# Activities 2009

# Contents

# Preface

**The Kennedy Center is a National Research and Counseling Center for Genetics, Visual Impairment and Mental Retardation. It is a government research institution under the Ministry of the Interior and Health.**

The purposes of the institution are

- Strategic biomedical research at the international level in rare genetic diseases causing mental retardation or visual handica
- Tight integration of research with diagnostics, lifelong counselling, and treatment, ensuring prevention of disease and provision of patient care of the highest quality
- Assembling unique bio- and databanks based on diagnostic laboratory analyses
- Keeping registries on patients with visual impairment, including a mandatory national registry for children
- Knowledge distribution and education in the fields covered by the Center

The Kennedy Center houses the National Center for the dietary treatment of the genetic metabolic diseases Phenylketonuria (PKU) and alkaptonuria, as well as the National Eye Clinic for patients with severe visual impairment, especially children and patients with rare genetic eye diseases.

Furthermore, Centers for Rett syndrome and for Fragile X syndrome have been established.

The Kennedy Center further provides clinical genetic services to Eastern Denmark together with other hospital departments.

The total annual budget including income generating activities amounted to approx. 68 mill DKK.

The Center's staff corresponded to 89 man-years. For detailed overview of economy, budget, contract with the Ministry, board, management etc., we refer to the annual report in Danish (search for "årsrapport") available on our website www.kennedy.dk.

In the present report for 2009 we aim to describe key activities during the past year at the Kennedy Center.

The report is intended for national and international collaborators, funding agencies, and other interested parties.

We hope to convey an impression of a many facetted and dedicated Institution.

The report is divided into three parts, one describing the clinical activities (Part A), one dealing with research and education (Part B), and Part C briefly summarizing the Management and the Board. The addendum contains literature list, contributions from private foundations, and the laboratory's analytic repertoire.

Part A

# Clinical and Diagnostic Activities

## Center for PKU

**PKU is an inborn error of protein metabolism, due to a defective enzyme (PAH) which normally converts phenylalanine to tyrosine.**

The defect leads to increased phenylalanine. To avoid brain damage a strict protein restriction is needed from birth, supplemented with amino acid supplements.

Newborns in western countries are screened for PKU a few days after birth.

In Denmark, all newborn heel prick blood samples are screened at the Serum Institute, and all patients with increased phenylalanine are referred to the Kennedy Center.

We are currently treating approx 250 patient. The level of phenylalanine is monitored regularly with blood samples. The Center is staffed with a head of department (pediatrician), nurse and auxiliary staff, dieticians, and psychologists, in total 10 persons.

**New children**

In 2009 six children were diagnosed with hyperphenylalaninaemia. Two had classic PKU, the most severe form, two had mild PKU, and all four are in treatment with the protein-restricted diet.

Two of the newborns only had a mild increase in blood phenylalanine and were categorized as having mild hyperphenylalaninaemia, MHP, which does not need treatment.

In pregnancy (and preconceptionally) women with PKU have to adhere to a strict diet, to avoid fetal damage. At the start of 2009 one woman was already pregnant and gave birth to a healthy boy later in the year. Five more women started the very strict diet for pregnancy, 2 miscarried, and 3 are expected to give birth in 2010.

**Head of department (PKU and Rett)**
**Jytte Bieber-Nielsen**

**New treatment**

We had hoped to be able to use a new medical treatment (BH4) for mild PKU, with Kuvan® which was approved by EMEA, but the condition for payment is not yet clarified. The patients are looking forward to this treatment, because it for selected patients may replace the strict diet.

**Activities at the Center in 2009**

We had 213 outpatient visits, 175 to the doctor, 27 to the nurse, and 199 of the visits had diet counselling. One patient had 11 visits for blood sampling.

Once a week all the results for blood phenylalanine for infants and women on pregnancy diet are given directly to the patient or the parents by telephone or by mail. Beside this there are several daily telephone calls and mails to be answered, especially with questions about dietary problems.

The patients' cognitive performances are routinely tested by a psychologist with the Weschler Intelligence scale (for the infants The Bayley Test) at 1, 4½, 6 10, 14 and 22 years of age. 37 children and adults were tested in 2009. Our psychologist had 10 families for counselling.

26 children between 7 and 14 years of age joined our four-day PKU summer camp, which took place in the start of August. Seven staff members supervised the camp with the help of 6 young people with PKU.

## Center for Rett syndrome

**Rett syndrome is a severe congenital genetic disease with multiple mental and physical impairments, mostly in girls, requiring lifelong care and treatment.**

The center was started in 2007 with funding from the state.

The center offers multidisciplinary counselling to patients, families and caretakers.

The staffing includes medical doctors, physiotherapist, social worker, and a PhD student.

In Denmark approx 100 patients are known, most of who have the mutation in the MECP2 gene identified. In 2009 six new patients were diagnosed with Rett syndrome, RTT, five with a MECP2 mutation, one without, but with clinical RTT. Two patients were 20 months at the time of diagnosis; the other new-diagnosed patients were 4½, 17, 30 and 53 years of age respectively.

Twenty previously diagnosed patients were included in the ongoing research project about fractures and osteoporosis in Rett syndrome during the year, see part B, research projects.

A total of 64 patients have joined this study, which is now closed for inclusion.

20 patients were clinically examined at the Rett Centre during a one day session. Another day was spent at Hvidovre Hospital, where blood sampling and X-raying took place. We had nine more outpatients with RTT in our clinic.

A doctor and a physiotherapist together examined all 29 patients.

## Center for Fragile X

### Fragile X syndrome is the most common cause of familial mental retardation.

This national knowledge center offers genetic and psychosocial counseling to patients, families, professionals, schools, institutions, municipalities, etc.

In Denmark we know about 300 patients but approx 1000 are expected, meaning that the condition is under-diagnosed.

Boys are mostly affected.

Mental retardation is moderate to severe, with IQ typically in the 30-60 range.

The genetics of this X-linked disorder is complex, as both females and males can be carriers of a premutation that changes from generation to generation.

See also part B, research projects.

The center is staffed with a psychologist and a medical consultant.

In 2009 the center arranged a successful course for professionals (social workers, teachers etc) as well as meetings for families.

Collaboration with Nordic countries is established.

Many outgoing consultations were carried out by the psychologist, and the center also received families for counseling.

# Clinical Genetics

### Medical Genetics Laboratory and Genetic Counseling Clinic

The Kennedy Center, being a part of the National Clinical Genetic Unit for East Denmark, is authorized to provide a clinical genetic specialty service for the population of East Denmark.

The service includes diagnostic laboratory investigations on pre- and postnatal samples, by the medical genetics laboratory, and genetic counseling by the genetic counseling clinic.

## Medical Genetics Laboratory

### Medical Genetics Laboratory performs laboratory analysis to support and enable the Kennedy Center in its core business of patient diagnosis, treatment and research.

It provides national and international laboratory services to hospitals and specialized clinics concerning cytogenetic and molecular-genetic & -epigenetic issues.

The diagnostic service is income generating, as the laboratory charge for the analyses carried out. In addition, the laboratory performs research and development of relevant analytical methodologies.

The analytic repertoire and pricing can be seen in addendum on last pages of this document, and is accessible by the Kennedy Center home page.

The Kennedy Center is a non-for-profit public entity, and the prices are related only to the basic costs in performing the analysis and the developments of new analyses for diagnosing genetic disorders.

The staff includes a director (medical doctor), a head technician and 22 technicians. In addition, 3 molecular geneticists and a professor in molecular biology carry out both research and diagnostic activities.

**Head of Department**
**Peter McNair**

In the provision of laboratory services, the laboratory applies recommended standards for analysis and interpretation of results, and assures the quality by participation in relevant external quality assurance programs issued by e.g. EMQN, ERNDIM and UKNeqas.

The laboratory is in the process of implementing a quality management system, aiming at becoming accredited according to the European standard DS/EN ISO 15189:2008.

