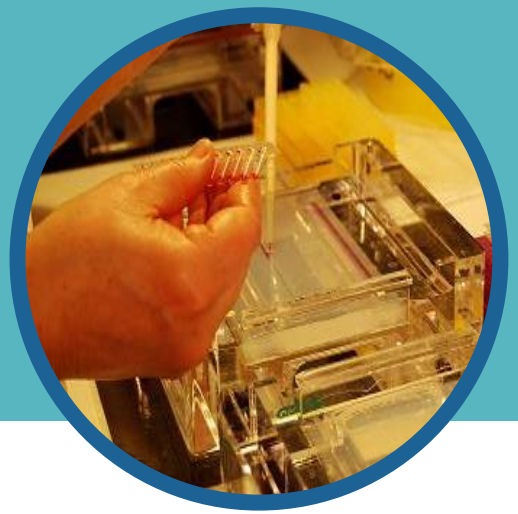
Klinisk Genetisk Afdeling, Odense Universitetshospital
Department of Clinical Genetics, Odense University Hospital

Research unit Clinical Genetics
Clinical Genome Center
Department of Clinical Research
University of Southern Denmark



ANNUAL REPORT 2023

OUH
Odense
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SDU

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Clinical Genome Center

WELCOME

This annual report from the research unit Clinical Genetics at Department of Clinical Genetics, Odense University Hospital (OUH), provides an overview of research activities, awards and publications. Our research activities are performed in collaboration with the Department of Clinical Research at University of Southern Denmark (SDU). Our research focuses on rare and complex hereditary diseases and cancer.

The Department of Clinical Genetics houses the Clinical Genome Center (CGC), led by professor Mads Thomassen. CGC is a resource centre offering support to research projects at OUH and SDU as well as collaboration with other institutions. The department moreover houses the Center of Rare and Complex Diseases (CAKS) that supports the multidisciplinary care of patients with rare genetic diseases.

Department of Clinical Genetics is a member of ERN-ITHACA, the European Reference Network for Rare Malformation Syndromes, Intellectual and Other Neurodevelopmental Disorders.

At the end of 2023, there are 9 ongoing PhD projects, two of them in collaboration with other departments. Two PhD students defended their thesis in 2023. You can read more about these in the report.

Within the past year, two professors have been employed in our department. Professor of Neurobiology, dr. med. Vijay Tiwari, was employed in a part-time position, divided between our department and the Department of Clinical Research, SDU, on 1 January 2023. And on 1 January 2024, we welcome Anja Lisbeth Frederiksen, who is employed 50% as chief physician, 50% as clinical professor at the Department of Clinical Genetics.

In 2023, more than 50 peer-reviewed publications were published. See the total list on page 34 in this report.

Thank you to all researchers, employees and collaborators for their contributions, enthusiasm and commitment to our research unit.

Enjoy the reading!

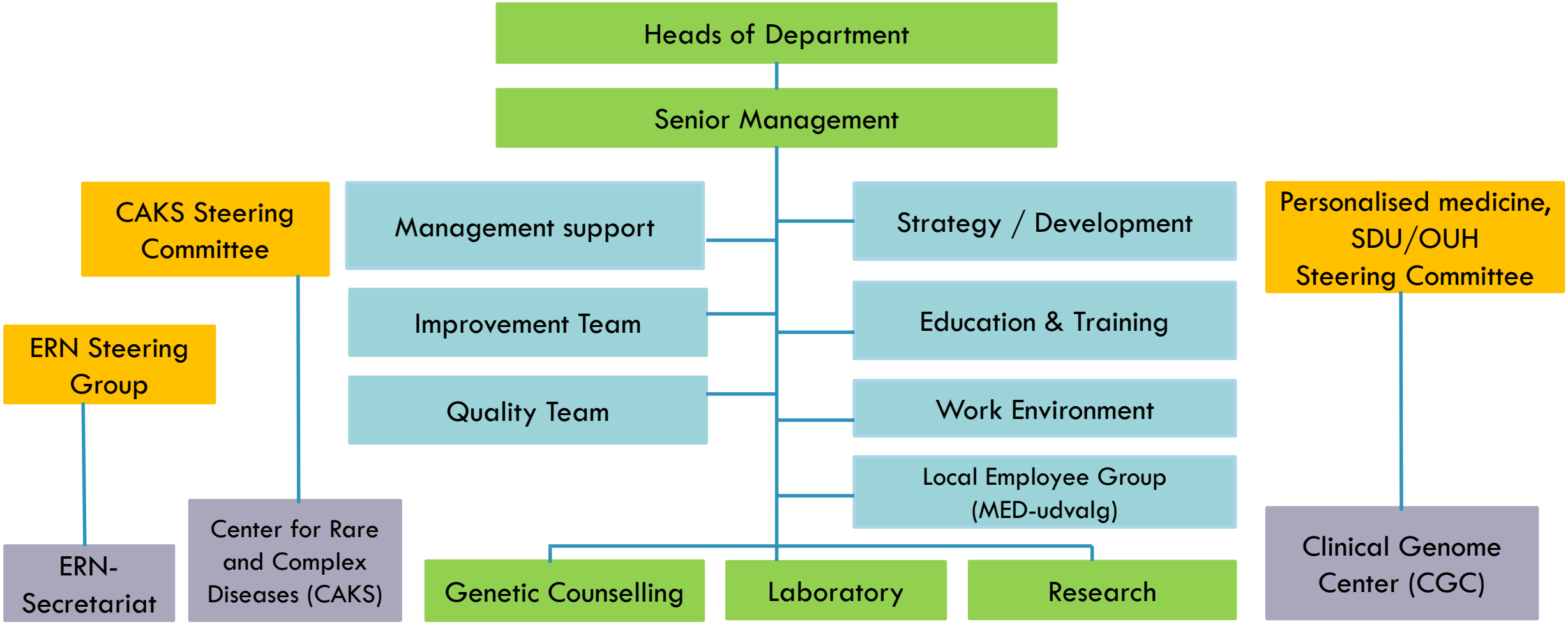
Professor Lilian Bomme Ousager
Head of Department, Head of Research

