

# The Impact of Generalized Dystonia on the Jewish Community

## Introduction

Dystonia is a painful, disabling disease for which there is no cure. For almost three decades, a small but growing group of scientists has labored to understand how and why dystonia occurs—and how to stop it. The answers needed to cure this disease may very well lie in the study of one specific form that is particularly prominent in persons of Ashkenazi Jewish descent, called *early onset torsion dystonia*. Originally described by Oppenheim in 1911, the disease was first called, “Oppenheim’s Dystonia.” Subsequently, this form of Dystonia was discovered to be caused by a mutation in a gene called DYT1. The impact of DYT1 dystonia on Ashkenazi Jews is significant—tens of thousands of families in North America are besieged by this insidious genetic disorder that disables children, hides in carriers who show no symptoms, skips generations only to recur, and devastates families. This community has suffered greatly from this disease, and it is believed that better treatments and ultimately a cure are possible by paying close attention to how dystonia affects Ashkenazi Jews both as a population and as individuals.

## Background

There are several forms of dystonia. Dystonia is a neurological movement disorder characterized by involuntary muscle contractions that cause uncontrollable movements and force the body into abnormal postures. Dystonia is an incurable, chronic disorder that affects men, women, and children of all ages and backgrounds. Dystonia may specifically affect the muscles of the neck and shoulders, trunk, limbs, face, eyes, and vocal cords, or it may be generalized throughout all major muscle groups. The disorder causes varying degrees of disability and pain, from mild to excruciating. Dystonia affects all aspects of a person’s life: health, daily activities, career, relationships, social activities, and self-perception. Available treatments can only temporarily relieve symptoms without resolving the actual disease. Results from treatments vary, and there is no single therapy that helps the majority of patients. Those who are severely affected may require a wheelchair or may even become homebound.

The exact cause of most forms of dystonia remains unknown. Most forms are likely due to a combination of genetic predisposition and environmental factors. Thanks to pioneering research<sup>1</sup> supported by the Dystonia Medical Research Foundation, the origins of DYT1 dystonia have recently been identified rather precisely.

Most cases of early onset torsion dystonia are directly associated with a genetic mutation on the human chromosome 9q34.<sup>2</sup> Specifically, the mutation affects a specific gene that scientists discovered in 1997 and named the DYT1 gene. In its normal state, the DYT1 gene is responsible for providing the body with the genetic instructions to produce a protein called torsinA. The

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<sup>1</sup> Ozelius, L, Kramer PL, Moskowitz CB, et al. Human gene for torsion Dystonia located on chromosome 9q32-q34. *Neuron* 1989;2:1427-1434.

<sup>2</sup> Ozelius L., Kramer PL, de Leon D, Risch N, Bressman SB, Schuback DE, Brin MF, Kwiatkowski DJ, Burke RE, Gusella JF, Fahn S, Breakefield XO. Strong allelic association between the torsion Dystonia gene (DYT1) and loci on chromosome 9q34 in Ashkenazi Jews. *Am J Hum Genet* 1992; 50:619-628.

existence of the protein was completely unknown prior to 1997, and at this writing its function remains largely a mystery.<sup>3</sup> What we do know, however, is that the mutated DYT1 gene results in an abnormal form of torsinA, and this abnormal protein starts a chain reaction of biochemical processes that somehow disrupts the communication between the brain and muscles. This disruption of the nervous systems leads to the debilitating physical symptoms of DYT1 dystonia.

We know that there is a higher prevalence of DYT1 dystonia in Ashkenazi Jews. Medical literature is lacking in definite data regarding the frequency and prevalence of this disorder, but the latest sources state that less than 1% of the overall population are carriers of the DYT1 mutation. Among Ashkenazi Jews, the frequency is at least 3-5 times higher.<sup>4</sup>

There are a number of factors scientists must consider in order to understand DYT1 dystonia well enough to proceed with new therapeutic approaches. We know that a mutation in the DYT1 gene is associated with early onset dystonia, but not all persons who develop this disease have the mutation. Interestingly, 90% of Ashkenazi Jews who develop early onset disease have the DYT1 mutation, but only about 50% of non-Jews with the same disorder have the mutation. Therefore, there are probably other genes that are involved in some individuals, especially non-Jews.

