Monogenic diabetes mellitus in Norway

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ABSTRACT

Here, we review data on monogenic diabetes mellitus in Norway based on the Norwegian MODY Registry at Haukeland University Hospital, Bergen. This registry comprises established or suspected cases of maturity-onset diabetes of the young (MODY) referred to our laboratory for genetic testing. We also present data on neonatal diabetes, another group of monogenic diabetes. To date, we have genetically diagnosed nearly 500 MODY cases in Norway. Mutations in the \textit{HNF1A} gene (MODY3) were detected in about 50\% of families with clinical MODY. GCK-MODY (MODY2) was the second most prevalent type, but may be underreported. We have also found mutations in the monogenic genes \textit{ABCC8}, \textit{CEL}, \textit{HNF1B}, \textit{HNF4A}, \textit{INS}, \textit{KCNJ11} and \textit{NEUROD1}. Based on genetic screening in the Norwegian MODY Registry and HUNT2, we estimate the number of MODY cases in Norway to be at least 2500-5000. Founder effects may determine the geographical distribution of MODY mutations in Norway. The molecular genetic testing of MODY and neonatal diabetes is mandatory for correct diagnosis and prognosis as well as choice of therapy.

INTRODUCTION

Whereas type 1 and type 2 diabetes are caused by a combination of several genetic and environmental factors, monogenic diabetes is caused by defect in a single gene only. The two main types of monogenic diabetes are maturity-onset diabetes of the young (MODY) and neonatal diabetes mellitus (1). In both types, a molecular genetic classification is necessary to choose the best possible treatment, and also for adequate prognosis prediction. In Norway, genetic testing of monogenic diabetes is performed at the Center for Diabetes Genetics and Center for Medical Genetics and Molecular Medicine at Haukeland University Hospital in Bergen. Patients can be referred for clinical investigations and genetic counseling as well as genetic testing. Necessary forms and addresses are available at the web site www.mody.no.

The purpose of the present article is to provide an update on monogenic diabetes in Norway, focusing on classification, prevalence and phenotypic expression. It should be noted that in patients with suspected monogenic diabetes mellitus, the results of pancreatic imaging could help to guide the molecular and genetic investigation (2). The results presented are mainly from the Norwegian MODY Registry (see below). Data were also obtained from the HUNT2 Study and from the Norwegian Childhood Diabetes Registry.

Studies on monogenic diabetes in Norway date back to the late 1960ies (3), whereas MODY type diabetes was first recognized in a family on the north-west coast of the country (4). In this “type 2-like diabetes” family, which we later designated the N1 family (Figure 1) and classified as \textit{HNF1A-MODY} (5), clinical features of affected members were severe diabetic eye disease and increased sensitivity to sulfonylurea (6).

THE NORWEGIAN MODY REGISTRY

The Norwegian MODY Registry was established in 1997 as a nation-wide registry of patients with monogenic diabetes, for diagnostic and research purposes. A patient referral to the registry should fulfill at least two of the following criteria: 1) first degree relative with diabetes, 2) onset of diabetes before age 25 years in at least one family member, 3) low-dose of insulin requirement, 4) early-onset type 2 diabetes, i.e. diagnosed between age 25 and 40 years, and 5) unusual type 1-like diabetes (low-dose insulin requirement, no antibodies, or atypical history).

Data have also been received from the HUNT2 study (1995-1997), in which 66 140 persons from the county of Nord-Trøndelag participated, i.e. 71\% of the eligible population (7). Furthermore, we have obtained some data from the Norwegian Childhood Diabetes Registry, which operates closely with the Norwegian Study Group of Childhood Diabetes.
MODY

The Norwegian MODY Registry serves scientific and diagnostic purposes. Available data also shed light on classification and epidemiological parameters, in particular prevalence. As of September 1st 2012, around 1500 subjects were registered of which 458 patients from 198 MODY families had a genetic diagnosis (Table 1). The distribution of the most common MODY forms was as follows: HNF1A-MODY 53%, GCK-MODY 30%, HNF4A-MODY 7.5%, and HNF1B-MODY 5.6%. Families with CEL and insulin gene mutations occur sporadically. Mutations in NEUROD1 were not found by routine diagnostic screening of Norwegian non-classified (MODYX) patients (8), although we have identified four cases from two families by whole-exome sequencing (Table 1).