CONTENTS

ORGANISATION

Heads of Department	Lilian Bomme Ousager, Professor, MD, Lilian.Bomme.Ousager@rsyd.dk Anja Christoffersen, Chief Biomedical Laboratory Scientist, Anja.Christoffersen@rsyd.dk
Head of Research	Lilian Bomme Ousager, Professor, MD
Head of Clinical Genome Center	Mads Thomassen, Professor, Mads.Thomassen@rsyd.dk
Heads of Laboratory	Lotte Nylandsted Krogh, MD, Lotte.Krogh@rsyd.dk Dorthe V. Pedersen, Leading Bioanalyst, Dorthe.V.Pedersen@rsyd.dk Morten Buch Engelund, Leading Molecular Biologist, PhD, Morten.Buch.Engelund@rsyd.dk
Head of Medical Education	Lone Krøldrup Kristensen, MD, Lone.Kroeldrup@rsyd.dk
Heads of Genetic Counselling unit	Marianne Præstegaard, Head Nurse and genetic counsellor, Marianne.Praestegaard@rsyd.dk Anita Bille Nielsen, Senior Medical Secretary, Anita.Bille.Nielsen@rsyd.dk
Head of Center for Rare and Complex Diseases (CAKS) & ERN-secretariat	Louise Lehmann Christensen, PhD, MD, Louise.Lehmann.Christensen@rsyd.dk

Department of Clinical Genetics



Senior Mangement: Heads of Department, Medical Head of Laboratory, Head of Research, Head of Medical Education and Head of Clinical Genome Center. In addition, the Executive Secretary participates in the senior management meetings.

Ongoing PhD Studies (1)

Project title: Whole genome sequencing of cell-free DNA from metastatic breast cancer patients: A study of accuracy and response.

Alexander's PhD project involves the use of circulating tumor DNA (ctDNA) analysis to detect and monitor metastatic breast cancer prior to and during treatment. For breast cancer patients with suspected or confirmed metastases, traditional CT scans are currently used to detect and monitor the disease. However, a significant study (MESTAR) has already shown that PET scans are more sensitive than CT scans.

Alexander's study will investigate whether ctDNA analysis also has a potential to improve current practice. By analysing serial blood samples collected through the MESTAR study at each CT- and PET scan, the project will estimate the fraction of ctDNA in the blood as a measure of disease progression during treatment. Through comparison with PET and CT results, it can be assessed whether non-invasive ctDNA analysis can improve practice and complement or even replace scans completely. A significant part of the project concerns the optimisation of ctDNA detection and measurement through bioinformatics to increase accuracy and sensitivity.

Supervisors: **Professor Mads Thomassen, Professor Torben Kruse,** Department of Clinical Genetics, OUH.

ALEXANDER VENZEL RUDBECK

PHD STUDENT

Ongoing PhD Studies (2)

Project title: Identification of the underlying genetic mechanisms in patients with skeletal dysplasias to improve diagnosis, genetic counseling and patient follow-up.

ASTRID SKOV MIDTIBY

PHD STUDENT

Astrid's project investigates patients and foetuses with skeletal dysplasia where the molecular genetic diagnosis is unknown. Included patients will be clinically examined and subsequently offered comprehensive genetic analysis. The aim of the study is to identify the genetic mechanism behind each individual skeletal dysplasia and thereby improve both the medical follow-up of the individual patient and the genetic counselling of both patient and family.

The project is carried out in collaboration with both Department of Clinical Genetics and the Center for Rare Diseases at Rigshospitalet.

Main supervisor: **Professor Lilian Bomme Ousager,** Department of Clinical Genetics, OUH.
Co-supervisors: **Professor Jens Michael Hertz, Professor Zeynep Tümer and Chief senior consultant Hanne Buciek Hove.**

Ongoing PhD Studies (3)

Project title: Long-Read Whole Genome Sequencing - 3rd Generation Nanopore Sequencing In Clinical Genetic Diagnostic.

Emilie's PhD project aims to harness the potential of Nanopore sequencing technology for genetic diagnostics. The project seeks to address the limitations of traditional short-read sequencing methods by offering comprehensive insights into complex genetic variants, including structural chromosomal rearrangements, repeat expansions, imprinting diseases, and detailed methylation profiles. The project is focused on integrating Nanopore sequencing into clinical practice by developing a diagnostic workflow, particularly for diagnosing previously unresolved cases. The project is a collaboration with the Departments of Clinical Genetics at Vejle Sygehus and at Rigshospitalet.

