Acute intermittent porphyria (AIP) is an autosomal dominantly inherited disorder, classified as acute hepatic porphyria. It is characterized by a deficiency of hydroxymethylbilane synthase (HMBS, EC 4.3.1.8), the third enzyme in heme biosynthesis. Clinical features include gastrointestinal, neurologic and cardiovascular symptoms, but the most common clinical presentation is abdominal pain caused by neurovisceral crises.

The purpose of this study was first to perform molecular analysis of the AIP patients. Once a mutation is detected in a patient, molecular testing is offered to family members. In each affected family, this becomes an important tool for individualised medicine, allowing for careful drug prescription; in addition, it is very important for the asymptomatic carriers to be warned of precipitating factors, thus avoiding an acute attack.

The proper DNA diagnostics can be achieved by a combination of a robust and effective pre-screening method and a confirmatory DNA sequencing step. We decided to establish a new generation pre-screening method, which will be highly sensitive and relatively time- and cost-effective. Our method of choice was high-resolution melting (HRM) analysis using the LightScanner instrument.

Another important aspect of this project was to study the molecular heterogeneity of AIP in relation to the HMBS protein. We aimed at characterisation of the impact of the HMBS gene mutation on the structure and function of the enzyme, and demonstration of how this aids the interpretation of clinical, biochemical and genetic data in establishing an AIP diagnosis. To demonstrate this, we used expression and characterisation of mutant HMBS enzymes in the prokaryotic system together with the use of predictive computer-assisted structure-function correlation studies.