The HUNT Study and potential for innovation and industry research collaboration

Professor Kristian Hveem, MD, PhD,
Director of HUNT biobank, NTNU
Head of Biobank Norway (BBMRI.no)
Head of K.G. Jensen Center for Genetic Epidemiology
The HUNT study

- Consent based
- Longitudinal, prospective design with repeated measurements
- Linkage by PIN to registry data and EHR form the local hospitals
- State-of-the-art, large scale biobank
- 170 PhDs, 100 peer reviewed papers annually
Biomarker discovery
Incident cancer cases from HUNT2 (1995-1997) to 2012 based on linkage to the Cancer Registry

<table>
<thead>
<tr>
<th>Years from HUNT2 visit to cancer diagnosis</th>
<th>0 to 1 year</th>
<th>1 to 2 years</th>
<th>2 to 3 years</th>
<th>3 to 4 years</th>
<th>4 to 5 years</th>
<th>5 to 10 years</th>
<th>&gt; 10 years</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>57</td>
<td>73</td>
<td>77</td>
<td>78</td>
<td>77</td>
<td>443</td>
<td>590</td>
<td>1395</td>
</tr>
<tr>
<td>Colon</td>
<td>42</td>
<td>55</td>
<td>50</td>
<td>56</td>
<td>44</td>
<td>310</td>
<td>439</td>
<td>996</td>
</tr>
<tr>
<td>Breast</td>
<td>42</td>
<td>53</td>
<td>51</td>
<td>48</td>
<td>56</td>
<td>312</td>
<td>429</td>
<td>991</td>
</tr>
<tr>
<td>Lung</td>
<td>37</td>
<td>38</td>
<td>31</td>
<td>25</td>
<td>38</td>
<td>239</td>
<td>365</td>
<td>773</td>
</tr>
<tr>
<td>Melanoma</td>
<td>18</td>
<td>17</td>
<td>11</td>
<td>27</td>
<td>20</td>
<td>127</td>
<td>204</td>
<td>424</td>
</tr>
<tr>
<td>Rectum</td>
<td>22</td>
<td>24</td>
<td>18</td>
<td>17</td>
<td>21</td>
<td>143</td>
<td>171</td>
<td>416</td>
</tr>
<tr>
<td>Ureter, bladder</td>
<td>15</td>
<td>22</td>
<td>16</td>
<td>29</td>
<td>24</td>
<td>139</td>
<td>163</td>
<td>408</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>14</td>
<td>13</td>
<td>17</td>
<td>10</td>
<td>15</td>
<td>96</td>
<td>114</td>
<td>279</td>
</tr>
<tr>
<td>Leukemia</td>
<td>12</td>
<td>7</td>
<td>8</td>
<td>11</td>
<td>15</td>
<td>82</td>
<td>144</td>
<td>279</td>
</tr>
<tr>
<td>Pancreas</td>
<td>12</td>
<td>13</td>
<td>7</td>
<td>11</td>
<td>16</td>
<td>66</td>
<td>108</td>
<td>233</td>
</tr>
<tr>
<td>Kidney</td>
<td>14</td>
<td>8</td>
<td>11</td>
<td>11</td>
<td>13</td>
<td>76</td>
<td>100</td>
<td>233</td>
</tr>
<tr>
<td>Stomach</td>
<td>8</td>
<td>11</td>
<td>27</td>
<td>11</td>
<td>16</td>
<td>79</td>
<td>73</td>
<td>225</td>
</tr>
<tr>
<td>Uterus</td>
<td>13</td>
<td>12</td>
<td>7</td>
<td>12</td>
<td>15</td>
<td>64</td>
<td>83</td>
<td>206</td>
</tr>
<tr>
<td>Ovaries</td>
<td>5</td>
<td>9</td>
<td>11</td>
<td>7</td>
<td>12</td>
<td>37</td>
<td>65</td>
<td>146</td>
</tr>
<tr>
<td>Myeloma</td>
<td>2</td>
<td>6</td>
<td>4</td>
<td>9</td>
<td>2</td>
<td>46</td>
<td>56</td>
<td>125</td>
</tr>
<tr>
<td>Cervix</td>
<td>1</td>
<td>4</td>
<td>6</td>
<td>4</td>
<td>5</td>
<td>15</td>
<td>32</td>
<td>67</td>
</tr>
<tr>
<td>Testis</td>
<td>3</td>
<td>2</td>
<td>6</td>
<td>3</td>
<td>6</td>
<td>27</td>
<td>20</td>
<td>67</td>
</tr>
<tr>
<td>Thyroid</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>15</td>
<td>28</td>
<td>54</td>
</tr>
<tr>
<td>Liver</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>12</td>
<td>24</td>
<td>38</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>15</td>
<td>8</td>
<td>35</td>
</tr>
<tr>
<td>Total</td>
<td>321</td>
<td>374</td>
<td>364</td>
<td>374</td>
<td>398</td>
<td>2343</td>
<td>3216</td>
<td>7390</td>
</tr>
</tbody>
</table>
HUNT biobank
(European Research Biobank of the year – 2013)