Main supervisor: **Associate Professor Martin Jakob Larsen,** Department of Clinical Genetics, OUH.

EMILIE BOYE LESTER

PHD STUDENT

Ongoing PhD Studies (4)

LOUISE ADEL JENSEN
MOLECULAR BIOLOGIST

PHD STUDENT

Project title: The Molecular Characterization of Familial Breast Cancer with no Confident Genetic Explanation - Identification of Subgroups and Classification of Genetic Variants.

The aim of this study is to identify molecular subgroups of hereditary breast cancer using whole genome sequencing (short-read, Illumina). The subgroups will be used in combination with long-read sequencing (Oxford Nanopore) to classify variants of unknown significance (VUS).

Main supervisor: **Professor Mads Thomassen,** Department of Clinical Genetics, OUH.

Ongoing PhD Studies (5)

MIKKEL MØLLER HENRIKSEN

PHD STUDENT

Project title: Characterization of tumor load and mutational profile in patients with gastroesophageal cancer using circulating tumor DNA.

Mikkel's PhD project, which is part of the GenUGI project, will investigate the use of plasma-derived circulating tumor (ctDNA) as a biomarker for clinical use in gastroesophageal cancers (GEC). The project will characterise and evaluate the tumor burden and mutational profiles of GEC cancer through Next Generation Sequencing of ctDNA as a non-invasive diagnostic tool through simple blood taking. This can be used as a supplement and/or alternative to conventional diagnostic tools, including structural (CT) and molecular (PET) imaging techniques.

The overall aim of this project is to investigate sequencing analysis of ctDNA as a tool for monitoring tumor burden and mutational profile in GEC patients throughout the course of the disease, including the treatment regimen and the follow-up period after surgical resection. This will include ctDNA analysis as a tool to monitor treatment response and mutation that cause resistance towards treatment during neoadjuvant and adjuvant chemotherapy, and to monitor GEC patients after curative treatment has been performed to determine whether ctDNA analysis is able to detect recurrence before it is detected by conventional methods. In addition, the prognostic and predictive value of ctDNA in terms of clinical outcome (disease-free survival and overall survival) will be determined and tumor-guided and –independent analysis methods of ctDNA will be compared.
Supervisors: **Professor Mads Thomassen, Professor Torben Kruse.**

Ongoing PhD Studies (6)

NHU DO

PHD STUDENT

Project title: Integrated genomic analysis of primary breast tumors. A possible tool towards reduction of overtreatment.

Nhu Do is currently working on a PhD project on prognosis in breast cancer. In a unique tumour material, she has studied molecular profiles of primary tumours to predict whether the patient will experience recurrence of the disease many years later in the form of metastases in other organs. These patients did not receive medical treatment after their primary diagnosis and there is a very long follow-up time and very well-preserved frozen tumour material. Nhu's studies show that different RNA molecule profiles (mRNA, miRNA, lincRNA) have different strengths in predicting relapse. The best of the profiles are highly accurate and have the potential to reduce a huge amount of medical overtreatment that takes place for breast cancer patients today. This saves patients from side effects and saves the healthcare system large amounts of money on medication. Nhu is also investigating cancer-specific genetic variants (somatic mutations) in the tumour samples. This information could potentially be combined with the RNA profiles for multi-omics classification. Nhu will also use the extensive data to investigate the mechanisms involved in the proliferation of breast cancer cells in patients who are not receiving medical treatment.

Supervisors: **Professor Mads Thomassen, Professor Torben Kruse,** Department of Clinical Genetics, OUH.

Upcoming PhD defences (1)

Project title: Clinical and genetic characterisation of palmoplantar keratoderma. PhD defence: 26 April 2024.

The PhD project is about the rare and hereditary disease palmoplantar keratoderma (PPK), a disease characterised by hard and thickened skin on the palms and soles, but complicated by a very heterogeneous nature including several different clinical subtypes and numerous different genetic types from isolated skin disease to syndromes with risk of other diseases. The project consists of three studies (I-III). **In Study I,** a large cohort of 142 patients (78 families) with PPK was established (making it the largest cohort of its kind at the time of publication). The study describes the clinical characteristics and results of systematic genetic testing. A genetic diagnosis was found in 80 percent, which testified to the relevance of genetic testing for patients with PPK. **Study II** investigated a frequent variant (*AAGAB*, c.370C>T) in the study population with punctate PPK in the Region of Southern Denmark. The variant was found to be a founder variant with an estimated age of 12.1 generations. Based on these results, we recommend testing for the variant as initial screening in our region and potentially for all Danish patients presenting punctate PPK.

Main supervisor: **Professor Lilian Bomme Ousager.**
Co-supervisors: **Professor Klaus Brusgaard, Professor Anette Bygum.**

STINE BJØRN GRAM

PHD STUDENT

Study III was a systematic review evaluating the literature on the suggested risk of malignancy for patients with punctate PPK. The existing literature was found to be of too poor methodological quality to answer our research question, but based on our review, not sufficient evidence was found to confirm an association. It is therefore highly questionable that this subgroup of patients would benefit from malignancy screening.

Completed PhD defences (1)

IEVA MICEIKAITÉ

PHD

Title: Advancing Prenatal Diagnostics with High-Throughput Sequencing: From Invasive to Non-Invasive Testing and Beyond.
PhD defence: 18 august 2023.

