Clinical diagnosis versus molecular diagnosis of familial hypercholesterolaemia

Sara Berguete
Instituto Nacional de Saúde Dr. Ricardo Jorge

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Estudo Português de Hipercolesterolemia Familiar

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Introduction

Familial hypercholesterolemia (FH)

- Inherited disorder of cholesterol metabolism
- Monogenic disease
- Autosomal dominant
- Heterozygous prevalence of 1/500
- Increased cardiovascular risk
- WHO recommends FH screening

Clinical diagnosis

- Clinical history
- Physical signs
- Biochemical Markers
- Family history

Simon Broome Register Group (SBRG)

Dutch MEDPED Program (DMP)

Molecular diagnosis

LDLR

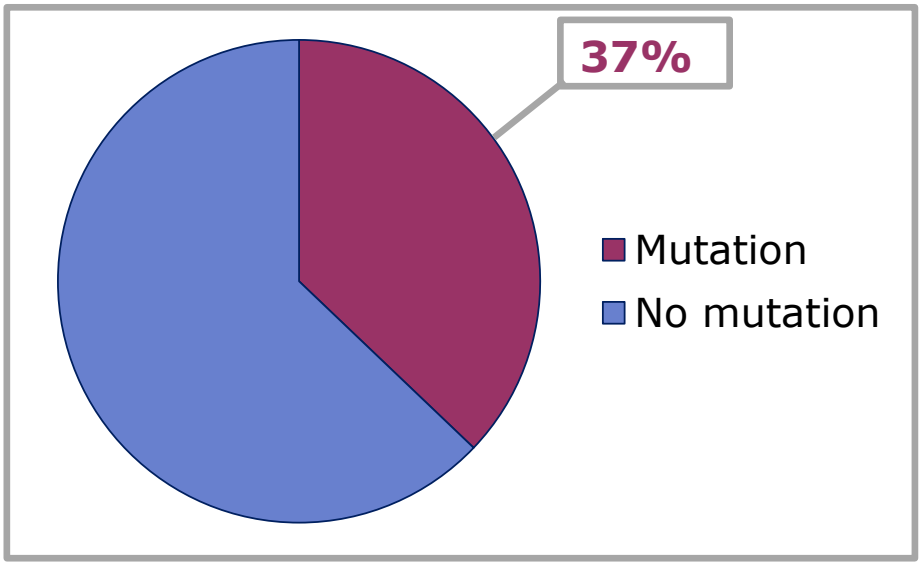
APOB

PCSK9

Introduction

Portuguese FH Study (PFHS)

13 years of PFHS



Mutation detection rate of 37%

AIM

- Use different clinical criteria to evaluate if is possible to improve the mutation detection rate
- Compare efficacy of the application of SBRG and DMP criteria to Portuguese índex patients with results of molecular study

Introdução

***Simon Broome Register Group* (SBRG) criteria for clinical diagnosis of FH**

	Criteria
Biochemical measurements	A. TC >290 mg/dL (>7.5 mmol/L) or LCL-C >190 mg/dL (>4.9 mmol/L) in an adult patient or TC >155 mg/dL (>4.0 mmol/L) or LDL-C >155mg/dL (>4.0 mmol/L) in a child patient under 16 years
Physical signs	B. Tendon xanthomas in the patient or in a first- or a second-degree relative of the patient
Family history	C. Myocardial infarction before 50 years in a first- or a second- degree relative or before 60 years in a first-degree relative of the patient
	D. TC >290 mg/dL (>7.5 mmol/L) in a first- or a second-degree relative of the patient
Molecular study	E. Mutation in LDLR gene or in any other gene that is related with HeFH
Diagnosis: **Definite HeFH → A+B or E** **Probable HeFH → A+C or A+D**	

Introdução

***Dutch MEDPED* (DMP) criteria for clinical diagnosis of FH**

	Criteria	Score
Family history	First-degree relative with premature coronary and vascular disease	1
	Plasma LDL-C>95th centile for age and sex in an adult relative	1
	Plasma LDL-C>95th centile for age and sex in a first-degree relative <18 years of age	2
	Tendon xanthomas or arcus cornealis in a first-degree relative	2
Personal clinical history	Premature coronary artery disease in the patient	2
	Premature cerebral or peripheral vascular disease in the patient	1
Physical signs	Tendon xanthomas in the patient	6
	Arcus cornealis in a patient under 45 years	4
Biochemical measurements	Patient with LCL-C >330 mg/dL (>8.5 mmol/L)	8
	Patient with LCL-C 250-329mg/dL (6.5-8.4 mmol/L)	5
	Patient with LCL-C 190-249 mg/dL (5.0-6.4 mmol/L)	3
	Patient with LCL-C 155-189 mg/dL (4.0-4.9 mmol/L)	1
Molecular study	Mutation in LDLR gene or in any other gene that is related with HeFH	8