Taking the new domicile of the Kennedy Center into full use late 2008, the year 2009 provides good statistics for judging the productivity and efficiency of the laboratory function.

| Table 1: Turn Around Time for 2009 | | | | | |
|---|---|---|---|---|---|
| **Prenatal chromosome analysis** | | 5 days | 10 days | 14 days | Number of analyses |
| QF-PCR | Goal | 100% | | | |
| | Result | 95% | | | 561 |
| Karyotyping | Goal | | 50% | 80% | |
| | Result CVS | | 60% | 94% | 459 |
| | Result Amniotic fluid | | 8% | 80% | 134 |
| | Result (all) | | 48% | 90% | 593 |
| **Postnatal chromosome analysis** | | | 5 weeks | 7 weeks | |
| Karyotyping | Goal | | 50% | 80% | |
| | Result | | 94% | 97% | 1300 |
| **Fragile X syndrome analysis** | | | 5 weeks | 7 weeks | |
| All methods | Goal | | 50% | 80% | |
| | Result | | 79% | 93% | 172 |

Goals for laboratory investigation turn around time was set and documented in the agreement contract for 2009 between the Ministry and the Kennedy Center.

The achievements of these goals are presented in table 1.

In table 2 the number of analyses produced in 2008 and 2009 are shown distributed on type of analysis.

Year 2009 shows an increase due to a small delay in the production of 2008 related to the process of moving the entire laboratory into the new domicile of the Kennedy Center and introducing new ITC systems. This delay was remedied during the first few months in 2009.

**New analyses**

In 2009 the major emphasis in developing new methods were focused on 1) changing from Southern Blot analysis to MLPA for methylation analysis in Angelman syndrome and Beckwith-Wiedemann syndrome; and on 2) introducing molecular genetics analysis for diagnosing glaucoma (WDR36; OPTN; MYOC and CYP1B1 genes) and microphtalmia (SOX2; OTX2 genes).

| Table 2: Number of analyses | 2008 | 2009 |
|---|---|---|
| DNA extractions & measurements | 1.094 | 1.598 |
| Analysis on DNA materials | 721 | 1.170 |
| QF-PCR analysis, prenatal | 405 | 641 |
| Chromosome analysis, prenatal | 517 | 606 |
| Chromosome analysis, blood samples, postnatal | 550 | 796 |
| Chromosome analysis, bone marow | 294 | 332 |
| Chromosome analysis, aborted tissues and stillborn | 152 | 179 |
| Array CGH | 70 | 141 |
| FISH analysis | 83 | 96 |
| Phenylalanine / Tyrosine measurements in blood | 3.723 | 3.421 |
| Other | 231 | 477 |
| Total number | 7.840 | 9.457 |

# Genetic Counseling Clinic

## Genetic service to patients and their families mainly living in Eastern Denmark is provided by the Genetic Counseling Clinic at the Kennedy Center.

The service covers all types of genetic disorders and when relevant our clinic collaborates with other national and international genetic departments and laboratories.

General practitioners and hospital departments can refer patients and family members for genetic counseling.

The genetic services of the genetic counseling clinic are income generating activities.

### Training and Education

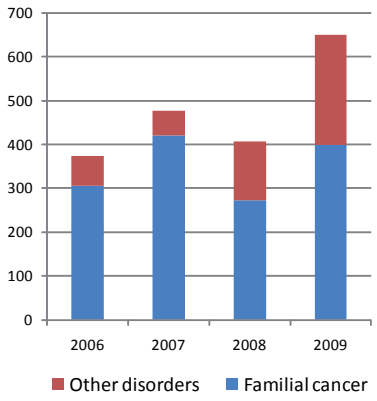
The Kennedy Center takes part in the postgraduate training of medical doctors for the medical specialty clinical genetics. In 2009 the staff consisted of two trainees, a clinical geneticist and a non-medical genetic counselor, and secretarial assistance. Apart from the genetic counseling activities the medical doctors in the clinic report the results of the laboratory tests, and in addition provide genetic consulting to other health care professionals. In order to strengthen the interdisciplinary collaboration and optimize our services regular staff meetings and mini symposia are held with participation of the clinicians from the departments of gynecology, pediatrics and fetal pathology as well as surgeons and oncologists.

**Head of Department**
**Susanne Timshel**

### Genetic counseling

Genetic counseling is a health care service aimed at helping individuals and families understand the science of genetics and how it may relate to them. Genetic counselors provide information that helps families make personal decisions about pregnancy, child care and genetic testing. Counselors are trained to help translate and simplify the information, and act as an emotional resource.

There is a growing demand for genetic counseling. In 2009 650 consultations were registered in the clinic. The temporary decline in the activities in 2008 was due to vacancy and relocation to our new domicile.




### Familial Cancer

A family history of cancer is often the cause for referral to the clinic. Familial cancer accounts for 60 % of the genetic counseling activity, mainly the hereditary breast and ovarian cancer syndrome. During the first clinic visit, a medical and family history assessment will be performed by the genetic counselor. A second clinic visit is arranged within the next 2-3 months with a clinical geneticist for counseling and risk assessment as well as recommendations for surveillance programs if relevant. If eligible for genetic testing a blood specimen will be collected.

### Prenatal genetic diagnosis and counseling

According to the prenatal screening program launched by the Danish National Board of Health in 2004, First Trimester Combined Screening (fetal nuchal translucency and maternal serum biochemistry) is offered to all pregnant women which allows for early diagnostic testing (CVS) when screen positive. When an abnormal test result is provided by our laboratory the mother to be is offered genetic counseling by our medical staff. Also prenatal genetic counseling is recommended to families with a family history of birth defects, mental retardation or developmental delay, stillbirths or childhood deaths, chromosome disorders, severe genetic childhood conditions (muscular dystrophy, cystic fibrosis), and consanguinity. When appropriate, we offer genetic testing, including prenatal diagnosis. We aim to give our patients the necessary information to enable them to make decisions that are right for them, and to support them throughout the process.

### Pediatric and adult genetic diagnosis and counseling

Our clinic has a well established collaboration with the pediatric departments in Eastern Denmark. The pediatric patients are referred for diagnostic evaluation of genetic syndromes, mental retardation, congenital malformations and other conditions suspected of being caused by a genetic or developmental defect. Counseling is given also to persons with a risk of adult-onset diseases for example Huntington Disease with the potential of presymptomatic testing. We aim to provide an unbiased, complete and accurate view of the situation, the nature of the genetic or birth defect being investigated in order to determine the risk of occurrence or recurrence, and the availability of tests for it.

# The Eye Clinic

## National Center for diagnosis and rehabilitation of severe visual impairment

The Eye Clinic receives patients from throughout the country concerning examination, diagnostic evaluation, treatment and counseling of severe visual impairment in children, adolescents and adults. Referring and cooperating agencies are ophthalmologists, both in practice and in hospitals, doctors in hospital departments, visual consultants, low vision centers, the Institute for the Blind and Partially Sighted etc. Opticians with specialized training in low vision optics and special contact lenses make a comprehensive visual rehabilitation of the visually impaired with sophisticated low vision optics.

The Eye Clinic makes a large number of specialized examinations for example special optical recordings of the corneal surface and refractive errors, and electrophysiological examinations in which the function of the retina and the optic nerve are measured.

In addition, a number of other special examinations as part of diagnosing and monitoring rare eye diseases.

Whilst 2008 was a year of change due to relocating the clinic from Hellerup to Glostrup, a new head of the department and replacement of personnel etc., 2009 has been the year in which the Eye Clinic was successfully established in the new environment.

Most of the activities at the Eye Clinic now take place at the headquarters in Glostrup, whilst the clinic in Hellerup primarily focuses on activities in collaboration with the Institute for the Blind and Partially Sighted (IBOS). These activities include patient cases dealing with the safeguarding of business in spite of progressive eye disease, counseling of the social workers at the Institute, Reading Vision Clinic and cooperation with the affiliated trainees and students.

The permanent staff of the Eye Clinic consists of four specialists in ophthalmology, one doctor training to be an ophthalmologist, five specially trained opticians, six nurses and three secretaries.

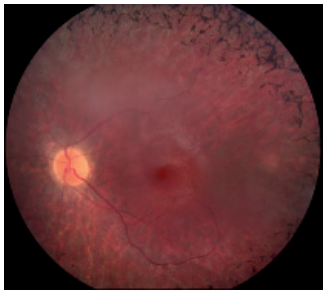
**Head of Department**
**Nynne Christoffersen**

## Registries

### Genealogy

The Eye Clinic at the Kennedy Center administers the Danish Family Archive for Hereditary Eye Diseases - a registry which holds about 36,000 persons spread over nearly 2,400 genera. In the latter half of 2008 a process concerning modernizing the registry has started. All four databases that previously constituted the registry has merged into one common database making it easier to update, and also easier to make statistic calculations for research etc. In 2009 the process converting the old databases into a modern platform was completed. During 2010 we expect the registry to become operational.

