

# Connecting genomics and clinical research

*Molecular medicine...*

**T**he research group in Molecular Medicine at the Department of Medical Sciences, Uppsala University, is interested in methods for large-scale genomic analyses and applies them to human diseases, with a focus on paediatric leukaemia and autoimmune diseases.

The group headed by Professor Ann-Christine Syvänen was established in 1998 at Uppsala University Hospital with the aim to introduce modern molecular methods into clinical research. Since its start the group has worked towards this goal by creating close collaborations with clinical scientists at the hospital and by hosting the SNP&SEQ Technology Platform in Uppsala that offers large-scale SNP genotyping and second generation sequencing services to academic researchers in Sweden and other countries.

### Epigenetic biomarkers for acute lymphoblastic leukemia

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer in the Western world. Although there has recently been great progress in treatment protocols for ALL, about 20% of the patients do not respond to drug treatment for unknown reasons. The aim of the research project on ALL in the Molecular Medicine group is to identify genetic and epigenetic signatures to improve stratification of the ALL patients into groups for alternative treatment protocols.

In these studies a unique collection of bone marrow and blood samples from children with ALL that have been collected in the Nordic countries by the Nordic Society for Paediatric Oncology (NOPHO) are being analysed. The project involves a close collaboration with paediatric oncologists at the Children's University Hospital in Uppsala.

The Molecular Medicine group also strives to elucidate the functional



Members of the Molecular Medicine group and the staff of the SNP&SEQ Technology Platform in Uppsala

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roles of epigenetic modifications of DNA and histones in the transformation of normal blood progenitor cells into leukemic cells.

### From genes to function in systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is regarded as the prototype for autoimmune disease because it involves most immune cell types and can affect all organs of the human body. SLE has a strong heritable component. There are about 35 confirmed genetic risk loci for SLE that have been identified by genome-wide association studies and consequent large follow up-studies.

By analysis of a collection of well-characterised Swedish patients with SLE, the Molecular Medicine group has contributed to the identification of 13 of these loci. Via a national network for SLE research with participants from most university hospitals in Sweden, a large number of Swedish patients with SLE that have been carefully investigated by clinicians can be included in genetic studies of SLE.

The genes at the SLE-associated loci belong to the type I interferon (IFN), B-cell and T-cell signalling pathways. Several of the risk genes for SLE also confer risk for other autoimmune disease. To identify the actual

functional, disease-causing alleles in the risk loci for SLE, the Molecular Medicine group uses new technology for second generation DNA sequencing in combination with functional analysis of fractionated human blood cells.

The project involves a close collaboration with the research group in Systemic Autoimmune Diseases and the Rheumatology Clinic at Uppsala University Hospital.

### Providing access to genotyping and sequencing

The objective of SNP&SEQ Technology Platform in Uppsala, headed by Professor Ann-Christine Syvänen, is to make large-scale SNP genotyping and 'second generation' DNA sequencing of a high quality available to academic researchers at the lowest possible costs.

The SNP&SEQ Platform has a professional staff of 20 research engineers, scientists or biocomputing specialists. To assure a high quality of the data produced, the SNP&SEQ Platform works according to the ISO/IEC 17025:2005 quality standard, and the genotyping and sequencing process is accredited by the Swedish Board for Accreditation and Conformity Assessment (SWEDAC).

Genome-wide SNP panels facilitate association studies in human

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The SNP&SEQ Platform in Uppsala offers a wide range of genotyping services, from genotyping of individual SNP markers to genome-wide studies with up to five million SNP markers in hundreds or thousands of samples using six different genotyping systems to match the needs of all projects. 'Second generation' DNA-sequencing is offered using HiSeq2000 systems

complex diseases and traits, determination of copy number alterations and DNA-methylation across the genome. 'Second generation' sequencing is applied to sequence large and small genomes, discovery of SNPs in targeted regions of large genomes, functional analyses of gene regulation by analysis of chromatin immunoprecipitated DNA and transcriptome sequencing.

The SNP&SEQ Technology Platform constitutes a major part of the recently established Science for Life Laboratory - Uppsala and participates in large collaborative EU projects, including the FP7 project European Sequencing and Genotyping Infrastructure (ESGI).

The research group first develops or establishes methods that can later be implemented at the SNP&SEQ Platform, while the SNP&SEQ Technology Platform makes the most advanced genotyping and sequencing technology easily accessible to the research in the Molecular Medicine group.

In ongoing projects, the Molecular Medicine group is using genome-wide genotyping of RNA transcripts to map genes with cis-acting regulatory factors based on allele-specific gene expression (ASE). This approach has been used as a guide to genes with cis-acting regulatory genetic and epigenetic factors in bone marrow cells from ALL patients and for mapping genes with cis-acting regulatory SNPs in human primary monocytes and other blood cells.

In combination with deep bioinformatic analysis, ASE analysis of relevant cell types provides functional hypotheses for the risk alleles for SLE identified by genetic association studies.

### Large collaborative projects

The Molecular Medicine group participates in collaborative projects, in which its competence in genomic technology is combined with the capacity of the SNP&SEQ Technology Platform for large-scale SNP genotyping and second generation sequencing. In the EU FP7 'Engage' project the group performs genome-wide analysis of DNA methylation in samples from European twin cohorts.

As partner of the EU FP7 'Geuvasis' consortium the Molecular Medicine



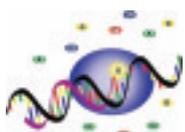
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Professor Ann-Christine Syvänen

group and the SNP&SEQ Technology Platform work together with 11 major sequencing and genotyping centres across Europe to define best laboratory practices for second generation transcriptome and exome sequencing.

The Molecular Medicine group is part of the EU FP7 'European Sequencing and Genotyping Infrastructure (ESGI)' to which it contributes by laboratory protocols and bioinformatics tools for allele-specific gene expression, while the SNP&SEQ Platform offers transnational access to SNP genotyping and second generation DNA sequencing.

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The reaction principle of 'minisequencing' single base primer extension

### Technology for genomics

Professor Ann-Christine Syvänen is an internationally recognised expert in SNP genotyping technology. Previously working in Helsinki, Finland, she and her co-workers pioneered the principle of single nucleotide primer extension ('minisequencing'), which underlies several leading commercial genotyping systems, like the Infinium assay for genome-wide genotyping.

The well-documented competence in SNP genotyping of the Molecular Medicine group was the incitement for placing the SNP Technology Platform in Uppsala in close connection with this group.



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