Ieva's PhD project investigates new sequencing technologies in prenatal genetic screening and diagnostics and shows how the new methods can detect a wide range of genomic variants including chromosomal and sequence variants. In doing so, the methods can help provide a deeper understanding of the genetic composition and heterogeneity of the placenta.

One of the most exciting parts of Ieva's project was the development of the desNIPT assay, a new non-invasive method to examine the foetus based on deep exome sequencing of cell-free DNA from maternal plasma. A method with great potential. This assay has the potential to become a new method for risk-free screening for all known monogenic diseases in early pregnancy.

Main supervisor: **Associate Professor Martin Jakob Larsen.**
Co-supervisors: **Associate Professor Christina R. Fagerberg, Associate Professor Charlotte Brasch Andersen,** Department of Clinical Genetics, OUH.

Ongoing PhD studies in collaboration with other departments (1)

Project title: Predicting response to medical treatment of inflammatory bowel disease (IBD) using transcriptomics analysis on intestinal biopsies and blood: a prospective cohort study of personalised medicine.

After a while of not getting patients for her second study, which involved running single cell RNA sequencing on fresh biopsies, Zainab decided to switch to using already collected surgical samples from patients with inflammatory bowel disease. After receiving authorisation from the RES, she set about comparing fresh vs fixed single cells from 10x genomics and comparing cell expression in inflamed vs non-inflamed tissue to gain an understanding of the disease activity in these patients.
In 2023, Zainab received a grant of DKK 857,000 from the Region of Southern Denmark's pool for Independent and Strategic Research. The grant was for operations, including running single cell RNA sequencing and spatial transcriptomics as well as an automated cell counter.
In February 2024, Zainab is going to AAU for environmental exchange. There she will work with her co-supervisor, Tue Bjerg Bennike, at the Department of Health Science and Technology. There Zainab will learn how to analyse Proteomics and Metabolomics data in addition to Multi-Omics Data integration.

ZAINAB HIKMAT, PHD STUDENT

Main supervisor: **Professor Vibeke Andersen,** Sygehus Sønderjylland, and Dep. of Regional Health Research.

Co-supervisors: **Professor Mads Thomassen,** Dep. of Clinical Genetics, OUH, **Maja Dembic, PhD,** CGC, and **Associate Professor Tue Bjerge Bennike,** University of Aalborg.

Upcoming PhD defences, in collaboration with other departments (1)

KIRSTINE ØSTER ANDERSEN

PHD STUDENT

Project title: Genetic alterations in insulinomas with and without multiple endocrine neoplasia type 1: Understanding tumourigenesis in beta-cells. PhD defence: 8 March 2024

Kirstine's project focuses on DNA, RNA, protein and epigenetic markers in insulinoma tissue. Insulinomas are rare, benign tumours that arise in the beta cells of the pancreas. The increased cell count leads to an overproduction of insulin, causing blood sugar levels to drop and can lead to a condition called hyperinsulinaemic hypoglycaemia. The only way to cure insulinomas is through surgery.

Main supervisor: **Professor Henrik Christesen,** H.C. Andersen Childrens' Hospital.
Co-supervisor: **Professor Klaus Brusgaard,** Department of Clinical Genetics, OUH.

Upcoming PhD defences, in collaboration with other departments (2)

NANNA ELMAN ANDERSEN

PHD STUDENT

Project title: Mechanisms of chemotherapy neurotoxicity in iPSC-derived schwann cells and sensory neurons.
PhD defence: 8 March 2024

The project aims to understand the neurotoxic mechanisms behind three commonly used chemotherapeutics which cause chemotherapy-induced peripheral neuropathy. Chemotherapy-induced peripheral neuropathy is an adverse side effect of several chemotherapeutics that leads to pain, numbness in hands and feet and a tingling and burning sensation. This affects patients' quality of life negatively.
We want to understand the mechanisms behind this toxic side effects and our findings might aid in the development of future treatment or prevention of chemotherapy-induced peripheral neuropathy.

Main supervisor: **Professor Tore Bjerregaard Stage**, Clinical Pharmacology, Pharmacy and Environmental Medicine, Department of Public Health, University of Southern Denmark.
Co-supervisors: **Professor Mads Thomassen**, Department of Clinical Genetics, OUH, and **Professor Kate Lykke Lambertsen**, Department of Neurobiology Research, Institute of Molecular Medicine, SDU.

Completed PhD defences, in collaboration with other departments (1)

JEANNE BANG VEJEN

PHD

Title: The Splicing Regulatory Protein RBM10, its role in a new syndrome, in TARP syndrome and in cancer.
PhD defence: 16 March 2023.

The project has gathered information on more than 25 patients with changes in the RBM10 gene. The project sheds light on the effect of variants with functional studies. While loss of function variants of RBM10 are well known to cause a severe syndrome called TARP syndrome, the study has shown that other variants, for instance missense variants, can also cause disease and be associated with other less severe phenotypes. The genotype-phenotype association has proven to be complex. The results from the study will be published later.

Main supervisor: **Professor Brage Storstein Andresen,** Institute of Biochemistry and Molecular Biology, SDU.
Co-supervisor: **Associate Professor Christina Fagerberg,** Department of Clinical Genetics, OUH.

