FAMILIAL DYSAUTONOMIA AND THE PURSUIT OF GENETIC HEALTH

Miri Mandelbaum

In loving memory of Michael Zauder a"h, who inspired us with his strength and warmed our hearts with his smile.

Familial dysautonomia (FD) is an Ashkenazi Jewish genetic disease affecting the sensory and autonomic nervous systems. Among other symptoms, children born with the disease cannot control their blood pressure, body temperature, and heart rate. They have trouble swallowing and digesting food properly, have reduced sensitivity to pain and temperature, and cannot produce tears [1].

An estimated, 1 in 27 Ashkenazi Jews are carriers of the FD mutation [1]. The mutation is found on the long arm of chromosome 9 (on the IKBKAP gene). Since the mutation is recessive, a person will only exhibit the FD trait if he carries the mutation on both #9 chromosomes. A heterozygote, with one mutated and one normal functioning gene, is a carrier of FD. Although he will not exhibit any adverse symptoms, if he conceives a child with another carrier, there is a 1 in 4 chance that their child will inherit the mutation from both parents and will have the disorder [2].

It is speculated that the FD mutation originated in Eastern Europe as a result of the founder effect [3]. The Ashkenazi Jewish population descended from a significantly small number of ancestors. Any mutations they carried were passed on to their children and amplified throughout the generations. The founder effect is one major cause of Jewish genetic diseases [4].

In Europe prior to the twentieth century, technology was not yet advanced enough to maintain the lives of FD babies. Because child mortality was fairly common, no attention was paid to these babies in particular. It was not until the 1940s that the disease was identified. Doctors Riley and Day, while working in Columbia Presbyterian Babies Hospital, discovered similarities between some of the sick babies. The disease they uncovered became known as Riley-Day Syndrome.

As modern medicine progressed, children born with Riley-Day Syndrome, also known as familial dysautonomia, began to live longer, allowing for more research [3]. Parents of children with FD founded the Dysautonomia Foundation in 1951, a public charity dedicated to improving the lives of people with FD [1]. In 1970, Dr. Felicia Axelrod formed a treatment center for these children at New York University Medical Center.

Towards the end of the 1980s, scientists began to work to identify the gene carrying the FD mutation. Understanding the advantages of having the gene identified, Dr. Axelrod suggested that the Dysautonomia Foundation fund the discovery of the gene. A Harvard Medical School laboratory funded by the foundation discovered genetic markers, i.e., similar DNA sequences, within FD families. The markers did not identify the FD gene, but they did open the option of preimplantation genetic diagnosis (PGD) for couples who already had a child with FD. PGD is a procedure developed by Jewish researchers, originally to allow carriers of the Tay-Sachs gene to have healthy children. In this procedure, cells from a preembryo produced by *in vitro* fertilization (IVF) are tested for mutations before being implanted in the mother. In the case of FD, preembryo cells could be tested for the DNA markers common amongst FD families. This option was difficult, not 100% reliable, and could only be used for affected families. The gene carrying the FD mutation was identified in 2000. A carrier-screening test became available to the public in 2001 as an easy way for anyone to know if he carries the FD mutation.

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Two different mutations on the IKBKAP gene account for 99% of FD cases. A third mutation was discovered in one or two cases. Dysautonomia treatment centers test patients for these mutations. If a patient does not carry one of the three known mutations, a new mutation can potentially be found.

By identifying the gene and through the use of modern technology, couples in which both parties carry the FD mutation can avoid conceiving a child with the disease. PGD is much more reliable now that the actual gene can be tested for instead of the DNA markers. Additionally, much genetic research is being done. By researching the discrepancies between what the gene should be doing and what it actually does, genetic therapies are being de-

veloped. These therapies try to correct the gene by constructing the correct protein. Another research methodology is through laboratory animal models. The defective gene is inserted into the genome of an animal, commonly a mouse. Researchers can perform tests on the animal to learn more about the effects of the mutation and how it can be corrected [3].

The Dysautonomia Foundation, headquartered in New York City, continues to provide the largest source of funding for FD research. It also funds the world's two FD treatment centers, one at New York University Medical Center and the other in Hadassah Hospital in Jerusalem. As a result of the work of these centers, the quality of life for people with FD has improved significantly. Life expectancy has risen from 5 years to 40 years. However, affected individuals still suffer from symptoms that prevent them from leading normal lives [1].

With the availability of genetic screening for the FD mutation, the birth of children with FD can be completely avoided. However, as long as people remain unaware of the importance of genetic testing, not only for FD but for all genetic diseases, affected babies are still being born. Rabbinical leaders should be aware, ensuring that couples are tested before getting married. It is extremely important that couples know if they are carriers for a genetic disease before having children. Appropriate measures can then be taken to ensure the birth of a healthy baby [3]. ■

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