The Genetics of Familial Hypercholesterolemia (FH)

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Potential COI disclosure

- No conflict of interest (COI) to disclose

Learning Objectives

- At the conclusion of this activity, participants will be able to:
  - Describe the main known genetic causes of familial hypercholesterolemia (FH)
  - Articulate the criteria for genetic testing in FH
  - Explain recent developments, utility and limitations of monogenic and polygenic genetic testing

Introduction – FH

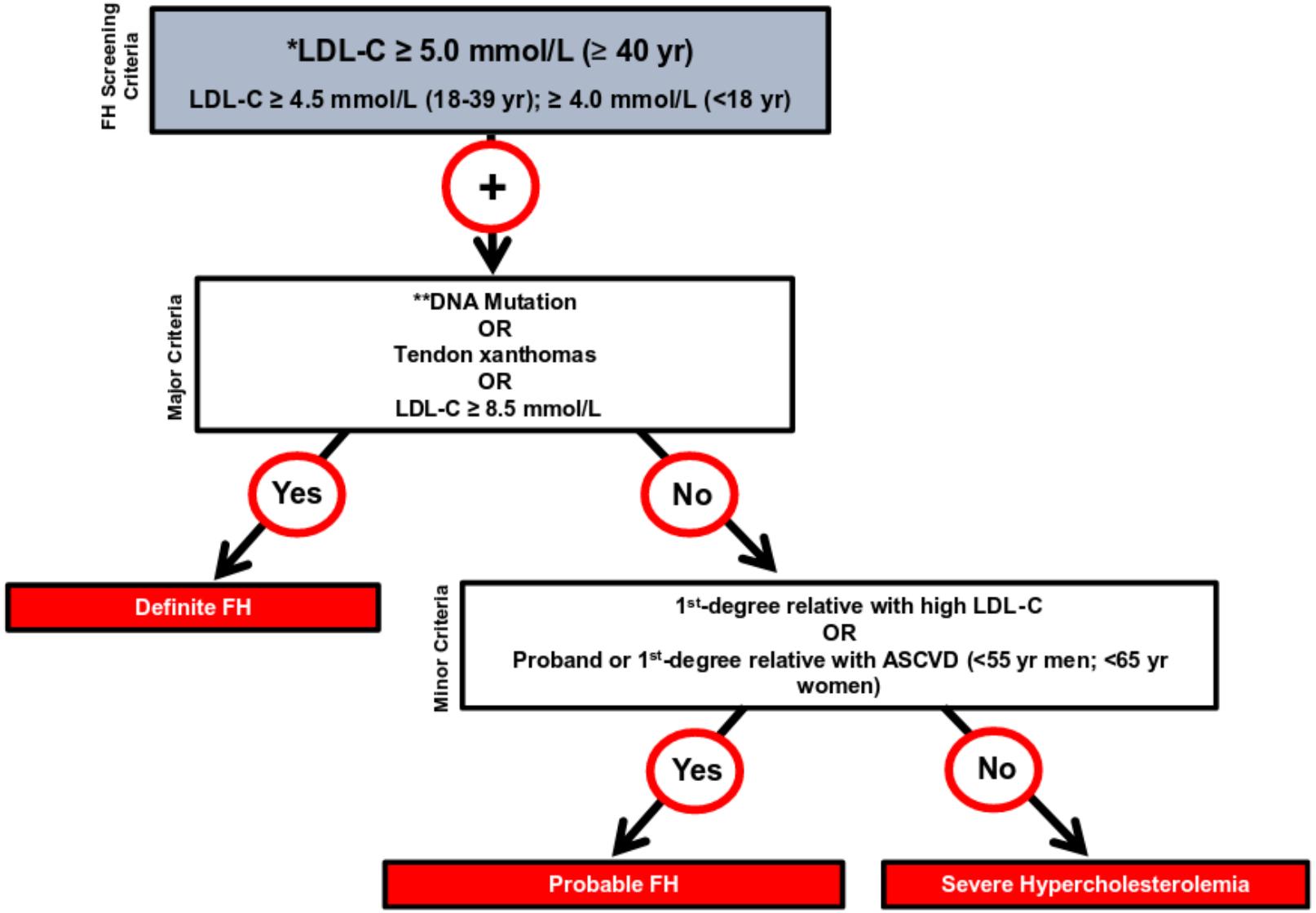
- **Familial hypercholesterolemia (FH):**
  - An inherited lipid disorder
  - Lifelong exposure to highly elevated LDL levels
  - High risk of premature coronary artery disease (ASCVD)
  - Untreated men are at a 50% risk for a coronary event by age 50 years. Untreated women are at a 30% risk by age 60 years.
- **One of the most common monogenic disorder** encountered in clinical practice (~1/250 individuals)
- Formal **diagnostic criteria** (Western countries):
  - UK Simon Broome FH Registry
  - Dutch Lipid Clinic Network
  - US MEDPED Program

Canadian Journal of Cardiology 34 (2018) 1210–1214

Training/Practice
Contemporary Issues in Cardiology Practice

Simplified Canadian Definition for Familial Hypercholesterolemia

Isabelle Ruel, PhD,[a] Diane Brisson, PhD,[b] Sumayah Aljenedil, MD,[a] Zuhier Awan, MD, PhD,[c]



Efficacy of statins in familial hypercholesterolaemia: a long term cohort study

Jorie Versmissen, researcher,[1] Daniëlla M Oosterveer, researcher,[1] Mojgan Yazdanpanah, epid
Joep C Defesche, senior researcher,[2] Dick C G Basart, clinician,[3] Anho H Liem, clinician,[4] Jan H
statistician,[5] Jacqueline C Witteman, professor of epidemiology,[5] Peter J Lansberg, clinician,[2]
John J P Kastelein, professor of vascular medicine,[2] Eric J G Sijbrands, associate professor[1]

AHA Scientific Statement

The Agenda for Familial Hypercholesterolemia

A Scientific Statement From the American Heart Association

Samuel S. Gidding, MD, FAHA, Chair; Mary Ann Champagne, RN, MSN, FAHA; Sarah D. de Ferranti, MD, MPH; Joep Defesche, PhD; Matthew K. Ito, PharmD; Joshua W. Knowles, MD, PhD, FAHA; Brian McCrindle, MD, MPH, FAHA; Frederick Raal, MD, PhD; Daniel Rader, MD, FAHA; Raul D. Santos, MD, PhD; Maria Lopes-Virella, MD, PhD, FAHA; Gerald F. Watts, DSc, MD, PhD; Anthony S. Wierzbicki, MD, PhD, FAHA; on behalf of the American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, and Council on Lifestyle and Cardiometabolic Health

