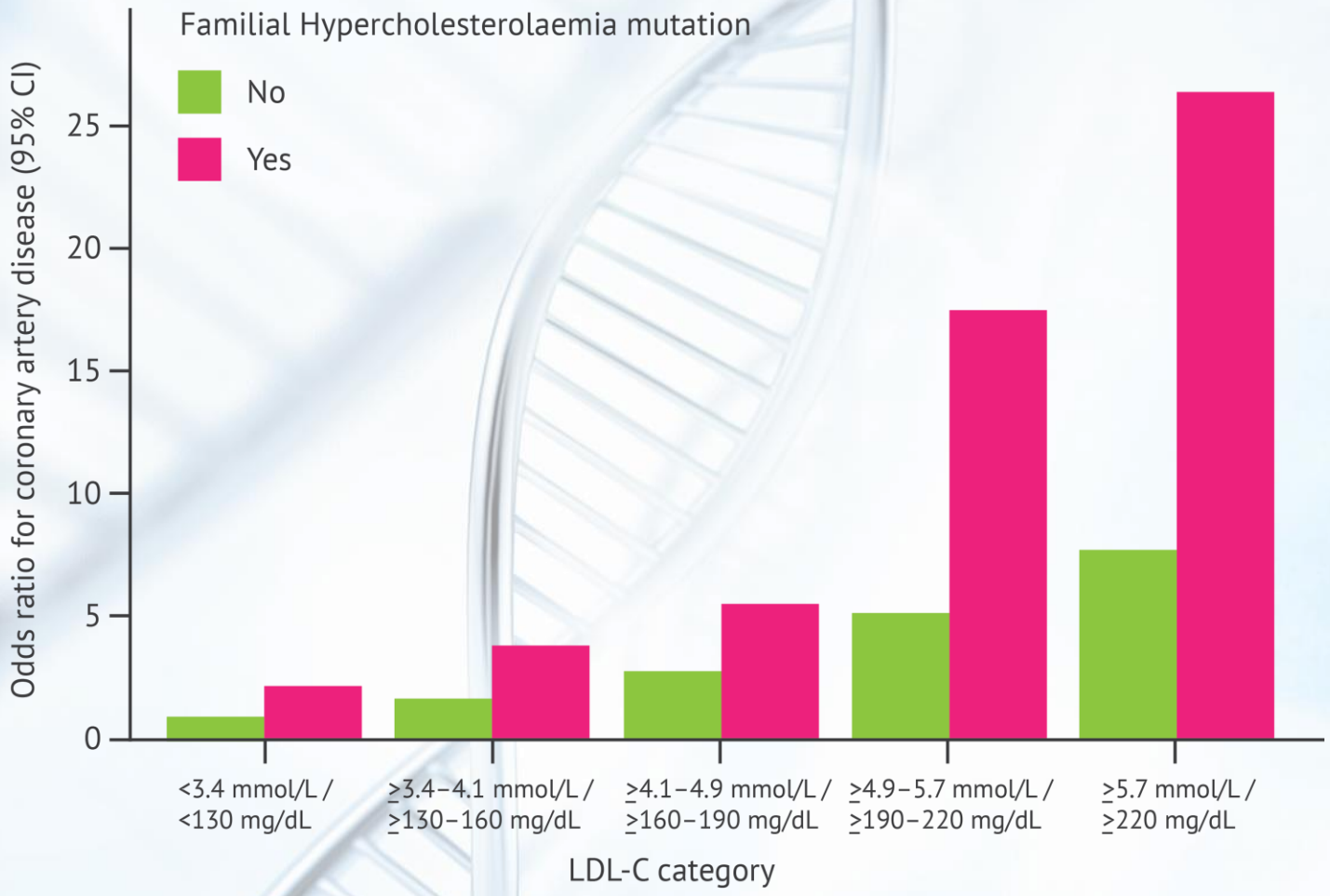
1. Wiegman A, et al. *Eur Heart J* 2015; 36: 2425–37. 2. Khera AV, et al. *J Am Coll Cardiol* 2016; 67: 2578–89. 3. Wald DS, et al. *NEJM* 2016; DOI: 10.1056/NEJMoa1602777. 4. Nordestgaard BG, et al. *Eur Heart J* 2013; doi: 10.1093/eurheartj/eht273.

FH is one of a number of disorders associated with hypercholesterolaemia

	Polygenic hypercholesterolaemia	HeFH	HoFH
CV risk	1 mmol/L (38 mg/dL) increase in LDL-C is associated with a 22% increase in risk for CV mortality	Increased x13	Death before 20 years
Frequency	Very frequent	1/200–500	1/300,000–1 million
Usual range of LDL-C levels	2.5–4.9 mmol/L (100–190 mg/dL)	4.9–6.4 mmol/L (190–250 mg/dL)	>12.9 mmol/L (>500 mg/dL)
Genetics	Approx. 30 factors	LDL-R/APOB/PCSK9	LDL-R/APOB/PCSK9

1. ATP III Final Report. *Circulation* 2002; 106: 3329–45. 2. Ference BA, et al. *JACC* 2012; 60: 2631–9. 3. Khera AV, et al. *J Am Coll Cardiol* 2016; 67: 2578–89. 3 Wald DS, et al. *NEJM* 2016; DOI: 10.1056/NEJMoa1602777. 4.Nordestgaard BG, et al. *Eur Heart J* 2013; doi: 10.1093/eurheartj/eht273.

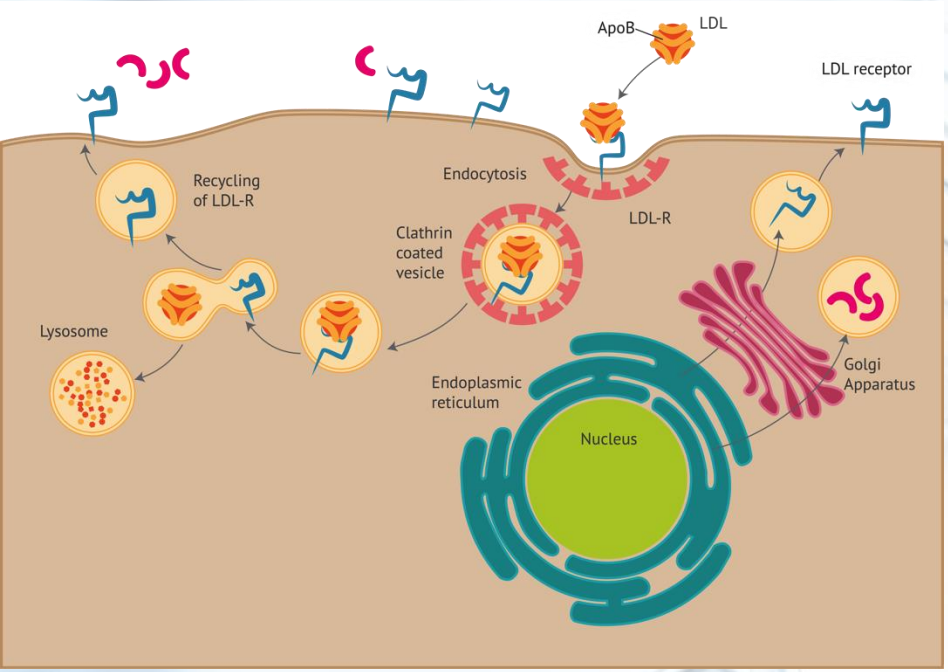
The risk of CAD is markedly higher in patients with FH mutations



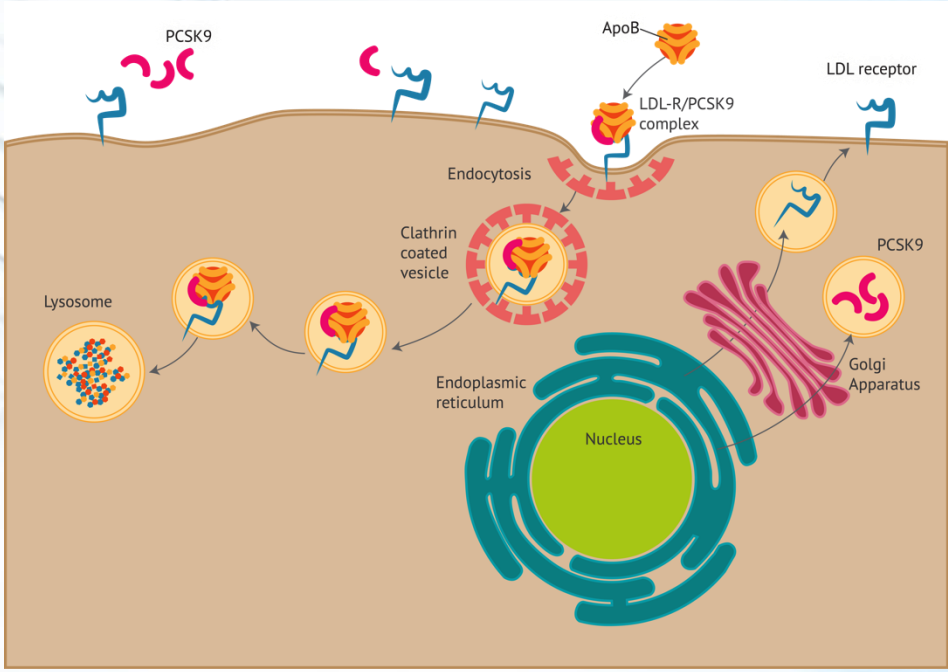
Khera AV, et al. *J Am Coll Cardiol* 2016; 67: 2578–89.

