

Overall research theme:

Long QT syndrome and cardiomyopathy: Genotype-phenotype relationship, pathogenetic mechanisms and gene-specific treatment

Latest update:

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Characteristics of the research group:

The research group combines competences in molecular genetics, molecular cardiology, genetic epidemiology, biochemistry, cell biology, clinical chemistry and diagnostic medicine. The focus is on the identification of genetic substrates for the development of cardiac disease, in particular genetic arrhythmic syndromes and cardiomyopathies, and the elucidation of the mechanism of disease, the clinical significance of genetic diagnostics and the importance for choice of treatment. The group collaborates extensively with groups in many countries.

Running projects: Titles and abstracts:

Identification of novel genes involved in long QT syndrome

Long QT syndrome is caused by mutations in genes coding for subunits of potassium and sodium ion channel channels, but present technology can only identify mutations in ca. 60% of cases, why we screen new ion channel genes in patients with long qt syndrome, where screening of known genes, *KCNQ1*, *KCNH2*, *KCNE1*, *KCNE2*, *SCN5A*, have not resulted in identification of mutations.

Genotype-phenotype relationship in long QT syndrome

Based on, at present, 175 long QT syndrome families from all over the world we study the phenotypic characteristics, e.g. clinical course, electrophysiological characteristics and effect of different pharmacologic treatments. Mutations are expressed in HEK293 cells and the biochemistry and expression is studied.

The genetic basis of hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is caused by mutations in at least 10 genes coding for sarcomeric proteins. We use a large cohort (>1000 families) from Scandinavia, South Africa, Turkey, New Zealand and Great Britain to study the genotype-phenotype relationship and – in particular – the mechanism of disease. We believe that haploinsufficiency caused by mRNA surveillance are a far more important pathogenetic mechanism than previously thought and may explain why some polymorphism can be associated with some forms of disease. We particularly focus on the the differential splicing and control of transcription in myosin binding protein C.

Genetic causes of sudden death

We use the PKU-biobank to study genetic polymorphisms in genes associated with sudden death and have identified mutations in *KCNH2* as a cause of cot-death. The study is based on high-throughput genetic screening.



Recent publications related to the projects described above:

Andersen PS, Larsen LA, Kanters JK, Havndrup O, Bundgaard H, Brandt NJ, Vuust J, Christiansen M. Mutation detection by Cleavase in combination with capillary gel electrophoresis analysis : Application to mutations causing hypertrophic cardiomyopathy and Long QT syndrome. **Mol Diagn** 1998; 3: 105-111

Kanters JK, Larsen LA, Orholm M, Agner E, Andersen PS, Vuust J, Christiansen M. Novel donor splice site mutation in the KVLQT1 gene is associated with Long QT syndrome. **J Cardiovasc Electrophysiol** 1998; 9: 620-624

Larsen LA, Andersen PS, Kanters JK, Jacobsen JR, Vuust J, Christiansen M. A multiplex single stranded conformation polymorphism/heteroduplex (SSCP/HD) method for detection of mutations in 15 exons of the KVLQT1 gene, associated with Long QT syndrome. **Clin Chim Acta** 280:113-125, 1999.

Larsen LA, Christiansen M, Vuust J, Andersen PS. High throughput single strand conformation polymorphism (SSCP) analysis by automated capillary electrophoresis: robust multiplex analysis and pattern-based identification of known allelic variants. **Hum Mutat** 13: 318-327, 1999.

Larsen LA, Fosdal I, Andersen PS, Kanters JK, Vuust J, Wettrell G., Christiansen M. Recessive Romano-Ward syndrome associated with compound heterozygosity for two mutations in the KVLQT1 gene. **Eur J Hum Genet** 7: 724-728, 1999.

Bundgaard H, Havndrup O, Andersen PS, Larsen LA, Brandt NJ, Vuust J, Kjeldsen K, Christiansen M. Familial hypertrophic cardiomyopathy associated with a novel missense mutation affecting the ATP-binding region of the cardiac beta-myosin heavy chain. **J Mol Cell Cardiol** 31: 745-750, 1999.

