Scanning Population-Based Biobanks to Identify a Rare Gene Variant for Myocardial Infarctions

The HUNT Biobank and Lifandis AS provide access to biological samples and corresponding clinical data from more than 250,000 individuals in the Norwegian population.

Introduction

Biobanks are time capsules for genomic information, storing biological samples, such as blood, saliva, cells, or tissues, with the anticipation of discovery at a future date. They provide a snapshot of a specific moment in time that we can use to learn more about human disease and disorder, as well as human health and well-being. With today's current technological advancements, these samples are gaining even more importance. We now have the tools to mine the data hidden within them and the bioinformatics support to interpret the findings. We can genotype these stored samples, identify variants, and connect genetic changes to disease.

Kristian Hveem and Ove V. Solesvik are linking this data to electronic medical records (EMRs) and national health registries, using this information to increase disease understanding in the Norwegian population, with the overall goal of improving health care. There are two crucial components to making the connection between genetics and disease: sample access and analysis methods. Enter the HUNT Biobank, providing access to samples from 80,000 participants in the HUNT Study collected over the last 20 years plus DNA from 250,000 individuals in a national biobank[1].

In the early 1990s, Dr. Hveem, a clinical epidemiologist with specialization in internal medicine and gastroenterology at the Norwegian University of Science and Technology (NTNU) joined the Nord-Trøndelag Health Study (HUNT Study). The goal of the HUNT Study, one of the largest and most comprehensive health studies ever performed, was to collect samples over the years from a representative cohort of the Norwegian population. In the process, the HUNT Study became a unique database of personal and family medical histories, establishing a ready sample source for genome-wide association studies (GWAS).

Kristian Hveem, M.D., PhD., (left) is a Professor at the Norwegian University of Science and Technology (NTNU) and the Director of the HUNT Biobank. **Ove V. Solesvik, M.Sc.**, (right) is Chief Executive Officer of Lifandis AS (formerly Hunt Biosciences).

To analyze this multitude of samples, Dr. Hveem is collaborating with a core genotyping facility at NTNU using the Infinium® HumanExome BeadChip. The HumanExome BeadChip consists of > 247,000 SNPs and can analyze 12 samples simultaneously. Based on these results, Dr. Hveem, Dr. Oddgeir Lingaas Holmen (a researcher at NTNU), and their collaborators at the University of Michigan were able to draw correlations between genotype and susceptibility to disease within the Norwegian population. Recently, they used this approach in a cardiovascular disease study that identified a gene with a protective effect against myocardial infarctions.

To stimulate further innovation and share the rich HUNT Biobank and Databank with industry researchers, HUNT Study stakeholders established Lifandis AS, a publicly owned commercial-operated company. Ove Solesvik, CEO of Lifandis, has been the lead on this endeavor, linking samples and data from the HUNT Study with various drug discovery, diagnostics, and

personalized industry partners. iCommunity spoke with Dr. Hveem and Ove Solesvik to learn more about their partnership and how they see the HUNT Study and Lifandis contributing to the development of better strategies for disease prevention, diagnosis, and treatment.

Q: What is the HUNT Biobank?
Kristian Hveem (KH): In addition to storing all samples from the HUNT Study, the HUNT Biobank is part of a national biobank establishment called Cohort of Norway (CONOR) used for all of the major population studies in Norway. There are about 250,000 donors. It contains samples from 80,000 individuals from the County of Nord-Trøndelag from the second and third wave of the HUNT Study, which started in 1984 and has been repeated every 10 years. The biobank also contains samples from the Tromsø Study.

Q: What information do you have for each sample?
KH: We have an advanced databank, called the HUNT Databank, where we have detailed information about all of the participants collected through self-reported questionnaires and medical examinations. In total, it contains 6,000 data variables. Our well-annotated samples can be linked to donor information using local, regional, and national registries in Norway.

Q: How are samples selected for a study?
KH: We select individuals from the HUNT Databank with the disease outcome of interest. We also match HUNT participants with the relevant hospital-based diagnostic registries using a unique personal identification number. This is done every time we want to initiate a large study to find exactly who in the HUNT Study has developed the relevant phenotype.

Q: How did the idea for your cardiovascular disease study published in *Nature Genetics*[2] originate?
KH: This project initiated in 2010 when we visited colleagues at the University of Michigan and discussed another possible collaboration. We had been working together on type II diabetes studies (FUSION) since 2007, generating several publications, some based on the Illumina HumanCardio-Metabo BeadChip. We also shared an interest in cardiovascular diseases, in particular myocardial infarctions. We knew that the HUNT samples held excellent quality, good annotations, and linkage opportunities to highly validated phenotypes. We were able to identify, in a very detailed way, samples of people who had, or experienced, a myocardial infarction after being enrolled in the HUNT Study.

Q: How did you decide which samples to include in the study?
KH: We began by selecting 3,000 myocardial infarction cases within the HUNT cohort and selected the youngest ones, matched that with 3,000 controls. So 6,000 study participants in total were recruited from the HUNT Study.

