Genotypic and phenotypic spectrum of mitochondrial diseases with focus on early onset mitochondrial encephalopathies

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet, kommer att offentligen försvaras i sal Tallen, Drottning Silvias Barn- och Ungdomssjukhus, fredagen den 24 oktober 2014, kl. 13:00 av

Kalliopi Sofou

Fakultetsopponent: Professor Anna Wedell
Institutionen för molekylär medicin och kirurgi, Karolinska Institutet, Stockholm

Avhandlingen baseras på följande delarbeten:

I. Sofou K, Moslemi AR, Kollberg G, Bjarnadóttir I, Oldfors A, Nennesmo I, Holme E, Tulinius M, Darin N.

Phenotypic and genotypic variability in Alpers syndrome. Eur J Paediatr Neurol, 2012. 16(4): p. 379-89.

II. Sofou K, Kollberg G, Dávila M, Darin N, Gustafsson C, Holme E, Oldfors A, Tulinius M, Asin-Cayuela J.

Whole exome sequencing reveals mutations in *NARS2* and *PARS2*, encoding the mitochondrial asparaginyl-tRNA synthetase and prolyl-tRNA synthetase, in patients with Alpers syndrome. Submitted.

III. Sofou K, De Coo IF, Isohanni P, Ostergaard E, Naess K, De Meirleir L, Tzoulis C, Uusimaa J, De Angst IB, Lönnqvist T, Pihko H, Mankinen K, Bindoff LA, Tulinius M, Darin N.

A multicenter study on Leigh syndrome: disease course and predictors of survival. Orphanet J Rare Dis, 2014. 9(1): p. 52.

IV. Sofou K, Steneryd K, Wiklund LM, Tulinius M, Darin N.

MRI of the brain in childhood-onset mitochondrial disorders with central nervous system involvement. Mitochondrion, 2013. 13(4): p. 364-71.

UNIVERSITY OF GOTHENBURG

Göteborg 2014

Genotypic and phenotypic spectrum of mitochondrial diseases with focus on early onset mitochondrial encephalopathies

Kalliopi Sofou

Institute of Clinical Sciences, Sahlgrenska academy, University of Gothenburg

ABSTRACT

Early-onset mitochondrial encephalopathies comprise a challenging group of neurodegenerative disorders. This is due to their progressive nature, often leading to major disability and premature death, as well as their diagnostic complexity and lack of customized treatments.

The overall aim of the research presented in this thesis was to explore the phenotypic and genotypic spectrum of childhood-onset mitochondrial diseases with central nervous system involvement. The present thesis focuses on early-onset mitochondrial encephalopathies with particular emphasis on Alpers and Leigh syndromes.

We studied 19 patients with Alpers syndrome and showed specific genotype-phenotype correlations depending on the presence or not of *POLG1* mutations. We have further identified, with the help of whole exome sequencing, mutations in *NARS2* and *PARS2* in two of our patients with Alpers syndrome not associated to *POLG1*, being the first to link mutations in these genes to human disease and to Alpers syndrome.

We also present the natural history data on a unique cohort of 130 patients with Leigh syndrome, along with predictors of long-term outcomes. Disease onset before six months of age, failure to thrive, brainstem lesions on neuroimaging and intensive care treatment were associated with poorer survival. Based on the findings from this study, we suggest revised diagnostic criteria for Leigh syndrome.

We also studied the brain MRIs of 66 patients with mitochondrial disorders with central nervous system involvement. We describe the optimal use of brain neuroimaging in the diagnostic work-up of suspected mitochondrial disorders, as well as its role in the differential diagnosis among mitochondrial encephalopathies and from other diseases with similar features.

This thesis advances our knowledge of the phenotypic and genotypic spectrum of early-onset mitochondrial encephalopathies and discusses the applicable diagnostic methods, from the diagnostic criteria used to define clinical syndromes, to the role of the traditional and modern methodologies in the diagnostic work-up of these complex disorders. The study of patients with Leigh syndrome is the first joint research work between eight centers from six European countries specializing in mitochondrial diseases, creating a strong platform for ongoing collaboration on mitochondrial research projects.

Keywords: mitochondrial encephalopathy, Alpers syndrome, Leigh syndrome, neuroimaging, whole exome sequencing **ISBN:** 978-91-628-9110-7; 978-91-628-9111-4