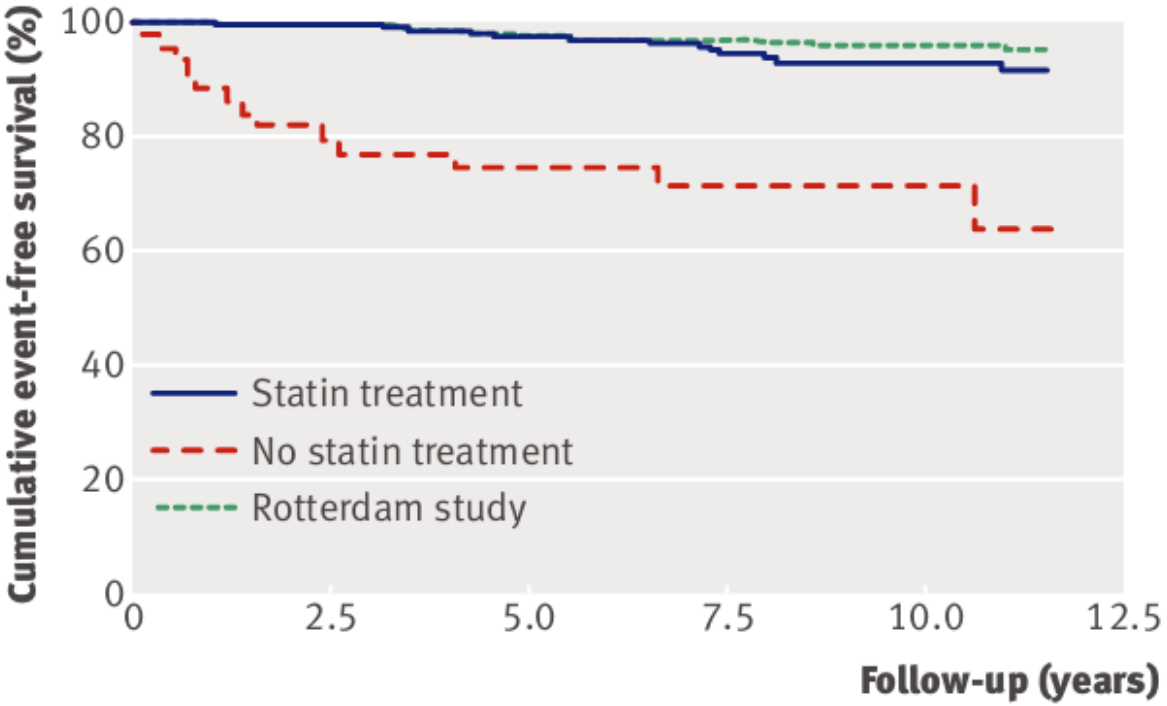
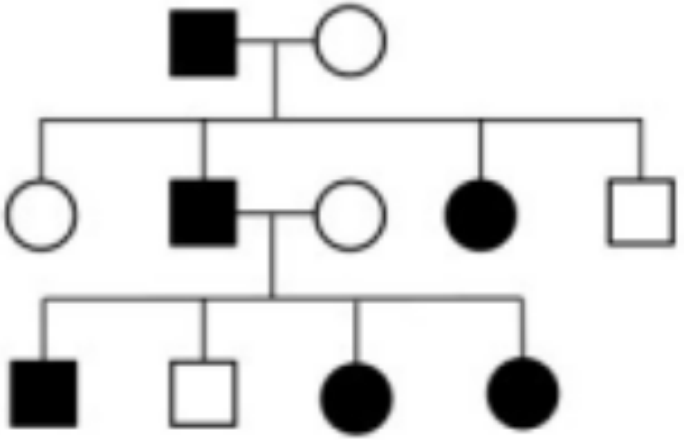


Fig 4 | Kaplan-Meier curve estimates of cumulative myocardial infarct-free survival among patients with familial hypercholesterolaemia older than 55 years according to statin treatment compared with a sample from the general population (Rotterdam study). (P<0.001 for difference between untreated patients and general population; P=0.07 for difference between treated patients and general population)

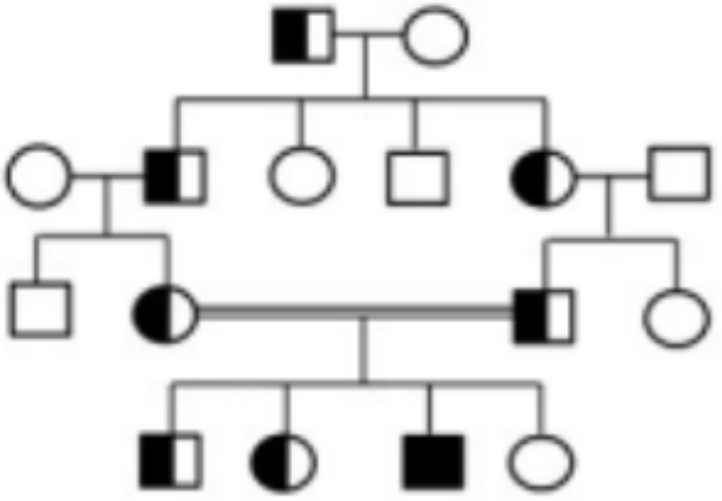
- Early diagnosis and treatment can **normalize life expectancy**

The genetics of FH

- **Inheritance**
  - Autosomal **dominant** (Heterozygous FH [HeFH])
  - Autosomal **recessive** (Homozygous FH [HoFH])
  - "**Polygenic**" inheritance



Autosomal dominant



Autosomal recessive

The genetics of FH

- Heterozygous pathogenic variants in one of 3 genes (***LDLR***, ***APOB***, ***PCSK9***) in 28-80% of cases
- Rare autosomal recessive form (homozygous FH, HoFH)

Gene [1]	Proportion of FH Attributed to Pathogenic Variants in This Gene [2]	Proportion of Pathogenic Variants [3] Detectable by This Method	
		Sequence analysis [4]	Gene-targeted deletion/duplication analysis [5]
APOB	1%-5%	>99%	1 individual [6]
LDLR	60%-80%	>90% [7]	~2.5%-10% [8]
PCSK9	0%-3%	~100%	None reported [9]
Unknown [10, 11]	20%-40%	NA	

