1. English Summary

The aim of this thesis was to find out the etiology of diabetes mellitus in patients with a family predisposition to the disease. The world-wide increase in the incidence of diabetes in the past years has lead to intensive research of its etiological and pathophysiological mechanisms. This research has helped to discover many genes whose mutations were proved to cause diabetes without a contribution of other factors. Such cases where a mutation in a single gene crucial for glucose control is sufficient to result in diabetes are referred to as monogenic diabetes. This group includes a broad spectrum of hyperglycaemic conditions that differ significantly in their prevalence, course, treatment as well as prognosis. The so called MODY (maturity onset diabetes of the young) belongs to this group and is characterized by early onset before 25 years of age and no need of insulin substitution initially. In this study we were looking for mutations in genes that may be a rare cause of monogenic diabetes. We examined patients with hyperglycaemia occurring in several generations of their families and in whom mutations in more prevalent MODY genes had been previously excluded.

We performed a genetic analysis of genes NEUROD1, IPF-1 and ABCC8. The protein NEUROD1 is a crucial transcription factor that affects the development of pancreas and is one of the enhancers of insulin gene expression. Its mutations were connected with diabetes mellitus later referred to as MODY 6. IPF-1 is the gene coding insulin promoter factor-1 and its mutations has led to sporadic MODY 4 type of diabetes. The gene ABCC8 encodes the SUR1 subunit of voltage controlled potassium channel in beta cell membrane, which is necessary for appropriate insulin secretion. Activation mutations of this gene were found in patients with transient and permanent diabetes mellitus as well as other forms of diabetes of various severity.

The genetic analysis of these genes revealed unique types of diabetes that occur extremely rarely world-wide. Firstly, we managed to find a so far unpublished mutation H241Q in the NEUROD1 gene in two unrelated families, where obesity in affected members most likely also contributed to the development of diabetes. Secondly, we found a new V841 variant of gene ABCC8 in one family,
where the carriers had only mild hyperglycaemia without further progression and without need of treatment. This phenotype is the least severe among so far published cases with mutations in this gene. Both findings were reported in articles published in an acknowledged journal with an impact factor. There was no mutation identified in the *IPF-1* gene. This corresponds with recent findings, that disorders in this gene is very rare cause of diabetes.

To conclude, the results of our study have increased the knowledge about less common forms of monogenic diabetes and have helped to reveal rare patients, whose genetic variant consegregated in their families with hyperglycaemia or diabetes.