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Department Paediatric Laboratory Medicine

Division of Molecular Genetics

CARRIER TESTING FOR PERSONS OF ASHKENAZI JEWISH ANCESTRY

Background

All around the world certain ethnic groups have been identified as having an increased risk for certain genetic diseases. In individuals of Ashkenazi (Eastern European) Jewish descent, a number of such inherited diseases are known.

In Ontario, carrier screening for seven of these genetic diseases, Bloom syndrome, Canavan disease, familial dysautonomia, Fanconi anemia (group C), Niemann Pick disease (type A & B), mucolipidosis IV and Tay-Sachs disease is available to individuals of Ashkenazi Jewish descent and their partners.

You have recently had a blood test to learn about your specific chances of having a child affected with one of these conditions. Please refer to the attached screening report for details about the results of your screening test.

Bloom Syndrome

Individuals with Bloom syndrome usually have short stature, recurrent respiratory and ear infections, and a characteristic redness of the skin mainly across the bridge of the nose and upper cheek area which is sensitive to the sun. These individuals are at an increased risk for the development of cancer and diabetes. DNA testing for one mutation in the Ashkenazi Jewish population is performed.

Canavan Disease

Canavan disease is a progressive neurological disorder in which the brain and nervous system degenerate. The majority of individuals with Canavan disease die in childhood. DNA testing for the four common mutations in the Ashkenazi Jewish population is performed.

Familial Dysautonomia

Familial dysautonomia (FD) is a progressive degenerative disorder that affects the autonomic nervous system which is responsible for controlling body temperature and blood pressure. Individuals with FD have generalized weakness, feeding difficulties recurrent pneumonia and developmental delay. DNA testing for the two common mutations in the Ashkenazi Jewish population is performed.

Fanconi Anemia Group C

Fanconi anemia (FA) is a genetically complex condition since it is caused by gene alterations (mutations) in a number of different genes. Individuals with FA have variable clinical symptoms that can differ between patients and even within the same family. Some clinical findings in patients with FA include: anemia (iron deficiency), progressively reduced number of blood cells; skin discolouration; short stature; and/or multiple malformations of the bones and organ systems. Individuals with FA are at increased risk for cancers of blood and solid tumours. Fanconi anemia group C (FA-C) is the most common form of FA seen in the AJ population DNA testing for two mutations in the FANCC gene is performed.

Mucolipidosis IV

Mucolipidosis IV is a storage disorder characterized by delayed development, eye abnormalities, and iron deficiency. Most patients present at 2-3 years of age and remain in an apparent steady-state for the next 2-3 decades. DNA testing for two mutations common in the Ashkenazi Jewish population is performed.

Niemann Pick Disease (Types A & B)

Niemann Pick disease type A and B are storage disorders resulting from a buildup of material in the cells of affected individuals due to a deficiency of an enzyme needed to break down these substances. Niemann Pick type A (NPA) presents in infancy with enlarged organs and rapid neurodegeneration leading to death by -3 years of age. Individuals with Niemann Pick type B (NPB) can have multiple findings including enlarged liver and spleen, growth retardation, frequent respiratory infections and fatigue. Lifespan is usually into adulthood. DNA testing for three mutations common in the Ashkenazi Jewish population for NPA and one mutation in NPB is performed.

Tay-Sachs Disease

Tay-Sachs disease is caused by a lack of the enzyme hexosaminidase A (Hex-A). Without this enzyme a harmful substance builds up in the brain leading to progressive weakness and loss of motor skills beginning between three and six months of age, and death occurs by age 5. DNA testing for the three common mutations in the Ashkenazi Jewish population and for two pseudodefiency alleles is performed. Carrier couples of the pseudodeficiency allele are not at increased risk to have a child with TSD. TSD is seen at a increased frequency in the French Canadian and Cajun populations as well. DNA testing for two mutations seen at a higher frequency in the French Canadian population are also part of the panel. Individuals screened for their carrier status of TSD by DNA testing may also have been screened by enzyme analysis.

Other Conditions Common in Ashkenazi Jewish Population

Carrier screening for cystic fibrosis, Gaucher disease, glycogen storage disease type 1a and maple syrup urine disease is available for Ashkenazi Jewish individuals. Testing can be arranged and could be covered by OHIP when there is a positive family history.