Fundus photo of the retina showing retinitis pigmentosa.



### Low Vision Registry of Children

The Eye Clinic at the Kennedy Center keeps a mandatory National Registry of Blind and Low Vision Children in Denmark, which means that all children under 18 years living in Denmark with a visual impairment to a certain limit or less have to be registered. All children with retinitis pigmentosa regardless of vision are also included in the registry. Members of the registry obtain particular financial assistance for the purchase of glasses, and receive offers to be registered with a visual consultant, who can visit and counsel the institution, the school and the home of the child.

At the end of 2009, a process converting of the registry to an electronic record was started, and is expected to be finished during 2010.

The Eye Clinic publishes an annual report in Danish of the Low Vision Registry. This can be downloaded on our website www.kennedy.dk (search for "Registre"), where all the previous annual reports are available.

### "Web Vision"

It is not known how many visually impaired citizens in total there are in Denmark. The Eye Clinic at the Kennedy Center has launched an internet-based system ("Web Vision") in order to collect and register data and activities in local low vision centers in Denmark. In addition to statistics, the aim of the registry is to record the need for rehabilitation.

In 2009 the Kennedy Center requested the National Board of health to have the database formally accepted as a Clinical Database. Once approved, the system will be operational.

The Web Vision project has a website, www.websyn.dk where more information can be found.

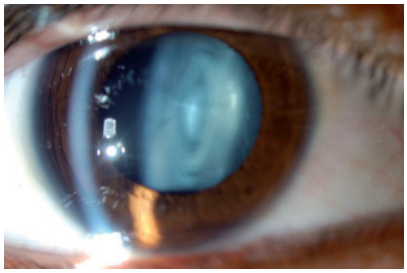
## Cooperative Agreements

By the end of 2009 a cooperation agreement between the Kennedy Center and Glostrup Hospital was formally approved by the parties involved.

The aim of the cooperation is to share and divide the work on well-defined patient groups for the benefit of patients and caregivers, as well as professionals.

A part of the cooperation agreement concerns children with congenital cataracts. This cooperation is already established. The children have the initial ophthalmic examinations and surgery at the Eye Department at Glostrup Hospital.

After the operation the children will appear at the Eye Clinic at the Kennedy Center for adjusting the optics.



Lens with congenital cataracts.

Another part of the agreement describes the cooperation around patients undergoing electrophysiological examinations and other special examinations of the eye as part of diagnosing and monitoring rare (hereditary) diseases of the eye.

According to agreement the Eye Department at Glostrup Hospital can refer the patients for electrophysiological examinations to the Eye Clinic at the Kennedy Center, where the investigations are conducted and described followed by a joint conference.

Vice versa, patient from the Kennedy Center can be referred to Glostrup Hospital for special photographic examinations of the eye.

The joint conferences involve staff from both departments (doctors and researchers, etc.) and are designed to share knowledge, educate students and younger colleagues as well as developing new areas of research and collaboration.

**Consultations in 2009 compared with the previous four years**

| Type of consultation | 2005 | 2006 | 2007 | 2008 | 2009 |
|---|---|---|---|---|---|
| Optical rehabilitation | 1122 | 1021 | 1070 | 1713 | 1922 |
| Ophthalmological examinations | 1154 | 1095 | 1067 | 1414 | 1647 |
| Total | 2276 | 2116 | 2137 | 3127 | 3569 |

Conclusion: The number of consultations in 2009 has generally risen over the past five years.

**Special examinations in 2009 compared with 2008**

| Type of examination | 2008 | 2009 |
|---|---|---|
| Examinations in general anaesthesia | 25 | 19 |
| Electrophysiology | 380 | 454 |
| Topography (corneal) | 142 | 167 |
| Fundus photography | 420 | 330 |
| Slit lamp photography | 60 | 487 |
| Other (color vision tests, visual field and dark vision examination etc.) | 499 | 523 |

Conclusion: Generally there is an increase in the number of special examinations in 2009 compared with 2008. Particularly noteworthy is the increase in the number of slit lamp photographies which is due to new equipment in the clinics.

## Facilities

The Eye Clinic in Glostrup has five equally equipped clinics. There are three examination rooms for special examinations inclusive electrophysiology, a room for photography, and rooms for specialized examinations in optics and an optic laboratory. In addition to this there are offices, secretarial, archival, reception and waiting room. The clinic in Hellerup consists of three clinics, waiting room, office, secretarial and one room for special examinations.

## Education and training

### Training of Opticians

The Eye Clinic at the Kennedy Center held in the autumn of 2009 the first training course for low vision opticians. The course was previously held at the optician schools, but they wanted to give the mandate to the Kennedy Center. Opticians and eye doctors from the Eye Clinic were together with external lecturers responsible for the teaching, which was subsequently evaluated with a very satisfactory result.

### Visual Vocational Training

In spring 2009 ophthalmologists and opticians from the Eye Clinic taught at a course of visual professional training at the Institute for the Blind and Partially Sighted.

### Training of doctors

Decided in 2009, a doctor in training to be an ophthalmologist will from spring 2010 be associated to the Eye Clinic at the Kennedy Center. This means that the Kennedy Center helps to train future specialists in ophthalmology.

# Part B

## Research and Education

In the following significant research projects in 2009 are described.

The ultimate aims of our research is to identify new genes and genetic mechanisms in mental retardation and visual impairment, to improve diagnosis and treatment, furthermore research is conducted in order to gain understanding of pathophysiological processes in disease. Clinical research in core competence areas is also an important issue.

Research is a fundamental activity at the Kennedy Center, and all departments contribute. The research is focused in 5 main areas:

1. Mental retardation and neurodevelopmental disorders,
2. Visual impairment, clinical and molecular aspects,
3. PKU and related disorders,
4. Copper metabolism, functional studies and genetherapy,
5. Epigenetics

Some of the PhD students, technicians and scientists employed at the Kennedy Center on a windy day with professor Zeynep Tümer far right.

# Area 1

# Mental Retardation and Neurodevelopmental Disorders

## Tourette Syndrome

**Tourette syndrome (TS) is a hereditary, chronic, neurobiological disorder, characterized by multiple motor and vocal tics that begin in childhood or early adolescence.**

TS is often accompanied by co-morbidities, where the most prevalent ones are attention deficit hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD), each of which is observed approximately in 60% of TS patients.

Furthermore, sleeping disorders, stuttering, anxiety, depressive symptoms, outbursts of extreme anger, and learning disabilities are often seen. TS is 4 times more common in males and prevalence is around 1% among school children.

Genetic factors are suggested to play an important role in the aetiology, but these factors are largely unknown.

Our aim is to unravel the molecular genetic changes by investigating a unique cohort of 214 clinically well-described TS patients, with or without co-morbidity disorders, and families with several affected members.

Combining several new high throughput technologies with detailed phenotype data from a large patient cohort and families may enable to identify novel genes and mechanisms in TS and co-morbidity disorders.

This project has been supported by a grant from Lundbeck Foundation.

**Contribution from KC**
Zeynep Tümer, Karen Brøndum Nielsen, Kate Nielsen, Linea Melchior, Kirstine Ravn, Karen Grønskov, Judy Rasmussen

**Collaborators**
Liselotte Skov, Nanette Mol Debes (Tourette Clinics, Glostrup Hospital); Helle Hjalgrim (Danish Epilepsy Hospital); Søren Brunak (DTU); Kasper Lage (Broad Institute, Boston); Jørgen Nielsen, Lena Hjermind, Anya H. Simonsen (Rigshospitalet, Copenhagen); Steven Haugbøl (Hillerød Hospital); Kirsten Ohm Kyvik (Twin Register and Odense Universitet).

