Hereditary transthyretin amyloidosis (ATTR V30M)

- from Genes to Genealogy

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av medicine doktorsexamen framläggs till offentligt försvar i Sal D, 9 trappor, byggnad 1D, Norrlands Universitetssjukhus fredagen den 31 januari, kl. 09:00.
Avhandlingen kommer att försvaras på engelska.

Fakultetsopponent:

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Title
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Abstract
Background: Hereditary transthyretin amyloidosis is an autosomal dominant disease with a reduced penetrance. The most common mutation in Sweden is the V30M mutation in the transthyretin gene. Endemic areas of the disease can be found in Northern Sweden, Portugal, France, Brazil and Japan, although sporadic cases exist worldwide. Despite being caused by the same mutation, there are large differences in onset, penetrance and symptoms of the disease. Swedish V30M patients typically have a later onset with a lower penetrance compared to those from the endemic Portuguese V30M areas. The reasons for these differences have not been fully understood. The aim of this thesis is to study mechanisms that may influence onset and symptoms and investigate why patients carrying the same mutation have different phenotypes.

Methods: Genealogy studies were performed on all known V30M carriers in Sweden using standard genealogy methods. DNA samples from patients, asymptomatic carriers and controls from different countries were collected and the transthyretin gene was sequenced. Liver biopsies from patients were used for allele specific expression analysis and a cell assay was used for miRNA analysis with the mutated allele. Gene expression analysis was performed on biopsies from liver and fat tissue from patients and controls.

Results and conclusions: Genealogic analysis of all known Swedish V30M carriers managed to link together 73% of the Swedish ATTR V30M population to six different ancestors from the 17th and 18th century, thus dating the Swedish V30M mutation to be more than 400 years old. A founder effect was also visible in descendants to one of the ancestors, producing a later age at onset. Sequencing of the transthyretin gene revealed a SNP in the 3’ UTR of all Swedish V30M carriers that was not found in any of the Japanese or French V30M carriers. The SNP was present on the Swedish transthyretin haplotype and defined the Swedish V30M population as separate from others. However, the SNP itself had no effect upon phenotype or onset of disease. Gene expression analysis of liver and fat tissue revealed a change in genetic profile of the patients’ livers, in contrast to the unchanged profile of the fat tissue. A changed genetic profile of the liver could explain why domino liver recipients develop the disease much earlier than expected.

Keywords
Hereditary transthyretin amyloidosis, Familial amyloid polyneuropathy, transthyretin, genealogy, founder effect, miRNA, allele-specific expression, gene expression, PCA, liver biopsies, fat biopsies

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