Biological material
H1-3 DNA from 80 000
H2 Serum from 65 000,
H3 Serum/plasma from 50 000, immortalized cells 20 000, Trace metals 20 000, mRNA 14000, urine 12 000
H4 50 000 (serum, plasma, buffy coat, urine, saliva, fecal samples)

National CONOR-biobank –
DNA from 230 000 (HUNT, Tromsø, HUSK, HUBRO, Oslo 1 og 2, Troms og Finnmarksus. + +)

Automatized solutions
• DNA-extraction, QC and normalization
• - 80 °C automated storage (13 mill samples)

Manual/semi-manual solutions
• - 196 °C nitrogen storage (3 mill samples)
• - 80 °C freezers, (3 mill samples)

ISO-9001 certified since 2011
HUNT Databank, unique resource for researchers nationally and internationally

(ISO-9001 certified since 2011)

HUNT Databank

HUNT Databank manages the data gathered in the HUNT Study and associated studies. This web application presents the associated metadata - i.e. not the actual, individual results from the various questionnaires, interviews and measurements that constitute the HUNT Study, but descriptions of them: An overview of HUNT's surveys, studies and study parts; of the selections and response rates of each; of the variables they encompass, with question text, sources and references, frequencies and descriptive statistics. It contains no person-level data from the HUNT participants.

Organisation

Questionnaires, interviews and measurement/analysis sets are collectively called Study Parts. A typical example is Questionnaire 1 from HUNT3. A Study Part is a collection of Variables, as well as the unit of participation in HUNT. Related Study Parts are grouped into Studies (e.g. the HUNT2 Lung Study), which in turn are grouped into the main HUNT Surveys (HUNT1, HUNT2, HUNT2, the Young-HUNT Surveys etc.) This structure is reflected in the tree list to the left, under the tab Study Parts.

An alternative organisation is presented under the tab instruments. Variables may be characterised as belonging to or arising from a particular instrument - be it a physical piece of laboratory equipment like an osteometer, or a validated questionnaire like HADS.

About HUNT Databank

The HUNT Databank software is created and maintained by Jon Heggland.

Organisation and quality assurance of the HUNT data is managed by Annuf Langhammer and Bitte Dillan.

This web application is a work in progress. Planned improvements/extensions include facilities for applying for research rights and variable data, and alternative organisations of variables (e.g. based on topics or disease cohorts).
Selection criteria and method: Questionnaire sent together with the invitation to everyone aged 20 years or more.


Responsible for collection: HUNT

Cohorts
The following participants/cohorts were invited to participate in this studypart.

<table>
<thead>
<tr>
<th>Cohort Name</th>
<th>Cohort Description</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT3inv</td>
<td>HUNT 3 invites. Basically, this is all Nord-Trøndelag residents aged 20 or more at the time.</td>
<td>93860</td>
</tr>
</tbody>
</table>
HUNT Data center and computer cloud
Oddgeir Lingaas Holmen, Tom Erik Røberg, Sandor Zeestraten

- Secure storage of sensitive data
- Open stack-solutions for secure access and analyses with sufficient computational resources to provide analytical resources and preserve data on data owner’s hand
- ISO-9001 certified June 2017
- ISO 20017 Oct 2017
The all-in project

- GWAS-genotyping of 72,000 HUNT-participants (Human Core Exome, 604,000 genetic markers including 60,000 custom “HUNT SNPs”)
- Imputed up till 30 mill genetic markers against HRC-reference panel
- CVD as main focus, 64 sub-studies on various other disease categories
- Challenging the ethics with variants such as FH, BRCA

- > 150 collaborating clinicians (phenotype experts)
- EthiCert
  - Introducing an ethical certificate (OL Holmen, S. Gartmann, L Ursin)