LDL-R, PCSK9 and ApoB play key roles in LDL metabolism

LDL metabolism with no PCSK9



LDL metabolism in the presence of PCSK9



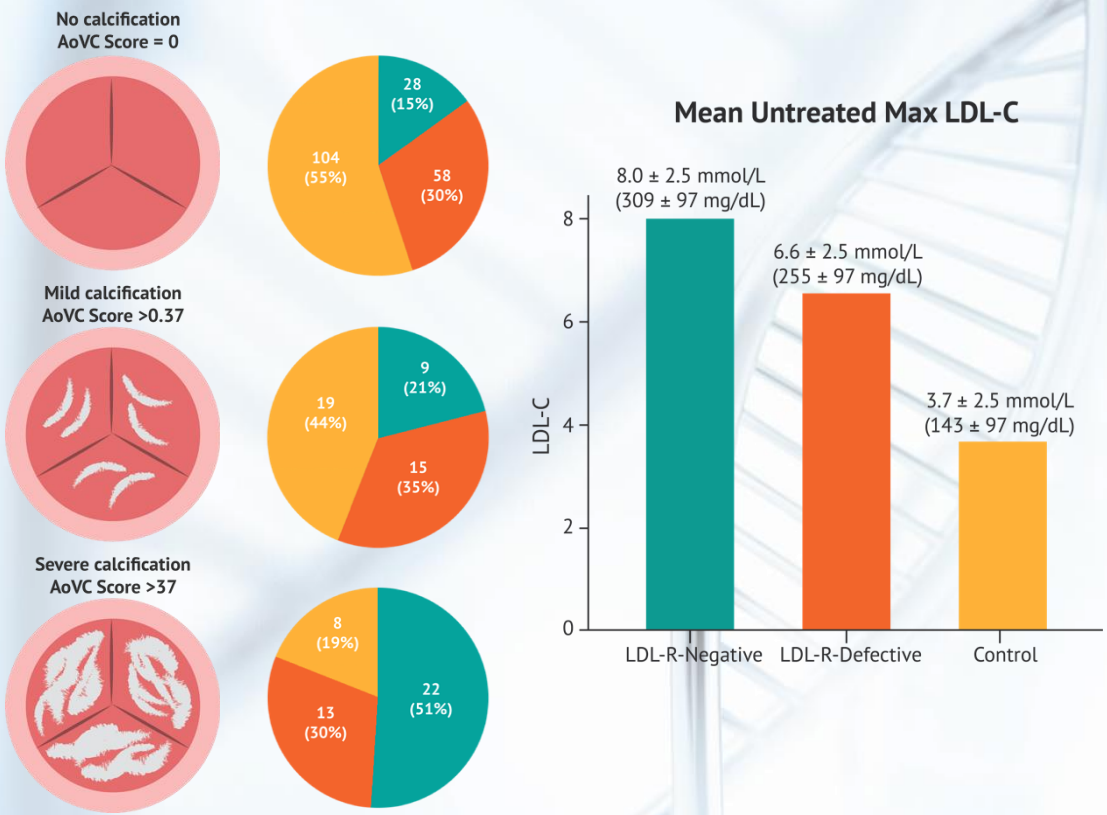
FH has a broad impact on lipid metabolism

FH has a broad impact on lipid metabolism:

- ↓↓LDL uptake and catabolism (the primary defect)
- ↑↑Cholesterol synthesis within cells (compensating for decreased cellular uptake), mediated via the up-regulation of HMG-CoA reductase pathway
- ↑ in Lp(a) levels of unknown mechanism

FH also impacts aortic valve calcification

Severity of AoVC in patients with he-FH and control subjects, and their unrelated LDL-C levels



Calcification is present in 41% of FH patients versus 21% of control patients

Note: the link between FH and aortic valve calcification is still being elucidated

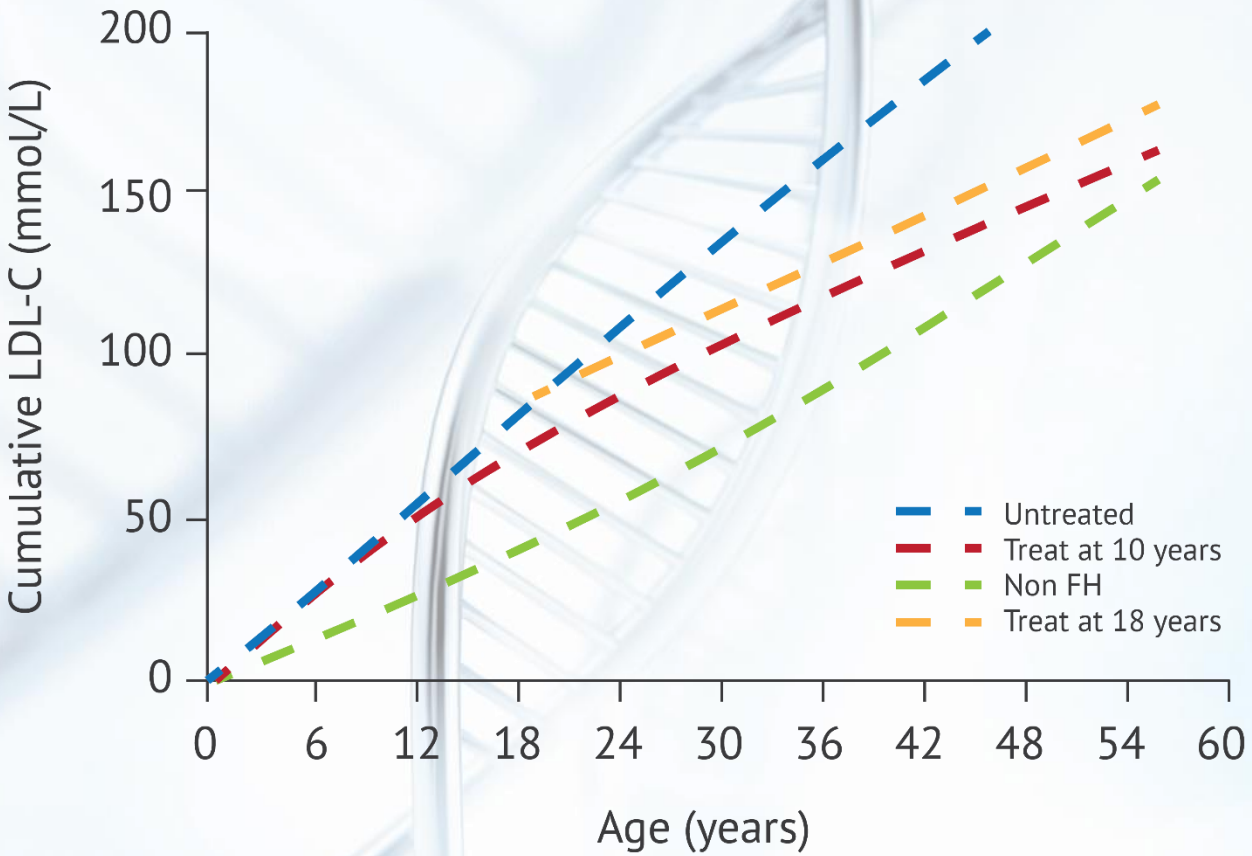
ten Kate G-JR, et al. *JACC* 2015; 66: 2687–95.

Identifying FH patients has many benefits

- The FH population is at high CVD risk – once identified they can be managed with appropriate LDL-C treatment targets
- Diagnosis of FH is the basis for cascade screening, which can identify previously undiagnosed FH patients
- Identification through screening allows FH treatment to start as early as possible (over 8 years of age)
- Diagnosis of FH gives the opportunity for improved medical care and compliance
- Diagnosis of FH may be useful for reimbursement in some countries and might be an indication for future therapeutic options

1. Nordestgaard BG, et al. *Eur Heart J* 2013; doi: 10.1093/eurheartj/eht273.
2. Goldberg AC, et al. *J Clin Lipidol* 2011; 5: S1–S8.

