The development of a peptide SRM-based tandem mass spectrometry assay for prenatal screening of Down syndrome

Down’s syndrome (DS) is the most common chromosomal abnormality in humans. Prenatal screening for Downs syndrome (DS) involves a combination of nuchal translucency scanning and analysis of the serum biomarkers using antibody ELISA based tests. Using results from these tests and combining them with an algorithm that takes into account maternal age, a risk factor for an affected pregnancy is produced. Women with pregnancies considered a high risk are currently then offered a diagnostic test from fetal material obtained using amniocentesis or chorionic villus sampling, which have a ~1-2% risk of miscarriage. With the discovery of free fetal DNA (ffDNA) in maternal blood there has been rapid research and development for a safer non-invasive alternative test to amniocentesis and CVS. The technology used in ffDNA Down syndrome testing is expensive and therefore is not economically viable to replace the primary screening test and would miss other congenital disorders that can be detected by prenatal screening. Therefore, there is still a requirement to improve the specificity of initial screening tests whilst maintaining low running costs. Funded by SAFE—the ‘Special Non-invasive Advances in Fetal and Neonatal Evaluation Network, (a European Union Framework VI network of excellence), researchers at the biological mass spectrometry facility (BMSF) at the UCL Institute of Child Health London have discovered new serum biomarkers for Down syndrome pregnancies. In addition, they have developed these biomarkers into a rapid quantitative mass spectrometry based assay. Two new markers were validated for first and second trimester pregnancies using this novel approach which has recently been published (1).

This method used involves the quantitation of peptides from biomarker proteins. Traditionally mass spectrometers are used to quantitate small molecules and not proteins as they are too large. However proteins can be digested into smaller fragments or ‘peptides’ for which typical mass spectrometers used in many chemical pathology laboratories can then be used to analyse. The quantity of the biomarker peptides is then used to indirectly quantitate the biomarker protein. This method eliminates the need for antibodies which have limited shelf lives, batch to batch variation and also allows for multiple markers to be measured in the same assay ‘multiplexing’. The use of mass spectrometry is also significantly more specific, accurate and more cost-effective than immuno-based assays. Thereby development of this assay for prenatal Down syndrome screening will create a robust rapid multiplexed assay to improve specificity, reliability and reduce cost. The GOSH BRC is further funding this research using the GOSomics facility at ICH to develop the existing screening markers into this test alongside the new ones. This study is cross centre collaboration with other BRC funded centres that are providing sample cohorts for evaluation of the assay against current methods.

Reference List