Source: GeneReviews

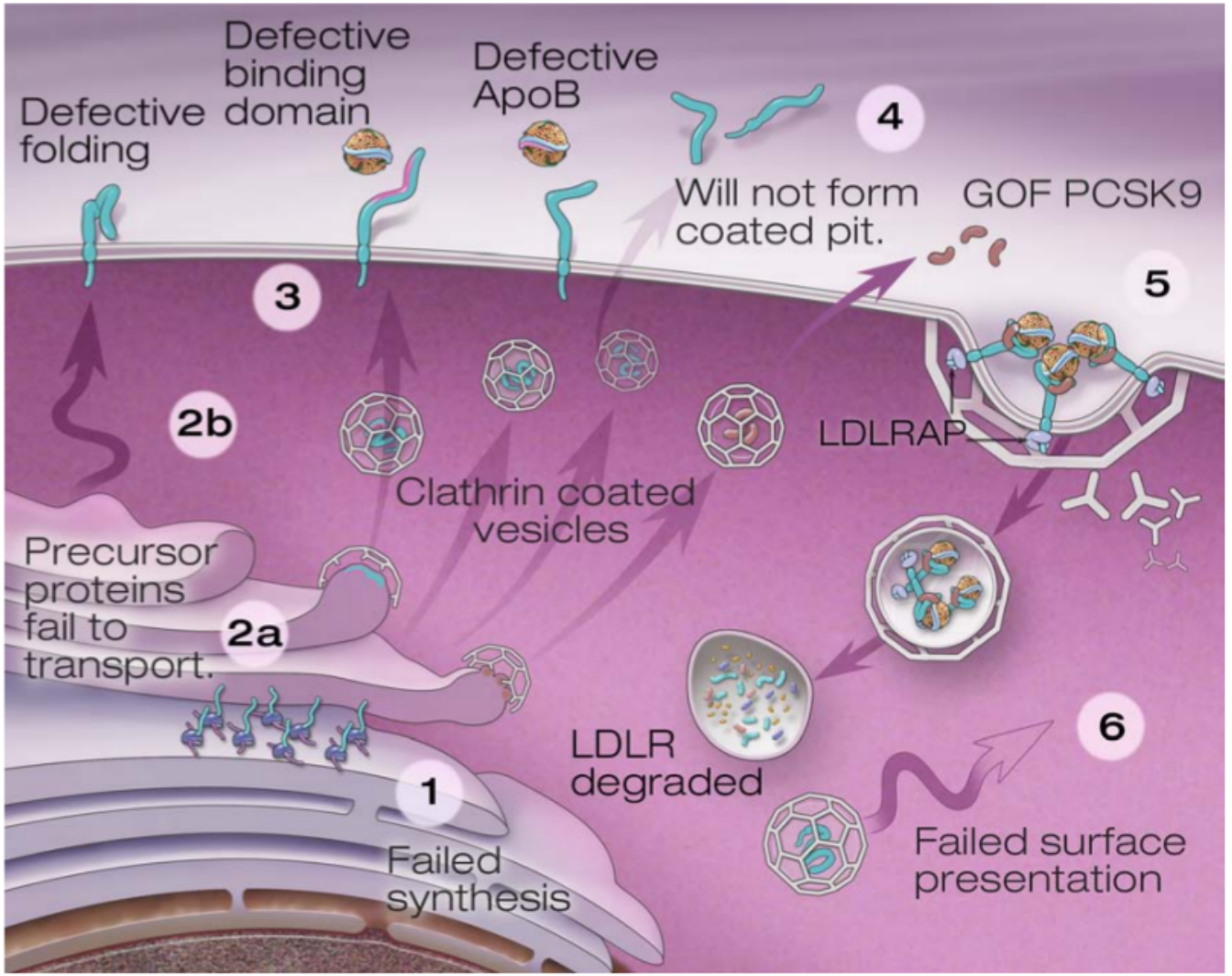


Figure 2. The known mechanisms causing familial hypercholesterolemia linked to low-density lipoprotein (LDL) receptor (LDLR) function. Numbers 1 through 6 correspond to the mechanisms of LDLR dysfunction discussed in the text and Table 3. Familial defective apolipoprotein B (apoB) impairs the ability of the apoB to bind with the LDLR. LDLR adaptor protein (LDLRAP) impairs the ability of the LDLR to interact with LDL particles to extract cholesterol. Proprotein convertase subtulisin/kexin type 9 (PCSK9) gain-of-function (GOF) mutations inhibit LDLR function and increase the degradation of LDLRs.

LDLR gene

- Main disease-causing gene
- ~80% of disease-causing variants
- **Loss-of-function** variants
- > 2,000 known pathogenic variants

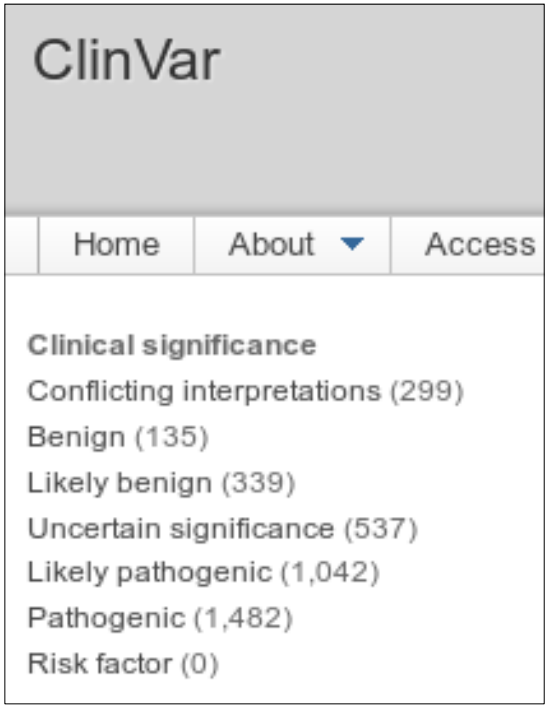


TABLE 1 | Overview of common monogenic FH mutations.

Gene	Protein	Role of normal protein	Type of FH-causative mutation	Notes
LDLR	Low-density lipoprotein receptor	Uptake of low-density lipoprotein cholesterol (LDL-c), thus decreasing systemic LDL-c levels	Loss-of-function	60–80% of FH-causative monogenic variants Patients with null *LDLR* mutations may not may not benefit from PCSK9 inhibitors or respond well to statin therapy
APOB	Apolipoprotein B-100	Binding of LDL-containing lipoproteins to the LDL receptor	Loss-of-function	Up to 5% of FH-causative monogenic variants (may be higher in some populations)
PCSK9	Proprotein convertase subtilisin/kexin 9	Promotes intracellular LDL receptor degradation	Gain-of-function	Up to 3% of FH-causative monogenic variants

Detailed overview of pathogenic allelic variants for each gene may be found in ClinVar, HGMD (Human Gene Mutation Database), and LOVD (Leiden Open Variation Database) (16).

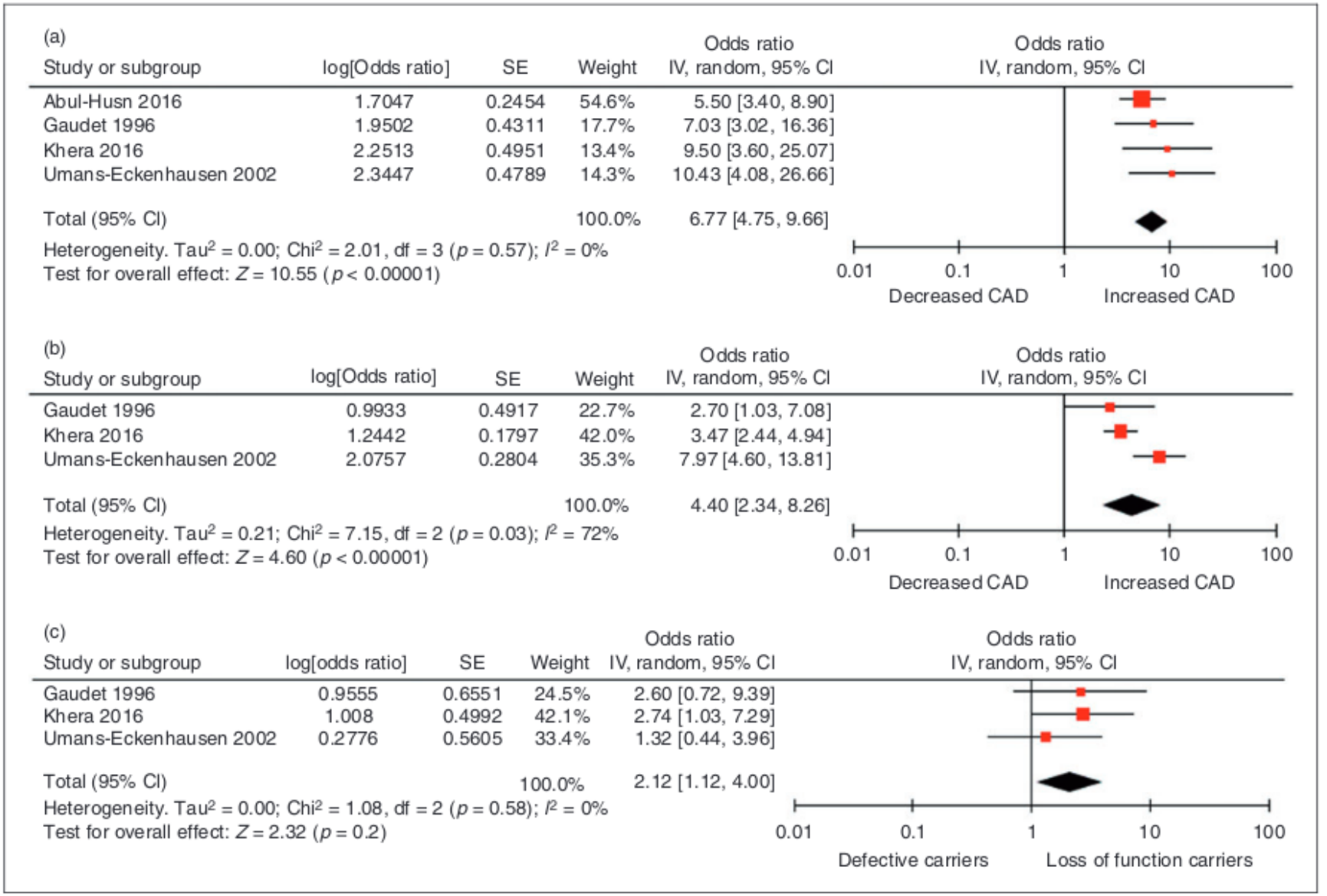
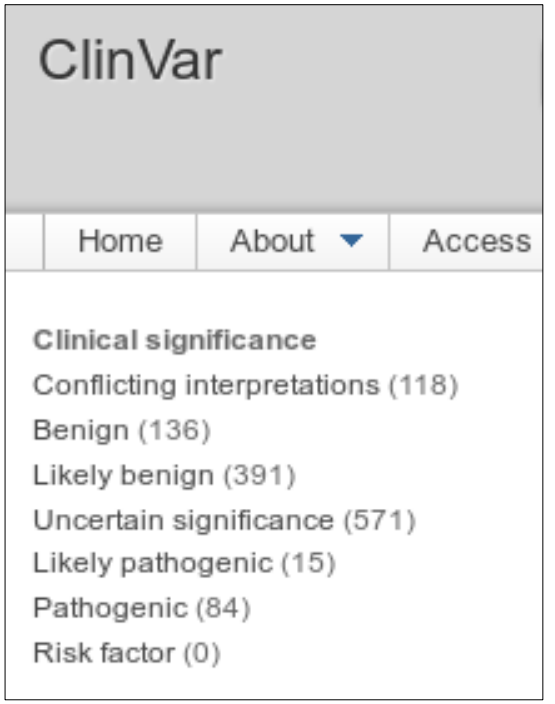