To estimate the prevalence of HNF1A-MODY in Norwegian pedigrees with diabetes, Bjørkhaug et al. (5) screened 130 families for mutations in HNF1A. Mutations were found in 22 of 42 families with clinical MODY, 15 of 75 families with suspected MODY, and in one of 13 families with multiplex type 1-like diabetes. Thus, mutations in HNF1A were detected in about 50% of families with clinical MODY, in agreement with present updated numbers (Table 1).

Sagen et al. (9) screened for GCK mutations in 122 probands referred to the MODY Registry. Two novel and 13 previously reported mutations were found in 23 probands and in 33 of their family members. From this study, we concluded that GCK-MODY is less prevalent than HNF-1A-MODY.

Ræder et al. (10), sequencing the HNF4A gene of 95 MODY3-negative probands from the MODY Registry, identified three novel HNF4A mutations and a 3.7-MB haplotype, which was linked with diabetes. Of particular interest was the finding of two unrelated families with several subjects with the P2 promoter haplotype who were originally perceived as late-onset lean diabetes patients with a mean age of onset at 45 years. In conclusion, HNF4A variants were considered to cause diabetes in 9% of HNF1A-negative probands.

So far, we have identified HNF1B mutations in 19 cases from 11 families (Table 1). These patients typically present with progressive renal dysfunction and renal cysts prior to the development of diabetes (11-13).

Ræder et al. (14) identified CEL mutations to be a novel cause of MODY, which later was denoted MODY8. Subsequent screening of 38 MODY patients negative for mutations in the common MODY genes...
identified another CEL-MODY family. These patients have both diabetes and pancreatic exocrine dysfunction with diabetes onset usually around the age of 35 years. CEL-MODY seems to be extremely rare (15).

Molven et al. (16) searched for INS mutations in 62 patients with MODY and 30 patients with suspected MODY from the MODY Registry, and identified the INS mutation c.137G>A (R46Q) in one proband, his father, and a paternal aunt. They were diagnosed with diabetes at 20, 18 and 17 years of age, respectively, and treated with small doses of insulin or diet only. In 223 type 1 diabetic patients from the Norwegian Childhood Diabetes Registry, selected on the basis of autoantibody negativity or family history of diabetes, the INS mutation c.163C>T (R55C) was found in a girl who had presented with ketoacidosis and antibody-negative diabetes at 10 years of age. INS mutations have been established as the third most common cause of neonatal diabetes (17). Our study suggests that INS screening should be considered also in MODY and in selected cases of type 1 diabetes.

By studying 1972 diabetic subjects from the HUNT2 Study, Eide et al. (18) identified a subgroup of 43 suspected MODY cases, based on clinical and laboratory findings. Thus, in the HUNT2 cohort, 2.2% of all subjects with self-reported diabetes could be classified as suspected MODY cases by clinical criteria. Within this group, HNF1A mutations were found in three subjects, two with an R229Q mutation and one subject with a novel S6N alteration. Genotyping the total cohort of diabetic HUNT2 subjects revealed five additional R229Q-positive subjects. The minimum prevalence of HNF1A MODY in Nord-Trøndelag could therefore be estimated to 0.4% of subjects with a diabetes diagnosis.

