# Adolescents at Risk for MODY3 Diabetes Prefer Genetic Testing Before Adulthood

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Mutations in the hepatocyte nuclear factor (HNF)-1α gene cause an autosomally, dominantly inherited form of diabetes, maturity-onset diabetes of the young (MODY) type 3, which is characterized by poor insulin secretion in response to glucose together with good sensitivity to insulin and sulfonylurea medication and 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. 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 A1C value. Diabetes 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 steeply increases in puberty, at least 20% remain nondiabetic until their 30s (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 a clinical or specific gene test, may have some negative impact on the adolescents' self-esteem and their future plans, as they may feel predestined to become diabetic. In the 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 in MODY3 families.

## RESEARCH DESIGN AND METHODS

— Adolescents (aged 12–18 years), their parents, and other adults from families with HNF-1α mutations from the Botnia Study (10,11) were offered genetic counseling 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 counseling were collected by questionnaires before and 1 year after the counseling and possible gene test. The counseling 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 Fisher's exact test, $\chi^2$ test with Yates correction, or Mann-Whitney *U* test.

## RESULTS

— Of the 39 invited adolescents, 29 (11 male and 18 female) from 17 sibships participated in the study and took the gene test. Of these, 4 of 5 diabetic and 5 of 24 nondiabetic subjects were found to be carriers. Those declining had parents who had previously declined participation (10). Twenty-five parents, at least one per adolescent (8 males and 17 female, 14 MODY3 carriers), and 105 other adults (34 male and 17 female, 14 carriers) also participated. Most participants (78%) irrespective of age considered that genetic testing should be performed before adulthood (Fig. 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 as early an age as possible, and the opinion of children aged ≥12 years must be heard (14). Although the majority of parents (89%) preferred joint decision-making, many (60%) also favored testing before the age of 12 years, when the decision would be made solely by the parents. This differed from the adolescents' preference (<12 years: 28%, $P = 0.005$). Two parents favored prenatal testing. Before counseling, the adults were also specifically asked about their attitudes toward prenatal diagnosis of MODY3: 38% considered the possibility to be good, 23% bad, and 40% were hesitant. Most of them were critical toward the suggestion, as a prenatal diagnosis of MODY3 was either regarded as 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%) wanted to make the decision alone, and as many as 55% actually chose to receive their test results alone. By contrast, before the counseling, the majority of their parents considered that they

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**Abbreviations:** MODY, maturity-onset diabetes of the young.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

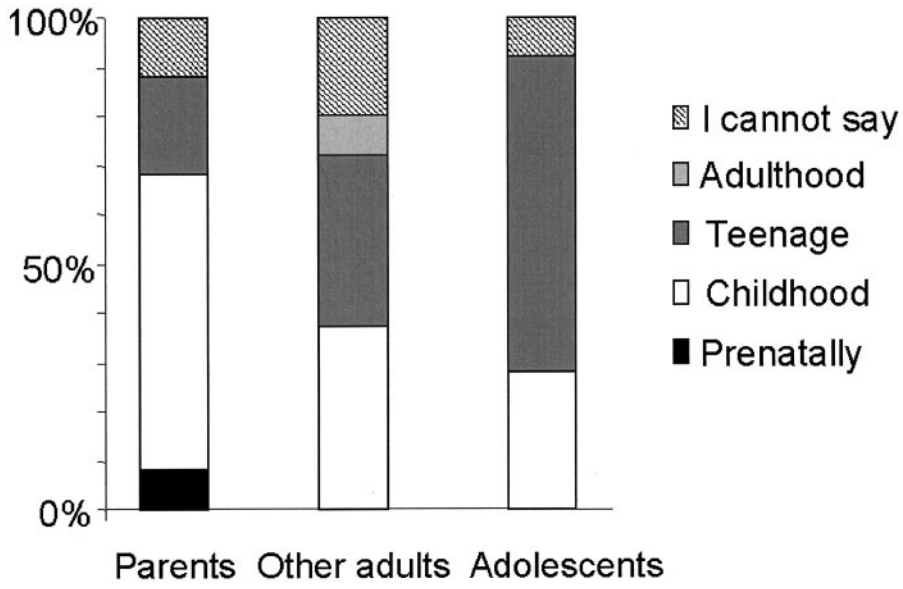


**Figure 1**—*Opinions before genetic counseling of the three groups of subjects (parents,* n = *25; other adults,* n = *105; and adolescents,* n = *29) from MODY3 families on the age at which gene testing should be performed (%). None of the subjects opted for "never", which was an alternative.* P = *0.005 for the difference between parents and adolescents with respect to testing in childhood.*

should be present at their children's test disclosure (80%, $P = 0.039$ vs. adolescents). After the counseling, the adults changed their opinion toward allowing the adolescents to receive the results alone, if they wished (16 vs. 27% before vs. after counseling, respectively; $P = 0.0355$).

One year after the disclosure of test results, 21 adolescents returned the follow-up questionnaire. All 12 noncarriers and 8 of the 9 mutation carriers correctly reported their test result and its interpretation, but 1 carrier could not say what the result meant. Most (17 of 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 who was in the same situation. However, four subjects (three carriers and one noncarrier) were dissatisfied with having taken the test. One had not really reacted to learning that he/she was a carrier but was angry at having been tested when diagnosed with diabetes 1 year later at a clinical follow-up. This shows that the adolescents may be more disposed to "natural optimism," in that they understand but do not necessarily internalize the risk of diabetes. Also, at least one of the eight nonresponders (four carriers and four noncarriers) aggressively reacted immediately after hearing that he/she was a carrier. Not returning the posttest 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 counseling. Both adolescents and adults considered that such testing should already be offered 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 counseling needs to be provided.

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