Researchers in the research unit Human Genetics and the Department of Clinical Research, SDU

- **Anette Bygum**, Professor, PhD
- **Britta Schlott Kristiansen**, MD
- **Caroline Hey Bækgaard**, MSc in Molecular Biology
- **Charlotte Brasch Andersen**, Associate Professor, PhD, MSc in Molecular Biology
- **Christina Fagerberg**, Associate Professor, MD
- **Klaus Brusgaard**, Associate Professor, PhD, MSc in Molecular Biology
- **Lilian Bomme Ousager**, Professor, PhD
- **Lotte N. Krogh**, MD
- **Martin J. Larsen**, Associate Professor, PhD, MSc in Bioinformatics
- **Mie Bohnensack Larsen**, MSc in Molecular Biology
- **Pernille M. Tørring**, PhD, MD
- **Qin Hao**, PhD, MSc in Molecular Biology
- **Susanne Eriksen Boonen**, Associate Professor, PhD, MD
- **Torben Kruse**, Professor, lic.scient.

Researchers in Clinical Genome Center

- **Mads Thomassen**, Professor, PhD, Head of CGC
- **Maja Dembic**, PhD, MSc in Molecular Biology
- **Mark Burton**, Associate Professor, PhD, MSc in Bioinformatics
- **Sepideh Sadegh**, MSc in Bioinformatics
- **Steffen Møller Bøttger**, PhD, MSc in Molecular Biology
- **Torben Kruse**, Professor, lic.scient.
- **Vijay Tiwari**, Professor, PhD, dr. Med.
- **Zainab Hikmat**, PhD student, maternity cover for Maja.

The research field examples on the following pages were presented in the department's internal newsletter during 2023. Other examples will be presented in 2024.

CURRENT RESEARCH FIELD

Examples of research fields (1)

Mads Thomassen, Professor of Genomic Medicine and Head of the Clinical Genome Center

Current projects:
Mads is involved in a number of research projects at CGC. They span many different diseases. The main research area is cancer, especially breast cancer. The projects deal with, among other things, cancer risk based on inherited genetic changes. Mads is also involved in a number of projects investigating tumour profiles, typically RNA profiles or DNA profiles of tumour-specific (somatic) mutations. The aims of the projects are to understand tumour development and spread of disease (metastasis), as well as to develop better biomarkers for prognosis, treatment response or monitoring of possible relapse.
A very interesting field is circulating tumour DNA. Here, cell-free DNA originating from cancer cells in the body is studied. The big challenge is that there are often very small amounts of this DNA and detecting it is a challenge. The project group is in the process of testing exome and genome sequencing for this purpose, as this is a way to see many different mutations and thus get a very high sensitivity of the analysis. in a number of cancers, many blood samples have been collected and will be analysed in the near future.

What do you think is the best thing about spending time on research?
It's meaningful to contribute to better diagnostics and treatment of future patients. At the same time, it's very exciting to find out how biological mechanisms in the body work. The most exciting part is when you see new data for the first time. It's a bit like unwrapping presents.

CURRENT RESEARCH FIELD

Examples of research fields (2)

Maja Dembic, PhD, MSc in Molecular Biology

Maja is the project coordinator and bioinformatician at the Clinical Genome Center (CGC).

She is involved in the coordination of projects from CGC users, where she provides scientific and operational guidance to find the best course of action. These projects include a wide range of applications from DNA and RNA sequencing to single cell applications.

Maja also follows and mentors students associated with CGC.

Maja's main research focus is on genetic causes and splicing defects in rare disorders. She has specialised in the functional characterisation of metabolic disorders, heart arrhythmias, and neuromuscular disease.

At CGC, she specifically follows single cell sequencing projects. Furthermore, her expertise as bioinformatician includes genetic variant calling, copy number analysis, and genetic demographic data analysis, applied mainly to tumor studies and other genetic disorders.

One of Maja's main priorities is to implement single cell applications that fit the necessities of the different projects that CGC supports and their research questions. This is a challenging and rapidly expanding field and -to Maja- very exciting to be a part of.

CURRENT RESEARCH FIELD

Examples of research fields (3)

Christina Ringmann Fagerberg, Associate Professor, MD

The Region of Southern Denmark funded Christina's research time for a 20% buyout over 3 years.

Christina has been working on different projects, triggered by the patients she has met in the clinic. A main project is the RBM10 project. It has been known for many years that loss-of-function variants in the RBM10 gene cause a very serious disease called TARP syndrome - a disease that affects boys who die shortly after birth or in infancy. Almost 10 years ago, Christina counselled a teenager with intellectual disability. The project group found a missense variant in the RBM10 gene in him and his uncle, who also had intellectual disability. The significance of the variant was uncertain because, at the time, it was only known that loss-of-function variants could be significant. Since then, Christina collected about 30 patients from all over the world with different variants in the RBM10 gene. She established a collaboration with Brage Andresen from BMB, SDU, and PhD student Jeanne Bang Vejen. A number of functional studies were conducted to elucidate the effect of different types of variants in the gene. It was shown that missense variants in the gene can also be significant, and that the genotype-phenotype correlation in the gene is quite complex. Jeanne defended her PhD on 16.3.2023 and, consequently, an article summarising the findings was published.

Furthermore, Christina is working on a project about pain. It is based on the suspection that in the group of chronic pain patients, there are some patients with monogenic diseases (rare genetic diseases) that have not been diagnosed.

