ay-Sachs is a recessive genetic disease characterized by a mutation in the gene coding for the enzyme hexosaminidase-A. Normally, hexosaminidase-A breaks down fatty acids in nerve cells but when the enzyme is defective, there is a build up of fatty acids called gangliosides. This build up interferes with normal biological processes and children with this disease usually decease by age four. Tay-Sachs has a high incidence in the Ashkenazi Jewish community, with a carrier frequency of 1 in 27 [1, 3].

Puzzled by the high frequency of the Tay-Sachs mutation within the Ashkenazi population, scientists searched to find an explanation. Several theories have been proposed, some of which have resulted in great controversy. Most of the theories have a historical foundation, and are based on the status or conditions of the Jewish population during the past 900 years [2]. Because of the varied possible origins for the Tay-Sachs mutation, much uncertainty and division exists among researchers concerning an explanation for its elevated frequency within the Jewish population.

In 1962, Myrianthopoulos and colleagues proposed the idea of heterozygote advantage as an explanation for the high frequency of the Tay-Sachs mutation among Ashkenazi Jews [3]. In typical Mendelian genetics, a given gene can exist in one of two forms, either dominant wild type or mutant recessive. An individual normally has two copies of each gene. “Dominant homozygous” refers to a genotype possessing two copies of the wild type allele, while “recessive homozygous” usually indicates a genotype that possesses two mutant alleles for a given trait. A heterozygote, therefore, is an individual who possesses one wild type allele and one mutant allele for a given gene, but only exhibits characteristics of the dominant allele. Heterozygote advantage is a phenomenon in which a heterozygote has higher fitness than an individual with a homozygous dominant or recessive genotype [4]. A well-known example of heterozygote advantage is that of carriers of sickle cell anemia. Studies have shown that individuals who have one allele for sickle cell have a greater resistance to malaria. Therefore, in addition to not being affected by the sickle-cell disease, the heterozygote condition (i.e. being a carrier) has an added advantage in that it provides a higher resistance to malaria [2, 4, 5].

In the case of Tay-Sachs, it was proposed that being a carrier for this disease could provide greater resistance to tuberculosis (TB) [6]. Historically it was shown that Jews have a lower rate of TB as compared to their non-Jewish counterparts living in similar conditions. Myrianthopoulos suggested that there is a link between TB resistance and the high frequency of Tay-Sachs alleles [6]. However, in 1981, Spyropoulos and colleagues published an article challenging the link proposed by Myrianthopoulos. Spyropoulos and colleagues performed a similar study to Myrianthopoulos, investigating the causes of death for grandparents of carriers and noncarriers of Tay-Sachs in order to assess whether the grandparents of the noncarriers died from TB more often than those of carriers. The difference in the frequency of death due to TB was not significant, and therefore there is no link between the heterozygous genotype with a mutant Tay-Sachs allele and resistance to TB [6].

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ditionally, because of persecution against Jews throughout Jewish European history, genetic drift occurred.

Tay-Sachs is one of four genetic diseases common among Ashkenazi Jews that is related to sphingolipid disorder. All four of these diseases, Tay-Sachs, Gaucher, Neimann-Pick, and mucolipidosis type IV, are caused by a mutation in different enzymes that affect the cell's management of sphingolipids [2, 5]. This scientific fact weakens the likelihood that the mutation occurred merely by chance, thereby strengthening the case for some advantage in being a carrier. Perhaps carrying one mutated allele offers some benefit other than resistance to TB and inheritance of the recessive disease is a by-product of heterozygote advantage [2, 5].

Although the advantage of the Tay-Sachs mutation in providing TB resistance was debated and possibly disproven, the support for the view of a heterozygote advantage did not subside. Instead, a different advantage for heterozygosity was proposed. Historically, as a result of persecution, Jews often were banned from many professions. In order to make a living, Jews had to excel intelligently and think of new ways to earn a living. Because of this, natural selection led to the survival of the smartest Jews. Furthermore, some researchers suggest that smarter men had increased reproductive success because men with greater intellectual abilities married wealthy women and had many children, passing down the “intelligence gene” to many offspring [2].

The cause of the high frequency of genetic mutations in the Jewish population has been hotly debated more recently as well. Researchers at the University of Utah built upon this historical idea and tested the theory that carrying an allele for Tay-Sachs was a result of natural selection for enhanced intellectual ability. Gregory Cochran and Jason Hardy of the University of Utah proposed that not only were Jews barred from the common professions during medieval times, but they were restricted to positions of management, which required a lot of intellectual acuity. Furthermore, those who were successful had more children, causing an elevation in the frequency of the gene that promotes intelligence [5].

Cochran and Hardy substantiate their argument by explaining that sphingolipid disorders promote growth and connections between brain cells, enabling faster communication between different areas of the brain [5]. Throughout history, Jews have been recognized for their great academic accomplishments and groundbreaking discoveries. Statistically, Jews make up a very small percentage of the world, yet they have won 27 percent of America's Nobel prizes [5]. While these facts support the suggestion that Jews tend to be smarter, they do not prove that increased intellectual ability within the Jewish population is due to an allele for the Tay-Sachs mutation.

On the other hand, Dr. Neil Risch, a geneticist at the University of California, is a proponent of the founder effect as the cause for the high frequency. Dr. Risch found that many of these genetic diseases arose around the same time, most likely due to the same cause. Therefore, founder effects must be the reason that the mutations are so common among Ashkenazim. Other researchers disagree with the heterozygote advantage as an explanation for increased intelligence because it is far-fetched and challenging to prove.

Each view answers some of the mysteries of Jewish genetic diseases, but still leaves scientists unfulfilled with respect to other puzzling factors of these phenomena. We may never be able to pinpoint how the Tay-Sachs mutation arose. However, it is important not only to focus on the origin of the disease, but also how the disease takes its course. This knowledge will help us work toward the future and find solutions that prevent the disease from being passed to offspring.

Another question can be raised with regard to the correlation between heterozygosity for the Tay-Sachs mutation and increased intelligence. If individuals with one copy of the mutated gene have an added dose of intelligence, do individuals with two copies of the mutated gene have two doses of added intelligence? It is probably impossible to answer this question, as children with Tay-Sachs die at a young age, before their intelligence can be evaluated. However, the possibility suggests that there is much more research to be done in order to properly evaluate and understand genetic disease.

It is my hope that understanding the possible benefit of being a carrier for Tay-Sachs may lessen the stigmatization that sometimes occurs when someone is found to be a carrier of a genetic disease. Although it is not recommended to reproduce with someone who has an identical mutation, as there is a 25 percent risk of having an affected child, being a carrier should not be looked at as a flaw. It is a physical attribute of a person just like eye color, and may even carry with it the added advantage of increased intelligence.

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