Introdução

***Dutch MEDPED* (DMP) criteria for clinical diagnosis of FH**

Diagnosis	Score
Definite HeFH	>8
Probable HeFH	6-8
Possible HeFH	3-5

Methods

Sample

609 index patients already studied by the PFHS

- 236 children
- 373 adults

Molecular study

- ***LDLR***
- ***APOB***
- ***PCSK9***

Classification according to criteria for clinical diagnosis of FH

- SBRG criteria
- DMP criteria

Results and discussion

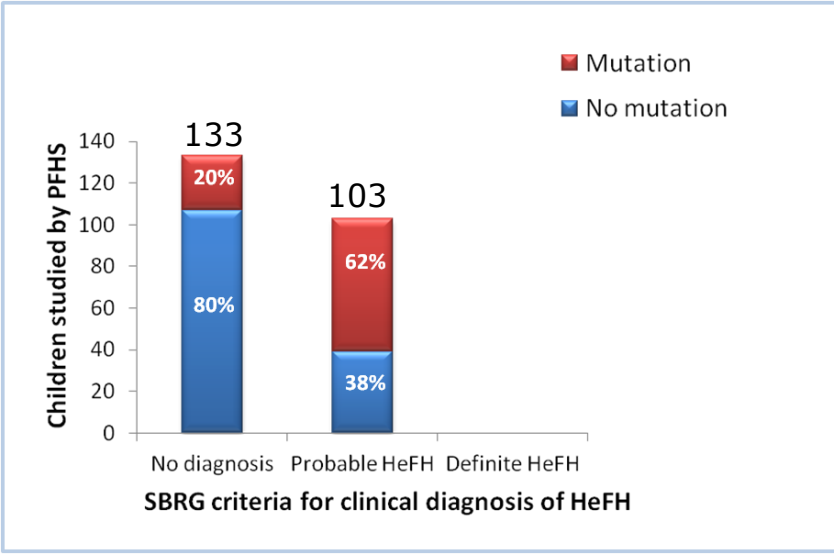
Criteria for clinical diagnosis of FH

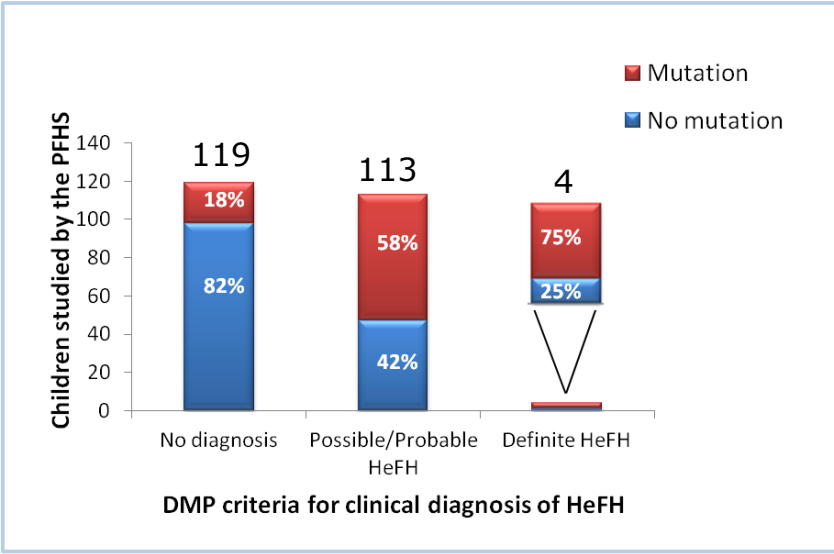
236 children – 90 with mutation (38%)

- **SBRG criteria**
  - Detection rate of 62% in probable HeFH
  - 26 false negative diagnosis
- **DMP criteria**
  - Detection rate of 59% in possible/probable/definite HeFH
  - 21 false negative diagnosis

Similar results

- False negative clinical diagnosis of FH is probably due to insuficient data or because the phenotype is milder in children (no environmental effect)
- Similar results when índex patients in each classification were divided by type of mutation