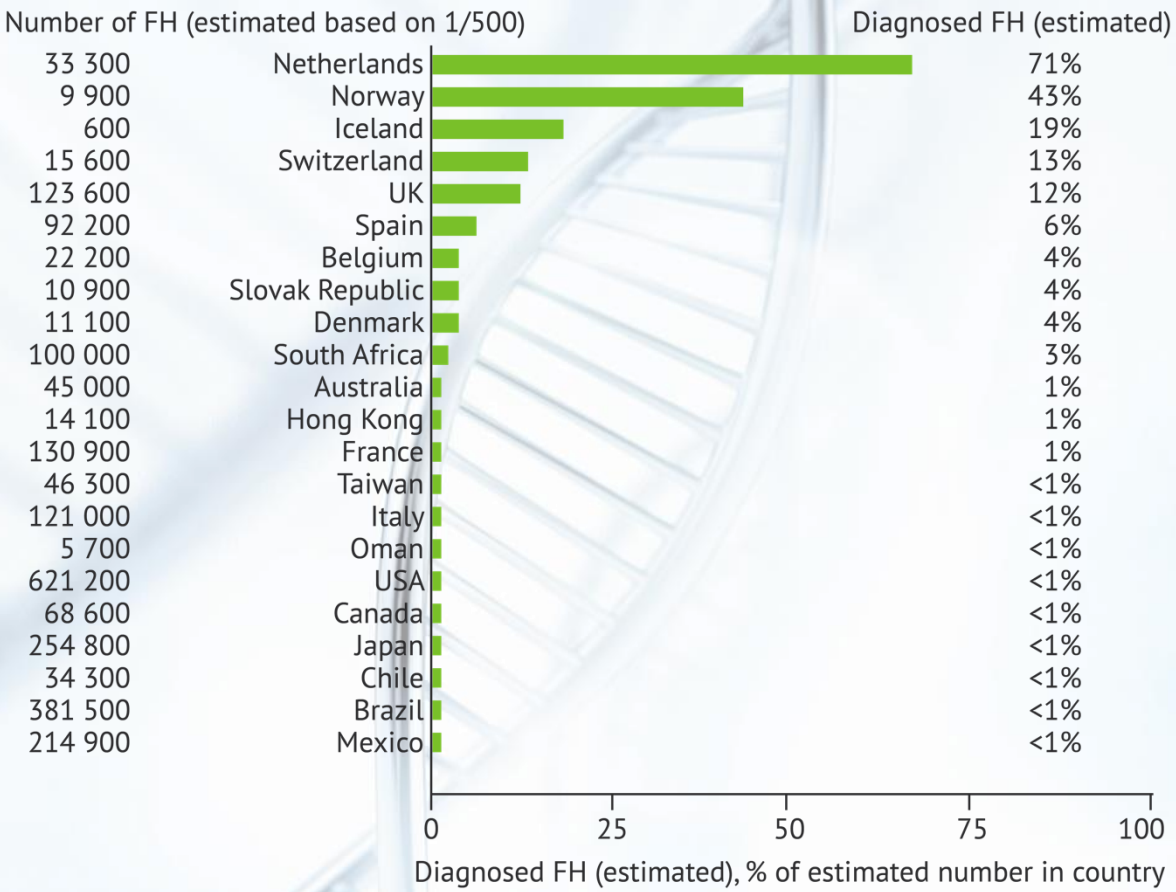
Early identification and treatment leads to improved outcomes in FH



- Every 1 mmol/L reduction in LDL-C is associated with a 22% reduction in CV mortality and 12% reduction in total mortality over 5 years

1. Wiegman A, et al. *Eur Heart J* 2015; 36: 2425–37.
2. Nordestgaard BG, et al. *Eur Heart J* 2013; 34: 3478–90.

Estimated real-world diagnostic rates for FH do not reflect prevalence



As most countries do not have valid nationwide registries for FH, several values in this figure represent informed estimates from clinicians/scientists with recognized expertise in and knowledge of FH in their respective countries

Nordestgaard BG, et al. *Eur Heart J* 2013; 34: 3478–90.

Summary

- heFH affects ~1 in 200–500 births
- FH patients are at markedly higher risk of CVD than non-FH patients with the same levels of LDL-C
- LDL-R, PCSK9 and ApoB are critical elements in lipid metabolism
- Early diagnosis and screening are key for improving outcomes in FH patients
- Currently, rates of diagnosis of FH are very low in most parts of the world

Clinical presentation of FH

Introducing the patient case studies

Introduction

The following section will focus on FH diagnosis, supported by patient case studies based on common patient types in FH

By the end of this section you should:

- Be able to list the key clinical diagnostic signs and symptoms for FH
- Understand how to use the DLCN diagnostic criteria for FH
- Recognise common patient types with elevated LDL-C

Key non-genetic diagnostic parameters in FH

Physical examination	• Tendon xanthomas • Arcus cornealis (if <45 years old) • Nodular xanthomas • Palpebral xanthelasmas • Personal history of CVD
Family history	• Close family members with history of: – Elevated LDL-C (above 95th percentile for age) – Early MI – Early cardiac death – Tendon xanthomas or arcus cornealis
Biological criteria	• Elevated LDL-C (>4.0 mmol/L [>155 mg/dL])

Nordestgaard BG, et al. *Eur Heart J* 2013; 34: 3478–90.

FH diagnosis: DLCN diagnostic criteria

	Score
Family history	
I. First-degree with premature coronary or vascular disease	1
II. First-degree relative with LDL-C levels >95th percentile	1
III. First-degree relative with tendon xanthomas and/or arcus cornealis	2
IV. Children <18 years old with LDL-C levels >95th percentile	2
Clinical history	
I. Premature (<55 years for men, <60 years for women) coronary heart disease	2
II. Premature (<55 years for men, <60 years for women) cerebrovascular or peripheral vascular disease	1
Physical examination	
I. Tendon xanthomas	6
II. Arcus cornealis (<45 years old)	4
Biochemical results (LDL cholesterol)	
8.5 mmol/l (>325 mg/dL)	8
6.5–8.4 mmol/l (251–325 mg/dL)	5
5.0–6.4 mmol/l (191–250 mg/dL)	3
4.0–4.9 mmol/l (155–190 mg/dL)	1
DNA analysis	
Causative mutation shown in LDL-R, APOB or PCSK9 genes	8

Diagnostic total score:

- Definite FH: >8
- Probable FH : 6–8
- Possible FH: 3–5
- Unlikely FH: 0–2

For example: xanthomas with LDL-C 5 mmol/l (191 mg/dl), give a score of 9 (i.e. a certain diagnosis of HeFH)

Genetic testing is recommended for all individuals with a score >5

DLCN: Dutch Lipid Clinic Network

Nordestgaard BG, et al. *Eur Heart J* 2013; 34: 3478–90.

The DLCN diagnostic criteria have limitations

- Patients with young parents may not have a clear family history of CVD
- Patients receiving statins for hypercholesterolaemia prior to FH diagnosis may not present with a personal history of CVD
- Tendon xanthoma and arcus cornealis are infrequently seen in younger patients
- Threshold LDL-C levels can change with age, and are not known for statin-treated patients

AHA recommendation for simplified FH diagnostic criteria

FH Category	Clinical criteria	With genetic testing performed
Heterozygous FH	• LDL-C ⩾4 mmol/L (⩾160 mg/dL) for children and ⩾5 mmol/L (⩾190 mg/dL) for adults and with one first-degree relative similarly affected or with premature CAD or with positive genetic testing for an LDL-C–raising gene defect (LDL-R, APOB, or PCSK9)	• Presence of one abnormal LDL-C–raising (LDL-R, APOB or PCSK9) gene defect • Diagnosed as heterozygous FH if LDL-C–raising defect positive and LDL-C <4 mmol/L (<160 mg/dL) • Occasionally, heterozygotes will have LDL-C >10 mmol/L (>400 mg/dL); they should be treated similarly to homozygotes • Presence of both abnormal LDL-C–raising (LDL-R, APOB or PCSK9) gene defect(s) and LDL-C–lowering gene variant(s) with LDL-C <4 mmol/L (<160 mg/dL)
Family history of FH	• LDL-C level not a criterion; presence of a first-degree relative with confirmed FH	• Genetic testing not performed

Gidding SS, et al. *Circulation* 2015; 132: 2167–92.

Case studies

The following case studies will take you through some of the most frequently encountered scenarios in FH management; giving you insights into how patients present, how to pursue diagnosis, and how to put an effective treatment plan in place

Case one: Anna

Case two: Brian

Case three: Diana

Case study: Anna

Case study: Anna

- Anna, a non-smoker aged 25 presented with a sore ankle following a fall playing tennis
- On physical examination of her achilles tendon she was found to have tendon xanthoma
  - Note: Tendon xanthoma may also be confirmed with palpation of extensor tendons in the hands and knees
- Anna was questioned about her family history of CHD, and revealed a grandfather who died aged 50 from 'heart problems'
- While Anna had numerous close relatives, she was unclear on their cholesterol status
- Anna's lab test showed an LDL-C level of 6.4 mmol/L (250 mg/dL)
- Based on her phenotype, Anna's physician diagnosed FH

Case study: Anna

- Before starting treatment, Anna's physician explained the consequences of an FH diagnosis and the benefits of maintaining a healthy lifestyle
- As Anna is considering having children, her physician discussed the need to avoid pregnancy while taking statins and the benefits of genetic testing for any potential father
- Having agreed to the use of depot contraception, Anna started treatment with a high dose statin and ezetimibe

Case study: Brian

Case study: Brian

- Brian, aged 43 years, was hospitalised with chest pain and diagnosed with a small MI
- Tests revealed elevated blood pressure and an LDL-C of 5.5 mmol/L (213 mg/dL)
- A physical examination revealed no anomalies
- On discussion of his family history, Brian was not aware of any history of premature death or CVD, however his father died aged 40 in a car accident. His mother is still living and healthy
- Brian has three teenage children, none of whom show overt signs of elevated cholesterol levels
- Brian was started immediately on a high dose statin

Case study: Diana

Case study: Diana

- Diana, aged 50 presented to her family physician for a regular health check
- Following the menopause, Diana had gained weight and now had a BMI of 35. Her blood test results showed an LDL-C of 5.0 mmol/L (191 mg/dL)
- At her previous health check, aged 45, her LDL-C had been 3.6 mmol/L (140 mg/dL)
- Diana has two living parents. Her mother is overweight and has been taking a statin for a number of years
- Diana also has a sibling currently receiving treatment for early CHD and diabetes
- Her physical examination showed she is overweight, but no tendon xanthoma or arcus cornealis
- Diana's physician believed her elevated LDL-C levels were likely to be related to her recent weight gain and recommended diet and exercise along with a low dose statin

Patient Case studies overview

	Anna	Brian	Diana
Age	25	43	50
LDL-C	6.4 mmol/L (250 mg/dL)	5.5 mmol/L (213 mg/dL)	5.0 mmol/L (191 mg/dL)
CV history	None	MI	None
Family history	Premature cardiac death grandfather	None confirmed (father died in accident)	Sibling early CVD and diabetes Maternal overweight
Physical exam	Tendon xanthoma	No abnormalities	Overweight

