Genetic studies using dried blood spot samples with particular focus on cytokine SNPs and preterm birth

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ABSTRACT

Blood samples are conveniently handled and stored as dried blood spots on filter paper. Very large collections of archived dried blood spot samples are available worldwide for research purposes. However, as these samples contain very little genetic material, DNA, they are very precious and a scientific study is seldom granted more than two 3.2 mm disks per included individual. This is far from enough for carrying out a genetic study looking at a large amount of genetic markers. To overcome this challenge, the extracted DNA can be whole-genome amplified, an approach that has previously been met with some concerns regarding its usability, and the reliability of the genotyping results.

In four articles we investigate if dried blood spots, stored for over 25 years, can be used as reliable sample material in genetic studies. Aspects regarding DNA extraction as well as the whole-genome amplification are addressed and the best combinations suggested. Four different genotyping assays have been used, from the low throughput TaqMan assay genotyping one variation at the time, to Illumina genome wide scanning, genotyping >610,000 variations per sample. Overall the four articles prove that dried blood spots provide reliable results when used for genetic studies in complex diseases.

Archived dried blood spot samples are in this thesis used to investigate the genetic aspects of preterm birth. Being born preterm, before 37 weeks of gestation, is the direct cause of 75% of all prenatal mortalities and more than 50% of all long-term morbidities (cerebral palsy, asthma, vision, hearing impairments, and social and intellectual problems). Despite healthcare system improvements, the preterm birth rates have risen the past decades in most developed countries. In Denmark the rate reached 6.3% in 2004, affecting approximately 4000 families a year. The pathology of preterm birth is most likely multi-factorial and quite complex. In line with several epidemiological factors (smoking, alcohol, etc.), genetic variations in both mother and child are suspected to be involved as well. In two manuscripts, one maternal and one fetal, we found genetic variations to be associated to preterm birth. In the fetal study, the genetic variations were also found to be associated with diverse protein levels.

This thesis shows the potential of using biobank samples in the hunt for genetic markers of disease. Finally, we identified genetic variations in both mother and child which could be associated with preterm birth, hence larger studies are needed to replicate these results.