**International collaborators**
Ben Oostra (Erasmus University, Netherlands); Hans Hilger Ropers, Reinhard Ullmann (Max Planck Institute, Berlin)

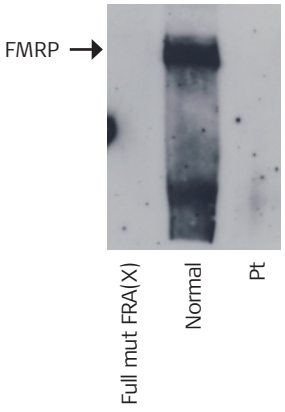
## Fragile X Syndrome, a Unique Case with a Rare Mutation

**Fragile X syndrome is a inherited form of mental retardation, and is in more than 99% of cases caused by an expansion of a untranslated trinucleotide repeat (CGG) located in the 5'UTR.**

In collaboration with an experienced clinical colleague we identified a clinically typical fragile X syndrome without CGG expansion, where western blot analysis showed no expression of FMR1 protein.

Sequence analysis revealed a missense mutation in the FMR1 gene.

This has been considered extremely rare; however with this finding the message clearly seems to be that patients with typical features of fragile X syndrome should have sequence analysis of FMR1.




Western blot analysis shows that pt. has no expression of FMRP.

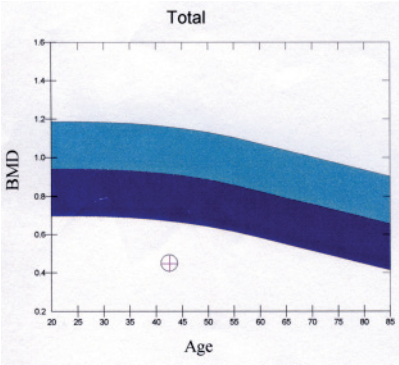
**Contribution from KC**
Karen Grønskov, Helle Hjalgrim, Karen Brøndum-Nielsen, Alma Dedic

## Clinical Study: Evaluation of the Occurrence of Bone Fractures in Patients with Rett Syndrome

**Rett syndrome (RTT) is a severe neurodevelopmental disorder, affecting mainly females due to mutations in the X-linked gene, MECP2 located at Xq28.**

RTT has a worldwide distribution with a prevalence of 1:10.000 in Denmark.

Classical as well as atypical forms of RTT have been described giving a very broad spectrum of symptoms. Patients with RTT are reported to be at almost 4-fold increased risk of getting a fracture.

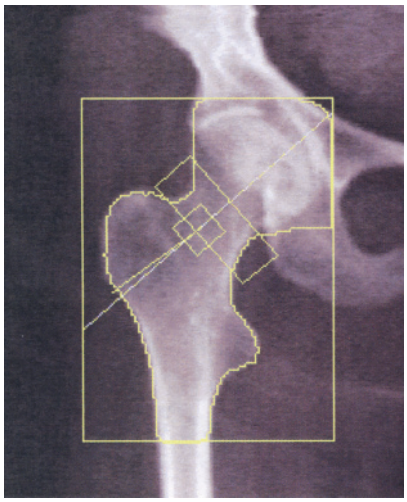



▲ Low bone mass in left hip for patient with Rett syndrome (42 years old).

DXA scan showing thin cortex of left hip in same patient. ▶

The aim of this case control study was to investigate the prevalence of fractures in the Danish population of patients with a known MECP2 mutation.

We wanted to compare fracture mechanism and age at first fracture event with healthy controls.



Furthermore, we wanted to examine whether possible risk factors such as mobility status, fall tendency, epilepsy and epileptic seizures, anti-epileptic drugs and vitamin D status were associated with fracture occurrence within RTT.

Our hypothesis was that RTT patients have an increased risk of fractures, and that possibly it could be related to MECP2 mutation type and/or risk factors associated with low-energy trauma.

**Contribution from KC**
Gitte Rønde (PhD student) Jytte Bieber Nielsen, Karen Brøndum-Nielsen

**Collaborators**
Jens-Erik Beck Jensen (The Osteoporosis Research Unit, Hvidovre Hospital)

## Rett Syndrome - Determining the Parental Origin of MECP2 Mutations

**The aim of the project is to determine the parental origin of MECP2 mutation in patients with Rett syndrome.**

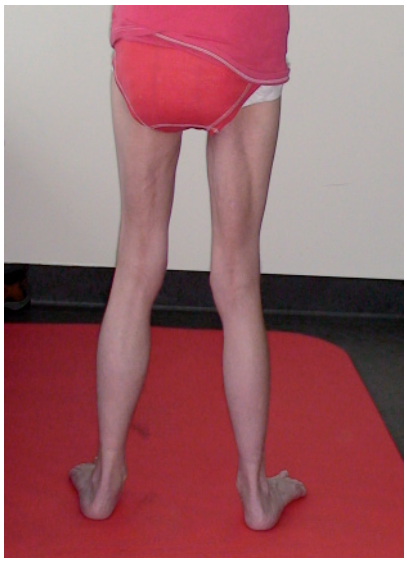
So far studies have revealed a high predominance of paternal origin of de novo C to T transition mutations.

We will expand these studies to include Rett patients with MECP2-deletions and -duplications.

The mechanisms involved in the occurrence of these types of mutations, are different from the C to T transition and therefore could be of maternal origin.

The project will involve 30 Rett patients.

So far all patients have been sequenced in 3000 bp for identification of SNPs, which is the basis to determine the parental origin of the MECP2 mutations.



**Contribution from KC**
Kirstine Ravn and medical staff from Center for Rett syndrome

**International collaborators**
Ola H Skjeldal (Department of Pediatrics, Rikshospitalet, Oslo, Norway)

◀ Older patient with Rett syndrome and characteristic growth retardation.

# Area 2 Visual impairment

## Primary Congenital Glaucoma

**Primary congenital glaucoma (as PCG) is characterized by developmental defect(s) of the trabecular meshwork and anterior chamber angle that prevent adequate drainage of aqueous humor, resulting in elevated intraocular pressure (IOP). Typically, the diagnosis is made in the first year of life.**

Depending on when treatment is instituted, visual acuity may be reduced and/or visual fields may be restricted. In untreated cases, blindness invariably occurs.

The diagnosis of PCG is based on clinical findings. CYP1B1, the gene encoding cytochrome P450 1B1, is the only gene currently known to be associated with PCG.

The aim of the project is to identify new genes involved in PCG pathogenesis.

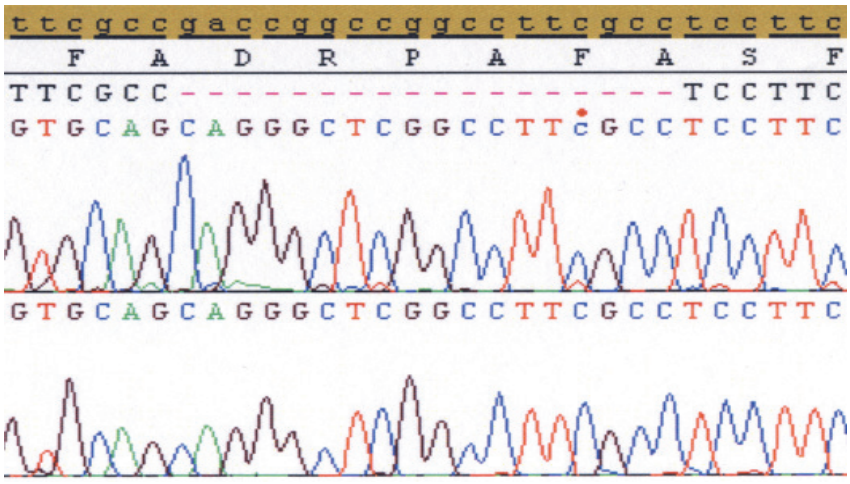
For this purpose we have initially investigated 30 patients with PCG for mutations in the CYP1B1 gene and detected mutations in app. 20% of the patients (=5).

The patients who do not show mutations in CYP1B1 will be screened for submicroscopic chromosome aberrations by genome wide screening for deletions/duplications using high resolution DNA microarrays.

These studies may enable finding new genes involved in PCG.

**Contribution from KC**
Alba Redo (Erasmus Student), Karen Grønskov, Zeynep Tümer

**National collaborators**
Daniella Bach-Holm Petersen, Lisbeth Sandfeld Nielsen (Glostrup Eye Clinic)




The deletion is shown with the dashed line

## Optic Atrophy, Kjer Type

**Autosomal dominant optic atrophy (ADOA, Kjer disease, MIM #165500) is the most common form of hereditary optic neuropathy.**

Mutations in OPA1 located at chromosome 3q28 are predominant, explaining between 60 and 80% of ADOA cases.