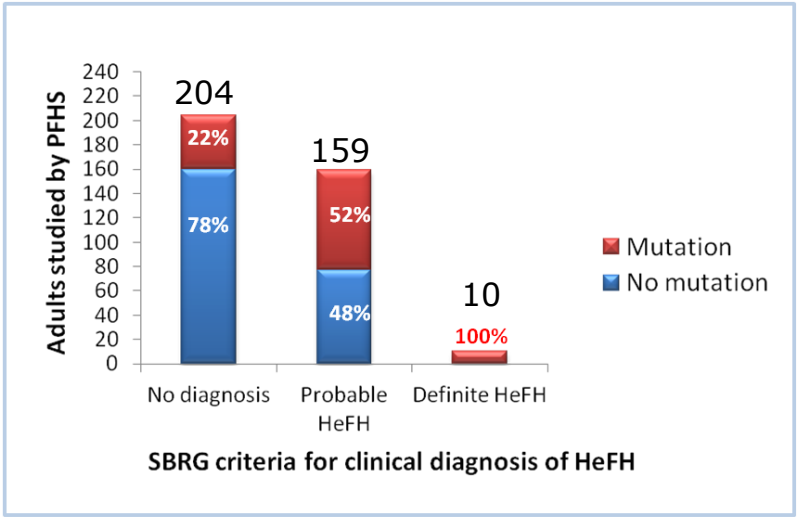


Results and discussion

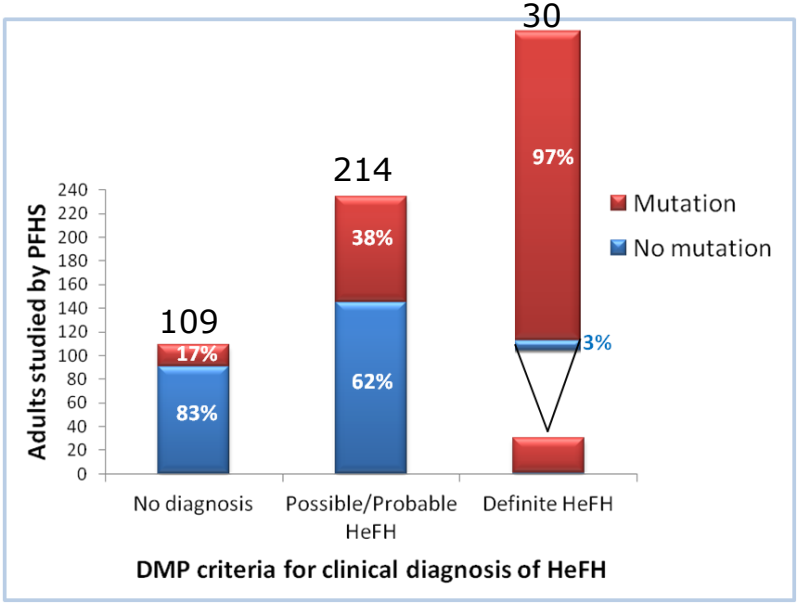
Criteria for clinical diagnosis of FH

373 adults – 136 with mutation (36%)

- **SBRG criteria**
  - Detection rate of 54% in probable/definite HeFH
  - 44 false negative diagnosis
- **DMP criteria**
  - Detection rate of 45% in possible/probable/definite HeFH
  - 18 false negative diagnosis



SBRG criteria for clinical diagnosis of HeFH



DMP criteria for clinical diagnosis of HeFH

Similar results

- False negative clinical diagnosis of FH is probably due to insuficient data
- Similar results when índex patients in each classification were divided by type of mutation

Conclusions

- Similar results with two criteria for clinical diagnosis of FH that misdiagnosed about 35% of the Portuguese índex patients
- Combine efforts to construct an international set of criteria in order to increase the detection of FH patients. It is necessary to improve the specifications of both criteria:
  - DMP
    - include a specific cut off for children
    - increase score for first relative with CAD
  - SBRG
    - include a diagnosis for probable FH for patients with established CAD
- This is a preliminary study that can open new ways to the clinical diagnosis of FH and improve the rate of identification of patients with high cardiovascular risk
- In the future we will perform a new evaluation of both criteria in Portuguese índex patients using the new specifications to see if we can improve the results

Grupo de Investigação Cardiovascular (GIC)
Departamento de Promoção da Saúde e Prevenção de Doenças Não Transmissíveis
Instituto Nacional de Saúde Dr. Ricardo Jorge
Lisboa, Portugal

Mafalda Bourbon

- Catarina Alves
- Ana Medeiros
- Flávia Leitão
- Elisete Duarte
- Isabel Picanço

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Portuguese Familial Hipercholesterolaemia Study

Center for Biodiversity, Functional & Integrative Genomics

Thank you