Figure 2. (a) Risk of coronary artery disease (CAD) in patients with *LDLR* loss-of-function variants for familial hypercholesterolemia relative to unaffected individuals. Studies are combined using a random-effects model. Square sizes are proportional to random-effects study weights with horizontal lines denoting 95% confidence intervals (CIs). (b) Risk of CAD in patients with *LDLR* hypomorphic variants for familial hypercholesterolemia relative to unaffected individuals. Studies are combined using a random-effects model. Square sizes are proportional to random-effects study weights with horizontal lines denoting 95% CIs. (c) Risk of CAD in patients with loss-of-function variants for familial hypercholesterolemia relative to hypomorphic changes. Odds ratios represent derived ratios of relative risk. Studies are combined using a random-effects model. Square sizes are proportional to random-effects study weights with horizontal lines denoting 95% CIs.

IV: inverse variance

APOB gene

- Ligand responsible for LDLR binding during LDL-C uptake
- ~5% of disease-causing variants
- **Loss-of-function** variants
- Typically less severe than *LDLR*



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PCSK9 gene

- Responsible for LDLR degradation in liver cells
- ~3% of disease-causing variants
- **Gain-of-function** variants (increased PCSK9 activity & LDLR degradation)

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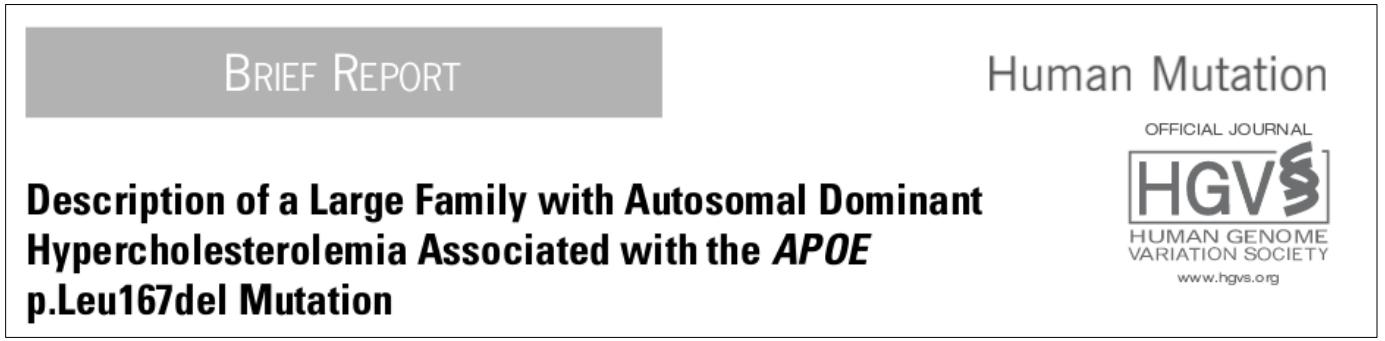
Other genes

- Rare reports of disease-causing variants in other genes (e.g. *APOE*, *LDLRAP1*, *ABCG5*, and *ABCG8*)
- Mostly autosomal recessive inheritance



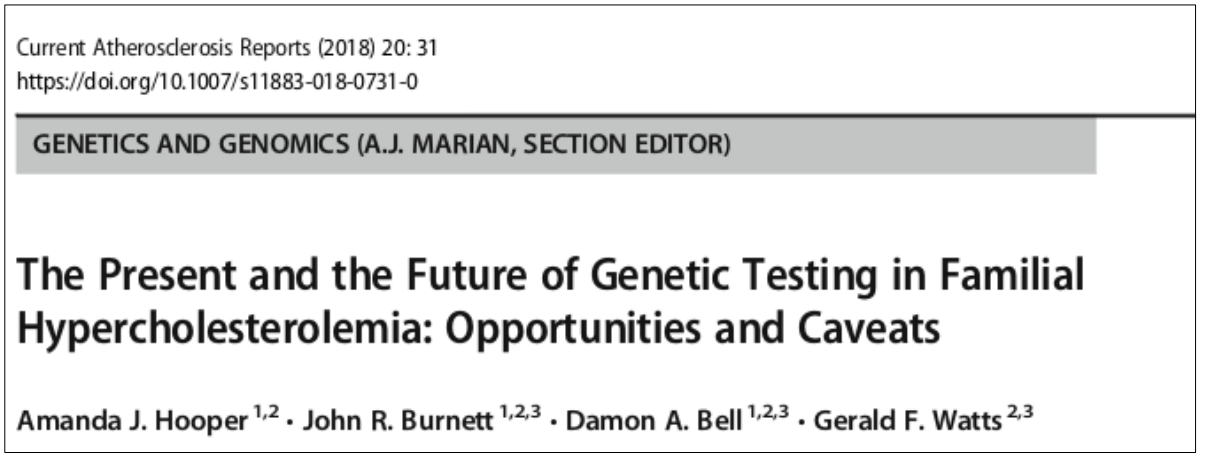
BRIEF REPORT

Human Mutation

OFFICIAL JOURNAL

HGVS HUMAN GENOME VARIATION SOCIETY www.hgvs.org

Description of a Large Family with Autosomal Dominant Hypercholesterolemia Associated with the *APOE* p.Leu167del Mutation



Current Atherosclerosis Reports (2018) 20: 31
https://doi.org/10.1007/s11883-018-0731-0