**NEONATAL DIABETES**

We have obtained a genetic diagnosis in 27 patients with neonatal diabetes (Table 2). The first patient molecularly characterized by us was a child with a homozygous GCK mutation (19). We have not identified additional cases with neonatal diabetes and GCK mutations in Norway, and homozygous or compound heterozygous GCK mutations seem to be most frequent in regions where consanguinity is common (20). Chromosome 6 abnormalities (21) along with mutations in **KCNJ11** and **ABCC8** are most numerous in Norway. Sagen et al. (22) sequenced the **KCNJ11** gene encoding the Kir6.2 subunit of the potassium channel of the β-cell, in 11 probands with permanent neonatal diabetes mellitus. There were nine mutation carriers in seven families from Norway, Israel, Turkey and the USA. In one Norwegian patient, glibenclamide was introduced in increasing doses. With a dose of 0.4 mg per kg per day, insulin could be discontinued. This was the first case in the world where, based on a genetic diagnosis, a neonatal diabetes patient could have her insulin injections substituted with oral medication (22). It was later concluded that patients with mutations in **KCNJ11** may be managed on oral sulfonylurea, even with sustained or improved metabolic control (23). This is now state-of-the-art treatment, not only in neonatal diabetes due to mutations in **KCNJ11**, but also in patients harboring mutations in the **ABCC8** gene (24).

### Table 2. Genetically verified neonatal diabetes mellitus cases and families in the Norwegian MODY Registry.

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Cases</th>
<th>Families</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCNJ11-PNDM</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>ABCC8-PNDM</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Chromosome 6 abnormality</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Wolcott-Rallison syndrome</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Homozygous glucokinase defect</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Sum</strong></td>
<td>27</td>
<td>26</td>
</tr>
</tbody>
</table>
Interestingly, we have found that common type 2 diabetes characterized by neither obesity nor hyperlipidemia.

The lack of population-based data clearly prohibits a definite conclusion on the geographical distribution of MODY in Norway.

In our work we found, not unexpectedly, admixtures of type 2 diabetes in families with monogenic diabetes. This should be kept in mind during the delineation of MODY phenotypes, since MODY as such is characterized by neither obesity nor hyperlipidemia. Interestingly, we have found that common type 2 diabetes risk variants of modest effect sizes reduce the age at diagnosis in HNF1A-MODY (28). Thus, clinical characteristics of a monogenic disease can be modified by common polygenic variants.

Neonatal diabetes, now defined as diabetes before 6 months of age, is a rare condition (29). The distinction between transient and permanent neonatal diabetes is difficult because “transient” cases may have relapses, and “permanent” cases may show remissions. Long-term follow-up is necessary to make a distinction between transient and permanent neonatal diabetes (30).

In many subtypes of neonatal diabetes and in some MODY subtypes, symptoms and signs other than diabetes may dominate the phenotype, eg. pancreatic aplasia, exocrine dysfunction, renal dysfunction or urogenital malformations (2,13,31).

Of particular importance is that certain types of neonatal diabetes may be treated with oral sulfonylurea, periodically or permanently. Whereas the beneficial effect of sulfonylurea in neonatal diabetes was demonstrated many years ago (3), the good news is that patients may now be selected for such therapy on the basis of genetic testing, providing a nice example of pharmacogenetics (22,23).

**CONCLUSION**

The Norwegian MODY Registry was established with the ultimate goal of improving diagnostics and treatment of monogenic diabetes. As shown by the examples discussed above, this registry has significantly increased our knowledge about the genetics of diabetes in Norway, and it will continue to serve scientific and diagnostic purposes in the years to come. We have registered more than 1500 suspected cases of monogenic diabetes and the number of patients who have received a genetic diagnosis is now approaching 500. In the future, we expect that more detailed phenotyping using radiological imaging and physiological characterization will improve the value of the registry, enabling us to diagnose monogenic diabetes more efficiently (32).
example is the use of ultrasound examination to diagnose HNF1B-MODY and CEL-MODY (13,33). In the near future, we think tailored hybridization capture for selected genes of interest and very high-coverage sequencing of specific gene panels will replace the traditional Sanger sequencing. Most likely, exome and possibly whole-genome sequencing will be the future state-of-the-art in molecular diagnostics of MODY (34). Also, we think the use of future “omics” (35) will be a step forward and we plan to add biomarker investigations in serum to the DNA analysis.

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