The plot thickens: DYT1 dystonia is an autosomal dominant disorder which means that only one parent needs to have the mutation for a child to inherit the disorder. Of the individuals (Jewish and non-Jewish) who have the DYT1 gene mutation, only 30%<sup>5</sup> manifest symptoms. In other words, close to 70% of persons with the mutation are “carriers” but do not develop any disease symptoms. The children of both asymptomatic and symptomatic carriers are at risk of inheriting DYT1 dystonia. Therefore, the child of a carrier has a 50% chance of inheriting the mutated gene; if the child does inherit the mutated gene, there is a 30% chance that symptoms will develop. So, each child of a carrier has about a 15% chance of developing DYT1 dystonia. This phenomenon is called *reduced penetrance*. To make matters more complicated, there is no way to predict how severe the symptoms will be. Some people within a family can be very severely affected while others only have mild symptoms—this is called *variable expressivity*. We don’t understand why reduced penetrance or variable expressivity occur, but again it points to additional genes or environmental factors that may activate symptoms in some individuals and/or suppress symptoms in others.

Most Jewish genetic diseases are severely incapacitating and some are tragically debilitating, leading to death in infancy or early childhood. Tay-Sachs may be the most notorious of the lot, but other diseases, just as prevalent and just as devastating, shatter the lives of Jewish families.<sup>6</sup> DYT1 dystonia certainly meets this description. A child who is affected cannot control the

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<sup>3</sup> Ozelius, LJ, Hewett JW, Page CE, et al. A strong candidate for the early onset torsion Dystonia gene (DYT1) encodes an ATP-binding protein. *Nat Genet.* 1997; 17: 40-48.

<sup>4</sup>Risch, N., de Leon D, Ozelius LJ, et al. Genetic analysis of idiopathic torsion Dystonia of Ashkenazim for a small founder population. *Nat Genet* 1995;9:152-159.

<sup>5</sup>Clinical Molecular Genetics Society web site <http://www.ich.ucl.ac.uk/cmgs/jewish.htm>

<sup>6</sup> <http://www.mazornet.com/genetics/index.asp>

movement of his/her limbs and body. The shoulders rise and the torso twists as multiple muscles contract in competition against each other; the neck swivels the chin down into the chest; muscle spasms in the jaw slur speech; the hands cramp up into unrelenting fists; the feet turn inward while the legs are forced back toward the spine.

Dystonia is exhausting—both physically and emotionally—and often painful. Living with the symptoms and stigma of dystonia can be an overwhelming burden to even the most secure adult, let alone a child. Although treatments exist, dystonia is a chronic and unpredictable disorder that children must endure for the extent of their lives. Because of the reduced penetrance, more than one child may be born before parents realize they are carriers. And every child carrying the gene risks developing symptoms, although they may not manifest prior to about age 6.

A genetic test is available to determine if a person is a carrier. The test is not recommended unless it is preceded by a consultation with a skilled genetic counselor, to inform the person of the potential risks and benefits of testing. While the test is very helpful for adults with DYT1 dystonia or adult relatives of a person with this disease, genetic counseling guidelines strongly discourage testing asymptomatic children<sup>7</sup>:

Consensus holds that children at risk for adult-onset disorders should not have testing in the absence of symptoms. The principal arguments against testing children who do not have symptoms are that it removes their choice to know or not know this information, raises the possibility of stigmatization within the family and in other social settings, and could have serious educational and career implications [[Bloch & Hayden 1990](#) , [Harper & Clarke 1990](#)]. In addition, no preventative treatment is available.

It is the unpredictability of dystonia, both in terms of its penetrance and expressivity that is perhaps the biggest source of heartache and anxiety for affected families and an equivalent source of puzzlement for researchers. The most urgent questions for research to answer are:

- How does the mutated protein torsinA affect the nervous system and thus lead to symptoms of dystonia?
- Why do 30% of mutated DYT1 carriers develop symptoms and 70% do not?
- Why do some people with DYT1 dystonia develop very severe symptoms while others remain relatively mild?

The answers to these questions will illuminate new treatment approaches and ultimately a cure. In the meantime, The Dystonia Medical Research Foundation is committed to serving the needs of all dystonia-affected individuals and families.

### **Why is the DYT1 Mutation More Prevalent in Ashkenazi Jews?**

The Ashkenazim accounts for 80% of all Jews. This population originated from a group that colonized the Rhineland (now Germany) and then migrated to Eastern Europe in the 15<sup>th</sup>-16<sup>th</sup> centuries, and more recently migrated to North America and Israel (19<sup>th</sup> century). The Ashkenazim is a group in which a number of genetically inherited diseases occur at an unusually high frequency as compared to non-Jewish populations. For many of these disorders, a causative gene has been identified and 2-3 mutations are found to cause most cases (90%+) of the disease

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<sup>7</sup> GeneReviews website: [www.genetests.org](http://www.genetests.org) “Early Onset Primary Dystonia (DYT1)”

within the group. These mutations are often found exclusively within the Ashkenazi population. Examples of such disorders include Tay-Sachs disease and Gaucher disease type I, both of which are inherited in an autosomal recessive manner. (Unlike a dominant mutation like DYT1, in the case of an autosomal recessive disorder, a child must inherit defective genes from both parents to inherit that disease.)