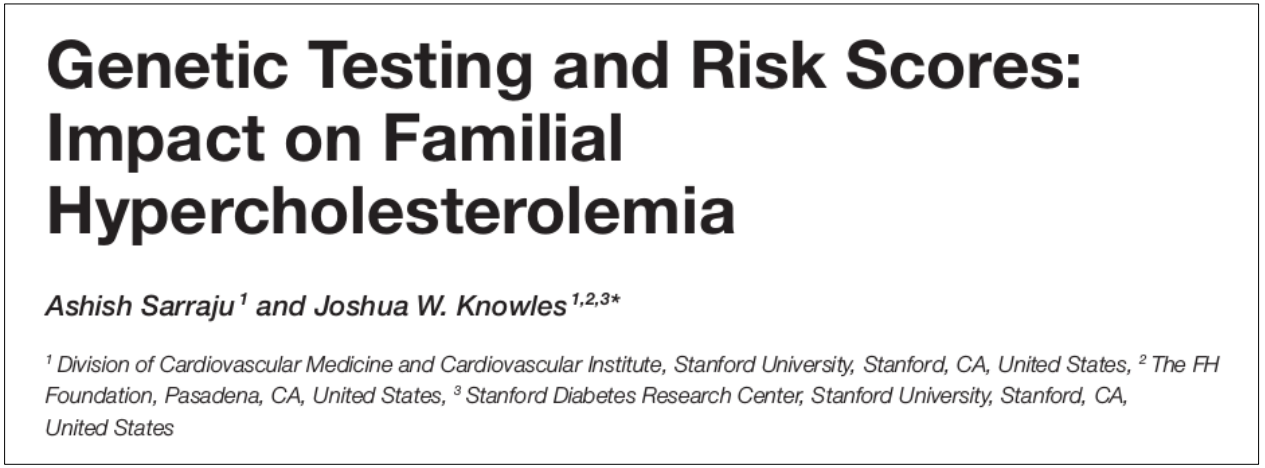
GENETICS AND GENOMICS (A.J. MARIAN, SECTION EDITOR)

The Present and the Future of Genetic Testing in Familial Hypercholesterolemia: Opportunities and Caveats

Amanda J. Hooper [1,2] · John R. Burnett [1,2,3] · Damon A. Bell [1,2,3] · Gerald F. Watts [2,3]

Clinical validity of genetic testing

- Genetic testing of *LDLR*, *APOB* and *PCSK9*
- Monogenic forms of FH
- **Severe cases**: sensitivity of > 80%
- **Milder presentations** (e.g. no xanthomas): sensitivity of ~50%
- **LDL-C > 4.9 mmol/L**: ~2% of cases



Genetic Testing and Risk Scores: Impact on Familial Hypercholesterolemia

*Ashish Sarraju[1] and Joshua W. Knowles[1,2,3]**

[1] Division of Cardiovascular Medicine and Cardiovascular Institute, Stanford University, Stanford, CA, United States, [2] The FH Foundation, Pasadena, CA, United States, [3] Stanford Diabetes Research Center, Stanford University, Stanford, CA, United States

Who to test?

- Untreated LDL-C ≥ **5.0 mmol/L for age ≥ 40**
- Untreated LDL-C ≥ **4.5 mmol/L for age 18-39**
- Untreated LDL-C ≥ **4.0 mmol/L for age ≤ 18**
- **AND** at least one of the following:
  - **Major criteria (definite FH):**
    - Tendon xanthomas in proband
    - Known FH-causing mutation in a 1st-degree relative
    - High LDL-cholesterol in proband (≥ 8.5 mmol/L)
  - **Minor criteria (probable FH):**
    - 1st-degree relative with high LDL-C
    - Proband or 1st-degree relative with early onset atherosclerotic cardiovascular disease (men < 55; women < 65 yr)

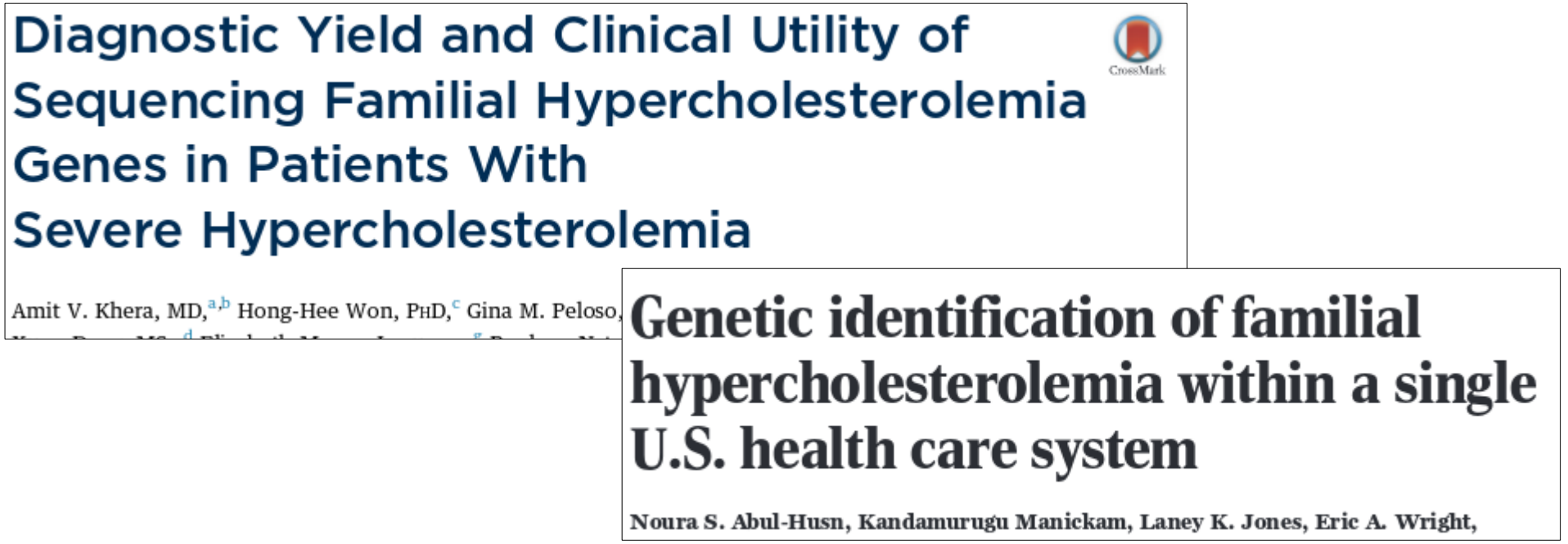
Who to test?

- **Additional details:**
  - Elevated LDL-C **not due to secondary causes:**
    - Severe or untreated hypothyroidism
    - Nephrotic syndrome
    - Hepatic disease (primary biliary cirrhosis)
    - Medication (especially antiretroviral agents)
  - **If baseline LDL-C is unknown:**
    - Imputed level using the CardioRisk Calculator
    - http://www.circl.ubc.ca/cardiorisk-calculator.html

CardioRisk Calculator ™

Who to test?

- **No evidence of the cost-effectiveness of broad population-based screening for FH**
  - **Khera *et al.*:** FH-causing variant in 1.7% (27/1,386) of cases with an LDL-C > 4.9 mmol/L
  - **Abul-Husn *et al.*:** FH-causing variant in 2.5% (112/4,433) of cases with an LDL-C > 4.9 mmol/L



Who to test?

- **Confirm diagnosis ≠ Exclude diagnosis**
  - Most genetic tests **do not exclude** a clinical diagnosis
  - This test should be used to confirm, not to rule out a diagnosis of FH
  - "*A negative result does not rule out the possibility that this individual harbors a pathogenic variant not detected by this assay*"

Who to test?

