

# Tay-Sachs Disease

## 23andMe Established Research Report

Andrew Yates - May 10, 2010

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Intended for research and educational purposes. Not for diagnostic use.

### Your Genetic Data

**Your result** - Does not have any of the four most common Tay-Sachs mutations or two variations that cause false positive results for Tay-Sachs blood test that measures hexosaminidase A activity. Most likely no disease and not a carrier. May still be a carrier due to other mutations in the HEXA gene (not reported here).

#### Technical Report:

23andMe Name	Other Name(s)	DNA Change	Genotype
i4000436	G269S	C to T	CC
i4000391	1278insTATC	— to TATC	—,—
i4000393	IVS12+1G>C	C to G	CC
i4000438	IVS9+1G>A	C to T	CC
i4000440	R249W	G to A	GG
i4000442	R247W	G to A	GG

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### The Genetics of Tay-Sachs Disease

Tay-Sachs disease is caused by mutations in the HEXA gene, which encodes a subunit of the hexosaminidase A enzyme (HEXA). These mutations lead to loss of enzyme activity and a nerve cell-destroying accumulation of a fatty substance called GM2 ganglioside in the brain.

A person must inherit a mutated copy of the HEXA gene from each parent in order to have Tay-Sachs disease. If two parents are carriers of a mutation, there is a 25% chance their child will be born with the disorder. There is a 50% chance that their child will be an unaffected carrier for Tay-Sachs disease. Each unaffected sibling of an affected child has a two in three chance of being a carrier.

More than 100 mutations that cause some form of Tay-Sachs have been identified in the HEXA gene. 23andMe reports data for the four most common disease-causing mutations, as well as two non-disease causing variations that can affect the results of Tay-Sachs screening tests. If your data does not indicate that you are a carrier of a Tay-Sachs mutation, you could still carry one of the other mutations associated with the disease. If you are concerned about

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Tay-Sachs disease, consult a health professional.

Some mutations (including the 1278insTATC, IVS12+1G>C and IVS9+1G>A mutations reported by 23andMe) in the HEXA gene cause a complete lack of the hexosaminidase A activity, which is needed for the normal breakdown of GM2 gangliosides. A person born with one of these mutations in each of their two copies of the HEXA gene will have the infantile form of Tay-Sachs disease. Symptoms usually develop around three to six months of age and death usually occurs between ages two and four.

Other HEXA mutations cause the juvenile form of Tay-Sachs disease, which is characterized by later onset of symptoms similar to those seen with infantile Tay-Sachs. Death generally occurs by age 15. 23andMe does not report data for any mutations associated with the juvenile form of Tay-Sachs disease.

The adult-onset form of Tay-Sachs disease is caused by mutations in the HEXA gene that only partially reduce the activity of the hexosaminidase A enzyme. People with this form of the disease have far milder symptoms than children with the infantile or juvenile forms of Tay-Sachs. Symptoms usually begin between adolescence and the mid-30s, although they can begin in childhood. Life expectancy is variable, and in some cases appears to be unaffected. The G269S mutation reported by 23andMe is associated with adult-onset Tay-Sachs.

23andMe also reports data for two HEXA mutations, R247W and R249W, known as "pseudodeficiency alleles." These mutations are considered normal variations because they do not actually affect the activity of the hexosaminidase A enzyme. They do, however, cause false positive results in blood tests that measure hexosaminidase A activity that are used to screen for Tay-Sachs disease. People with one copy of either the R247W or R249W mutation would be identified as carriers for Tay-Sachs disease by this type of screening test. People who have one of these mutations in one copy of the HEXA gene and a true Tay-Sachs mutation in the other copy of the gene would be identified as having Tay-Sachs disease, even though they are actually unaffected carriers. It is important to note, however, that these people still have a 50% chance of passing on the disease-causing mutation to a child.

In the general population, about one out of every 300 people carries a mutation in the HEXA gene. The prevalence is higher, however, in certain ethnic groups.

About one out of every 30 people with Ashkenazi Jewish ancestry is a carrier for Tay-Sachs — most often the 1278insTATC mutation. Extensive screening programs and genetic counseling in this population have reduced the number of children born with infantile Tay-Sachs by more than 90% since carrier testing became available in the 1970s.

French-Canadians have about the same carrier rate as Ashkenazi Jews. 23andMe does not provide data for the mutation most commonly found in this population. The Cajun community of Louisiana also has about a one in 30 carrier rate, with the most common mutation being the same 1278insTATC mutation commonly found in Ashkenazi Jewish carriers. People with Irish ancestry are also at increased risk for Tay-Sachs. Current research indicates the carrier rate is about one in 50 for Irish Americans.

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The high prevalence of Tay-Sachs mutations in select groups, particularly Ashkenazi Jews, has prompted some scientists to speculate that being a carrier for these mutations provides some sort of evolutionary advantage, similar to the protection from malaria conferred by carrying one copy of the mutation that causes sickle cell anemia. Several theories for what this advantage might be have been proposed. One suggests that Tay-Sachs mutations provide protection against tuberculosis, an infectious bacterial disease that ran rampant through the cramped ghettos many Jews inhabited in Europe in the historical past. Another theory is that Tay-Sachs mutations and others affecting the brain increased in the Jewish population as a by-product of cultural selection for intelligence. For more information on this controversial theory, check out [the Spittoon review](#) of the book *The 10,000 Year Explosion*. At present, no theory of a selective advantage for Tay-Sachs mutations has been proven.

### Citations

[Myerowitz \(1997\)](#) . "Tay-Sachs disease-causing mutations and neutral polymorphisms in the Hex A gene." *Hum. Mutat.* 9(3):195-208.

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[Martin et al. \(2007\)](#) . "Evaluation of the risk for Tay-Sachs disease in individuals of French Canadian ancestry living in new England." *Clin. Chem.* 53(3):392-8.

[Spyropoulos et al. \(1981\)](#) . "Heterozygote advantage in Tay-Sachs carriers?" *Am. J. Hum. Genet.* 33(3):375-80.