Patient Case studies overview

	Anna	Brian	Diana
Age	25	43	50
LDL-C	6.4 mmol/L (250 mg/dL)	5.5 mmol/L (213 mg/dL)	5.0 mmol/L (191 mg/dL)
CV history	None	MI	None
Family history	Premature cardiac death grandfather	None confirmed (father died in accident)	Sibling early CVD and diabetes Maternal overweight
Physical exam	Tendon xanthoma	No abnormalities	Overweight
DLCN SCORE	**10**	**5**	**4**

Summary

- FH diagnosis focuses on a combination of personal and family history of:
  - premature CVD
  - presence of xanthomas or early arcus cornealis
  - presence of significantly elevated LDL-C levels
- The DLCN diagnostic criteria give an effective approach to identifying potential FH patients
- All patients who score 5 or higher on the DLCN diagnostic criteria should be considered for genetic testing
- A positive genetic test is definitive for FH

Genetics and FH

Introduction

The following section will discuss the genetics of FH, including how to obtain informed consent, the most common gene variants, how FH variants are passed through families, and how different variants can effect patient outcomes

By the end of this section you should:

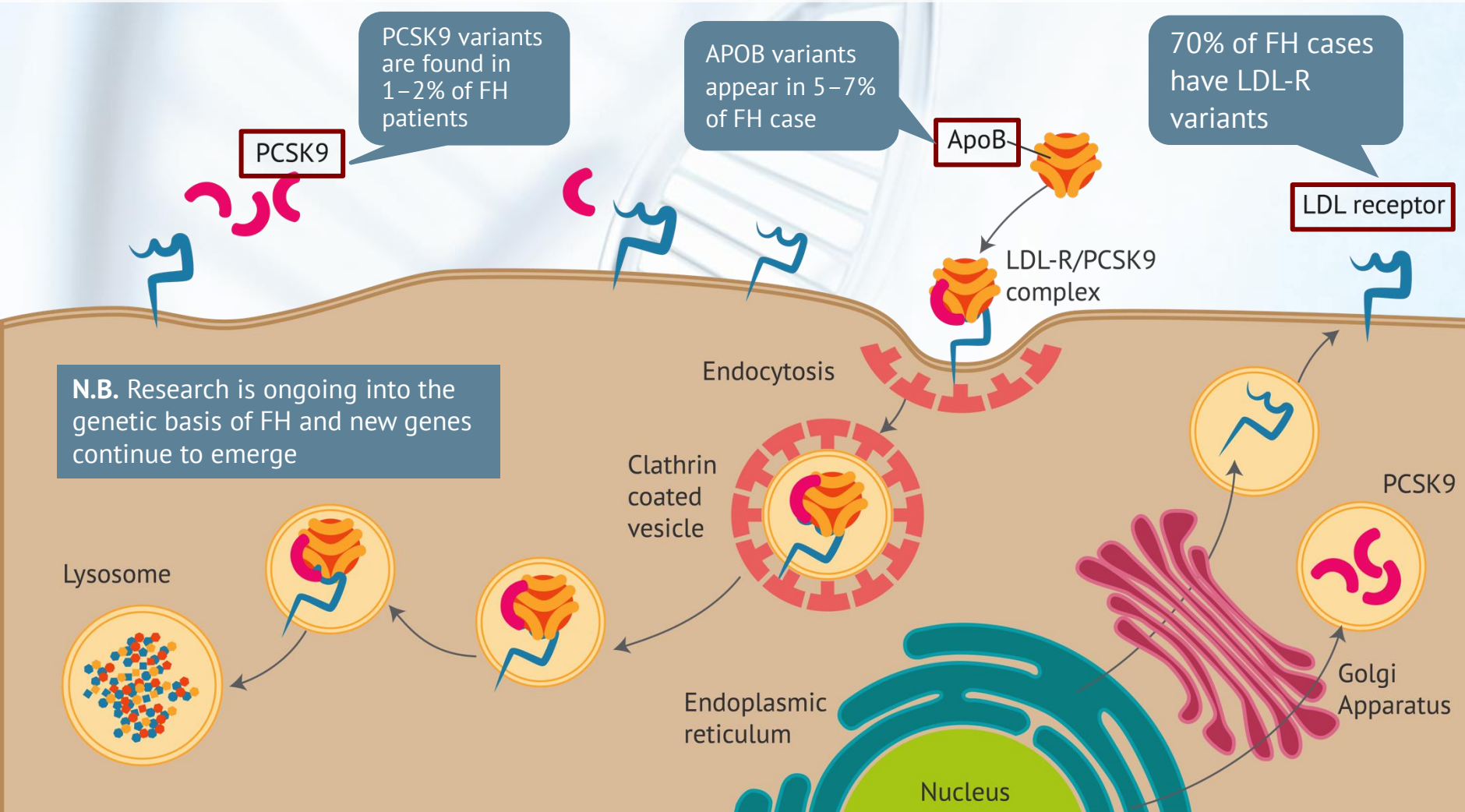
- Know the key genes involved in FH
- Understand how FH variants are transmitted through families
- Understand how different variants can have different effects on patients

Ensuring informed patient consent for genetic testing

- While not always legally required in every country, wherever possible, specific informed consent should be obtained before any genetic testing is carried out on a patient or family member (during screening) to ensure that the full implications of the test are understood
- When explaining genetic testing for FH, the following points should be conveyed:
  - This is a DNA test that may allow us to confirm the presence of FH, and to understand how it is likely to progress
  - The results will have implications for you, but also for other members of your family as it may reveal that they are at risk of also having FH
  - The test can be done using a sample of your blood or saliva

Key genes in FH

Genetic testing for FH is focused primarily on variants in the genes encoding three key proteins of lipid metabolism



Key concepts in the genetics of FH

Homozygous mutations: the SAME mutation appears on both chromosomes

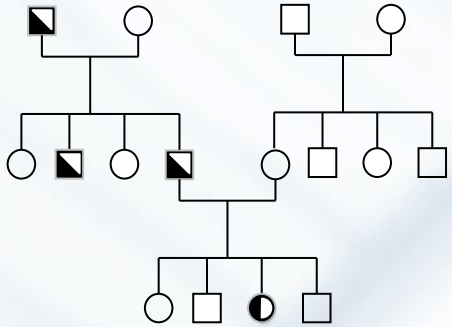
Heterozygous mutations: a mutation appears on only ONE chromosome

Dominant inheritance: a SINGLE mutated copy of a gene in a dominant disorder is enough to change function and for the disease to appear

Recessive inheritance: TWO mutated copies of a gene in a recessive disorder are required before a change in function is expressed and the disease appears

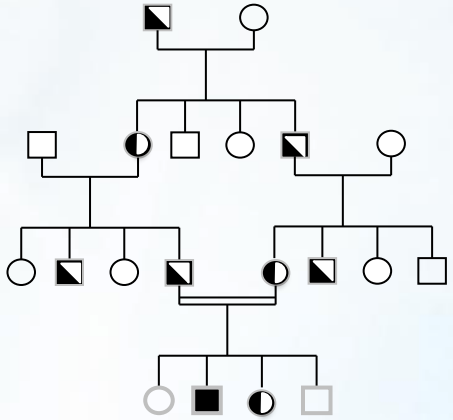
How does FH transition within a family?

Heterozygous autosomal dominant pedigree



Patient has one 'normal' and one mutated version (allele) of a gene. This is the most common presentation of FH

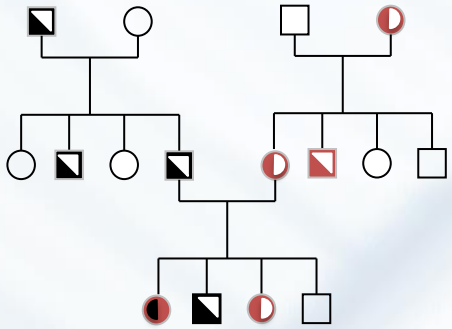
Homozygous pedigree



Patient has two identical versions (alleles) of a gene

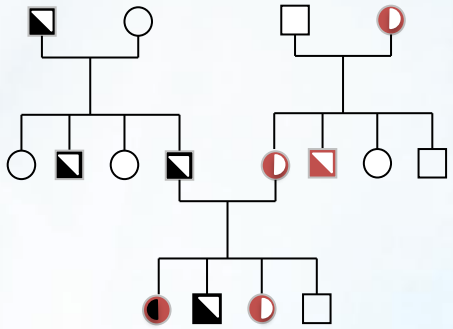
How does FH transition within a family?

Double heterozygous pedigree



Patient has two different mutations on two different genes (e.g. LDL-R and ApoB). Also known as digenic. Patients with both double and compound heterozygous FH can present phenotypically similarly to homozygous patients

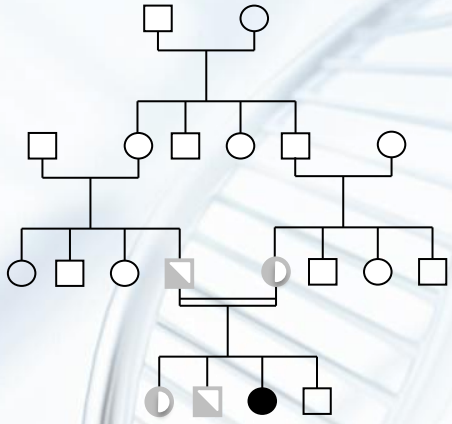
Compound heterozygous pedigree



Patient has two different mutated versions (alleles) of the same gene

How does FH transition within a family?