Human Core Exome
604,000 genetic markers
• GWAS-analyses has so far been conducted on > 1500 binary or quantitative traits based on > 7000 unique variables from HUNT Data bank
• A second round on GWAS is ongoing based on ICD-codes
• A Phewas approach is running in parallel and a HUNT Pheweb has been established
HUNT Pheweb

4 : 88,766,218 G / GGAAA

Category
- Macro-skeletal system & connective tissue
- Macro-skeletal system & connective tissue
- Macro-skeletal system & connective tissue
- Macro-skeletal system & connective tissue
- Macro-skeletal system & connective tissue
- Macro-skeletal system & connective tissue
- Macro-skeletal system & connective tissue
- Circulatory system

Phenotype
- BV-OUHCor NT23MV01
- BV-OUHCor NT23MV01
- BV-OUHCor NT23MV01
- BV-OUHCor NT23MV02
- BV-OUHCor NT23MV02
- BV-OUHCor NT23MV02
- BV-OUHCor NT23MV02
- LBBB

P-value
- 2.6e-17
- 1.4e-13
- 2.6e-13
- 2.6e-10
- 4.7e-6
- 2.6e-7
- 5.0e-6
- 1.2e-5

Number of samples
- 19966
- 19950
- 19579
- 19500
- 5591
- 5524
- 5399
- 85 / 68314

www.ntnu.no

Norwegian University of
Science and Technology
Scientific approach

- **Precision medicine** - studying health and disease outcome related to genetic variation
- **GWAS-approach** based on self-reported and measured health data and phenotypic classification (validated ICD-codes)
- **Prioritizing genes for functional follow-up**
- **Mendelian randomization** for identifying causal relations
- **Identifying rare variants** as potential drug targets
- **Pharmacogenomics**
Systematic evaluation of coding variation identifies a candidate causal variant in TM6SF2 influencing total cholesterol and myocardial infarction risk

Oddgeir I. Holmen1,3,13, He Zhang1,3, Yanbo Fan1,3, Daniel H Hovelson1,3, Ellen M Schmidt1,3, Wei Zhou2, Yanhong Guo2, Ji Zhang1, Arnulf Langhammer1, Maja-Lisa Lochen1, Santhi K Ganesh1, Lars Vatten2, Frank Skrøpen2, Håvard Dalen3,10, Jifeng Zhang6, Subramaniam Pennathur11, Jin Chen1, Carl Platou3, Ellisiv B Mathiesen12,13, Tom Wilskaard1, Inger Njølstad2, Michael Boehnke12, Y Eugene Chen1, Gonçalo R Abecasis4, Kristian鲱een1,3 & Cristen J Willer3,4,6

Blood lipid levels are heritable, treatable risk factors for cardiovascular disease. We systematically assessed genome-wide coding variation to identify new genes influencing lipid traits, fine map known lipid loci and evaluate whether low-frequency variants with large effects exist for these traits. Using an exome array, we genotyped 80,137 coding variants in 5,643 Norwegians. We followed up 18 variants in 4,666 Norwegians and identified ten loci with coding variants associated with a lipid trait (p < 3 × 10⁻⁸). One variant in TM6SF2 (encoding p.Glu162Ivs), residing in a known genome-wide association study locus for lipid traits, influences total cholesterol levels and is associated with myocardial infarction. Transient TM6SF2 overexpression or knockdown in mouse serum lipid profiles, consistent with the association observed in humans, identifying TM6SF2 as a functional gene within a locus previously known as NCAN-CHRF-PBX4 and 19q13. This study demonstrates that systematic assessment of coding variation can quickly point to a candidate causal gene.

- Exome chip analyses of 5643 HUNT participants
- Replicated in 4666 participants from the Tromsø study.
- Genotyped at GCF/NTNU
- Functional follow-up in mouse models (E Chen/UM)
- Financed by NTNU, RCN and NIH
Protective gene against type 2 diabetes

Loss-of-function mutations in SLC30A8 protect against type 2 diabetes.