Q: How did you genotype 6,000 samples?
KH: We have a close collaboration with our Illumina-certified genotyping core facility at NTNU. They are highly experienced with chip arrays and can accommodate an impressive level of throughput. At the biobank, all of our DNA samples are stored in a freezer with automatic retrieval and output to make it easy to select samples. Liquid handlers plate the samples in the format specified by the core facility to make them directly available for genotyping. We have a good setup for quality control and data management. Illumina off-the-shelf and custom-designed arrays have worked well in our hands.

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Q: What did you find in your myocardial infarction study?
KH: We identified one gene of interest that had a protective effect on myocardial infarction and was favorable in terms of lipid profiles, cholesterol levels, and other lipids. This gene was the *TM6SF*2 variant. Then we replicated this finding in another Norwegian population–based cohort, the Tromsø Study. Finally, we tested the gene in a functional mouse model, in

collaboration with Dr. Cristen Willer and Dr. Eugene Chen from the University of Michigan.

Q: Were you surprised by the results?
KH: Chip array–based studies don't always lead to the novel findings you hope for. It was quite unexpected, yet very satisfactory, that we were able to identify something as interesting as the *TM6SF2* gene, based on 6,000 HUNT samples and replicated in 5,500 Tromsø Study samples.

Q: How do the Illumina BeadChips enable your studies?
KH: We have worked with various Illumina BeadChip arrays in a number of studies, including the more disease-specific arrays such as the MetaboChip and ImmunoChip, with good results.

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Q: Why did you choose Illumina technology to perform the genotyping studies?
KH: Apart from our previous good experience with Illumina technology, it was equally important to use the same chip array within the same studies. Illumina has been supportive in discussing ways to increase the throughput on our platform. Things are moving forward quickly in our research field and the fact that you can turnaround quickly, with an efficient service provider and a flexible genotyping platform, is important.

Q: What are your future plans?
KH: In collaboration with Dr. Goncalo Abacasis and Dr. Cristen Willer, of the University of Michigan, we will conduct a follow-up project genotyping the whole HUNT cohort using the HumanCoreExome BeadChip with ~50,000 additional custom-designed SNPs. Already, about 2,000 samples have been selected for whole-genome and whole-exome sequencing as a basis for imputation. Close collaboration with Illumina has been important in helping us move fast. We're quite optimistic about the scientific potential with this approach.

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Q: How is Lifandis expanding the number and types of studies performed with HUNT Biobank samples?
Ove V. Solesvik (OS): Let me start with some background about the company. In 2006, the Norwegian government made a huge investment in the third round of the HUNT Study. They wanted to see more than scientific publications coming from the study. They wanted us to work with industry to create better diagnostic, drugs, or health services; something that would really benefit all of the donors as well as the whole population.

So the owners of HUNT, together with the Central Norway Regional Health Authority and the Nord-Trøndelag County, incorporated a company, HUNT Biosciences AS, designed to be a professional interface with industry and promote innovation and the possibility to do advanced industry-sponsored research with the HUNT Biobank and Databank. In April 2014, the company name changed to Lifandis to reflect the new strategy of expanding our inventory and working with all of the biobanks in Norway. We have this ambition to become the single national commercial company that interfaces with all of the Norwegian biobanks when it comes to industry collaboration. We want to provide a one-stop shop that makes it easier for industry to access the right groups and resources. Lifandis provides professional project management as

well as data management, biostatistics, reporting, and publication services.

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Q: How does Lifandis collaborate with industry?
OS: Our role is that of a project manager and sometimes a contract research organization. We have all the necessary competence in-house to run a study for industry partners. We set up agreements and design study protocols with industry clients. We arrange for any necessary approvals and applications for various registries. We assist with feasibility studies, lab work (outsourced to university core facilities), statistical analysis, access to medical journals, and linkage to relevant health registries.

One key asset for Lifandis is our access to richly annotated and genotyped pre-diagnostic samples and the ability to find matched controls. The fact that we also can access EMRs for diagnosis verification, makes HUNT a perfect set-up to look for, or verify, new disease-specific biomarkers for risk or early detection.

If we receive requests from academic groups, we connect them with the scientists at the HUNT Research Center. If the HUNT Research Center gets interest from industry, they will refer them to Lifandis and we find a way to work together. All of our industry projects are research-based with the goal of creating a publication.

Q: How is Lifandis collaborating with Illumina?
OS: We have had several interesting discussions with Illumina about how we can work together. We are discussing a joint pilot study to demonstrate the value of the Illumina technology combined with the high-quality HUNT biobank to the pharma and diagnostic industry. This pilot study aims to support idea of an Illumina Biobank Network, a network of high-quality biobanks that work closely with Illumina and industry to present the opportunities available in this field.

References

1. Krokstad S, Langhammer A, HVeem K, et al. Cohort profile: The HUNT study, Norway. *Int J Epidemiol* 2013, 42(2): 968-977.
2. Holmen O, Zhang H, Fan Y, et al. Systematic evaluation of coding variation identifies a candidate causal variant in *TM6SF2* influencing total cholesterol and myocardial infarction risk. *Nature Genetics* 2014, 46: 345-351.

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