

## Spotlight on...

### Interview

Orphanet's new country coordinator is bringing rare disorders out of isolation in Greece

Dr. Michael B. Petersen, Director of the Department of Genetics at the Institute of Child Health, Athens, Greece, studied Medicine at the University of Copenhagen and subsequently specialised in Clinical Genetics. He went on to complete a postdoctoral Fulbright fellowship in Molecular Genetics at the Center for Medical Genetics, Johns Hopkins University School of Medicine. From 1993 Dr. Petersen has served as Director in the Department of Genetics at the Institute of Child Health, in Athens, Greece. His principle research interest encompasses the origin and mechanisms of chromosomal aneuploidies. In recent years Dr. Petersen has concentrated on monogenic disorders of deafness and blindness. He has published more than 150 articles in peer-reviewed international genetics journals. Last year, Dr. Petersen also agreed to serve as Orphanet coordinator for the country of Greece. *OrphaNews Europe* took the opportunity to learn more about Dr. Petersen's activities in the field of rare diseases in Greece.



*Dr. Michael Petersen in Northwest Greece, where the GLC1C glaucoma family was identified*

***OrphaNews Europe:*** One of your recent publications (Am J Med Gen Part A 2008;146A: 2221-2226) presents a fascinating study of Cohen syndrome in an isolated Greek island population. Could you tell us more about this study?

***Dr. Petersen:*** It was known for decades that in this small isolated island population (around 2,000 inhabitants) there was an increased frequency of mental retardation. So, ten years ago we started to travel to these remote islands, as the patients very rarely come to mainland Greece for medical care. We understood that we were dealing with a syndromic form of mental retardation segregating as an autosomal recessive trait. Nearly all 15 affected

individuals could be assigned to one huge pedigree and we were obviously dealing with a high degree of consanguinity. Blood samples were drawn from all family members and, with the help of Italian colleagues, we realized that we were probably dealing with Cohen syndrome. Soon after this, the genetic defect (*COH1* gene mutation) was discovered, so that we can now offer both carrier testing and prenatal diagnosis. It has been a big accomplishment and a source of immense satisfaction to be able to help this isolated population with a severe health problem.

**OrphaNews Europe:** How do inhabitants in an isolated area cope with the manifestations of the disease?

**Dr. Petersen:** The majority of this population is occupied as fishermen and sailors. Most patients are severely affected and taken care of by their families in their own homes. They rarely come to nearby, bigger islands for proper medical attention. For this reason, we have planned a trip to the islands this spring together with an ophthalmologist, so that the patients can have an eye exam (for many of them for the first time in their life). In the early years, it was not easy to get access to the families, but in more recent years we see a big change, and we are now accepted by these families.

**OrphaNews Europe:** Has your study led to carrier screening in this population?

**Dr. Petersen:** We have so far analysed about 200 samples of individuals from the affected families. This has thus far been accomplished in collaboration with the IRCCS Neurological Institute “C. Besta”, Milan, on a research basis. We have estimated that we need to screen 1,000 individuals of child-bearing age and we have applied for funding to do this from the Ministry of the Aegean Sea.

**OrphaNews Europe:** With more than 200 of the total 6000 Greek islands inhabited (of which over 80 have populations of more than 100 persons), might other islands have founder migrations? Does the unique archipelago geography contribute to an increased number of rare monogenic conditions in Greece?

**Dr. Petersen:** This is indeed possible, though the subject has not been extensively studied. Another known example in Greece is Naxos disease, an autosomal recessive disorder characterised by palmoplantar keratoderma and arrhythmogenic right ventricular failure. Founder migrations, such as the ‘Finnish disorders’ for example, are well-known phenomena in several places around the world.

**OrphaNews Europe:** Greece is currently developing a national plan for rare diseases. Could you give us some details on this plan?

**Dr. Petersen:** One important goal of the National Plan of Action for Rare Disorders 2008-2012 is the improvement of the quality of services involved in the diagnosis and therapy of patients with rare disorders.

**OrphaNews Europe:** Will the Greek plan have to take into account its unique geography and the potential for rare autosomal recessive disorders amongst its more isolated populations?

**Dr. Petersen:** This is a very interesting idea, that I do not think anyone has ever looked at, but which could obviously be addressed through the planned National Registry of Rare Disorders.

**OrphaNews Europe:** What is the current policy in Greece for providing treatment for rare disorders?

**Dr. Petersen:** Greece wants to follow the European guidelines for rare disorders and is working for better access to treatment of rare disorders, including accreditation to referral centres for rare disorders. The goal of the Greek Ministry of Health is to improve the access of the patients to orphan drugs, including reimbursement from the public insurance system.

**OrphaNews Europe:** On another topic, you recently served as chairman for the “Chromosomal Disorders” session at the 1st Golden Helix Symposium on “Copy Number Variation (CNV) and Genomic Alterations in Health and Disease” that took place in November 2008 in Athens.

**Dr. Petersen:** Yes, it was a pleasure for me to be co-organiser of a symposium on such an exciting and new subject. The Symposium included lectures by 20 international leading scientists in the field and covered all aspects from technologies and population genomics, through chromosomal and other disorders, to validation and development of a uniform design and guidelines.

**OrphaNews Europe:** How many CNVs have been identified in the human genome and on average how big are they?

**Dr. Petersen:** The genomes of unrelated individuals can differ from one another with respect to the copy number of thousands of loci. A CNV is a DNA segment, longer than 1 kb, with a variable copy number compared with a reference genome. The definition makes no difference to the clinical impact of a given genomic imbalance, and CNVs are used to describe copy number differences in studies of both disease and normal controls.

**OrphaNews Europe:** What are some examples of rare diseases that result from copy number variants?

**Dr. Petersen:** Some well known examples of intellectual deficit syndromes include Prader-Willi, Angelman, Williams, DiGeorge, and Wolf-Hirschhorn syndromes, etc. But all microdeletion and microduplication syndromes are copy number variants, which can be detected by this new powerful technique called array-Comparative Genomic Hybridization (‘molecular karyotype’).

**OrphaNews Europe:** Are there population-specific copy number variants?

**Dr. Petersen:** Yes, marked variation among populations have been revealed, and several ongoing projects are being carried out to investigate CNVs as predisposing factors for a number of disorders. Inherited apparently benign CNVs can, in some cases, cause disease depending on copy number state, inheritance pattern, or genetic and environmental background. Furthermore, preliminary data show, that CNVs can influence gene expression.

**OrphaNews Europe:** Finally, you have conducted extensive research on the genetic causes of hearing and vision anomalies. Could you comment on some of your findings?

**Dr. Petersen:** First of all, we have started genetic diagnosis and counselling for deafness in this country and have become a referral centre (at the the Institute of Child Health). Greece

turns out to be the country with the highest carrier frequency in the world (together with Italy) of the 35delG *GJB2* mutation. With a carrier frequency of 3.5% in the normal population, *GJB2* deafness is the third most common autosomal recessive disorder in this country, after thalassemia and cystic fibrosis. This was unexpected to all of us.

Secondly, we have completed some good research on mapping new genes for rare monogenic disorders, again due to large families living in islands, villages or mountains. These include loci for adult onset autosomal dominant primary open angle glaucoma (*GLC1C*), autosomal dominant otosclerosis (*OTSC7*), and autosomal dominant macular dystrophy (*MCDR5*). The fine mapping of these loci and gene hunting are continuing with collaborators abroad.

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