Homozygous autosomal recessive pedigree

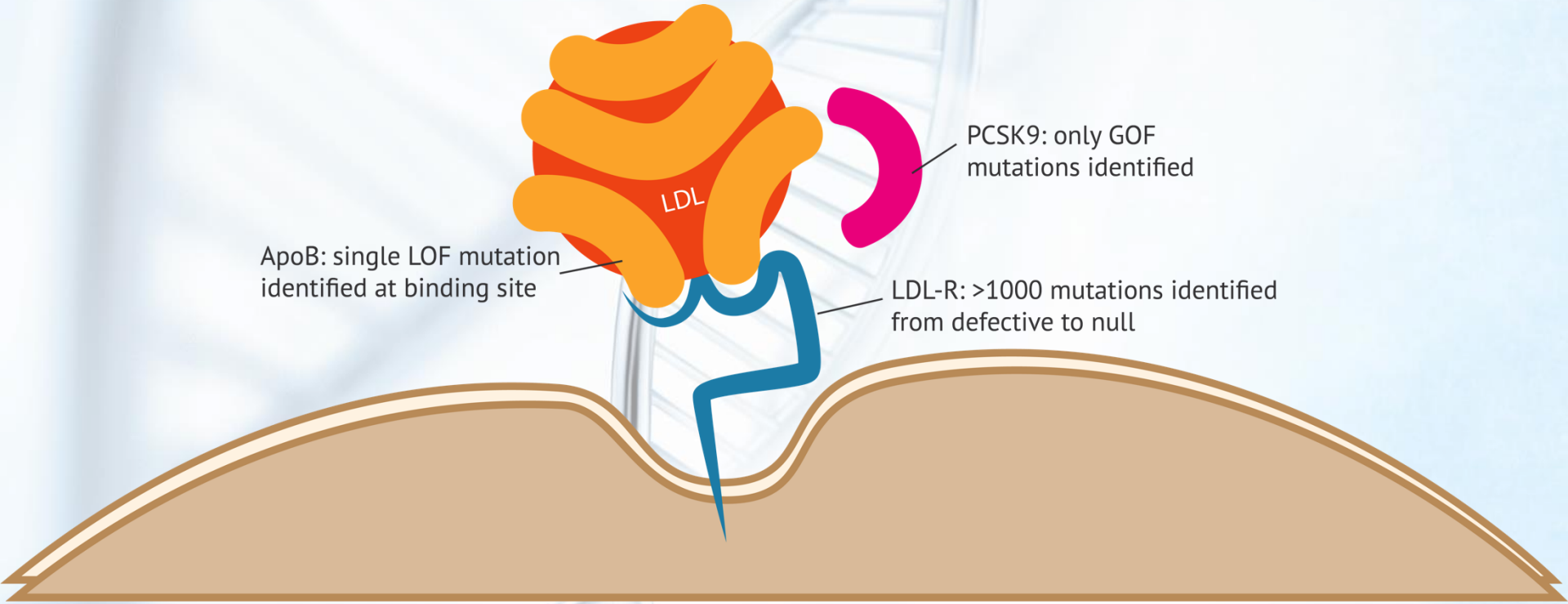


The disease appears only when the patient has inherited two mutated versions (alleles). The least common presentation of FH

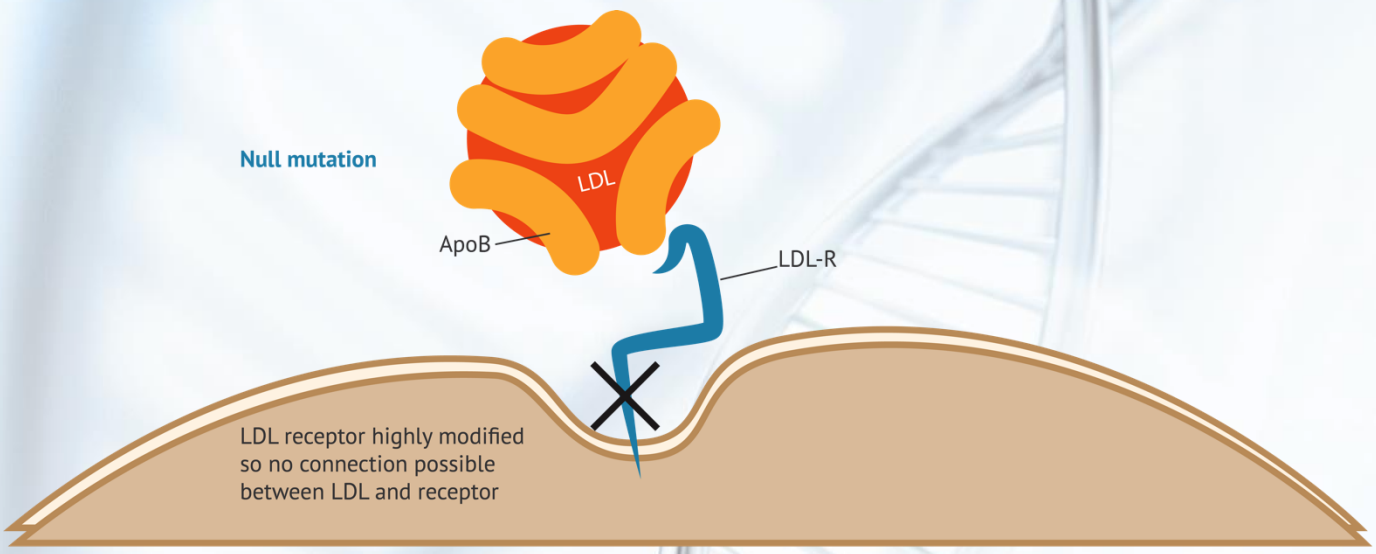
Not all genetic variants have the same clinical impact

- Some mutations cause **gain of function** (GOF)
  - Mutations of PCSK9 cause a GOF
- Some mutations cause **loss of function** (LOF)
  - Mutations of LDL-R cause LOF
- LOF can be **NULL** (causing a complete loss of function) or **DEFECTIVE** (causing partial loss of function)
  - Mutations of APOB cause a specific type of LOF known as ligand deficiency that affects only one of the functions of ApoB

A range of mutations are seen in FH



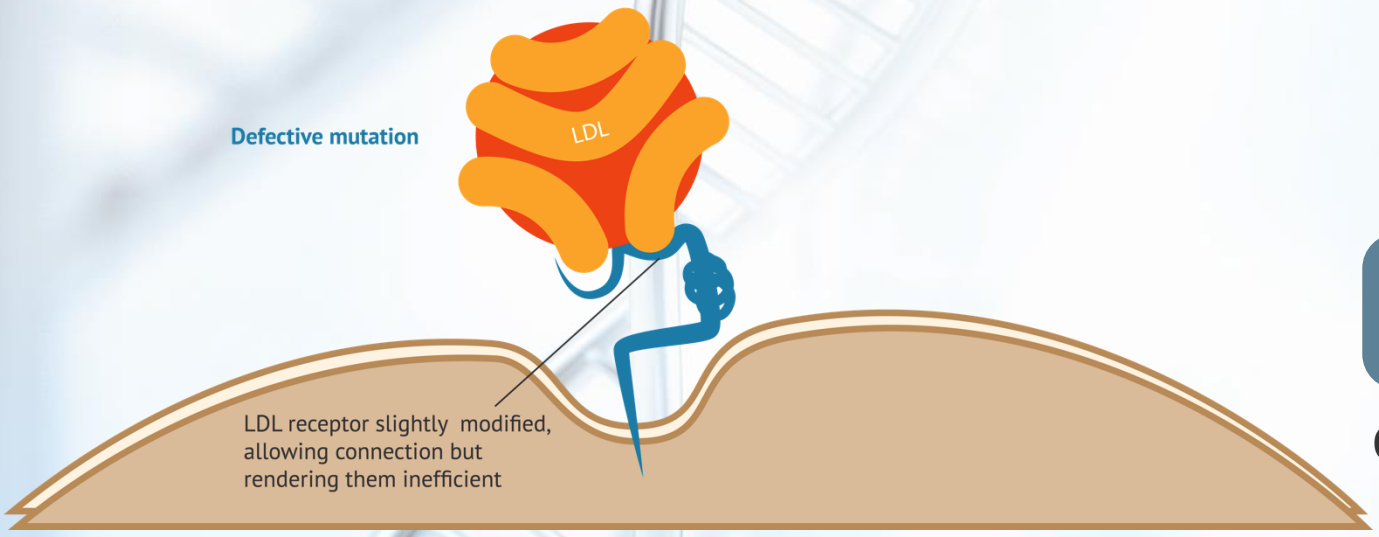
Differing impact of null and defective mutations



Types of null mutation in FH:

- Large genomic deletion
- Large genomic duplication
- Splice site
- Nonsense
- Small insertion /deletion

Cholesterol elevation



Types of defective mutation in FH:

- Missense

Cholesterol elevation

Differing impact of null and defective mutations

Large genomic deletion: Mutations caused by the loss of large genetic materials from a chromosome (from one exon to the complete gene)

Large genomic duplication: Mutations caused by the duplication of part of a chromosome containing from one exon to complete gene

