Clinical diagnosis versus molecular diagnosis of familial hypercholesterolaemia

Sara Berguete
Instituto Nacional de Saúde Dr. Ricardo Jorge

16ª Reunião Anual
Sociedade Portuguesa de Genética Humana

22 de Novembro de 2012
Porto
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

Molecular diagnosis

- LDLR
- APOB
- PCSK9

Simon Broome Register Group (SBRG)
Dutch MEDPED Program (DMP)
Introduction

Portuguese FH Study (PFHS)

13 years of PFHS

Mutation detection rate of 37%

AIM

Use different clinical criteria to evaluate if it is possible to improve the mutation detection rate.

Compare efficacy of the application of SBRG and DMP criteria to Portuguese index patients with results of molecular study.
### Simon Broome Register Group (SBRG) criteria for clinical diagnosis of FH

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biochemical measurements</strong></td>
<td>A. TC &gt;290 mg/dL (&gt;7.5 mmol/L) or LCL-C &gt;190 mg/dL (&gt;4.9 mmol/L) in an adult patient or TC &gt;155 mg/dL (&gt;4.0 mmol/L) or LDL-C &gt;155mg/dL (&gt;4.0 mmol/L) in a child patient under 16 years</td>
</tr>
<tr>
<td><strong>Physical signs</strong></td>
<td>B. Tendon xanthomas in the patient or in a first- or a second-degree relative of the patient</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td>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</td>
</tr>
<tr>
<td><strong>Molecular study</strong></td>
<td>D. TC &gt;290 mg/dL (&gt;7.5 mmol/L) in a first- or a second-degree relative of the patient</td>
</tr>
<tr>
<td><strong>Mutation</strong></td>
<td>E. Mutation in LDLR gene or in any other gene that is related with HeFH</td>
</tr>
</tbody>
</table>

**Diagnosis:**
- **Definite HeFH** → A+B or E
- **Probable HeFH** → A+C or A+D
### Dutch MEDPED (DMP) criteria for clinical diagnosis of FH

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-degree relative with premature coronary and vascular disease</td>
<td>1</td>
</tr>
<tr>
<td>Plasma LDL-C &gt; 95th centile for age and sex in an adult relative</td>
<td>1</td>
</tr>
<tr>
<td>Plasma LDL-C &gt; 95th centile for age and sex in a first-degree relative &lt; 18 years of age</td>
<td>2</td>
</tr>
<tr>
<td>Tendon xanthomas or arcus cornealis in a first-degree relative</td>
<td>2</td>
</tr>
<tr>
<td>Premature coronary artery disease in the patient</td>
<td>2</td>
</tr>
<tr>
<td>Premature cerebral or peripheral vascular disease in the patient</td>
<td>1</td>
</tr>
<tr>
<td>Tendon xanthomas in the patient</td>
<td>6</td>
</tr>
<tr>
<td>Arcus cornealis in a patient under 45 years</td>
<td>4</td>
</tr>
<tr>
<td>Patient with LCL-C &gt; 330 mg/dL (&gt; 8.5 mmol/L)</td>
<td>8</td>
</tr>
<tr>
<td>Patient with LCL-C 250-329 mg/dL (6.5-8.4 mmol/L)</td>
<td>5</td>
</tr>
<tr>
<td>Patient with LCL-C 190-249 mg/dL (5.0-6.4 mmol/L)</td>
<td>3</td>
</tr>
<tr>
<td>Patient with LCL-C 155-189 mg/dL (4.0-4.9 mmol/L)</td>
<td>1</td>
</tr>
<tr>
<td>Mutation in LDLR gene or in any other gene that is related with HeFH</td>
<td>8</td>
</tr>
</tbody>
</table>
### Dutch MEDPED (DMP) criteria for clinical diagnosis of FH

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite HeFH</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Probable HeFH</td>
<td>6-8</td>
</tr>
<tr>
<td>Possible HeFH</td>
<td>3-5</td>
</tr>
</tbody>
</table>
Methods

Sample

609 index patients already studied by the PFHS
• 236 children
• 373 adults

Molecular study

Classification according to criteria for clinical diagnosis of FH
• SBRG criteria
• DMP criteria

LDLR
APOB
PCSK9
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 insufficient data or because the phenotype is milder in children (no environmental effect)
• Similar results when index patients in each classification were divided by type of mutation

Introduction

Methods

Results and discussion

Conclusions
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

Similar results
- False negative clinical diagnosis of FH is probably due to insufficient data
- Similar results when index patients in each classification were divided by type of mutation
Similar results with two criteria for clinical diagnosis of FH that misdiagnosed about 35% of the Portuguese index 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 index 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
Thank you