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# Prevalence of monogenic diabetes in the Lithuanian pediatric and young adult population

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## Introduction

Monogenic diabetes is a heterogeneous group of metabolic disorders resulting from defects in single genes. Over 80% of the subjects remain undiagnosed, mainly because of lack of access to genetic testing. The aim of our study was to do a comprehensive genetic analysis of the whole pediatric and young adult autoimmune antibody negative diabetes population of Lithuania.

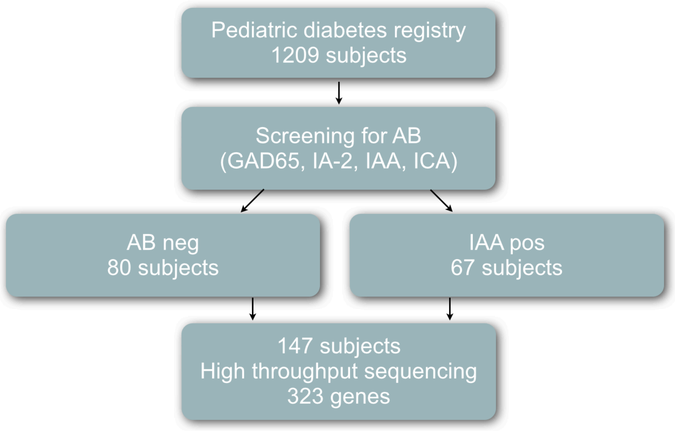
## Methods

Overall 1209 diabetic subjects, including 860 children (age 0-18 years) and 349 young adults (age >18-25 years), were screened for the presence of islet autoimmune antibodies (GAD65A, IA-2, ICA and IAA). **Genetic analysis** was performed by high throughput sequencing from DNA selected for all coding and splicing regions of 323 genes involved in diabetes and pancreas development (including the 13 MODY genes). Raw sequencing data was analyzed using a locally developed pipeline. The most prominent variants were selected according to the score of prediction of damaging effects on the respective proteins using SIFT, Polyphen-2, MutationTester-2 and confirmed by Sanger sequencing.

## Results

We screened 1209 subjects from the pediatric diabetes registry. The results are depicted in Fig 1.

**Figure 1:** Diagram of the screened subjects




Genetic analyses were performed in a total of 147 subjects subjects with suspected monogenic diabetes. We included the IAA positive probands under insulin treatment, because the antibodies were tested after introduction of insulin. The clinical characteristics at diabetes onset are summarized in table 1, the genetic results are depicted in Fig. 2.

**Table 1:** Clinical characteristics at diabetes onset

| | Diabetes onset <0.5 yrs | Diabetes onset 0.5-18 yrs | Diabetes onset >18-25 yrs |
|---|---|---|---|
| **Number of patients (total 147)** | 4 | 133 | 10 |
| **% of collection** | 2.7 | 90.5 | 6.8 |
| **% of female** | 50 | 52 | 30 |
| **Age at onset (years)** | 0.3 | 7.8 | 21.3 |
| **% Pos FHx** | 50 | 44.4 | 60 |
| **HbA1c (mmol/mol (%))** | 83.6 (9.8) | 66.1 (8.2) | 78 (9.25) |
| **Initial BG (mmol/l)** | 37.3 ±24.6 | 15.7 ±8.4 | 14.94 ±6.1 |
| **Ketosis %** | 50 | 52 | 33 |

**Figure 2: The genetic results of the 147 subjects with suspicion of monogenic diabetes.** Genetic analysis revealed mutations/variants in known MODY genes in 25.9% of the probands.

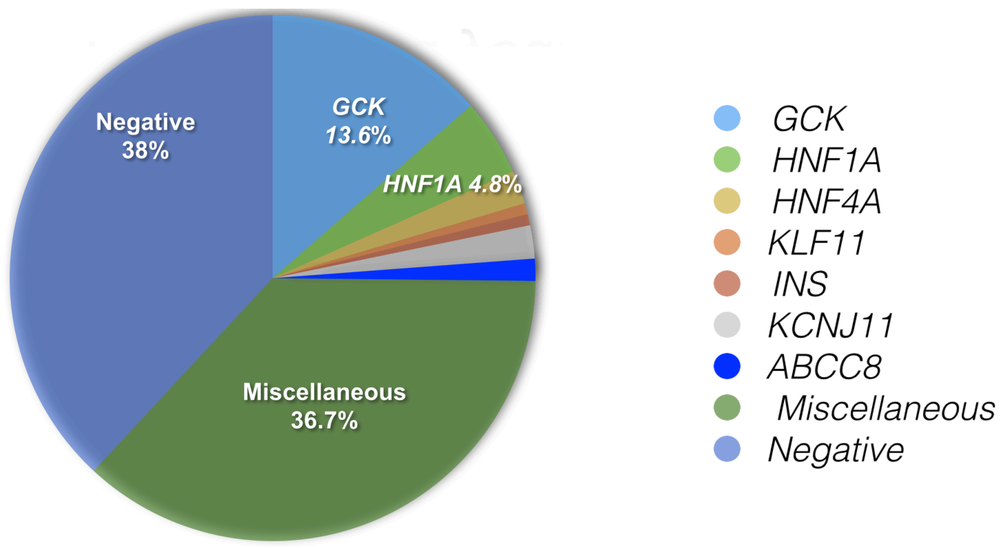



**Table 2:** The clinical characteristics of the different groups according to the gene defect are depicted.

| Characteristics at study entry | *GCK* | *HNF1A* | *HNF4A* | *INS* | *KCNJ11* | *ABCC8* | *KLF11* |
|---|---|---|---|---|---|---|---|
| Number of patients (total 38) | 20 | 7 | 3 | 1 | 4 | 2 | 1 |
| Age (yrs) | 12.48 | 18.28 | 23.3 | 17 | 11.72 | 22 | 1.5 |
| HbA1c (mmol/mol (%)) | 43 (6.1) | 45 (6.3) | 72 (8.7) | 93 (10.7) | 73 (8.83) | 113 (12.25) | 55 (7.2) |
| **Treatment** | | | | | | | |
| Insulin (%) | 0 | 57.1 | 100 | 100 | 100 | 100 | 100 |
| Oral agent (%) | 5 | 28.6 | | | | | |
| None (%) | 95 | | | | | | |
| **Complications (%)** | 0 | 0 | | 0 | | | 0 |
| Nephropathy (%) | | | 33.3 | | 66.67 | | |
| Retinopathy (%) | | | 33.3 | | 33.3 | | |
| Polyneuropathy (%) | | | 33.3 | | | 100 | |

**Table 3**: Prevalence of monogenic diabetes

| | Subjects | Diabetes onset | | |
|---|---|---|---|---|
| | | <0.5 yrs | 0.5-18 yrs | >18-25 yrs |
| Number of patients | 1209 | 4 | 1191 | 14 |
| AB neg cohort (except IAA) | 147 | 4 | 133 | 10 |
| MODY genes | 38 | 4 | 31 | 3 |
| Prevalence total cohort (%) | 3.1 | 0.3 | 2.6 | 0.2 |
| Prevalence AB neg cohort (%) | 25.9 | 2.7 | 21.1 | 2.0 |
| Prevalence AB neg cohort according to age (%) | | 100 | 23.3 | 30 |

## Discussion and Conclusion

This testing approach yields a high rate of positive results. In the whole Lithuanian pediatric diabetic and young adult population (1209 probands), *GCK* mutations are found in 1.65%, *HNF1A* mutations in 0.6% and *HNF4A* mutations in 0.25% of the patients.

*Authors have no conflict of interest*

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