Abstract

Loss-of-function mutations protective against human disease provide in vivo validation of therapeutic targets, but none have yet been described for type 2 diabetes (T2D). Through sequencing or genotyping of ~150,000 individuals across 5 ancestry groups, we identified 12 rare protein-truncating variants in SLC30A8, which encodes an islet zinc transporter (ZnT8) and harbors a common variant (p.Trp325Arg) associated with T2D risk and glucose and proinsulin levels. Collectively, carriers of protein-truncating variants had 65% reduced T2D risk (P = 1.7 x 10^-6), and non-diabetic Icelandic carriers of a frameshift variant (p.Lys34Serfs*50) demonstrated reduced glucose levels (-0.17 s.d., P = 4.6 x 10^-4). The two most common protein-
HUNT –
A national knowledge base for better public health strategies
Helseatlas HUNT
Variation in Diabetes
Obesity female
Total andel med fedme i HUNT3: 23,5%.

Adult obesity prevalence: Women age 30-69 years

Obesity, male
Total andel med fedme i HUNT3: 22,5%.

Fedme er mer utbredt utenfor tettbygde strek.
Organizational Phase Participants (Phase 1 Status)

- abbvie
- Merck
- Janssen
- TEVA
- Sanofi
- Bristol-Myers Squibb
- GSK
- Takeda Pharmaceutical Company Limited
- Biogen
- UCB
- WuXiNextCODE
- Genomics plc
- McKinsey & Company
- NTNU HUNT Research Centre
- Genomic Aggregation Project in Sweden (GAPS)
- Biobanking Partners (6)

- Yes (4)
- Pending (4)
- Tentative No (1)
- No (1)
- New Prospects (3)
## GRC’s Phase 1 bio-banking partnerships

### Key criteria

<table>
<thead>
<tr>
<th>Data scale and quality</th>
<th>Assessment</th>
<th>Target biobank partners</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Large, diverse population</td>
<td>Identified ~300 international biobanks</td>
<td>Go-SHARE, NTNU, Karolinska Institutet, UNIVERSITY-TARTU, biobank.uk</td>
</tr>
<tr>
<td>▪ Genomic and clinical/outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Select “Founder” cohorts</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Data accessibility</th>
<th>Surveyed and interviewed ~25 leading biobanks</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Broad patient consents</td>
<td></td>
</tr>
<tr>
<td>▪ Banks warrant proper consents</td>
<td></td>
</tr>
<tr>
<td>▪ Data access policies</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Openness to “win-win” partnerships</th>
<th>Targete9 key biobanks</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Strong Partnering Orientation</td>
<td></td>
</tr>
<tr>
<td>▪ Shared values/mission</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase 1 Research Collaboration</th>
<th>Engaged in partnership discussions and negotiations (5 initial BBs for Phase 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Large existing datasets</td>
<td></td>
</tr>
<tr>
<td>▪ General &amp; Disease projects</td>
<td></td>
</tr>
<tr>
<td>▪ Identify with GRC mission</td>
<td></td>
</tr>
</tbody>
</table>

* Phase 1 data and data handling feasibility studies bio-banking participants.
PPP Case study: HUNT collaboration with Somalogic

Value creation for HUNT:
- Publications
- Knowledge transfer
- Data points
- Add-on research
- Revenue

---

Development and Validation of a Protein-Based Risk Score for Cardiovascular Outcomes Among Patients With Stable Coronary Heart Disease

Peter Ganz, MD; Bettina Heidecker, MD; Kristian Hveem, MD, PhD; Christian Jonasson, PhD; Shintaro Kato, MS; Mark R. Segal, PhD; David G. Sterling, PhD; Stephen A. Williams, MD, PhD

ORIGINAL INVESTIGATION | INNOVATIONS IN HEALTH CARE DELIVERY

HUNT and industrial collaboration

- HUNT Biosciences 2007-2013
- Lifandis 2012-2015
- Christian Jonasson 2015 – Industrial/innovation officer – HUNT/NTNU

- Ongoing negotiations with several industry partners for large scale omics analyses
  - WES, WGS, Metabolomics
Thank you
BRCA-mutations in HUNT

- Recently started PhD-project
- Approval by REC dependent on the strategy for return of results
- Follow-up of incident cancers for > 20 yrs
- How many participants with BRCA-mutations have developed BRCA-related cancers, and how many have not?
- Retesting and clinical follow-up of cases
Summary

• There are reasonable guidelines
• We should be able publish frequency data, also on known genetic variants, without initial feedback to the participants
• We should be able to study the population based phenotypic penetrance of an actionable genetic variant before reporting back
• Communication with the donors, such as the establishment of “my page" is a necessary measure
• The participants are in favor of genetic recall
• We need an ongoing, dynamic communication with REK and NEM
Thank you