CURRENT RESEARCH FIELD

Examples of research fields (4)

Klaus Brusgaard, Associate Professor at SDU and Adjunct Professor at the European University of Lefke. Klaus is involved in both national and international projects, and is currently supervising 3 PhD and 2 Master's programmes.

Current projects:

- Development of diagnostic and prognostic non-invasive biomarker profiles in prostate cancer
- AMY2B gene expression in AR42j cells and its association with insulin resistance via TNF alpha.
- The utilization of tumor-derived exosomes as potent drug delivery systems.
- Improved genetic characterization and diagnostics in hereditary palmoplantar keratoderma.
- Genetic alterations in insulinomas with and without multiple endocrine neoplasia type 1: Understanding tumorigenesis in beta-cells.
- Advanced genetic investigations in patients with atypical genetic hyperinsulinism.
- Bioinformatic investigation of Ashkenazi Jews with idiopathic hypoglycemia.
- Bioinformatic analysis of British patients with idiopathic hypoglycemia using Genomic England GeCip.
- Functional studies related to hypoglycemia and hyperinsulinemia using CRISPR prime editing (PE)
- CELSR1 in brain malformations, neurodevelopmental delay, and epilepsy.

In more and more of the diseases I am involved in, it is becoming apparent that the cause is not only hereditary variation, but sometimes just somatic variation. In the long run, this could turn out to be something general; that we are just continuously acquiring mutations and that these mutations are the cause of all kinds of diseases. What I find really exciting is gaining a molecular understanding of the function of a gene/protein at the molecular level, and that depending on the location of the variant in the same gene, it can give rise to different phenotypes.

CURRENT RESEARCH FIELD

Examples of research fields (5)

Mark Burton, Assistant Professor at the Department of Clinical Sciences, SDU, and bioinformatician at the Clinical Genome Center (CGC).

Mark is involved in data analysis for a wide range of CGC users, but also in advising and mentoring students in data analysis and statistical design. His primary focus (and speciality) is associated with RNA-related data, such as bulk RNA sequencing, single cell RNA sequencing and microarray gene expression data analysis.

Single cell RNA sequencing is currently an expanding field that offers great opportunities to gain insights into the study of biological mechanisms at the single-cell level, and I find the approaches to analysing scRNA sequencing very exciting. Another field is the application and testing of new mathematical models and algorithms for supervised as well as unsupervised classification, which can be used predictively, prognostically or for the discovery of new sub-groupings among various diseases associated with altered gene expression patterns.

One of the biggest challenges is finding an optimal way to integrate data to further predictive and prognostic purposes. Many types of data can be included in such an analysis, such as expression data, copy number data, mutation signatures, or histological and demographic data. Integrating such data sources requires a lot of computing power, which can become a bottleneck.

CURRENT RESEARCH FIELD

Examples of research fields (6)

Susanne Eriksen Boonen, Associate Professor, PhD, MD.

Current projects:
All projects can be seen in a clinical perspective and originate from patient cases/analysis results, either in larger patient groups or in individual families/patients. All projects are in collaboration with many talented colleagues:

- **Functional Genomics.** The project is about determining whether a genetic variant of unknown clinical significance (VUS) explains the patient's/family's disease or whether it is harmless. Traditionally, attempts to clarify this have been made in highly demanding animal/cell models. In the operational context of a hospital, this is not feasible. Instead, genome-based analyses may be an option. In Functional Genomics, three different methods can be used for clarification (RNA sequencing, Tumour sequencing or Methylation analysis).
- **SWEA gene panel cohort** (oncogenetics). At the Department of Clinical Genetics, a patient group consisting of approx. 2,800 breast and ovarian cancer patients are currently being characterised. There are many sub-projects under this project in which several current and future medical students are involved.

In addition, there are two smaller but very interesting imprinting projects. Imprinting diseases can be caused by sequence changes in the DNA or epigenetic changes (not a change in the DNA strand itself, but a change outside the DNA strand, e.g. methylation). Below is an example of a DNA sequence variant and an epigenetic methylation change, respectively, which are currently under investigation:

- **Nanopore project** on a growth-impaired patient with the imprinting disease Silver-Russell syndrome based on a newly emerging IGF2 gene variant.
- **Whole genome sequencing and Nanopore.** A patient/family with the overgrowth disease Beckwith-Wiedemann syndrome who has methylation changes in not just one imprinted gene, but in multiple imprinted genes. This is known as Multilocus Imprinting Disturbance (MLID).

CURRENT RESEARCH FIELD

Examples of research fields (7)

Martin Jakob Larsen, Associate Professor, MSc in Bioinformatics, Clinical Laboratory Geneticist.
Current projects:

*In the **desNIPT project**, we have succeeded in developing a new and improved NIPT method based on deep exome sequencing. In parallel with the implementation of the department's prenatal exome analysis, plasma samples were collected from the pregnant women for the desNIPT project. We have demonstrated that sequencing the genes of the foetus via a blood sample from the pregnant woman is possible with a low error rate thanks to the deep sequencing technique.*

***Placenta mosaicisme:** In the project, we map the genetic architecture of the placenta. We examine multiple biopsies from the same placenta with deep genome sequencing. Based on somatic mutations, we have identified several clones, each with their own unique set of mutations - showing that placental mosaicism in the placenta is very common and most likely present in all placentas. This is important knowledge when using CVS samples for prenatal genome sequencing today.*

***Nanopore long-read genome sequencing:** a new sequencing technology with great potential in genetic diagnostics, as it overcomes many of the limitations of standard genome sequencing with NGS. In the project, we are testing Nanopore for various purposes, including complex structural chromosomal rearrangements, repeat diseases, as well as imprinting diseases and other methylation profiles (epi-signatures). The project runs in parallel with the implementation of Nanopore genome sequencing in operations. In the next part of the project, we are in the process of including "unsolved" patients where standard trio-genome sequencing has not been able to identify the genetic cause.*

In addition, I am involved in several other projects and projects in the pipeline, including Functional Genomics, foetal diagnostics, children with low height, and several cancer-related projects.

