Adolescents at risk for MODY3 diabetes prefer genetic testing before adulthood
Short title: Genetic testing of adolescents for MODY3

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Mutations in the HNF1α gene cause an autosomal dominantly inherited form of diabetes, Maturity-Onset Diabetes of the Young type 3 (MODY3), characterised by poor insulin secretion in response to glucose together with good sensitivity to insulin and sulphonylurea medication as well as low renal threshold for glucose (1). The lifetime risk of diabetes may be as high as 95% for individuals carrying the most common Pro291fsinsC mutation. The glucose tolerance deteriorates in most cases during the pubertal years (2-5). However, because of fasting normoglycemia clinical diagnosis is often delayed, despite high postprandial glucose concentrations and an increased HbA1c value. Diabetic complications are common and proliferative retinopathy has been detected already at diagnosis of diabetes in a 19-year-old carrier (6). On the other hand, while the incidence of diabetes among mutation carriers increases steeply in puberty, at least 20% remain non-diabetic until their thirties (2, 4, 5). Abnormal glucose tolerance in subjects at risk for MODY3 can be diagnosed with an oral glucose tolerance test. Urine glucose analysis after a large oral glucose load has also been advocated as a noninvasive screening tool in young children (7). Although an aberrant result from these tests has diagnostic value for diabetes and a certain predictive value in identification of probable carriers, they are not specific for MODY and a normal result cannot exclude future risk. A genetic test seems to be warranted before adulthood, either to confirm carrier status in these prescreened subjects or in all at risk subjects. A predictive test, whether it is a clinical test or a specific gene test, may have some negative impact on the adolescents’ self-esteem and their future plans as they feel predestined to become diabetic. In case of minors, predictive testing involves ethical questions regarding decision-making and the benefit of testing as opposed to possible negative effects (8, 9). We studied the attitudes to genetic testing in adolescents, their parents and other adults from families with HNF-1α mutations from the Botnia Study (10, (11), were offered genetic counselling and a gene test for MODY3 irrespective of their previous diabetes status. Data on glucose tolerance were obtained either earlier or at the time of the gene test. Data on attitudes to genetic testing and counselling were collected by questionnaires before and one year after the counselling and possible gene test. The counselling included information about MODY, its inheritance, and the nature of the gene defect, risk of MODY, and the methods available for follow-up and early detection of MODY. The benefits and disadvantages of the gene test were discussed. The subjects and their guardians gave informed consent to the study. Analyses were performed using the Fisher’s exact test, Chi-squared test with Yates correction or Mann-Whitney U-test.

RESULTS- Of the 39 invited adolescents, 29 (11M/18F) from 17 sibships participated and also took the gene test. 4/5 diabetic and 5/24 non-diabetic subjects were found to be carriers. Those declining had parents, who had previously declined participation (10). Twenty-five parents, at least one per adolescent (8M/17F, 14 MODY3 carriers), and 105 other adults (34M/17F, 14 carriers) also participated. Most participants (78%) irrespective of age considered that genetic testing should be performed before adulthood (Figure 1). Previously the decision about genetic testing of minors has been made by the parents (12, 13). Since 1992 in Finland, the child has a right to participate in the decision making at an as early age as possible and the opinion of children who have turned 12 years must be heard (14). Although the majority of parents (89%) preferred joint decision-making, they (60%) also favoured testing before the age of 12 years, when the decision would be made solely by the parents. This differed from the adolescents’ preference (< 12 yrs: 28%, P=0.005). Two parents favoured prenatal testing. Before the counselling the adults were also specifically asked about their attitudes towards prenatal diagnosis of MODY3: 38%
considered the possibility to be good, 23% bad and 40% were hesitant. Most of them were critical towards the suggestion as a prenatal diagnosis of MODY3 was regarded either unethical or as having no implications for the pregnancy.

While the majority of adolescents (72%) also preferred joint decision-making about taking the test, almost one-third (28%) of them wanted to make the decision alone and as many as 55% actually chose to receive their test results alone. By contrast, before the counselling the majority of their parents considered that they should be present at their children’s test disclosure (80%, P=0.039 vs. adolescents). After the counselling, the adults changed their opinion towards allowing the adolescents to receive the results alone, if they wished (16%/27%, P =0.0355 before vs. after counselling).

One year after the disclosure of test result, 21 adolescents returned the follow-up questionnaire. All 12 non-carriers and eight of the nine mutation carriers reported their test result and its interpretation correctly but one carrier could not say what the result meant. Most of them (17/21, 76%) were satisfied with their decision about taking the test and would have made the same choice again. They would also have recommended it to a friend, if he were in the same situation. However, four subjects (3 carriers, 1 non-carrier) were dissatisfied with having taken the test. One of them had not really reacted to learning that he/she was a carrier, but was angry at having been tested when found to have diabetes one year later at a clinical follow-up. This shows that the adolescents may be more disposed to “natural optimism”, they understand but do not necessarily internalise the risk of diabetes. Also at least one of the eight non-responders (4 carriers, 4 non-carriers) reacted aggressively immediately after hearing that he/she was a carrier. Not returning the post-test questionnaire presumably reflects dissatisfaction at having been tested or at the test result. All negative response came from newly identified MODY families, in whom the incident case had been diagnosed only 1-2 years earlier.

CONCLUSIONS - Genetic testing for MODY3 can be considered beneficial for early detection of MODY. Most adolescents at risk for MODY3 accepted and understood the gene test. However, at least 25% were dissatisfied with having taken the test although they had received proper counselling. Both adolescents and adults considered that such testing should be offered already before adulthood, but their views differed on whether to wait until the child is old enough to participate in the decision-making. In any case, educational counselling needs to be provided.

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Figure 1. Opinions before genetic counselling of the three groups of subjects from MODY3 families on the age at which gene testing should be performed (%). None of the subjects opted for “never”, which was an alternative. P=0.005 for the difference between parents and adolescents with respect to testing in childhood.