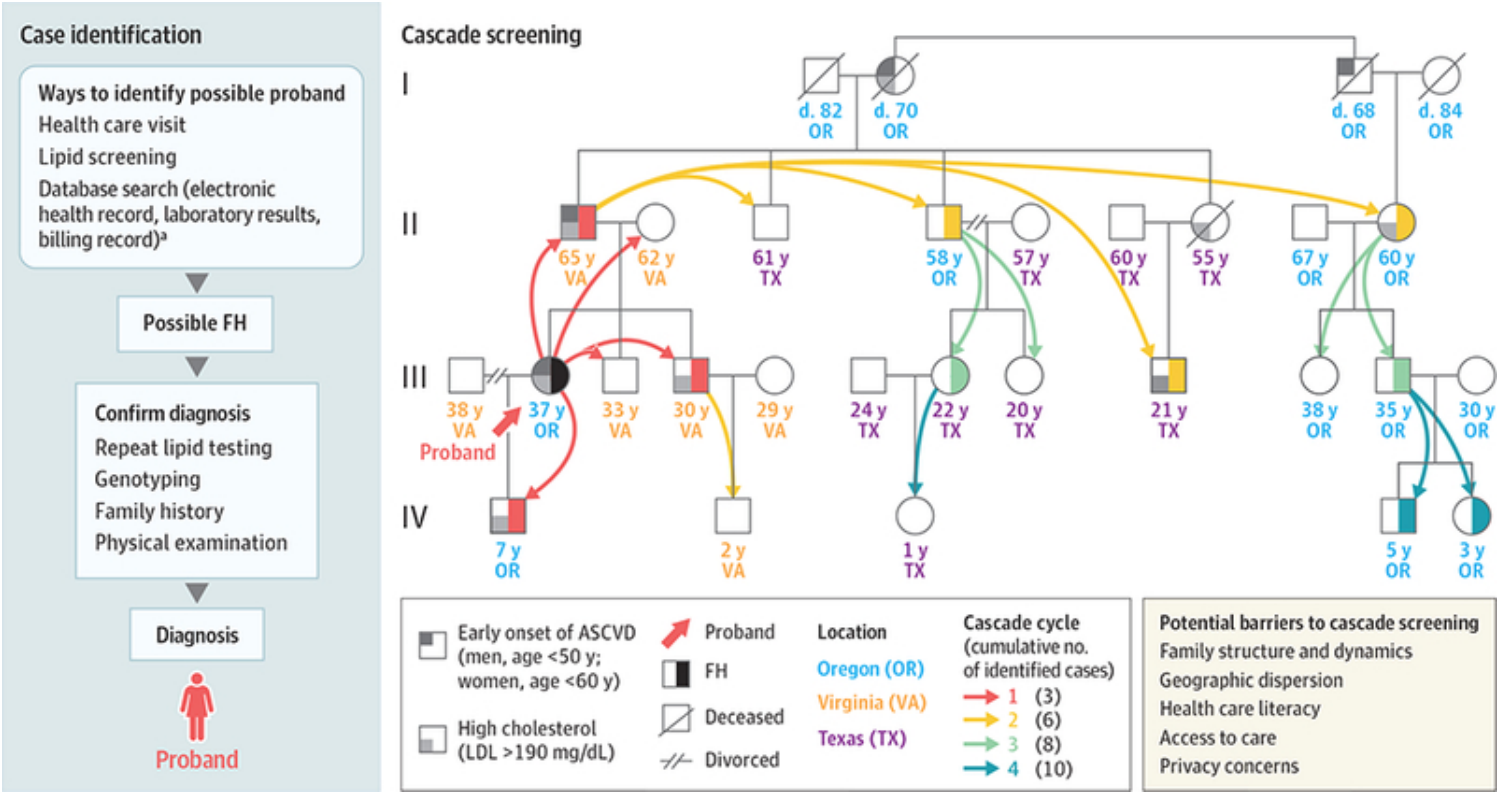
- **Testing of known familial variants:**
  - All 1st degree and relevant 2nd degree relatives (regardless of the LDL-C level)
  - Testing limited to the known familial variant (“cascade testing”)
  - **Exceptions:**
    - Familial variant not found in symptomatic case (phenocopy) => reflex to full panel
    - Suspicion of homozygous FH (HoFH): 2nd hit to be identified

Clinical utility of genetic testing

- Confirm diagnosis
- Cascade testing
- Risk stratification
- Genotype-phenotype correlation
- Overall management

Clinical utility of genetic testing

- FH is **under-diagnosed**
- Early diagnosis & management is important
- **Cascade testing** of known familial variants
- Known to be highly cost-effective



Clinical utility of genetic testing

- **Genetic counseling**
- **Cascade genetic testing** to assess the penetrance of familial variants
  - **Garcia-Garcia *et al.***: 7% of individuals positive for a FH-causing variant are asymptomatic

Reduced penetrance of autosomal dominant hypercholesterolemia in a high percentage of families: Importance of genetic testing in the entire family

Ana-Barbara Garcia-Garcia[a,b,*], Carmen Ivorra[b,c,3], Sergio Martinez-Hervas[a,b,d], Sebastian Blesa[a,b], M. José Fuentes[b,e], Oscar Puig[f,1], Jose Javier Martín-de-Llano[g,2], Rafael Carmena[a,d], Jose T. Real[a,d], Felipe Javier Chaves[a,b]

Clinical utility of genetic testing

Diagnostic Yield and Clinical Utility of Sequencing Familial Hypercholesterolemia Genes in Patients With Severe Hypercholesterolemia

Amit V. Khera, MD,[a,b] Hong-Hee Won, PhD,[c] Gina M. Peloso, PhD,[b,d] Kim S. Lawson, MS,[e] Traci M. Bartz, MS,[f]

BACKGROUND Approxi
lipoprotein [LDL] choleste
cholesterol elevations in F
by a single LDL cholesterc

OBJECTIVES This study
determined whether CAD risk varies according to mutation status beyond the observed LDL cholesterol level.

METHODS Three genes causative for FH (*LDLR*, *APOB*, and *PCSK9*) were sequenced in 26,025 participants from 7 case-control studies (5,540 CAD case subjects, 8,577 CAD-free control subjects) and 5 prospective cohort studies (11,908 participants). FH mutations included loss-of-function variants in *LDLR*, missense mutations in *LDLR* predicted to be damaging, and variants linked to FH in ClinVar, a clinical genetics database.

RESULTS Among 20,485 CAD-free control and prospective cohort participants, 1,386 (6.7%) had LDL cholesterol ≥190 mg/dl; of these, only 24 (1.7%) carried an FH mutation. Within any stratum of observed LDL cholesterol, risk of CAD was higher among FH mutation carriers than noncarriers. Compared with a reference group with LDL cholesterol <130 mg/dl and no mutation, participants with LDL cholesterol ≥190 mg/dl and no FH mutation had a 6-fold higher risk for CAD (odds ratio: 6.0; 95% confidence interval: 5.2 to 6.9), whereas those with both LDL cholesterol ≥190 mg/dl and an FH mutation demonstrated a 22-fold increased risk (odds ratio: 22.3; 95% confidence interval: 10.7 to 53.2). In an analysis of participants with serial lipid measurements over many years, FH mutation carriers had higher cumulative exposure to LDL cholesterol than noncarriers.

CONCLUSIONS Among participants with LDL cholesterol ≥190 mg/dl, gene sequencing identified an FH mutation in <2%. However, for any observed LDL cholesterol, FH mutation carriers had substantially increased risk for CAD.
(J Am Coll Cardiol 2016;67:2578–89)

Clinical utility of genetic testing

- Evidence of increased **adherence to treatment**
- **Umans-Eckenhausen *et al.***: 37.6% of patients treated at genetic screening, 92.5% and 85.9% 1 and 2 years after screening.