Material has been collected from Danish ADOA patients and investigated for mutations in the OPA1 gene.

By MLPA analysis deletions were found to be a frequent cause of optic atrophy, Kjer type.

Furthermore, several novel mutations were identified of which two are possible novel founder mutations.

**Contribution from KC**
Gitte J Almind (PhD student), Karen Grønskov, Karen Brøndum-Nielsen, Jakob Ek

**National collaborators**
Michael Larsen (Glostrup Hospital)

**International collaborators**
Dan Milea (Angers University Hospital, France)

## Oculocutaneous Albinism

**Oculocutaneous albinism (OCA) is a disease causing hypopigmentation of eyes, hair and skin.**

It is a genetically heterogeneous disorder and mutations in four genes (TYR, OCA2, SLC45A2, TYRP1) have been identified as the genetic cause.

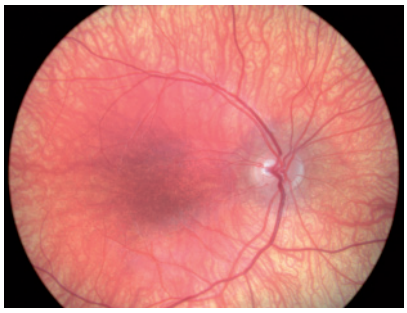
Mutations in these genes account for approximately 50% of patients, and thus a search for additional OCA genes are ongoing.

Published paper: Grønskov K et al, IOVS 2009, 50:1058-64.

Patients with OCA have been identified in the Faroe Islands.

Since these are in an isolated population, they have been the basis for identifying new OCA genes.

SNP6.0 analysis was performed and several homozygous shared regions have been identified, which are further investigated.



◂ Fundus photo of the retina showing Oculocutaneous albinism

**Contribution from KC**
Karen Grønskov, Thomas Rosenberg, Alma Dedic.

## The Molecular Nature of Usher Syndrome

**Usher syndrome (USH) is an autosomal recessive disorder, characterized by hearing impairment that may be congenital, progressive visual loss due to retinitis pigmentosa and variable vestibular dysfunction.**

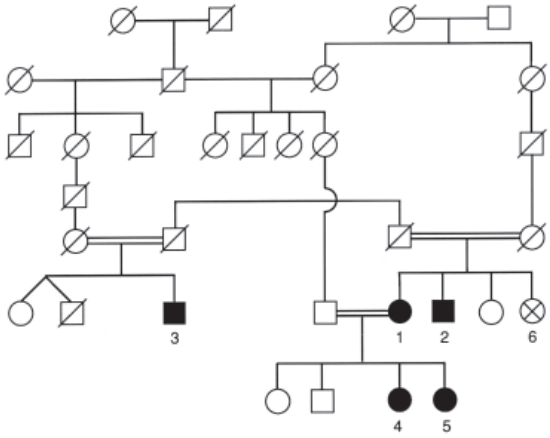
Clinically it has been divided into three subtypes; USH1, USH2 and USH3.

To date nine genes associated with USH have been identified. It is however assumed that additional genes exist.

In this project we are trying to identify a new USH3-like gene.

By homozygosity mapping of a consanguineous Danish family of Dutch descent, we have identified a novel locus for a rare USH3-like syndrome.

The affected family members have a unique association of retinitis pigmentosa, progressive hearing impairment, vestibular dysfunction, and congenital cataract.




Pedigree for the family, where the disease-causing gene is not yet identified.

Paper published in 2010 (Dad S et al)

We are now investigating the entire region for disease causing mutation by new generation sequencing in collaboration with the Panum Institute.

Furthermore, as part of an initiated PhD project we want to genotype further patients by screening of relevant Usher genes.

We have about 170 patients registered with Usher syndrome, of which only 80 have been genotyped.

We investigate Usher proteins interacting in a protein-network "USH protein interactome" by expression of Usher genes in cells forming cilia (murine pigment cells/hair cells/ fibroblast cell-line (NIH-3T3)) and in vitro investigate the effect of aminoglycosid suppression of premature stop mutations.

**Contribution from KC**
Shzeena Dad (Ph.D student), Lisbeth Birk Møller, Michael Larsen

**National collaborators**
Nanna Rendtorff and Lisbeth Tranebjerg (WJC, ICMM, University of Copenhagen/Bispebjerg Hospital)

# Area 3 PKU and related disorders

## Clinical study: Testing the effect of BH4 in selected Danish PKU patients

**Phenylketonuria (PKU) is an inherited metabolic disease characterized by phenylalanine (Phe) accumulation due to defects in the enzyme phenylalanine hydroxylase (PAH).**

Phe accumulation leads to cognitive impairment.

Treatment for prevent mental retardation is a strict protein restricted diet from birth supplemented with aminoacids minus phe.

It was discovered in 1999 that some individuals with PKU respond to tetrahydrobiopterin (BH4) treatment, the natural cofactor of PAH, by a reduction in blood Phe concentrations, paving the way for a new treatment principle.

In this study, we tested 12 patients with PKU, 8-29 years of age, all carrying the common Y414C mutation in the PAH gene.

Three were homozygous and nine were compound heterozygous.

During the study period, genuine protein was increased to approximately 1 g/kg.

The patients were treated with 20, 10, and 5 mg BH4/kg/day for 1 week on each dose, starting with 20 mg/kg.

A positive response was defined as a decline in blood Phe > 30%.

Eleven of 12 patients had a positive response with 20 mg/kg, 5/10 responded on 10 mg/kg, and 1/9 on 5 mg/kg.

Two were late responders, with a response on 20 mg/kg after >48 h.

We could confirm the previously reported inconsistent responsiveness of Y414C in the nine heterozygous patients, whereas the three homozygous patients had early median Phe declines of 73%, 51%, and 27%, respectively, on the three different doses.

No side effects were observed.

We conclude that extended testing (5 days) is necessary to determine BH4 responsiveness.

Manuscript published in 2010 (Nielsen JB et al, J Inherited Metabol Dis 2010, 33:9-16)

**Contribution from KC**
Jytte Bieber Nielsen Karen E Nielsen, Flemming Guttler

## Clinical study: - the effects on quality of life and plasma concentrations of phenylalanine and tyrosine of two different amino-acid-supplementations in different concentrations

**Supplementation of large neutral amino acid (LNAA) and a semi-free (SF) diet had possible positive effect on well being on adults with PKU.**

The aim of this study was to determine the effects of 2 different products, containing LNAA in different combinations, on plasma Phe levels and other metabolites in early treated adults with PKU, and to investigate the relationship between these metabolites and wellbeing.

This was a prospective, double blind, cross over study consisting of four consecutive three-week phases. Twelve subjects (6 males, 6 females) with PKU were recruited, 11 completed the study.

Each phase consisted of either LNAA1 or 2, either in low or high dosage.

Subjects were instructed to follow their usual SF diet, maintain energy intake, to complete a 3-day food record and a SF36 scheme during each phase, and to take blood samples every day for the week of each period.

At the end of each phase, plasma amino acid profile was quantified and other metabolites were measured.

The results showed that there was no correlation between plasma Phe level and LNAA dosage or type of LNAA supplement.

However, 2 patients stated that they felt better when taking LNAA 2 in high dosage.

We found that LNAA1 or 2 in higher dosage than usual does not lower Phe level.

However, LNAA supplementation has been used for PKU patients > 18 years for 25 years in Denmark and proved to be a useful alternative for adults with PKU.

**Contribution from KC**
Kirsten K. Ahring, Lisbeth Birk Møller

**National Collaborator**
J. R. Andersen, Department Human Nutrition, University of Copenhagen and Nutrition unit, Rigshospitalet, Copenhagen

# The Role of GTP Cyclohydrolase Gene, Involved in BH4 Synthesis, on Pain Threshold in Humans and Animals

**In a recent study a correlation between BH4 synthesis and pain threshold has been demonstrated in both rat and man suggesting that the processing of pain is regulated by the activity of the GCH1gene.**

The results indicate that the haplotype of the GCH1 gene, encoding the rate-limiting enzyme, GTPCH1 in the synthetic pathway of BH4, may predict the level of pain sensitivity and chronicity in patients with nerve injury.

The cofactor tetrahydrobiopterin (BH4) has previously been linked to the development of the human movement disorder, dopa-responsive dystonia (DRD) characterised by limb dystonia often starting in early childhood.

