The Pharmacogenomics Biobank of the University of Southern Denmark

Primary researchers
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Introduction

• Aim
• Approval
• Methods
• Study cohort
• Examples of use
• External user/ How to use the biobank?

• Information slides handed out on request
Aim of the biobank

1. To study the genetic variation and frequencies of genes coding for:
   1. Receptors
   2. Proteins related to pharmacokinetic and -dynamic processes relevant for drug response in a cohort of Danish healthy volunteers.

2. To recruit healthy volunteers, based on genotype, for future clinical pharmacological drug studies.

3. To have a passive healthy genotyped reference cohort for patients or other different cohorts.
Approval

• Established in the autumn of 2010.

• Approved by the Danish Data Protection Agency (J. no. 2010-41-5131)

• The Scientific Ethics Committee declared itself indifferent to the establishment

  – However, it was stated that future studies based on genotypes from the biobank must be evaluated individually by the Committee.
Methods

• **Blood samples:**
  – 2 samples of 5 mL K-EDTA blood

• **DNA extraction:**
  – Maxwell®16 (Promega corporation, Woods Hollow, Madison, WI, USA)
  – The DNA extractions are kept at -80°C.

• **Data analysis and security:**
  – All data are kept at protected servers at the Institute of Public Health, Clinical Pharmacology, University of Southern Denmark.
Genetic variation

• All genetic variations have a dbSNP ID:
  – Single nucleotide polymorphism database identification number.
  – Ex. rs72552763

• StepOnePlus
  – Few SNPs

• OpenArray
  – Many SNPs
  – Many samples

• Sanger sequencing
  – Long sequences
  – Deletions
  – Etc.

Determination of genotype of A270S in OCT2 in healthy volunteers. M MH Christensen 2010
Study cohort

• Recruited mainly among students and employees at the University of Southern Denmark, Odense, Denmark.

• Contains 387 self-declared healthy volunteers:
  – aged between 18 and 65 years
  – not taking medication on a regular basis, except contraceptives.

[Pie chart showing gender distribution: 52% Male, 48% Female]
Age distribution March 2011

Mean: 24 years, range: 19-58 years
Ethnicities

93% Caucasians (n 359)

7% Non-Caucasians (n 28)
- Mixed origin (n 11)
- African (n 3)
- Asian (n 8)
- Middle East (n 6)
### Genotype distribution within a cohort of ‘400’

<table>
<thead>
<tr>
<th>Allele frequency</th>
<th>Homozygote wildtype</th>
<th>Heterozygote</th>
<th>Homozygote variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>100</td>
<td>200</td>
<td>100</td>
</tr>
<tr>
<td>30%</td>
<td>196</td>
<td>168</td>
<td>36</td>
</tr>
<tr>
<td>10%</td>
<td>324</td>
<td>72</td>
<td>4</td>
</tr>
<tr>
<td>5%</td>
<td>361</td>
<td>38</td>
<td>1</td>
</tr>
</tbody>
</table>
Examples of use

Passive studies:
- Death among drug addicts caused by intoxication with morphine and methadone and the impact of pharmacogenetic factors
  - D Rollmann MSc, Department of Forensic Toxicology, Institute of Forensic Medicine.

Active studies:
- Pharmacokinetic:
  - Reduced/abolished inhibitory effect of oral contraceptives on the CYP2C19*17 allele
    - R S Pedersen MSc PhD, Department of Clinical Pharmacology, Institute of Public Health
  - A pharmacokinetic evaluation of metformin in relation to the polymorphism A270S in healthy volunteers
    - M MH Christensen MD, Department of Clinical Pharmacology, Institute of Public Health

- Pharmacodynamic:
  - Metformin’s Inhibition of the gluconeogenesis in relation to reduced-function polymorphisms in OCT1 in healthy volunteers
    - M MH Christensen MD, Department of Clinical Pharmacology, Institute of Public Health
The impact of pharmacogenetic factors on death among drug addicts

• Hypothesis:
  – Pharmacogenetic factors increase risk of fatal intoxication among drug addicts using morphine or methadone

• SNPs investigated in genes for:
  - Metabolism:
    CYP2B6, CYP2C19, CYP3A4
    COMT Catechol-O-methyltransferase
    UGT2B7 UDP glucuronosyltransferase
  - Transport:
    P-glycoprotein ABCB1
  - Receptor:
    µ-opioid receptor

Study design:
  - ‘Passiv’ case-control

Genotyping method
  Many samples + many SNPs = Open array
Inhibitory effect of oral contraceptives at CYP2C19*17

- **Hypotesis:** Oral contraceptives have reduced inhibitory effect in women with the CYP2C19*17 allele.

- **Study-design:** Active case-control study (n=33)

- **Method:**
  - OC ± omeprazol

**Not a classic clinical trial using a medicinal product**

Omeprazol is used as a study tool – not a drug.

The study should not be reported to The Danish Medicines Agency
Impact of **A270S** at the renal clearance of metformin

*Classic geno- to phenotype study*

**Hypothesis**
- The genetic variant A270S in *OCT2* changes renal clearance of metformin

**One period case-control study**
- Wildtype, heterozygote, homozygote variant

**Method**

\[
\text{AUC} = \frac{\text{Total Amount excreted unchanged}}{\text{Renal Clearance}}
\]
How can you use this?

• Your research must focus on:
  – ADME
  – Receptors
  – We do not explore genes related to a particular disease

• You need a healthy cohort to:
  – Set up a clinical geno- to phenotype study
  – know the distribution of genotypes within healthy Danish individuals for comparison with patients/other cohorts.

• Costs depend on:
  – the method
  – the number of SNPs
  – etc.
Interested?

• For more information:
  1. Email
     rspedersen@health.sdu.dk
     mmchristensen@health.sdu.dk
  2. Phone +45 6550 3788
Information for participants
Declaration of consent

Informeret samtykke for deltagelse i en forskningsbiobank.

Den frivillige deltager skal selv udfylde samtykket og de personlige oplysninger

<table>
<thead>
<tr>
<th>Samtykke til forskningsbiobanken</th>
<th>Sæt kryds.</th>
<th>Ja</th>
<th>Nej</th>
</tr>
</thead>
<tbody>
<tr>
<td>Har du læst den udeleverede information om biobanken?</td>
<td>☐</td>
<td>☐</td>
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<tr>
<td>Har du fået nok information og haft mulighed for at stille spørgsmål?</td>
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<tr>
<td>Har du haft tid nok til at tage din beslutning?</td>
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<tr>
<td>Jeg giver samtykke til, at mit biologiske materiale efter udelogelse må opbevares i en forskningsbiobank</td>
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<tr>
<td>Jeg giver samtykke til, at mit biologiske materiale må blive brugt til forskning i de genør, der påvirker lægemidler effekt og udstødning i kroppen.</td>
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<tr>
<td>Jeg giver samtykke til, at forskere og læger ved Elhoc Farmakologi, Sydhavn Universitetet, Odense må kontakte mig med hensyn på mulig deltagelse i fremtidige lægemiddelforsøg</td>
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Personal oplysninger (BLOKBRUGSTAVER)

<table>
<thead>
<tr>
<th>Navn:</th>
<th>E-mail:</th>
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<tbody>
<tr>
<td>Vej:</td>
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<td>Postnr.:</td>
<td>By:</td>
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<td>Telefon:</td>
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<td>Cpr.-nummer:</td>
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</tbody>
</table>

DATO: UNDERSKRIFT:

Udfyld af investigator ved bloxovertagning:

DATO:

NAVN:

Tildeling af deltagers ID: Initialet Nummer