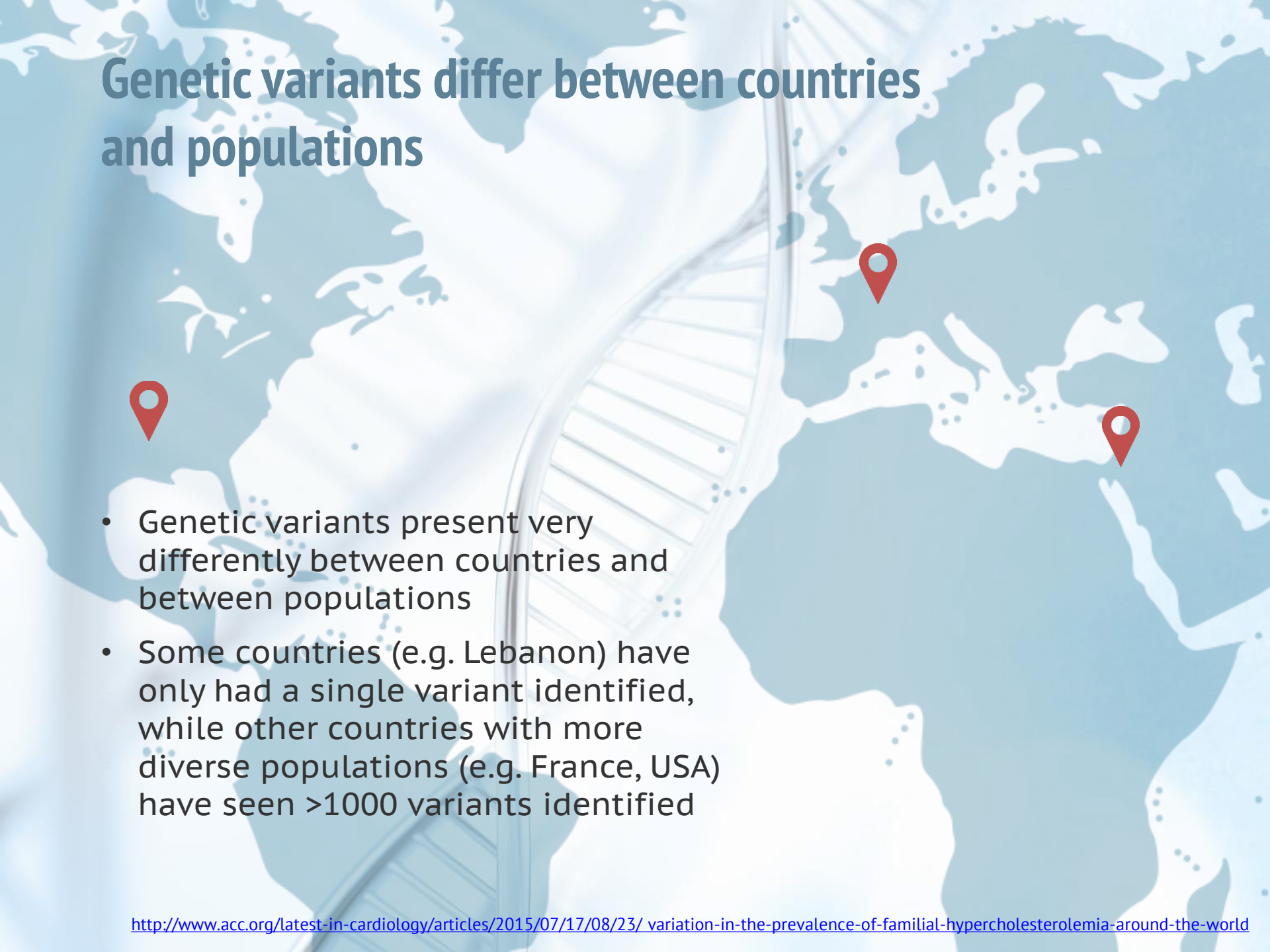
Splice site mutations: Mutations that affect the processing of mRNA, leading to abnormal protein synthesis

Nonsense mutations: Mutations that cause a premature stop codon to appear in the coding sequence of the gene, leading to incomplete (truncated) proteins or mRNA degradation

Small Insertion/deletion mutations: Mutations caused by the addition or loss of nucleotides in the coding sequence

Missense mutations: Mutations caused when a single nucleotide is changed, leading to the substitution of one amino acid for another in a protein. These may have a wide range of effects from major to relatively minor, depending on the role of the amino acid in the function of the protein

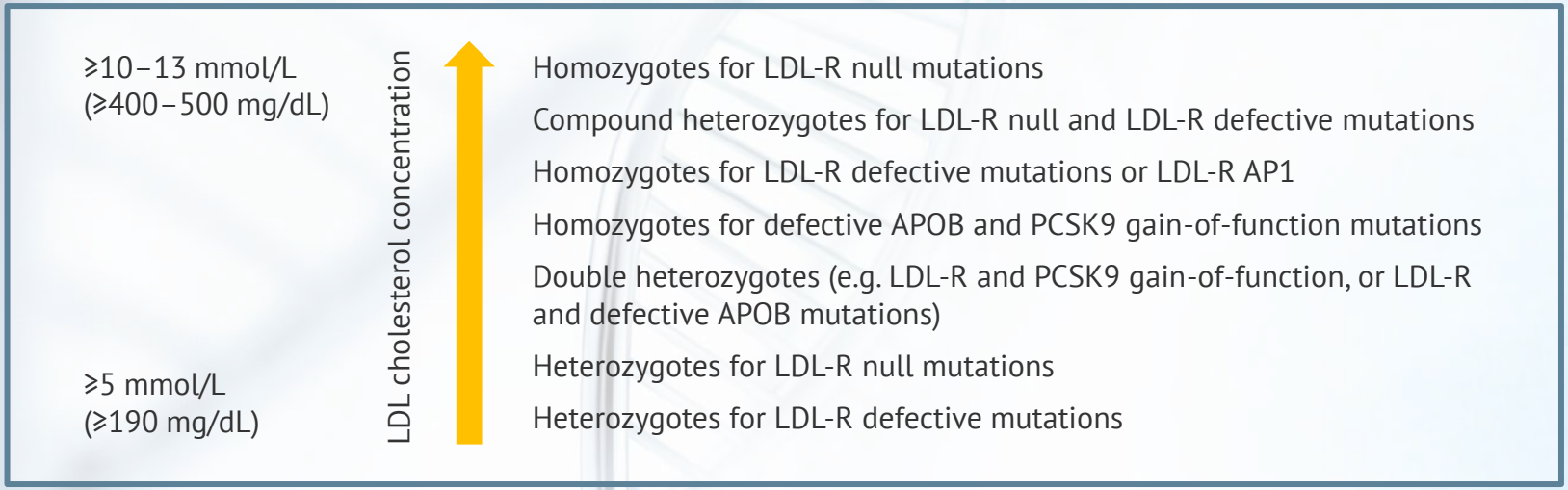
Genetic variants differ between countries and populations



- Genetic variants present very differently between countries and between populations
- Some countries (e.g. Lebanon) have only had a single variant identified, while other countries with more diverse populations (e.g. France, USA) have seen >1000 variants identified

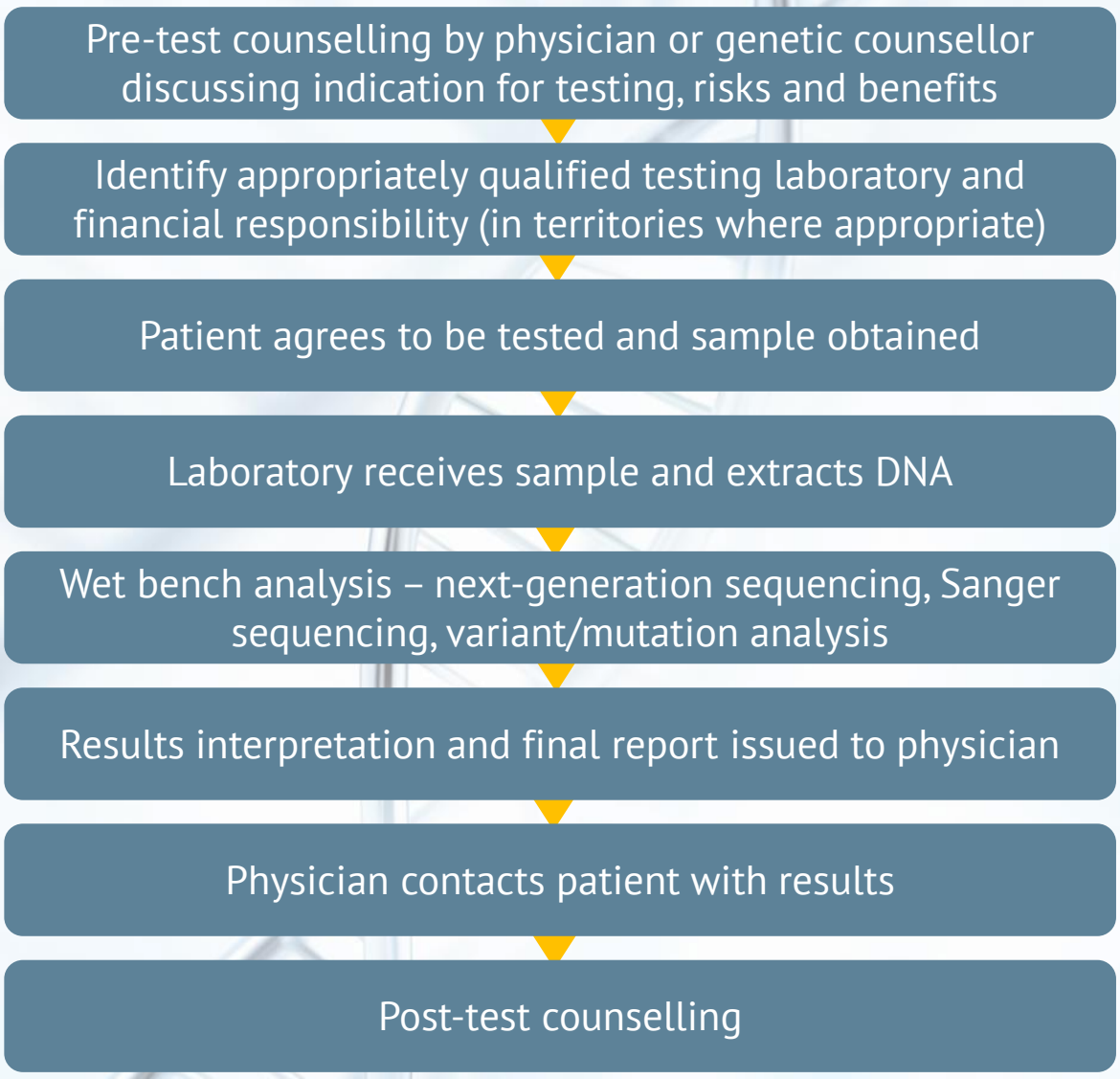
http://www.acc.org/latest-in-cardiology/articles/2015/07/17/08/23/ variation-in-the-prevalence-of-familial-hypercholesterolemia-around-the-world