There are several explanations for why a given population may have a higher prevalence of a genetic disorder than the general population. The most plausible explanation is a “founder effect.” A disease may become common within a population because all individuals within the population are descended from a small number of ancestors, and one or a few of the ancestors were affected by the disease. According to a recent summary compiled by the Public Broadcasting System for its lay audiences,

“When a small part of a population moves to a new locale, or when the population is reduced to a small size because of some environmental change, the genes of the ‘founders’ of the new society are disproportionately frequent in the resulting population.

If individuals in the group tend to marry within it, there's a greater likelihood that the recessive genes of the founders will come together in the cells that produce offspring. Thus diseases of recessive genes, which require two copies of the gene to cause the disease, will show up more frequently than they would if the population married outside the group.”<sup>8</sup>

Published scientific evidence clearly indicates that the DYT1 mutation arose in Ashkenazi Jewish populations due to a founder effect. The mutation was estimated to have arisen in a single Ashkenazi ancestor who had lived ~350 years ago in Lithuania or Byelorussia.<sup>9</sup> The founder effect, coupled with a history of social, religious, and geographic isolation provides a plausible explanation for the high incidence of certain genetic conditions within Jewish populations, including early onset torsion dystonia.

### **What is the Importance of Studying DYT1 dystonia?**

Much remains unknown about dystonia, and studying DYT1 will shed light on all forms of the disorder. The Dystonia Medical Research Foundation has devoted significant energy and resources to gaining a more complete understanding of all forms of dystonia, with special emphasis on DYT1 dystonia, in part because it is one of the most severe forms.

DYT1 dystonia serves as a unique model of dystonia because it is one of the few forms of dystonia for which a consistent gene mutation has been discovered in a large percentage of patients. Scientists have a “starting point” (the mutation in the DYT1 gene) and an end point (physical symptoms of dystonia)—and somewhere between these two points lies the secret to silencing or preventing the effects of the mutated gene. Researchers are working as “detectives” to trace how mutated torsinA ultimately undermines the nervous system and leads to physical symptoms. Once we can identify the ways in which the nervous system is affected, we can look

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<sup>8</sup> [http://www.pbs.org/wgbh/evolution/library/06/3/1\\_063\\_03.html](http://www.pbs.org/wgbh/evolution/library/06/3/1_063_03.html)

<sup>9</sup> Ibid, Risch et al. 1995

for additional sources of such disruption in other forms of dystonia and thus follow the trail to that biochemical point of origin, whether it's a gene or external factor.

Progress in learning about the DYT1 gene is steady and time-consuming. The Foundation needs to establish a fundamental understanding of the biochemical origins of the disease. Ongoing research about dystonia and the DYT1 gene is valuable, not only for the answers it helps provide, but also for the questions it inspires. Never before has dystonia captured the attention of so many researchers from such varied fields (neurology, biochemistry, protein chemistry, genetics, epidemiology, and others).

Dystonia has several features that suggest disruption of the basal ganglia, a crucial part of the brain involved in the control of movement. How torsinA may contribute to this disruption is not known. However, it appears as though this interference with the basal ganglia may be linked to the process by which the brain learns and develops as a child grows. When symptoms begin at a very young age (~9 years), they tend to occur most frequently in a foot and then spread to other body parts.<sup>10</sup> When symptoms begin later (~15 years), they usually start in the arm and are less likely to spread. Individuals who carry the gene and reach the age of 28 years without displaying symptoms (70% of all gene carriers), typically remain symptom-free for the rest of their lives. This relates to the concept of variable expressivity mentioned previously. Researchers are investigating the idea that there is a factor or phenomenon related to the development of the brain during childhood or adolescence that affects whether or not a carrier develops symptoms.

Brain imaging studies using positron emission tomography (PET) demonstrate that both symptomatic and asymptomatic DYT1 carriers show abnormal patterns of brain activity.<sup>11</sup> In addition to the pattern of brain activity seen in both patients and non-symptomatic relatives, a second pattern of activity is observed in patients. And this activity is apparent only when the patients experience dystonia symptoms. Scientists are thus again pointed to the possibility of a protective factor in asymptomatic carriers or a susceptibility factor in people who develop DYT1 dystonia.

