THE CHILDREN'S MEDICAL CENTER OF DAYTON

Pediatric Clips

A father unexpectedly dies with Marfan syndrome – Marvin Miller, MD

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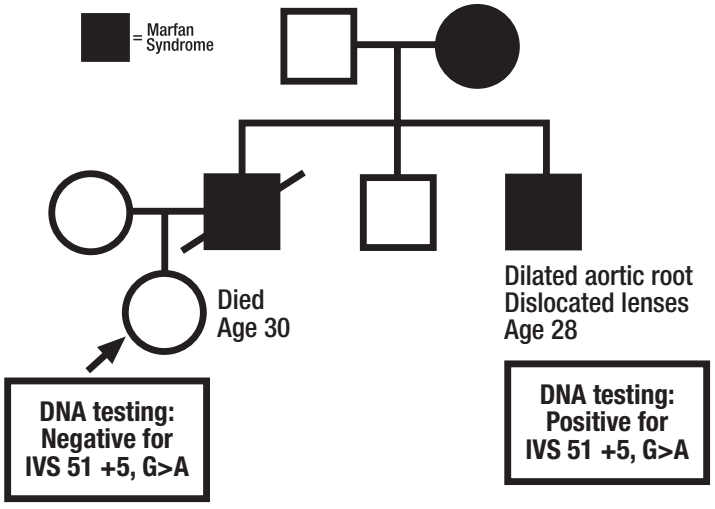
CASE: USING DNA TESTING TO PROVIDE INFORMATION ON MARFAN SYNDROME

A recently widowed woman came to the genetics clinic to request testing for Marfan syndrome in her 14-month-old child. Her husband had died suddenly at age 30, three months prior to this visit. His post-mortem examination revealed a ruptured aorta consistent with Marfan syndrome. The deceased had a history of high myopia, mitral valve prolapse and a dilated aortic root.

The child and surviving siblings of the deceased man with Marfan syndrome were referred to the genetics clinic at Dayton Children's. Unfortunately, no tissue or blood from the autopsy was saved for genetic testing. However, the 28-year-old brother of the deceased also has the disease and agreed to have DNA testing.

Marfan syndrome is caused by abnormalities in the protein fibrillin and molecular testing for mutations in the fibrillin gene (FBN1) is commercially available. Genetic testing on the living 28-year-old brother showed a disease-causing FBN1 mutation - IVS 51 +5, G>A. (This mutation is a single base pair change of a guanine to an adenine in the 5th position of intron 51).

Finding the disease-causing mutation in this family allowed for accurate genetic testing in at-risk relatives. The daughter of the deceased was then tested for the IVS 51 +5, G>A mutation. The good news for the family was that she tested negative for this mutation and thus did not have Marfan syndrome. The affected father of this child and his affected mother, however, presumably have the IVS 51 +5, G>A mutation. The pedigree with the molecular information is shown below:



CASE DISCUSSION

In this family, molecular testing was extremely helpful in the management of the 14-month-old child and her mother. First, the mother was reassured that her child did not have Marfan syndrome and her anxiety about this was abated. Second, the child was spared yearly eye exams looking for dislocated lenses and serial echocardiograms to evaluate aortic root dimensions. While the DNA testing for this family cost about $2,500, the costs saved over the years in not having eye exams and echocardiograms justified the molecular testing on economic grounds.

DNA testing for genetic disease should not be done just because the test is available. DNA testing can be costly and a core principle to remember is that the child or the family should benefit from the testing. Some genetic diseases are easily diagnosed by family history and physical examination (eg, neurofibromatosis-type1). Some genetic diseases can be accurately diagnosed by standard biochemical means (eg, sickle cell anemia). Thus, the use of molecular studies to diagnose genetic diseases should be done with thought and planning, so that the family has all the information. Table 1 summarizes important issues when considering molecular testing. Table 2 is a partial list of situations where clinical DNA diagnosis is possible.

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Table 1

Important issues to consider in molecular testing

1. The cost of the test for the family.
2. The turn around time for getting test results.
3. Knowing the types of mutations that cause the disease and whether there is genetic heterogeneity (more than one genetic locus).
4. For many genetic diseases, each family will have its own disease alleles. This information can be used in at-risk individuals in this family, but not in other families with the same genetic disease.
5. Determination of what the DNA test does—is it a complete sequencing of the gene or does it test for specific mutations? The former would be expected to have a greater chance of finding a disease mutation.
6. The experience of the lab with the test in distinguishing whether a DNA difference is a benign polymorphism or a disease mutation.
7. In testing at-risk individuals for a genetic disease with molecular studies, it is usually preferable to first test an individual in the family who is known to have the genetic disease. If the disease allele(s) in this affected individual are found, this information can then be easily and reliably applied to the at-risk individuals in the family.
8. How will the test influence your medical management of the child? DNA testing is not routinely offered to children less than 18 years of age unless the results of the test directly effect the medical management of the child.
9. DNA testing is best performed with consultation from a genetic counselor or medical geneticist who are well aware of the nuances in this ever-changing field.

Table 2

Examples of clinical situations where molecular studies may establish an etiologic diagnosis:

1. Hearing loss
2. Hypotonia
3. Muscle weakness
4. Pancreatitis
5. Mental retardation/ developmental delay
6. Thrombophilia
7. Bleeding disorders
8. Skeletal dysplasias
9. Craniosynostosis
10. Movement disorders
11. Cardiac arrhythmias
12. Sudden unexpected death
13. Seizures
14. Familial cancers
15. Iron overload
16. Neuronal migration abnormalities

FEATURED SPECIALIST

Marvin Miller, MD, is the medical director for the department of medical genetics and birth defects at Dayton Children's.

DEPARTMENT OF MEDICAL GENETICS AND BIRTH DEFECTS AT DAYTON CHILDREN'S

The department of medical genetics and birth defects at Dayton Children's accepts referrals for patients of any age with personal or family history of birth defects or genetic disease. The medical genetics department also provides genetic education to health care professionals, students and the community, and maintains an up-to-date video lending library on various topics in human genetics.

Services include medical genetics consultations and evaluations, genetics counseling (by appointment), molecular studies and plasma/urine amino acid qualification.

CONTACT INFORMATION

To contact the medical genetics department at Dayton Children's or to make a referral, call 937-641-3800.

For further information about The Children's Medical Center of Dayton or its specialists contact us at 937-641-3666 or marketing@childrensdayton.org.

DAYTON CHILDREN'S
The Children's Medical Center of Dayton

One Children's Plaza
Dayton, Ohio 45404-1815

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