Master thesis defences in 2023

1) **Caroline Hey Bækgaard**, MSc in Biochemistry and Molecular Biology: Identification of imprinting diseases using nanopore technology. Supervisors: **Martin J. Larsen, Steffen Møller-Larsen, Emilie Boye Lester.**

2) **Gina Therese Ransedokken Holte and Loan Anh Thi Tran**, both MSc in Medicine: Whole Exome and Genome Sequencing in Prenatal Care at a Danish University Hospital. Supervisors: **Pernille M. Tørring, Lilian Bomme Ousager, Martin J. Larsen.**

3) **Christina Hamkens Fisker**, MSc in Medicine: Female carriers of pathogenic variants in the RBM10 gene. Supervisor: **Christina R. Fagerberg.**

4) **Jakob Jersild Nielsen**, MSc in Computational Biomedicine: Detection of circulating tumor DNA by recalling patient-specific somatic variants in plasma samples using whole-exome sequencing. Supervisors: **Torben Kruse, Mads Thomassen, Lars Andersen, Kristina Magaard Koldby.**

5) **Elisabeth Simone Feldner**, MSc in Medicine: Genetic testing of 2540 patients with suspicion of hereditary disposition for breast and ovarian cancer in Western Denmark. Main supervisor: **Mads Thomassen**. Co-supervisors: **Susanne Eriksen Boonen, Qin Hao, Mark Burton, Thorkild Terkelsen.**

Ongoing Master studies

1) **Jens Christian Kraft**, Medical student:
   Analysis of the genetic background for dyslexia in a large Danish family.
   Supervisor: **Charlotte Brasch Andersen.**

2) **Naja Slemming-Adamsen**, Medical student:
   Splice prediction of pathogenic variants and variants of unknown significance in clinical relevant genes.
   Main supervisor: **Susanne E. Boonen.**
   Co-supervisors: **Mads Thomassen, Qin Hao, Caroline Hey Bækgaard.**

Selected grants

Mikkel Møller Henriksen received a 1-year PhD scholarship from SDU as well as a 1-year grant from the Region of Southern Denmark's PhD pool. Mikkel's PhD project investigates whether we can use circulating tumour DNA (ctDNA) to detect and monitor the disease progression in patients with esophageal and gastric cancer. He will test whether ctDNA can be used prognostically or predictively in relation to patients' treatment response, relapse and final outcome. The project is part of GenUGI, which Kristina Koldby has previously worked on at the department. See also page 8.

Alexander Venzel Rudbeck received a 1-year PhD scholarship from OUH's PhD pool. Alexander's PhD project also investigates the role of ctDNA as a tool for cancer detection and monitoring. However, he works with patients with suspected metastatic breast cancer. The project is part of MESTAR, which Stephanie Kavan's PhD was also part of. See also page 7.

Mikkel and Alexander are setting up a pilot project together, where they want to learn more about ctDNA analysis methods through a comparison of deep whole genome and whole exome sequencing of plasma, as well as both frozen and FFPE samples from normal and tumour tissue.

GRANTS

Selected grants

Maria Lissel Isaksson from the Department of Clinical Genetics at Vejle Sygehus received a grant for her PhD project: Genetic causes of short stature in children. Maria begins her PhD project on 1 March 2024.

The PhD project will be based at the Department of Clinical Genetics OUH with Professor Lilian Bomme Ousager as supervisor.

The grant is from the Region of Southern Denmark's PhD pool and corresponds to one year's salary.

GRANTS

Selected grants

Three grants from the Region of Southern Denmark's pool for Independent and Strategic Research 2023 for researchers at the Department of Clinical Genetics:

Zainab Hikmat received a grant of DKK 857.000 for her project: Predicting response to medical treatment of inflammatory bowel disease (IBD) using transcriptomics analysis on intestinal biopsies and blood: a prospective cohort study of personalized medicine.
The grant is for operation, including running single cell RNA sequencing and spatial transcriptomics as well as an automated cell counter. See also page 14.

Stine Bjørn Gram, Anette Bygum, Klaus Brusgaard and Lilian Bomme Ousager received a grant of DKK 200.000 for the project: Improved genetic diagnostics and characterisation of hereditary palmoplantar keratoderma. See also page 12.
The grant is for salary funds for Stine Bjørn Gram after completion of her PhD project.

Maria Lissel Isaksson received a grant of DKK 920.000 kr. for her coming PhD project on low height in children. The grant is given for operating expenses.
In addition, Maria received a 1-year PhD scholarship from the Region of Southern Denmark's PhD pool.