Andersen PS, Havndrup O, Bundgaard H, Larsen LA, Vuust J, Kjeldsen K, Christiansen M. Late-onset familial hypertrophic cardiomyopathy caused by a novel mutation, R694C, in the MYH7 gene. **Clin Genet** 56: 244-246, 1999.

Larsen LA, Svendsen IH, Jensen AM, Kanters JK, Andersen PS, Møller M, Sørensen SA, Sandøe E, Jacobsen JR, Vuust J, Christiansen M. Long QT syndrome with a high mortality rate caused by a novel G572R missense mutation in KCNH2. **Clin Genet** 57: 125-130, 2000.

Havndrup O, Bundgaard H, Andersen PS, Larsen LA, Vuust J, Kjeldsen K, Christiansen M. A novel missense mutation, L390V, associated with hypertrophic cardiomyopathy with a characteristic phenotype with interseptal hypertrophy. **Scand Cardiovasc Journal** 34: 558-563, 2000.

Havndrup O, Bundgaard H, Andersen PS, Larsen LA, Vuust J, Kjeldsen K, Christiansen M. The val606met mutation in the cardiac β -myosin heavy chain gene in patients with cardiomyopathy is associated with a high risk of sudden death at young age. **Am J Cardiol** 87: 1315-1317, 2001.

Bayes-Genis A, Ashai K, Lewis DW, Christiansen M, Oxvig C, Schwartz RS, Conover CA. Insulin-like growth factor binding protein-4 protease produced by smooth muscle cells increases in the in the coronary artery after angioplasty. **Arterioscler Thromb Vasc Biol** 21: 335-341, 2001

Mogensen J, Andersen PS, Steffensen U, Christiansen M, Gregersen N, Børglum AD. Development and application of linkage analysis in genetic diagnosis of familial hypertrophic cardiomyopathy. **J Med Genet** 38: 193-197, 2001.

Larsen LA, Andersen PS, Kanters JK, Svendsen IH, Jacobsen JR, Vuust J, Wettrell G, Tranebjærg L, Bathen J, Christiansen M. Screening for mutations and polymorphisms in the genes KCNH2, and KCNE2 encoding the cardiac HERG/MiRP1 ion channel: Implications for acquired and congenital long QT syndrome. **Clin Chem** 47: 1390-1395, 2001.

Andersen PS, Havndrup O, Bundgaard H, Larsen LA, Mogensen J, Børglum AD, Kjeldsen K, Vuust J, Christiansen M. Myosin light chain mutations in familial hypertrophic cardiomyopathy: Phenotypic presentation and frequency in Danish and South African populations. **J Med Genet** 38: e43, 2001.

Bayes-Genis A, Conover CA, Overgaard MT, Bailey KR, Christiansen M, Holmes DR, Virmani R, Oxvig C, Schwartz RS. Pregnancy-associated plasma protein-A is a sensitive and specific marker for acute coronary syndromes. **New Engl J Med** 345:1022-1029, 2001.

Jørgensen E, Kelbæk H, Helqvist S, Jensen GVH, Saunamaki K, Kastrup J, Havndrup O, Bundgaard H, Madsen JK, Christiansen M, Andersen PS, Reiber JHC. Predictors of coronary in-stent restenosis. Importance of angiotensin converting enzyme gene polymorphism and treatment with angiotensin converting inhibitors. **J Am Coll Cardiol** 38: 1434-1439, 2001 .

Larsen LA, Johnson M, Brown C, Christiansen M, Frank-Hansen R, Vuust J, Andersen PS. Automated mutation screening using dideoxy fingerprinting and capillary array electrophoresis. **Hum Mut** 18: 451-457, 2001.

Larsen LA, Christiansen M, Vuust J, Andersen PS. Recent developments in high-throughput mutation screening. **Pharmacogenomics** 2:387-399, 2001.