Clinical implication: genetic testing helps to diagnose severity of FH



Santos RD, et al. *Lancet Diabetes Endocrinol* 2016; http://dx.doi.org/10.1016/S2213-8587(16)30041–9.

Genetic testing process



Summary

- The LDL-R, APOB and PCSK9 gene variants are the most commonly seen variants in FH
- FH variants are transmitted through families in a number of ways, with heterozygous autosomal dominant inheritance the most common
- The key variants seen in FH are all different forms of mutation, understanding which variant type a patients has can help in understanding the severity of disease and may potentially impact on treatment

Clinical presentation of FH

Interpreting genetic test results

Introduction

The following section will look in more detail at the interpretation of genetic test results in FH, including patient case studies to examine how FH can appear in real-world practice, and discussion of how to manage negative test results.

By the end of this section you should:

- Be able to interpret genetic test results
- Know how to respond to common test result scenarios
- Understand the implications of negative FH test results

Understanding genetic test results

- Genetic tests may be for a specific gene, or a panel of genes
- Results may be presented in a number of formats depending on the specific lab performing the test
- In general, results should contain the following information:
  - Testing method
  - Description of variants found
  - Predicted functional impact of variant(s)
  - Whether variant is novel
  - Original source for variant identification

Genetic testing technologies

DNA sequencing is the most common approach to detecting point mutations (single base changes) or small deletion or insertion mutations. Other technologies are needed to identify large rearrangements, notably in the LDL-R gene.

DNA sequencing technologies determine the sequence of bases in DNA using tagged (fluorescent) base analogues that terminate chain building to reveal the position of each of the base pairs. By combining the positions of all the base pairs, it is possible to "read" the original DNA sequence.

Two main types of sequencing techniques are used in FH testing:

Sanger Sequencing:

- Established in the 1970s
- Sequential (exon by exon) single gene sequence testing
- Expensive, time consuming, 'gold standard' accuracy

Next Generation Sequencing:

- Massively parallel sequencing
- At base pair level: cheaper, quicker, requires less DNA, able to sequence large numbers of genes simultaneously

Case study: Anna

Case study: Anna

Anna's genetic test report showed:

- Pathogenic mutation
  - Stop codon
  - Functional study
  - Previously described

  LDL-R,c.2043C>A,p.Cys681*

  FH diagnosis confirmed

- The mutation found is a well known null mutation known as the Lebanese Mutation

Clinical implication: Anna's family should be tested to diagnose other members with FH

Case study: Brian

Case study: Brian

Brian's genetic test report showed:

- Likely pathogenic mutation
  - Missense
  - Variant not previously described
  - Mutation at the same codon previously described

  LDL-R,c.361T>C,p.Cys121Arg

  Molecular genetic results in favour of FH but diagnosis not confirmed

- Brian's children were also tested. Two of his children shared the same FH variant. Their LDL-C levels were 4.4 mmol/L (170 mg/dL). Both were started on low dose statins.

Clinical implication: Cascade screening is required to confirm FH diagnosis

EAS Cascade screening guidance

Cascade testing issues in Familial Hypercholesterolaemia
Notification of relatives at risk of Familial Hypercholesterolaemia should generally not be instituted without the consent of the index case.
National and local healthcare service protocols concerning disclosure of medical information without consent should be consulted.
A proactive approach that respects privacy, justice, and autonomy is required.
All material communicated to relatives and the telephone approach should be comprehensible and not cause alarm.
Pre-testing counselling should be offered to at risk family members of an index case prior to phenotypic or genetic testing.
If genetic testing detects a causative mutation, a definitive diagnosis of Familial Hypercholesterolaemia can be made in the tested individual particularly when the phenotype also suggests Familial Hypercholesterolaemia (Table 1: Figure 6: clinical diagnosis and mutation diagnosis).
If genetic testing does not detect a causative mutation, the diagnosis of Familial Hypercholesterolaemia can be excluded, except when the clinical phenotype is highly suggestive of Familial Hypercholesterolaemia (figure 6: clinical diagnosis wihtout mutation).
If genetic testing detects a causative mutation but the phenotypen does not suggest Familial Hypercholesterolaemia, then a definitive diagnosis of Familial Hypercholesterolaemia should not be made; however, the person and family should be monitored every 2–5 years for LDL cholesterol levels (Figure 6: mutation without clinical diagnosis).
Genetic testing may have implications for insurance cover in cerain countries.

Nordestgaard BG, et al. *Eur Heart J* 2013; doi: 10.1093/eurheartj/eht273.

Case study: Diana

Case study: Diana

Diana's genetic test report showed:

- Benign variant
  - Missense
  - Variant described at the same prevalence in FH and normocholesterolemic subjects

  LDL-R,c.1171G>A,p.Ala391Thr

  FH diagnosis not confirmed
  - **Possible polygenic origin**
  - **Or unknown molecular defect in known gene**
  - **Or molecular defect in unknown gene**
- Diana was referred to a lipidologist and a geneticist for further testing

Clinical implication: Investigate other lipid disorders. If family history and biology are particularly strong, consider possibility of currently undescribed FH variant

Negative test results still require treatment for high LDL-C

- Patients with negative test results may still have FH, as new variants continue to be discovered – follow-up testing may be warranted in future
- In all patients with hypercholesterolaemia, secondary causes should be ruled out through physical examination, patient history, and lab tests e.g. hypothyroidism and diabetes
- Patients remain at CV risk due to their elevated LDL-C levels, so will still require treatment – including discussion of diet and exercise and possible statin use
- Selected patients may be tested for other diseases which are sometimes confused with FH (e.g phytosterolemia or lysomal acid lipase deficiency [LIPA]) to rule out other conditions

Summary

- Genetic test results may be for a specific gene, or a panel of genes
- Positive genetic test results are often the trigger for screening for people with undiagnosed FH
- Negative test results do not fully exclude an FH diagnosis, as new variants continue to be discovered
- Other diagnoses should be explored for patients with hypercholesterolaemia and negative test results, and measures taken to address elevated LDL-C

Treatment strategies in FH

Introduction

The following section will discuss current treatment recommendations in FH

By the end of this section you should:

- Be able to apply the current treatment guidelines for FH
- Understand why statins are recommended as first line treatment for FH
- Understand the current guidance on the use of PCSK9 inhibitors

EAS FH treatment guidelines

Lifestyle modifications including smoking cessation and dietary advice – if needed from a certified dietitian

Treatment priority:

- Children: statin, ezetimibe and bile acid-binding resin
- Adults: maximal potent statin dose, ezetimibe and bile acid-binding resin, fibrate, (niacin, novel therapies)
- Lipoprotein apheresis in homozygotes and treatment-resistant heterozygotes with CHD

LDL-C targets:

- <3.5 mmol/L (<135 mg/dL) for children
- <2.5 mmol/L (<100 mg/dL) for adults
- <1.8 mmol/L (<70 mg/dL) for adults with known CHD or diabetes

Every 1 mmol/L (38 mg/dL) reduction in LDL-C is associated with a 22% reduction in CV mortality and 12% reduction in total mortality over 5 years

Maximal potent statin dose should be initiated at first consultation in adults (atorvastatin 80 mg, rosuvastatin 40 mg or pitavastatin 4 mg). Simvastatin 80 mg should not be used due to risk of myositis and rhabdomyolisis

Nordestgaard BG, et al. *Eur Heart J* 2013; 34: 3478–90.

NLA FH treatment guidelines

Lifestyle modifications including smoking cessation and dietary advice

- Initial treatment for adult FH patients: initial treatment with moderate to high doses of potent statins to achieve LDL-C reduction ⩾50% from baseline.
- If the initial statin is not tolerated, consider changing to an alternative statin, or every other-day statin therapy.
- If initial statin therapy is contraindicated or poorly tolerated, ezetimibe, a bile acid sequestrant (colesevelam), or niacin may be considered.
- For patients who cannot use a statin, most will require combination drug therapy.
- If the patient is not at LDL-C treatment goal with the maximum available and tolerable dose of statin, then combine with ezetimibe, niacin, or a bile acid sequestrant (colesevelam preferred).
- Decisions regarding selection of additional drug combinations should be based on concomitant risk factors for myopathy, concomitant medications, and the presence of other disease conditions and lipid abnormalities.