How accurate are these tests?

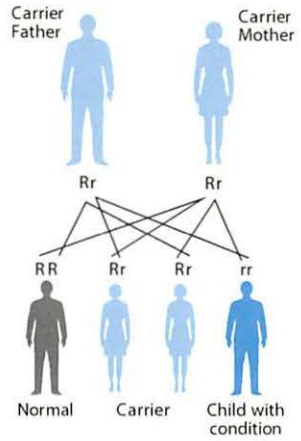
Disease	Carrier Frequency in AJ Population	Carrier Detection Rate in AJ Population
Bloom Syndrome	1 in 102	98%
Canavan Disease	1 in 57	99%
Familial Dysautonomia	1 in 32	99%
Fanconi Anemia group C	1 in 89	99%
Mucolipidosis IV	1 in 100	95%
Niemann Pick Disease (Type A&B)	1 in 90	95%
Tay-Sachs Disease	1 in 30	99% (DNA+ biochemical)

What is a carrier?

A carrier is a person who has one copy of the non-working gene and one copy of the working gene. Because having even one working copy of the gene is enough to prevent the disease, a carrier does not usually have any symptoms.

How are these diseases inherited?

All of the above diseases are autosomal recessive conditions. This means that a couple is at risk of having a child with one of these conditions only if both parents are carriers of the same disease-causing genetic alteration.



The diagram on the left shows that if both parents are carriers for the same disease (Rr), each child has a 1 in 4 (25%) chance to have the disease (rr) and a 3 in 4 (75%) chance of not having it. The chances are the same for each pregnancy, regardless of how many children the couple has.

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Summary of AJ Screening Panel

Below is a summary of the specific tests done at present as part of the AJ carrier screening program in Ontario. You may have been screened for any number of the conditions listed. Please refer to your personal screening report for details about the specific testing you had and your results.

Bloom Syndrome	2281del6ins7, 2281del6, 2407dupT
Canavan Disease	433-2A>G, Y231X, E285A, A305E, Y288C
Familial Dysautonomia	R696P, R696Q, IVS20+6T>C
Fanconi Anemia group C	322delG, IVS4+A>T
Niemann-Pick Disease(Type A&B)	DeltaR608, R496L, Phe333fs (fs330), L302P
Mucolipidosis IV:	IVS3-2A>G, Delta6.4kb
Tay-Sachs Disease (DNA)	R178H, R178L, G250D, G269S, 1278dupTATC, IVS12+1G>C, G250S**, delta7.6kb**, IVS9+1G>A** Pseudodeficiency alleles: R247W*, R249W*
Tay-Sachs Disease (Enzyme)	HexA activity

*Benign polymorphism
**Reported in non-Ashkenazi Jewish individuals

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IF YOU WERE IDENTIFIED AS A CARRIER

What is the next step? If you are pregnant or planning to get pregnant and currently have a partner who has not yet been tested, the next step would be to test your partner as soon as possible to see if s/he is also a carrier for the same disease.

What about others in my family? This result implies that your relatives (siblings/parents etc) may be carriers and we recommend that you inform them of this possibility so they may make decisions about being tested.

Is PRENATAL testing available? Yes. If both parents are found to be carriers for the same disease, prenatal diagnosis can be performed to determine whether or not the fetus is affected.

Genetic Counselling: Please refer to the Canadian Association of Genetic Counsellors website: (http://www.cagc-accg.ca) for a list of genetic centers in your area.

IF YOU ARE NOT A CARRIER

What about my partner? If your partner is also NOT a carrier for the same diseases, based on this analysis, your children would likely not be carriers and your chance of having a child with that particular disease would be extremely low.

If your partner were a carrier for one of these diseases your children would likely not be affected, but may still be carriers and should be tested when they reach adulthood.

If your partner has not been tested, s/he may request testing if s/he is also of Jewish descent.

For Further Questions: This information sheet contains some information about carrier screening for individuals of Ashkenazi Jewish descent.

Please speak with your referring healthcare provider if you have questions or concerns about your test results.