Dominant mutations in GCH1 lead to DRD.

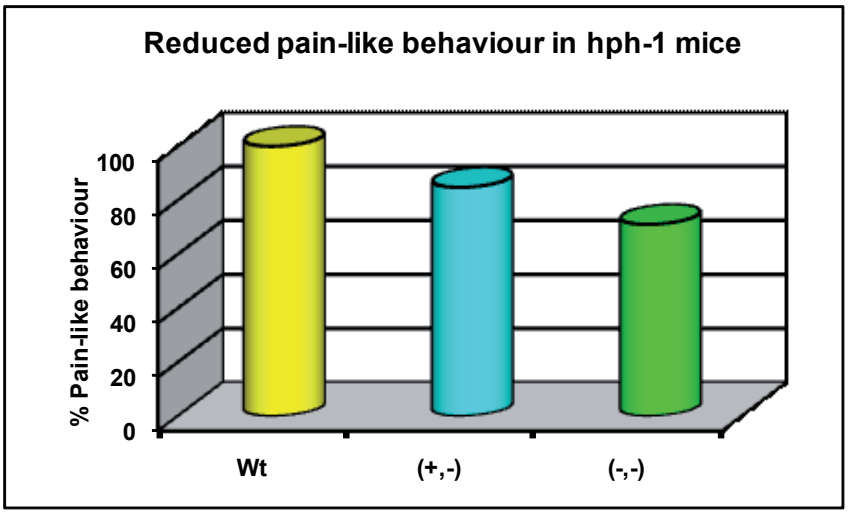
We are going to analyse the role of mutations in the GCH1 gene on pain perception in humans and on noxious responses in mice.

We will investigate patients suffering from DRD due to mutations in the GCH1 gene.

In parallel, a mouse mutant deficient in GTPCH1 will be examined.

Thus the patient group and the mouse model are unique for verification of the effect of the GTPCH1 activity on the individual pain threshold.

It is the first time this type of mice is investigated for responses to noxious stimuli.




Hph-1 mouse mutants show reduced pain-like behaviour after intraplantar injection of a diluted formalin solution into the right hind-paw.

We hypothesize that the reduced GTPCH1 activity will lead to an increased pain perception threshold (less sensitive) in both humans and animals.

The discovery that the concentration of BH4 modifies the sensitivity of the pain sensing system opens up to a new target for pharmacological intervention to modulate pain perception.

Only few genes have so far been linked to pain perception.

**Contribution from KC**
Arafat Nasser (Ph.D student), Lisbeth Birk Møller, Pia Hougaard

**National collaborators**
Ole J. Bjerrum and Anne-Marie Heegaard (Department of Pharmacology and Pharmacotherapy, University of Copenhagen),
Erik Dupont, Troels Staehelin Jensen, Anette Torvin Møller and Vibe Hellmund (Danish Pain Research Center, Aarhus University Hospital)

# Area 4 Copper Metabolism and Gene Therapy

## An immunofluorescence Analysis of Mutated ATP7A Proteins

**Menkes disease is a rare X-linked multisystemic lethal disorder of copper metabolism.**

The Menkes gene *ATP7A* encodes a copper transporter, ATP7A that belongs to the large family of P-type ATPases.

The protein has three cytoplasmic domain: the activation (A) domain, the phosphorylation (P) domain, and the nucleotide-binding (N) domain.

ATP7A has a dual role. It is responsible for the copper loading of several copper-requiring enzymes, which take place in the Trans Golgy Network (TGN), and it is responsible for the efflux of copper from the cell.

The efflux of copper from the cell, or copper transport into the lumen of TGN is ATP driven.

During the catalytic cycle an invariant aspartate residue located in the P domain is phosphorylated.

It is known that ATP7A at low copper concentrations is located in the membrane of TGN, whereas in response to increased amount of copper it is translocated, to the plasma-membrane.

This copper-dependent translocation is furthermore dependent on phosphorylation of the aspartate residue.

If the protein is not phosphorylated it will not be translocated to the plasma-membrane.

The Kennedy Center receives samples for molecular diagnose of Menkes disease form the entire world.

Until now we have identified about 350 mutations in 450 families.

A fraction of these mutations are missense-mutations.

To investigate the effect of these missense-mutations in more details we are investigating the cellular localisation and copper dependent trafficking of these protein variants.

The analysis is performed by immunofluorescence analysis of the ATP7A proteins expressed in fibroblasts from patients with Menkes Disease.

**Contribution from KC**
Lisbeth Birk Møller, Tina Christoffersen, Tina Skjørringe

**National collaborators**
Poul Nissen, Bjørn Panyella Pedersen (Centre for Membrane pumps in Cells and Disease, University of Aarhus)

## Non-viral Gene Delivery using Pegylated Immunoliposomes

**The aim of this project is to introduce a reliable and safe method for systemic non-viral targeted delivery of transgenes with focus on targeting the blood-brain barrier and the brain.**

Pegylated immunoliposomes (PILs) targeting specific receptors, with monoclonal antibodies, were employed.

A large part of the work was focused on designing and re-designing the liposomal strategy leading to more efficient DNA encapsulation and delivery.

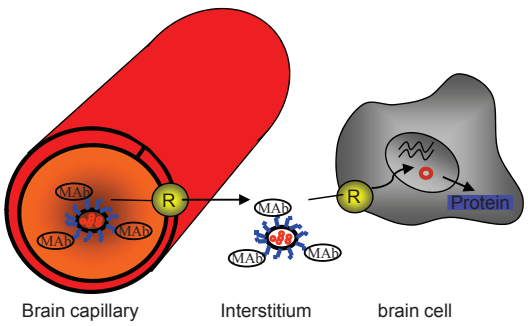
Obtained results:
A marked and significant increase in DNA encapsulation was obtained, leading to the ability of the liposomes to effectively transfect cells in vitro.

The cellular uptake has been shown to be specific and dependant on antibody/receptor interaction, which allows the liposomes to be taken up only by specific target cells, which is essential for directed delivery.

Papers published: Skjørringe T et al, J Control Release 2009,139:140-5. Liu J et al, BMC biotechnology 2009, 9:31.

**Contribution from KC**
Tina Skjørringe

**National collaborators**
Thomas G Jensen (University of Århus), Torben Gjetting and Thomas L Andresen (Risø, Roskilde)




Depiction of the project aim. Systemically delivered transgenes encapsulated in PILs are transported across the brain capillaries by receptor (R) mediated transport. Cells inside the brain take up the PILs, leading to transgene expression in the brain.

# Area 5 Epigenetics

## Hypomethylation of Multiple Imprinted Loci - HIL

**– is a novel imprinting syndrome, affecting a subset of patients with the rare disorder Transient Neonatal Diabetes Mellitus, TNDM.**

We contributed to the detection that HIL is in some patients caused by homozygous mutations in the gene ZFP57, being the first heritable global imprinting disorder described in humans that is compatible with life (Mackay et al., 2008).

Our research project is carried out as a collaborative PhD study with the Wilhelm Johannsen Center for Functional Genome Research, University of Copenhagen.

The project aims at increasing knowledge about imprinting and this novel imprinting syndrome, through more detailed clinical and laboratory studies of HIL patients and families.

**Contribution from KC**
Susanne Boonen (PhD student) Johanne Hahnemann, Karen Grønskov, Zeynep Tümer

**National collaborators**
Niels Tommerup, Mads Bak (WJC, ICMM, University of Copenhagen); Per Guldberg, Christina Dahl (Laboratory of Cancer Genomics, Danish Cancer Society)

**International collaborators**
Deborah Mackay (Wessex Regional Genetics Laboratory, Salisbury District Hospital, UK) and Karen I Temple (Human Genetics Division, Princess Anne Hospital, Southampton, UK)

## Age-dependent Reactivation of X-linked Genes

**The aim of the project is to investigate age dependent reactivation of X-linked genes and thereby to address the epigenetic mechanisms of X chromosome behaviour.**

We will investigate whether several X linked genes undergo an activation/reactivation process by studying the gene expression in two different cell lines obtained from the same individual with a time relapse of more than 20 years.

Material of this project will involve fibroblast cell lines obtained from 30 individuals.

We have identified three new loci for determine the X chromosome inactivation pattern.

The new loci are located on both arms of the X chromosome and will further be applied in this project.