- For adult FH patients (⩾20 years of age), drug treatment to achieve an LDL-C reduction ⩾50% should be initiated.
- Higher risk patients may need intensification of drug treatment to achieve more aggressive treatment goals (LDL-C <2.5 mmol/L [<100 mg/dL] and non-HDL-C <3.4 mmol/L [<130 mg/dL]).
- In FH patients without any higher risk characteristics, intensification of drug therapy may be considered if LDL-C remains ⩾4.1 mmol/L [⩾160 mg/dL] (or non-HDL-C ⩾4.9 mmol/L [⩾190 mg/dL]), or if an initial 50% reduction in LDL-C is not achieved.

Goldberg AC, et al. *J Clin Lipidol* 2011; 5: S1–S8.

ESC/EAS dyslipidaemia treatment guidelines

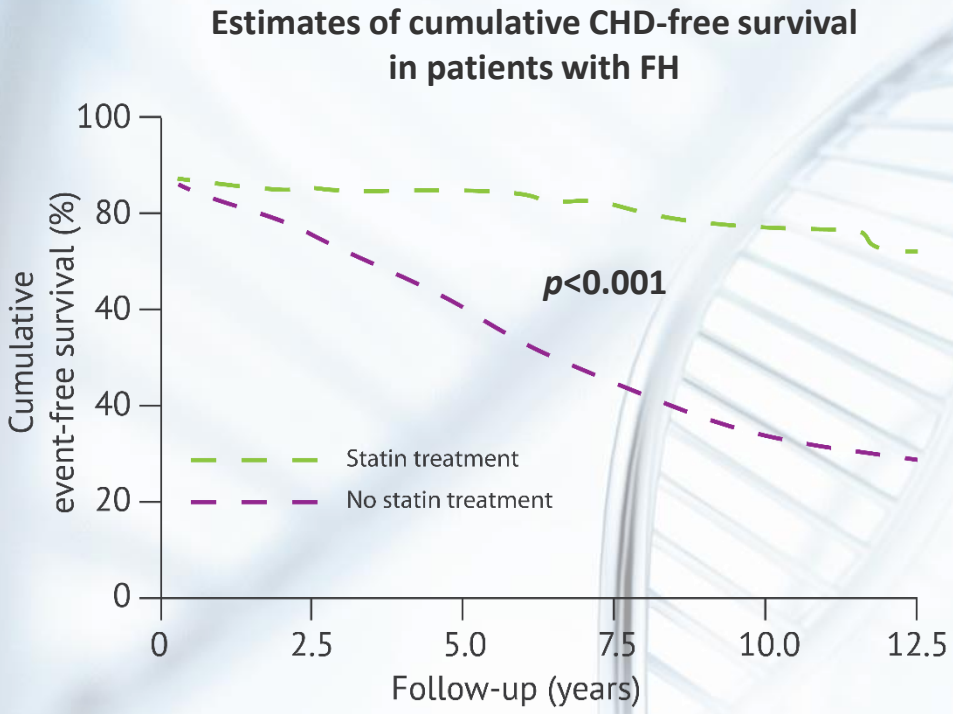
In HeFH high dose statin is recommended and whenever needed in combination with cholesterol absorption inhibitors and/or a bile acid sequestrant

Treatment is aimed at reaching the LDL-C goals for high risk subjects (<2.5 mmol/L, < ~100 mg/dL) or in the presence of CVD of very high risk subjects (<1.8 mmol/L, < ~70 mg/dL).

If targets cannot be reached, maximal reduction of LDL-C should be considered using appropriate drug combinations in tolerated doses

Reiner Z, et al. *Eur Heart J* 2011; 32: 1769–818.

Treating with statins markedly reduces mortality in FH



Patients with FH: n=2146

Mean follow-up: 8.5 years

Excludes secondary prevention

Mean age at first visit: 43.3 years

Follow-up after the first statin was available (1990)

Statins prescribed were mainly simvastatin (average dose: 33 mg) and atorvastatin (average dose: 49 mg)

- 408 patients had a CHD event
- Overall risk reduction: 76% (HR 0.24 [95% CI 0.18, 0.30]); 82% (HR 18 [95% CI 0.13–0.25]) after adjustment for **other risk factors**
- Risk is no longer different from that of the general population when treatment is given earlier **(risk of MI: HR 1.44 [95% CI 0.80, 2.60]; *p*=0.23)**

Versmissen J, et al. *BMJ* 2008;337:a2423.

Early treatment initiation is beneficial in FH

- Patients with FH are likely to be exposed to elevated LDL-C levels across their entire lifetime
- In patients with heFH, the cumulative LDL-C burden required to trigger CHD is on average reached at age 35 versus 55 years in the general population
- With early treatment initiation it takes longer for an heFH patient to reach this level, with treatment initiation in childhood reducing the gap to just two years
- Guidelines recommend initiation of statin treatment in children from age 8–10 years
- However, the impact of long-term treatment on the individual should be considered when discussing treatment options

Nordestgaard BG, et al. *Eur Heart J* 2013; 34: 3478–90.

Expert recommendations on PCSK9 inhibitor treatment

ESC/EAS Taskforce Consensus Statement on PCSK9 inhibitors[1]:

- "This panel recognizes that addition of a PCSK9 inhibitor is a very attractive and efficacious new option for HeFH patients who typically need 50–60% incremental LDL-C reductions to achieve LDL-C goal. However, until results from major outcomes trials are reported, the panel proposes that PCSK9 inhibitor treatment may be considered for severe FH patients with ASCVD, as well as those without ASCVD (clinical or on imaging) and LDL-C levels >5.0 mmol/L or >200 mg/dL despite maximally tolerated statin/ezetimibe therapy. For patients with additional risk factors [diabetes mellitus, elevated Lp(a) >50 mg/dL, marked hypertension, and premature familial ASCVD (<55 years in males and <60 years in females)], the LDL-C threshold is lower, i.e. >4.5 mmol/L or >175 mg/dL."

ACC expert consensus on the role of non-statin therapies for LDL-lowering[2]:

- "In the opinion of the expert consensus writing committee, in a patient with ASCVD and baseline LDL-C ≥190 mg/dL with <50% reduction in LDL-C (and may consider LDL-C ≥70 mg/dL) it is reasonable to consider a PCSK9 inhibitor as a first step rather than ezetimibe or BAS given PCSK9 inhibitors' greater LDL-C lowering efficacy."

PCSK9 inhibitors are not available or reimbursed in all countries at the time of preparation of this eLearning

1. Landmesser U, et al. *Eur Heart J* 2016; doi:10.1093/eurheartj/ehw480.
2. Lloyd-Jones DM, et al. *JACC* 2016; http://dx.doi.org/10.1016/j.jacc.2016.03.519.

Case study overview: Ongoing treatment

Patient status after 6 months:

	Anna	Brian	Diana
Treatment	High dose statin plus ezetimibe and PCSK9 inhibitor	High dose statin	Lifestyle modification plus low dose statin
LCL-C	2.5 mmol/L (100 mg/dL)	2.3 mmol/L (89 mg/dL)	1.8 mmol/L (70 mg/dL)

Summary

- The EAS and NLA FH treatment guidelines recommend lifestyle modification followed by the use of statins to control FH
- If LDL-C levels do not decrease sufficiently with statin treatment, the guidelines recommend the use of ezetimibe and bile acid-binding resin
- Statins are recommended as first line treatment for FH due to the 76% risk reduction seen with their use
- While formal guidelines on PCSK9 inhibitor use do not yet exist, consensus statements from the ESC/EAS and ACC are supportive of their use in more severe patients

Practical advice on FH genetic testing

Introduction

The following section offers simple, practical advice on delivering genetic testing and cascade screening in FH

By the end of this section you should:

- Understand the process for ordering genetic testing in FH
- Be able to apply the basics of cascade screening

Ordering genetic testing

1. Identify your local lab with FH testing capability
2. Contact to enquire about lipid disorder genetic testing
3. Inform yourself about the reimbursement/cost status in your country
4. Arrange pre- and post-test counselling where possible
5. Ensure informed consent
6. Provide lab with lipid data and family history of the patient

Performing cascade screening

- Cascade screening is recommended for all patients with a definite diagnosis of FH (DLCN score >8), however it may be appropriate to initiate cascade screening in patients with less definite diagnosis (i.e. to confirm the nature of genetic variant)
- Cascade screening should be implemented in primary family members (parents, children, siblings) initially, then rolled out to secondary family (cousins, aunts, uncles) and beyond where appropriate
- Cascade screening can be undertaken based on biochemistry alone, however genetic screening markedly improves accuracy
- Genetic testing can be considered as the first line of testing or later in the process
- Screening should always be accompanied by counselling to minimise distress

Overall Summary

E-Learning Summary

- FH affects ~1 in 200–500 births and leads to a markedly higher risk of CVD
- LDL-R, ApoB and PCSK9 are key elements of lipid metabolism – mutations in the genes coding for them are central to the appearance of FH
- Diagnosis of FH focuses primarily on elevated LDL-C, personal and family history of early CVD, presence of tendon xanthoma or arcus cornealis and the presence of known FH genetic variants
- Genetic screening is important to discover family members with undiagnosed FH, allowing earlier intervention
- FH patients should start treatment as early as possible (after 8 years of age) to minimise the impact of FH on long-term CV outcomes

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Improving management through genetic testing for Familial Hypercholesterolaemia (FH)

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