Review of first 5 years of screening for familial hypercholesterolaemia in the Netherlands

Marina A W Umans-Eckenhausen, Joep C Defesche, Eric J G Sijbrands, Robert L J M Scheerder, John J P Kastelein

- **Severe disease-causing variants**:
  - Patient may require more aggressive therapy
  - Early consideration of advanced lipid powering therapy (e.g. PCSK9 inhibitor)?

Clinical utility of genetic testing

ACMG STATEMENT | Genetics inMedicine

Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics

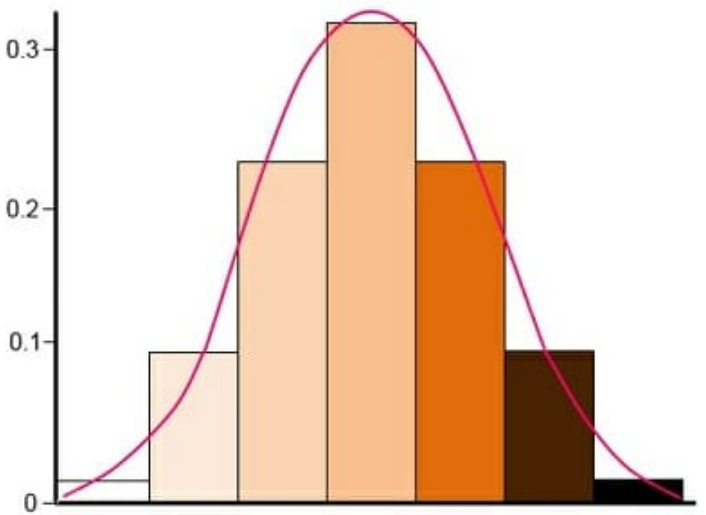
Table 1 Continued

Phenotype	MIM disorder	PMID Gene Reviews entry	Typical age of onset	Gene	MIM gene	Inheritance[a]	Variants to report[b]
Arrhythmogenic right ventricular cardiomyopathy	609040 604400 610476 607450 610193	20301310	Child/adult	*PKP2* *DSP* *DSC2* *TMEM43* *DSG2*	602861 125647 125645 612048 125671	AD	KP and EP KP KP and EP
Romano-Ward long-QT syndrome types 1, 2, and 3, Brugada syndrome	192500 613688 603830 601144	20301308	Child/adult	*KCNQ1* *KCNH2* *SCN5A*	607542 152427 600163	AD	KP and EP
Familial hypercholesterolemia	143890 603776	No GeneReviews entry	Child/adult	*LDLR* *APOB* *PCSK9*	606945 107730 607786	SD SD AD	KP and EP KP
Wilson disease	277900	20301685	Child	*ATP7B*	606882	AR[c]	KP and EP
Ornithine transcarbamylase deficiency	311250	24006547	Newborn (male), child (female)	*OTC*	300461	XL	KP and EP (hemi, het, hom)
Malignant hyperthermia susceptibility	145600	20301325	Child/adult	*RYR1* *CACNA1S*	180901 114208	AD	KP

Polygenic FH

- Accumulation of **common**, **small effect variants** affecting LDL-C levels
- Identified by genome-wide association studies (**GWAS**)
- Calculation of a **polygenic risk score** (or GRS)
- **12 alleles** from the Global Lipid Genetic Consortium (GLGC)

	ABC	*ABc*	*AbC*	*aBC*	*Abc*	*aBc*	*abC*	*abc*
ABC	6	5	5	5	4	4	4	3
ABc	5	4	4	4	3	3	3	2
AbC	5	4	4	4	3	3	3	2
aBC	5	4	4	4	3	3	3	2
Abc	4	3	3	3	2	2	2	1
aBc	4	3	3	3	2	2	2	1
abC	4	3	3	3	2	2	2	1
abc	3	2	2	2	1	1	1	0



Polygenic FH

- Individuals with **severe hypercholesterolemia**:
  - 20% with a high polygenic risk score
  - 2% with a rare disease-causing variant

ARTICLE

DOI: 10.1038/s41467-018-05747-8 OPEN

Deep-coverage whole genome sequences and blood lipids among 16,324 individuals

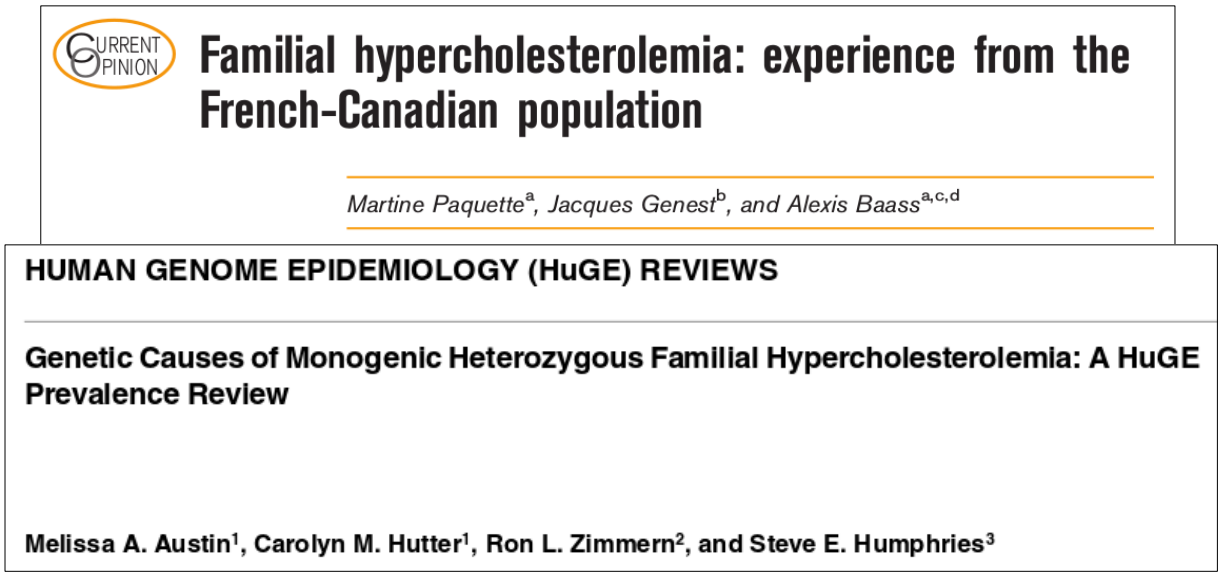
Pradeep Natarajan[1,2,3], Gina M. Peloso[4], Seyedeh Maryam Zekavat[3,5,6], May Montasser[7], Andrea Ganna[3,8], Mark Chaffin[3], Amit V. Khera[1,2,3], Wei Zhou[9], Jonathan M. Bloom[3,8], Jesse M. Engreitz[3,10], Jason Ernst[11], Jeffrey R. O'Connell[7], Sanni E. Ruotsalainen[12], Maris Alver[13], Ani Manichaikul[14], W. Craig Johnson[15], James A. Perry[7], Timothy Poterba[3,8], Cotton Seed[3,8], Ida L. Surakka[12], Tonu Esko[13], Samuli Ripatti[12], Veikko Salomaa[12], Adolfo Correa[16], Ramachandran S. Vasan[17,18,19], Manolis Kellis[3,20], Benjamin M. Neale[1,2,3,8], Eric S. Lander[3], Goncalo Abecasis[21], Braxton Mitchell[7], Stephen S. Rich[14], James G. Wilson[16,22], L. Adrienne Cupples[4,19], Jerome I. Rotter[23] NHLBI TOPMed Lipids Working Group, Cristen J. Willer[24] & Sekar Kathiresan[1,2,3]