**Contribution from KC**
Birgitte Bertelsen, Kirstine Ravn, Zeynep Tümer

**National collaborators**
Lis Hasholt (Section of Neurogenetics, Institute of Medical Biochemistry and Genetics, University of Copenhagen)

## Silver-Russell Syndrome (SRS)

**- is characterized by pre- and postnatal growth retardation**

It has recently been identified as the opposite syndrome, genetically and clinically, to Beckwith-Wiedemann syndrome (BWS), an overgrowth syndrome.

Both syndromes are imprinting disorders and can be caused by deficient imprinting of the H19/IGF2 imprinting control region (ICR) located at chromosomal region 11p15.

Furthermore, BWS can be caused by deficient imprinting of the KCNQ1OT1 ICR, and SRS can be caused by uniparental disomy of chromosomes 7 and 11.

The genetic etiology is unknown in a considerably fraction of SRS patients.

We have identified a new genetic mechanism causing SRS in a patient with a deletion of the enhancer region of H19/IGF2 genes on the paternal allele.

**Contribution from KC**
Karen Grønskov, Susanne E. Boonen, Zeynep Tümer, Karen Brøndum-Nielsen, Johanne MD Hahnemann, Kirstine Ravn, Linea Melchior, Alma Dedic

**International collaborators**
Deborah Mackay (Salisbury District Hospital, UK) and Karen I Temple (Princess Anne Hospital, Southampton, UK)

# Other Research and Education Activities

**Professor Zeynep Tümer**

### Phd Dissertations In 2009

Tina Skjørringe: Non-viral approaches for gene transfer –Towards effective and safe delivery to the brain. PhD degree in October 2009.

### Bachelor Degrees

Berit Lilje: Secreening age related cataract patients for mutations in a candidate gene –Bachelor Project in Molecular Biomedicine, Faculty of Health Sciences, Copenhagen University, February-June 2009

### Scientific Lectures And Posters

Many researchers, students and doctors at the Kennedy Center have attended a number of national and international scientific meetings and conferences, often with posters or oral presentations. Among these the ASHG, ESHG, ICIEM, and ARVO conferences were attended.

### Visiting scientists

Alba Redo - Primary congenital glaucoma: identification of candidate genes, Erasmus student, University of Barcelona (8 months)

Sena Özeker – Age related cataract: University of Istanbul (1 month)

### Education

Lectures were given by KC researchers in Medical Genetic Course for medical students and dentists (ICMM, University of Copenhagen); Human Genetics Course for Human Biology students (ICMM,KU); Clinical Genetics Course for dentists (Department of Odontology); Post-graduate course for medical doctors (Region Sjælland); Postgraduate course in clinical genetics .

Postgraduate course in ophthalmology : "Children, ophthalmology of the handicapped and social ophthalmology" was arranged by the Eye Clinic at Kennedy Center. Lectures were given by doctors, opticians and molecular biologist from the KC together with external lecturers.

The Eye Clinic was assigned by the NBH as responsible for the post graduate course for ophthalmologists:"Optics and refraction" for the next five years.

### Referee in International Journals/Grant Reviewing/Phd Assesment Committee Work

Researchers at the Kennedy Center carry out academic duties as they participate in evaluations of PhD and master degrees, as well as committees for professorships and grant applications, and act as refereees for several international journals.

### International Collaboration

We collaborate with international researchers from many departments and universities abroad, e g in Oslo, Berlin, Gottingen, Nijmegen, Rotterdam, Cardiff, Southampton, Salisbury, Dublin, Angers, and UBC,Canada, as evident also from the above project descriptions.

**Donations from Private Foundations** in support of ongoing projects

- **Lundbeck Foundation**
  Tourette Project - 3.000.000 DKK (2009-2010)
- **Neurocluster**
  Age Related X-inactivation - 600.000 DKK (2009)
- **Lundbeck Foundation**
  Pain project - 1.288.000 DKK (2008-2011)
- **Jascha Fonden**
  Usher project - 300.000 DKK (2009-2011)
- **Oticon**
  Usher project - 1.920.000 DKK (2009-2011)
- **Direktør Jacob Madsen og Hustru Olga Madsens fond**
  Imprintning and hypomethylation - 15.000 DKK
- **Danske Banks Fond**
  Rett and bone fractures - 25.000 DKK
- **Elsass Fonden**
  Rett and bone fractures - 200.000 DKK
- **Fonden til Lægevidenskabens fremme**
  Rett and bone fractures - 25.000 DKK
- **Fonden til Lægevidenskabens fremme**
  OPA1 - 50.000 DKK

Part C

# Management and Board

## Executive Management

**Director**
**Karen Brøndum-Nielsen**

**Vice director**
**IngerMarie Bruun-Vierø**

## The Board

| | |
|---|---|
| **Birgitte Nauntofte** | Director of Novo Nordisk Foundation, Dr Odont. PhD (chairman), appointed by the Ministry of the Interior and Health |
| **Svend Hartling** | Director, DMSci, Capital Region of Denmark (vice chairman), nominated by the Capital Region |
| **Henrik Lund Andersen** | Professor, University of Copenhagen, nominated the Danish Council for Strategic Research |
| **Frank Emanuelsen** | Nominated by PKU foreningen |
| **Thomas G. Jensen** | Professor, University of Aarhus, nominated by the Danish Council for Strategic Research |
| **Erik Kann** | Elected employee representative |
| **Birgit Kjer** | Head of Eye department, Hilleroed Hospital nominated by Danish Regions |
| **Ebba Nexø** | Professor, University of Aarhus, nominated by the Danish Council for Strategic Research |
| **Freddy Nielsen** | Physiotherapist, school leader, nominated by DBS |
| **Dorthe Pedersen** | Nominated by LEV |

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### Books


**Brøndum-Nielsen Karen**: Forebyggelse og Genetisk rådgivning, kap 25, I: Forebyggende sundhedsarbejde, eds: Kamper Jørgensen F, Almind G, Jensen , BB. Munksgaard, 2009


### Formidling og populærvidenskab


**Brøndum-Nielsen Karen**: Trisomi 21, den første kromosomafvigelse hos mennesket blev opdaget for 50 år siden. Kronik Ugeskrift for læger, 14. sept. 09
**Brøndum-Nielsen Karen:** Fosterdiagnostik. Kronik Ugeskrift for læger, 7. dec. 09
**Rønde Gitte**: Knogleskørhed og knoglebrud ved Rett syndrom. Rett nyt nr. 2, 09
**Rønde Gitte**: Et klinisk overblik. Rett nyt nr. 2, 2009
**Rønde Gitte**: D-vitamin status hos danske patienter med Rett syndrom. Rett nyt nr. 3, 2009
**Ravn Kirstine**: Rett muse modeller. Rett nyt nr. 1, 2009