One of the most exciting recent developments is that pioneer researchers in one of the Foundation's supported laboratories have discovered how to silence the mutated DYT1 gene in cultured cells.<sup>12</sup> The next step will be to recreate this effect in animal models. The Foundation currently supports several projects for the development of additional animal models because we believe they are a critical step in bridging the gap between the discovery of the DYT1 gene (as well as dystonia genes that may be discovered in the future) and understanding the function of that gene.

By pursuing the meticulous research investigations mentioned above and many others, it will become possible to narrow in on the precise biochemical flaw that ultimately results in symptoms of dystonia. Scientists will then have the opportunity to develop a therapy or

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<sup>10</sup> Ibid., Bressman et al. 1994

<sup>11</sup> Eidelberg D, Moeller JR, et. al. Antonini A. Functional brain networks in DTY1 dystonia. *Ann Neurol* 1998. Sept;44(3):303-312.

<sup>12</sup> Gonzalez-Alegre P, Miller VM, Davidson BL, Paulson HL (2003). Toward therapy for DYT1 dystonia: allele-specific silencing of mutant TorsinA. *Ann Neurol* 53:781-787.

application to “fix” the flaw with the hope of thereby preventing or reversing the onset of dystonia. The beginnings of a cure may very well be within the reach of this generation of researchers. This prospect is almost unbearably exciting to those within the Dystonia Foundation who have spent decades raising money for research and watching the progress. Since current treatments only cover up symptoms without altering the actual disease and no single treatment benefits all patients, a cure for this disorder would truly be revolutionary for the hundreds of thousands of persons—including tens of thousands of Jewish families—who are affected.

## **Conclusion**

A better understanding of DYT1 dystonia will contribute hugely to the greater field of dystonia research. These studies provide a helpful model of dystonia in terms of:

- How the DYT1 gene mutation biochemically affects cells and the nervous system
- How the familial forms of dystonia are inherited, and why symptoms within a family may vary
- Achieving a better understanding of how dystonia affects populations, and especially the Jewish community.

All of these elements will illuminate a route to better treatments and a cure.

Current dystonia research sponsored by the Foundation is focused on turning meaningful laboratory discoveries into practical applications that improve the lives of persons with the disorder. Dystonia scientists are contributing to the growing body of knowledge about dystonia at an inspiring rate, and the Dystonia Foundation is committed to perpetuating this progress until a cure is found.

We are proud that DMRF-sponsored research has made possible two very significant clinical services that are improving the lives of individuals and families in very tangible ways. The first is a genetic test to determine if a person carries the DYT1 gene mutation. This test is applicable to confirm a diagnosis in a patient with DYT1 dystonia symptoms and to identify asymptomatic carriers including the family members of patients. This test can also be used for prenatal testing.

New developments in reproductive sciences have created a second, very exciting option for couples who carry the mutated DYT1 gene. A process called pre-implantation genetic diagnosis (PGD), is making it possible for parents carrying a defective DYT1 gene to conceive a child who does not have the mutation. PGD is complex and expensive. The approach entails inducing *in vitro* fertilization and then, when the embryos grow to the minute size of 8 cells, testing them for the presence of the DYT1 gene mutation (using the genetic test described above). The embryos that do not have the mutation are implanted into the mother’s uterus and, if all goes well, a healthy DYT1 negative child is born. We have already witnessed this process play out successfully once, and expect it will be used again until a less complex way is found to prevent carriers from passing on the mutated gene to their children or until we have discovered a cure.

Why does the Foundation focus so much energy and attention on the DYT1 gene? The tragedy of dystonia is particularly devastating in a young child who unknowingly carries this gene and appears perfectly normal until about age 8. Then, once the gene is turned on, there is no going

back. The progression is gradual—the child does not experience a single loss but rather a series of losses within months or years. At first the child becomes unable to run the bases on the baseball field, then he can't control his handwriting, then he is unable to sit up at the kitchen table, then he must use a wheelchair at school, and then he can't speak clearly. The impact of this disorder on a child just as they begin their school age years cannot be overstated—not being able to sit at a desk or hold a pencil makes school a logistical hardship, pain and muscle spasms may make it difficult for a child to concentrate (and prescribed medications may make him sleepy or depressed), teachers may misinterpret symptoms, and schoolmates may distance themselves or be cruel. DYT1 dystonia wreaks havoc with the child, family, and loved ones, forever changing lives. We are determined to find ways to interrupt this process for those carry the mutation with the intent of bettering the lives of not only the families plagued with DYT1 dystonia, but for individuals afflicted with all forms of this ruthless disease.