EuroGentest: Harmonization, validation and standardization in genetic testing

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May 25th 2012
What is EuroGentest?

• = Coordination Action funded by the 7th Framework of the European Commission

• EuroGentest was set-up in 2004 by Prof. Jean-Jacques Cassiman as a response to a survey performed by IPTS/JRC-EC that highlighted major problems in genetic testing in Europe (Ibaretta et al., 2004)
Genetic testing

blood → DNA → laboratory

patient → counselling

analysis

interpretation & report

www.eurogentest.org
Main goals of EuroGentest

QUALITY

- **Harmonization** of genetic testing across Europe
- Support professionals in achieving **high quality** in all aspects of genetic testing services
- Provide **information** on genetic testing to professionals (e.g. CUGC’s and guidelines) and to the public (policy makers and patients)
Main goals of EuroGentest

Promote the implementation of **novel technologies** into current practice
What can EuroGentest do for you?

for Medical Professionals

Clinical Utility Gene Cards
Guidelines for Genetic Counseling
....

for Genetic Laboratories

Workshops
EQA
Best practice guidelines
...

for Patients & Family

Patient leaflets

www.eurogentest.org
Clinical Utility Gene Cards

= Disease specific guidelines
  – Clear
  – Concise
  – About the clinical utility of a genetic test
CUGC’s

DISEASE characteristics:
• Which gene(s)
• Which mutation(s)
• Which are the phenotypical and biochemical characteristics
• Sex or ethnicity correlation?
• validation options (guidelines, EQA) etc...

Clinical utility gene card for: haemophilia B

Peter Vincent Jenkins, Catriona Keenan, Steve Keeney, Tony Cumming and James S O’Donnell

European Journal of Human Genetics advance online publication, 25 January 2012; doi:10.1038/ejhg.2011.268

1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonym/s)
Haemophilia B, Hemophilia B, (Christmas disease, heritable Factor IX deficiency).

1.2 OMIM# of the disease
306090.

1.3 Name of the analysed genes or DNA/chromosome segments
Factor IX (F9).

1.4 OMIM# of the gene(s)
300746.

1.5 Mutational spectrum
Haemophilia B results from the deficiency of blood coagulation factor IX (FIX). All heritable cases of haemophilia B are due to mutations in or near the factor IX gene (F9). The gene located on Xq27.1–27.2 is ∼36 kb long and comprises eight exons. Severe haemophilia (FIX<1% of normal) is caused by a wide spectrum of mutations including...

1.6 Estimated frequency of the disease (incidence at birth (‘birth prevalence’ or population prevalence)
1.1–4.3 per 100,000 males.

1.7 If applicable, prevalence in the ethnic group of investigated person
No known ethnic variation in prevalence; however, there is variation in detection and diagnosis.

1.8 Diagnostic setting

<table>
<thead>
<tr>
<th></th>
<th>Differential diagnosis</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Predictive testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Risk assessment in relatives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Provenance</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comment: Haemophilia B is an X-linked disorder. Diagnosis of affected males is by laboratory measurement of functional factor IX levels (FIX:C). Possible carriers are definitively diagnosed by DNA analysis.
nonsense, missense, splice site mutations and less commonly by large and small indels. Moderate and mild haemophilia (FIX 1–4%, and 5–40%, respectively) are generally caused by missense mutations or less commonly splice-site alterations. A locus-specific database for haemophilia B mutations is available at http://www.kcl.ac.uk/ip/petergreen/haem8database.html.

1.6 Analytical methods
Typically standard PCR of genomic DNA and direct resequencing of essential coding and flanking regions is performed.1,2 Mutation screening methods have been described.3-5 Multiplex ligation-dependent probe amplification can be applied for determination of large insertions or deletions.6

1.7 Analytical validation
A guideline for recommended practice in the molecular analysis of haemophilia B is available.1 This discusses analytical design, mutation validation procedures, and analytical pitfalls. External quality assurance (EQA) should be carried out where available. An EQA scheme has been established for genetic investigation of haemophilia, details of this scheme are available from UK NEQAS for Blood Coagulation (http://www.ukneqasbc.org).7 Use of internal controls, especially in the analysis of extended family members is recommended.

analysis of the mutation site once the underlying mutation has been determined in a related affected male index. Molecular analysis can aid differential diagnosis by linkage of mild FIX deficiency to the F9 gene.

Predictive testing in general does not apply as males with a clinically significant F9 mutation will be affected as shown by a low FIX:C level. In certain rare cases molecular testing can predict amelioration of the disease with increasing age (see 2.4 below).

Prenatal diagnosis is available, preimplantation genetic diagnosis is possible for haemophilia B.9 Knowledge of carrier status can inform clinical management of antenatal delivery.

2. TEST CHARACTERISTICS

<table>
<thead>
<tr>
<th>Genotype or disease</th>
<th>A: True positives</th>
<th>B: False positives</th>
<th>C: False negatives</th>
<th>D: True negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td></td>
<td></td>
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<td></td>
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</table>

<table>
<thead>
<tr>
<th>Test</th>
<th>Positive</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>A/(A+Q)</td>
<td>D/(D+B)</td>
<td>A/(A+B)</td>
<td>D/(D+E)</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

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TEST characteristics:
- Sensitivity and specificity
- Analytical as well as clinical
Clinical utility: what is the clinical ‘value’ of performing the test:
- Are there alternative tests?
- Are these more expensive or burdensome for the patient?
- Does the result of the test has an impact on the patients life (therapy, way of life, reproductive choices)?
- What is the impact on relatives?
CUGC’s

- Peer-reviewed
- Published in the European Journal of Human Genetics (EJHG)
- Open access
- Up-to-date
- List available on the EuroGentest website
Workshops - Training on QAu and accreditation

• Several different workshops in different countries, languages
• Specific topics: ISO15189 accreditation for beginners, validation, quality management systems, etc...
• Interactive, sharing experiences with colleagues from all over Europe

Check the schedule on our website and join one of our future workshops!

www.eurogentest.org
EQA

= External Quality Assessment

="A system of **objectively assessing the laboratory performance by an outside agency.** ... The main objective of external quality assessment is to establish inter-laboratory compatibility" (WHO 1981)
EQA

Your laboratory

Look up in which EQA scheme you wish to participate and register online with the appropriate EQA provider

Test the sample with routine method

Analyze data and write report

Discuss with the laboratory

EQA provider

Sample preparation + mock clinical case or online clinical information*

Assessment of the results

General report and individual comments + certificate if successful

*Depending on the EQA type
15 different leaflets with general information on genetic testing:

What is a Genetic Test?
The Amniocentesis
Chorionic Villus Sampling (CVS) Test
Carrier Testing
Predictive Testing
Predictive Testing for Inherited Cancer
Dominant Inheritance
Recessive Inheritance
X Linked Inheritance
Chromosome Changes
Chromosome Translocations
Some Information About Your Genetic Appointment
What Happens in a Genetics Laboratory
Genetic Glossary
Frequently Asked Questions About Genetic Testing
Patient leaflets

- Available in 28 languages
- Free to download on the EuroGentest website
Thank you for your attention.