GRANTS

Selected grants

PhD student **Louise Adel Jensen,** MSc in Molecular Biology, received the Carl and Ellen Hertz Grant for Danish Medical and Natural Sciences of DKK 10,000.
The grant will be used to analyse VUS in breast cancer predisposing genes using somatic (cancer node) gene profiles. Louise also analyses samples from breast cancer patients where neither a significant gene variant nor a variant of unknown significance have been found (what we call BRCAX patients). This is also done using somatic (tumour) gene profiles. See also page 6.

PhD student **Stine Bjørn Gram,** MD, received DKK 70,000 from Robert Wehnert and Kirsten Wehnert's foundation to buy time off after completing her PhD programme and attending the 2nd World Congress on Rare Skin Diseases in June 2024.

GRANTS

AWARDS AND NOMINATIONS

Selected awards (1)

Top cited article 2021-2022:

In January 2023, PhD student **Ieva Miceikaité** had her research paper nominated 'Top Cited Article 2021-2022' by Wiley. The paper entitled *Total number of reads affects the accuracy of fetal fraction estimates in NIPT* is about how fetal fraction estimation, which is one of the quality criteria for NIPT, may be affected by the sequencing read depth used. The paper was published in Molecular Genetics & Genomic Medicine.

Best cfDNA Poster:

Ieva Miceikaité won the Best Poster Competition at the cfDNA2023 international conference in Copenhagen on 25-26 May 2023 for her poster about cell-free DNA and the development of a non-invasive and risk-free screening method in early pregnancy.

Publication in the recognised New England Journal of Medicine:

In November 2023, **PhD Ieva Miceikaité** and colleagues had their latest study of the desNIPT method published in the journal. The study entitled *Comprehensive Noninvasive Fetal Screening by Deep Trio-Exome Sequencing* shows how genetic diseases in the foetus are detected through deep exome sequencing (des) using a simple blood sample.

The NEW ENGLAND JOURNAL of MEDICINE

AWARDS AND NOMINATIONS

Selected awards (2)

Best PhD supervisor and Best PhD poster:

During Research Week 2023 at the Department of Clinical Research, University of Southern Denmark, **Professor Lilian Bomme Ousager** and **PhD student Stine Bjørn Gram** were awarded 'Best PhD supervisor' and 'Best PhD poster'.

The jury awarded Lilian with 'Best PhD supervisor' for being "a proficient and inspiring supervisor who always provides concrete guidance with the PhD student at the centre".

Stine's presentation of her research in palmoplantar keratoderma was awarded with 'Best PhD poster' because: "the poster presentation was memorable in both words and pictures, it engaged the audience and communicated a difficult and exciting topic in a good way".

PUBLICATIONS

The below list comprises 54 publications/articles written by 25 different authors from our research unit, 16 of these are authors of two or more publications.

nanoNIPT: Short-fragment nanopore sequencing of cell-free DNA for non-invasive prenatal testing of fetal aneuploidies and sex chromosome aberrations. Maria Winther Jørgensen, **Ieva Miceikaitė, Martin J. Larsen.** *Prenatal Diagnosis Mar 2023; 43(3):314-317.*

Survival, surveillance, and genetics in patients with Peutz-Jeghers syndrome: A nationwide study. Jelsig AM, van Overeem Hansen T, Gede LB, Qvist N, Christensen LL, Lautrup CK, Frederiksen JH, Sunde L, **Ousager LB**, Ljungmann K, Bertelsen B, Karstensen JG. *Clin Genet. 2023 Jul; 104(1):81-89.*

Identification of a Novel *PLCD1* Variant in a Danish Family with Hereditary Leukonychia. Lieberoth S, Kumar S, **Brusgaard K, Ousager LB**, Betz RC, **Bygum A**. *Skinmed. 2023 Mar 29;21(1):44-46.*

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Insulinoma in childhood: A retrospective review of 22 patients from one referral centre. Maria Melikyan, Diliara Gubaeva, Anna Shadrina, Maria Kareva, Anna Bolmasova, Anatoly Tiulpakov, Artem Efremenkov, Yuri Sokolov, **Klaus Brusgaard**, Henrik Thybo Christesen, Kirstine Andersen, Alexey Stepanov, Julia Averyanova, Sergey Makarov, Larisa Gurevich. *Front Endocrinol (Lausanne), 2023; 14:1127173.*

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CONTACT

Department of Clinical Genetics:
J.B. Winsløws Vej 4, Indgang 24, 5000 Odense C

Head of Research Professor Lilian Bomme Ousager
Lilian.Bomme.Ousager@rsyd.dk

Management support OUH.ODE.KGA.Ledelsessupport@rsyd.dk

- Executive Secretary, Medical secretary, Tine Koch Andreasen, Tine.Koch.Andreasen@rsyd.dk
- Research Secretary, MA, Susanne Kærn Christiansen, Susanne.Kaern.Christiansen@rsyd.dk

Outpatient clinic and Secretariat:
J.B. Winsløws Vej 15, 1. floor, 5000 Odense C

Phone: +45 65 41 17 25
E-mail: ode.kga@rsyd.dk

Klinisk Genetisk Afdeling / Department of Clinical Genetics
Human Genetik / Human Genetics
Klinisk Genom Center / Clinical Genome Center
Klinisk Institut / Department of Clinical Research

cgc Clinical Genome Center

OUH Odense University Hospital

SDU