# Laboratory Analyses

DKK 100 = Euro 7,40

| | Dkk | Euro |
|---|---|---|
| **Diagnosis related DNA-analyses:** | | |
| 1p-deletion: | | |
| Screening for deletion – MLPA | 1.850 | 250 |
| Xq28-duplication: | | |
| Screening for duplication – MLPA | 1.850 | 250 |
| Albinism: | | |
| Screening for mutation (OCA1) - sequencing | 5.316 | 718 |
| Screening for mutation (OCA2) - sequencing | 11.094 | 1.499 |
| Screening for mutation (OCA4) - sequencing | 5.924 | 801 |
| Carrier analysis | 4.265 | 576 |
| Prenatal diagnosis | 6.800 | 919 |
| Angelman syndrome: | | |
| Methylation & deletion analysis - MLPA | 2.150 | 291 |
| Uniparental disomy - UPD | 3.200 | 432 |
| Screening for deletion - FISH | 4.630 | 626 |
| Aniridi: | | |
| Screening for deletion (PAX6) - MLPA | 1.850 | 250 |
| Mutationsscreening (PAX6) - sequencing | 8.053 | 1.088 |
| Carrier analysis | 4.265 | 576 |
| Prenatal diagnosis | 6.800 | 919 |
| Bardet-Biedl Syndrome: | | |
| Screening for mutation (BBS1) - sequencing | 7.749 | 1.047 |
| Screening for mutation (BBS2) - sequencing | 8.661 | 1.170 |
| Screening for mutation (BBS4) - sequencing | 8.661 | 1.170 |
| Screening for mutation (BBS10) - sequencing | 5.924 | 801 |
| Screening for mutation (MKKS) - sequencing | 6.228 | 842 |
| Beckwith Wiedeman syndrome: | | |
| Methylation analysis - MLPA | 2.150 | 291 |
| Uniparental disomy - UPD | 3.200 | 432 |
| Screening for mutation (CDKN1C) - sequencing | 5.011 | 677 |
| BH4 deficiency: | | |
| Screening for mutation (QDPR), dihydropteridine reductase (DHPR) deficiency - sequencing | 5.924 | 801 |
| Screening for mutation (PTS), 6-pyruvoyltetrahydropterin synthase deficiency - sequencing | 5.620 | 759 |
| Screening for mutation (GCH1), GTP cyclohydrolase | 5.620 | 759 |
| Screening for mutation (SPR), sepiapterin reductase | 4.707 | 636 |
| Screening for mutation (GCH1) - MLPA | 1.850 | 250 |
| Carrier analysis | 4.265 | 576 |
| Prenatal diagnosis | 6.800 | 919 |
| Cri-du-chat syndrome: | | |
| Screening for deletion - MLPA | 1.850 | 250 |
| DiGeorge syndrome: | | |
| Screening for deletion - MLPA | 1.850 | 250 |
| Doparesponsive dystonia: | | |
| Screening for mutation (TH), tyrosin hydroxylase | 8.053 | 1.088 |
| Screening for mutation (GCH1), GTP cyclohydrolase | 5.620 | 759 |
| Screening for mutation in both TH and GCH1 - sequencing | 13.673 | 1.848 |
| Screening for mutation in both TH and GCH1 - MLPA | 1.850 | 250 |
| Carrier analysis | 4.265 | 576 |
| Prenatal diagnosis | 6.800 | 919 |
| Fragile X syndrome (FRAXA) (FMR1 gene): | | |
| Repeat analysis | 2.430 | 328 |
| Southern blot | 7.200 | 973 |
| Prenatal diagnosis | 9.629 | 1.301 |
| Glaucoma: | | |
| Screening for mutation (WDR36), primary open angle glaucoma (POAG) - sequencing | 10.790 | 1.458 |
| Screening for mutation (OPTN), primary open angle glaucoma (POAG) - sequencing | 7.749 | 1.047 |
| Screening for mutation (MYOC), primary open angle glaucoma (POAG, JOAG) - sequencing | 5.620 | 759 |
| Screening for mutation (CYP1B1), primary congenital glaucoma (PCG) - sequencing | 5.620 | 759 |
| Carrier analysis | 4.265 | 576 |
| Incontinentia pigmenti: | | |
| Screening for deletion (IKBKG, NEMO) | 4.860 | 657 |
| Carrier analysis | 4.265 | 576 |
| Prenatal diagnosis | 12.050 | 1.628 |
| Menkes disease: | | |
| Screening for mutation (ATP7A) - sequencing | 10.790 | 1.458 |
| Screening for mutation (ATP7A) - MLPA | 1.850 | 250 |
| Carrier analysis | 4.265 | 576 |
| Prenatal diagnosis | 6.800 | 919 |
| Mikrophthalmia / Anophthalmia: | | |
| Screening for mutation (SOX2) - sequencing | 4.707 | 636 |
| Screening for mutation (OTX2) - sequencing | 5.011 | 677 |
| Screening for mutation (SOX2) - MLPA | 2.280 | 308 |
| Screening for mutation (OTX2) - MLPA | 2.280 | 308 |
| Carrier analysis | 4.265 | 576 |
| Prenatal diagnosis | 6.800 | 919 |
| Miller-Dieker syndrome: | | |
| Screening for deletion - MLPA | 1.850 | 250 |
| Opticus atrophy: | | |
| Screening for danish founder mutation | 2.430 | 328 |
| Screening for mutation (OPA1) - sequencing | 12.311 | 1.664 |
| Screening for mutation (OPA1) - MLPA | 1.850 | 250 |
| Carrier analysis (founder mutation) | 2.430 | 328 |
| Carrier analysis | 4.265 | 576 |
| Prenatal diagnosis | 6.800 | 919 |
| Phenylketonuri (PKU): | | |
| Screening for mutation (PAH genet) - sequencing | 7.445 | 1.006 |
| Screening for mutation (PAH genet) - MLPA | 1.850 | 250 |
| Carrier analysis | 4.265 | 576 |
| Prenatal diagnosis | 6.800 | 919 |
| Prader-Willi syndrome: | | |
| Methylation & deletion analysis - MLPA | 2.150 | 291 |
| Uniparental disomy - UPD | 3.200 | 432 |
| Screening for deletion - FISH | 4.630 | 626 |
| Retinoblastoma: | | |
| Screening for deletion - FISH | 4.630 | 626 |
| Segawa syndrome: | | |
| Screening for mutation in both TH and GCH1 - sequencing | 13.673 | 1.848 |
| Screening for mutation in both TH and GCH1 - MLPA | 1.850 | 250 |
| Silver-Russell: | | |
| Methylation analysis - MLPA | 2.150 | 291 |
| Uniparental disomy - UPD | 3.200 | 432 |
| Smith-Magenis syndrome: | | |
| Screening for deletion - MLPA | 1.850 | 250 |
| Trichorhinophaleangal syndrome: | | |
| Screening for deletion - FISH | 4.630 | 626 |
| Tubeous sclerosis: | | |
| Screening for mutation (TSC2) - sequencing | 16.264 | 2.198 |
| Carrier analysis | 4.265 | 576 |
| Prenatal diagnosis | 6.800 | 919 |
| Velocardiofacial syndrome: | | |
| Screening for deletion - MLPA | 1.850 | 250 |
| WAGR: | | |
| Screening for deletion - FISH | 4.630 | 626 |
| Screening for deletion - MLPA | 1.850 | 250 |
| Williams syndrome: | | |
| Screening for deletion - FISH | 4.630 | 626 |
| Screening for deletion - MLPA | 1.850 | 250 |
| Wilsons disease: | | |
| Screening for mutation (ATP7B) - sequencing | 10.182 | 1.376 |
| Screening for mutation (ATP7B) - MLPA | 2.280 | 308 |
| Carrier analysis | 4.265 | 576 |
| Prenatal diagnosis | 6.800 | 919 |
| Wolfs syndrome: | | |
| Screening for deletion - FISH | 4.630 | 626 |
| X-linked mental retardation, West syndrome and XLAG: | | |
| Screening for mutation (ARX) - sequencing | 5.620 | 759 |
| Fragment size (ARX) | 2.430 | 328 |
| X-inactivation - PCR | 2.430 | 328 |
| Screening for deletions/duplication (MRX) - MLPA | 1.850 | 250 |
| Screening for duplication (MECP2) - MLPA | 1.850 | 250 |
| Carrier analysis | 4.265 | 576 |
| Prenatal diagnosis | 6.800 | 919 |
| **Method relaterede DNA-analysis:** | | |
| Array CGH | 10.752 | 1.453 |
| FISH | 4.630 | 626 |
| Interfase FISH (prenatal) | 5.310 | 718 |
| Interfase FISH (postnatal) | 4.630 | 626 |
| Multisubtelomer MLPA (2 kits) | 3.700 | 500 |
| Southern blot | 7.200 | 973 |
| Syndrome MLPA | 1.850 | 250 |
| **Karyotyping:** | | |
| Solid tissues (abortion, skin, other) | 5.045 | 682 |
| Tissues failure of growth | 2.225 | 301 |
| Blod | 2.850 | 385 |
| Amnion fluid or CVS | 4.825 | 652 |
| Bone marrow | 5.750 | 777 |
| Bone marrow without growth | 1.800 | 243 |
| QF-PCR amnion fluid or CVS | 780 | 105 |
| **Metabolism related analysis:** | | |
| (Menkes) - copper analysis, cell retention dynamics | 7.385 | 998 |
| (Menkes) - copper content analysis in prenatal cells | 14.035 | 1.897 |
| B-Tyrosin, substance concentration | 530 | 72 |
| B-Phenylalanin, substance concentration | 530 | 72 |
| U-Homogentisat, arbitrary substance concentration | 530 | 72 |


Gl. landevej 7
2600 Glostrup
Phone - +4543260100
Fax - 43431130
www.kennedy.dk
kennedy@kennedy.dk