Polygenic FH

- **High GRS**: Possible cause in FH patients with no disease-causing variant
- Currently used by direct-to-consumer genetic testing companies
- **Limited clinical applicability**
  - Individual risk difficult to assess
  - Ethnically biased (towards European ancestry)
  - Probable gene-environment (GxE) interactions
  - Unknown cost-effectiveness
  - The absence of a monogenic variant cannot be excluded

Genetic testing in Québec

- **What is currently offered in Quebec?**
  - Genotyping of 11 recurrent disease-causing *LDLR* variants in the French-Canadian (FC) population
  - Collectively account for up to 90% of FH cases in FC
  - **Limitations:** not tailored to the needs of a more diverse population (e.g. Montreal area)



CURRENT OPINION

Familial hypercholesterolemia: experience from the French-Canadian population

Martine Paquette[a], Jacques Genest[b], and Alexis Baass[a,c,d]

HUMAN GENOME EPIDEMIOLOGY (HuGE) REVIEWS

Genetic Causes of Monogenic Heterozygous Familial Hypercholesterolemia: A HuGE Prevalence Review

Melissa A. Austin[1], Carolyn M. Hutter[1], Ron L. Zimmern[2], and Steve E. Humphries[3]

Population	Prevalence
General population	1:250
French Canadian [1]	1:270
Old Order Amish [2]	1:10
Christian Lebanese	1:85
Tunisia	1:165
South African Afrikaners	1:72 to 1:100
South African Ashkenazi Jews	1:67

2018 | 2019

Répertoire québécois et système de mesure des procédures de biologie médicale

Les annexes

55008				D. mol. maladie héréditaire	Hypercholestérolémie familiale (gène récept. *LDL*) (del 5-15 Kb) (TAAN)	Rapport	Supra	70,0
55018				D. mol. maladie héréditaire	Hypercholestérolémie familiale (HF), gène *R-L* DL (TAAN, mutation unique)	Rapport	Supra	30,0
55010				D. mol. maladie héréditaire	Hypercholestérolémie familiale (HF), gène *R-LDL* Panel 1 (del 5, del 15 kb,Trp66Gly, Cys646Tyr) (TAAN)	Rapport	Supra	120,0
55012				D. mol. maladie héréditaire	Hypercholestérolémie familiale (HF), gène *R-LD* L Panel 2 (Glu207Lys, Cys152Trp, Arg329Xaa, Cys347Arg, Tyr468Xaa, Tyr354Cys, 681ins7) (TAAN)	Rapport	Supra	210,0

LDLR, *APOB* and *PCSK9* testing

- **Single-nucleotide variants (SNVs) and small indels**
  - Sequencing of *LDLR*, *APOB* and *PCSK9* coding regions and flanking intronic regions
  - Now performed by targeted NGS
  - Known familial variants: Sanger sequencing
- **Copy number variants (CNVs) for *LDLR***
  - Multiplex ligation-dependent probe amplification (MLPA)
  - Quantitative PCR (qPCR)
  - Gap-PCR (for recurrent CNVs with known breakpoints)

Summary – The genetics of FH

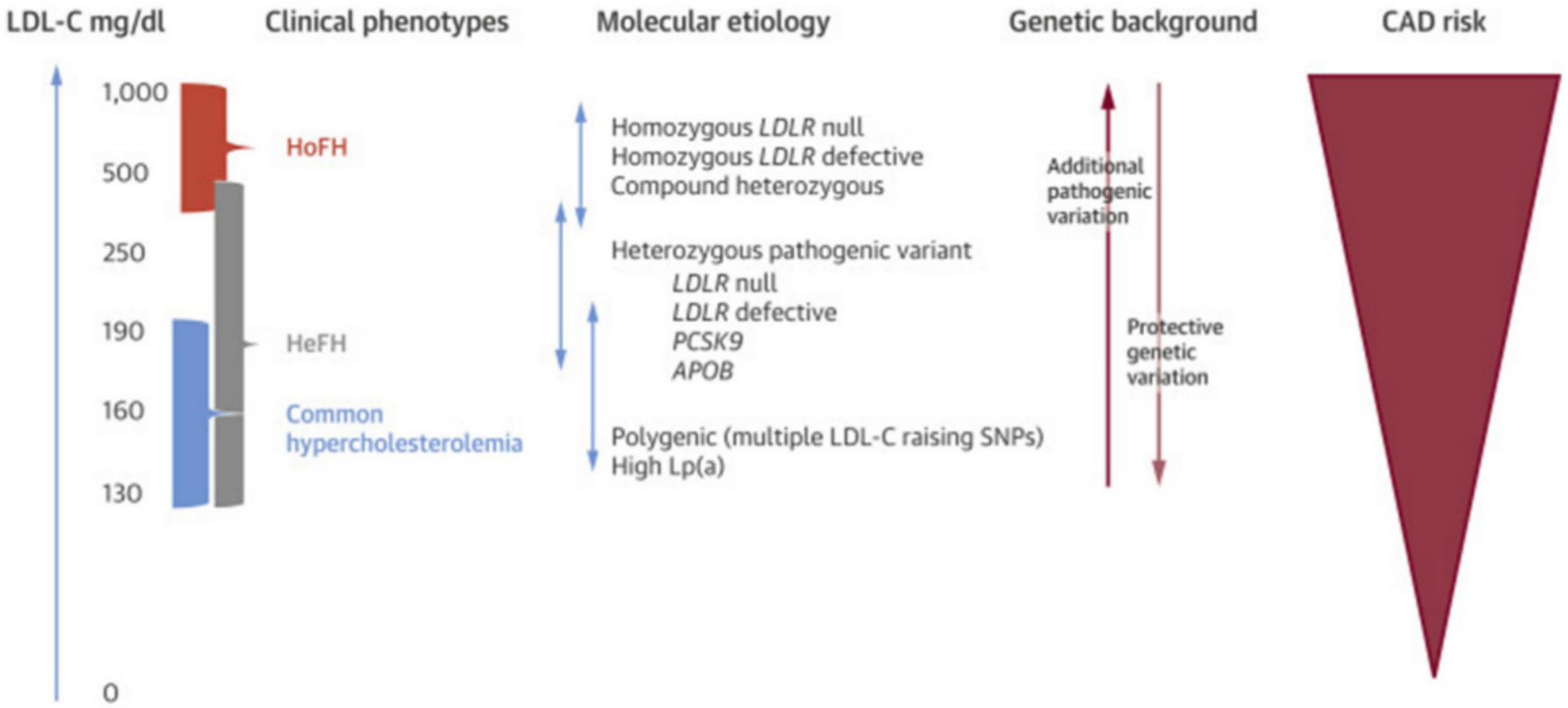


FIGURE 1 | Phenotypic, genotypic, and ASCVD risk spectrum of FH. Lp(a), lipoprotein (a). Other abbreviations as in text. Re-printed with permission from Elsevier (15).

Conclusion & Perspectives

- **Standard or care:**
  - Genetic testing for monogenic FH (*LDLR*, *APOB* and *PCSK9*)
  - Cascade screening in families
  - Should be offered in Québec province
- The use of **polygenic risk scores** requires further studies:
  - Management of FH patients NEG for monogenic testing
  - Risk assessment in FH patients POS for monogenic testing
  - Management of severe hypercholesterolemia patients
  - Clinical outcomes, feasibility, cost-effectiveness, reimbursement, ethics

Thank you!
Questions?