

Celiac Disease Genetics

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Celiac.com 08/17/2008 - Are you confused about genetic testing for celiac disease? Do you want to know what tests you should request and which laboratory to use? Have you already had celiac DQ genetic testing but are not sure what the results mean or what your risk is of developing celiac disease or gluten sensitivity? These are the questions I will answer in the next few pages.

What is [HLA DQ](#) celiac genetic testing?

To understand celiac DQ genetics and the risk estimates you must also understand how the DQ types are determined and some basic terminology. Each of us has 46 chromosomes, 23 pairs received from our parents. We all have two copies of chromosome 6, one from each parent. [homozygous](#) is when a person has two copies of the same gene, one from each parent. Our white blood cells ([leukocytes](#)) have proteins called human [leukocyte antigens](#) or HLA proteins that are inherited from our parents. The genetic code that determines our HLA patterns resides on chromosome 6. We all have two DQ patterns, one from each of parents, such that we are all DQx/DQx, where x is a number between 1 and 9. I am DQ2/DQ7 and my wife is DQ2/DQ5. We are both therefore heterozygous for DQ2. That is, we have only one copy of DQ2. Scott Adams, the founder of celiac.com is DQ8/DQ8. He is homozygous for DQ8. There are several HLA patterns. Some are proteins that reside within cells and others are on the outer surface of cells, and are called class II. The class II HLA proteins have very important immune functions. There are several class II HLA protein types but DQ have been found to be important in celiac disease, specifically DQ2 and DQ8.

What does it mean to be homozygous or heterozygous for celiac genes?

Homozygous means that you have two copies e.g. DQ2/DQ2, DQ8/DQ8 whereas heterozygous means you have one copy of DQ2 or DQ8. Some people have one copy of DQ2 and one of DQ8 (DQ2/DQ8) and they have a greater risk for celiac disease than someone with only one copy of either DQ2 or DQ8 but not as great a risk as someone with two copies of DQ2 (DQ2/DQ2). Since DQ2 is associated with a greater risk of celiac disease than DQ8, then one copy of DQ2 plus a DQ8 (DQ2/DQ8) indicates a higher risk than having two copies of DQ8 (DQ8/DQ8). Hopefully, I have not lost you yet but if I have please continue to read on because the information that follows will still be helpful to you.

What is this alpha and beta subunit typing and why is it important?

HLA DQ typing consists of two subunits of the DQ [molecule](#), an alpha and beta subunit. So, both DQ types that indicate a risk of celiac disease, DQ2 and DQ8, are made up of two protein subunits designated alpha and beta. They determine the complex letter and number combinations reported. For example, the full DQ2 molecule is typically HLA DQA1*05xx DQB1*02xx. The A1 is the alpha unit and the B1 is the beta subunit.

The beta subunit is the most important component of the DQ molecule, but the alpha subunit has also been shown to carry an increased risk for celiac disease. Unfortunately, since testing for both is more complicated and expensive it is not always done.

Also, some think that since the beta subunit carries most of the risk and the alpha unit only minor risk, testing for only the beta subunit is adequate. Several clinical laboratories have chosen this approach. They only test for, and report on, DQ2 and DQ8 based on beta subunit types, so their results typically look like this: HLA DQB1*02 detected, DQ2 positive, etc. This is the policy of the laboratory at Bonfils, who also does testing for Quest Diagnostics and Enterolab as well as many hospitals. However, the alpha subunit of DQ2 also carries some risk for celiac disease.

What if you are positive for the beta subunit of DQ2 or DQ8 by testing from Bonfils, Enterolab or Quest?

If the beta subunit is present then Bonfils, Enterolab and Quest tests will report DQ2 and/or DQ8 positive. Sometimes the report will just report DQ2 negative and DQ8 negative, especially when a hospital is reporting the results obtained from Bonfils. However, when the beta subunit is not present and they report DQ2 negative and/or DQ8 negative, it is still possible that an alpha subunit could be present. Results reported in this manner are, in my opinion, potentially misleading. I believe they can lead a doctor to assume that an individual is not at increased risk for, or cannot have celiac disease, when this may or may not be true. Unfortunately, the patient in such circumstances may be told that they can not have celiac disease, yet they may not only be at risk for the disease, they may well have it while being told it is impossible or extremely improbable.

What does Prometheus do and how do they report their results?

Prometheus, like Kimball and LabCorp, includes alpha and beta subunit typing. In the past they did not indicate whether there was one or two copies of DQ2 or DQ8 if someone was positive. If a patient was DQ2 and DQ8 positive then these labs reported their full genetic DQ type. However, if one or the other was negative, their exact genotype was not reported. Recently, not only has Prometheus started reporting the full DQ2 and DQ8 genotype, but they are now reporting whether someone is homozygous or heterozygous as well. They are also reporting the relative risk for celiac disease based on the pattern shown by testing. However, they are still not reporting the other DQ types.

What is the advantage of the new Prometheus reporting?

Since Prometheus results now include a calculation of the individual's risk of celiac disease, compared with the general population, the patient can see how high their risk of celiac disease is, as well as being able to estimate the risk for their parents and their children.

As you can see, the risk of celiac disease has a wide range of possibilities, which depend on the individual's DQ results. This risk can be below 0.1% if you do not have any portion of the high-risk genes DQ2 and DQ8. On the other hand, the risk may be very high (more than 31 times the risk of the general population) if you have two copies of the full complement of DQ2 molecule. Again, I would like to point out that if you have DQ2/DQ2, DQ2/DQ8, or DQ8/DQ8, then both of your parents and all of your children have to have at least one copy of an at-risk celiac gene. Your child's complete type will depend on the DQ contribution from their other parent.

What other laboratories do both alpha and beta subunit testing?

Kimball Genetics and LabCorp also report both alpha and beta subunit results but the advantage of their testing is that they report the other specific DQ types detected. Gluten sensitivity is found in all DQ types except DQ4. Other DQ types, particularly DQ1, DQ5, are associated with a risk of gluten related neurological and skin problems. Microscopic [colitis](#), food allergies and oral allergy syndrome reactions are also found in association with other DQ types. Though Enterolab does report other DQ types, including these markers of risk for gluten sensitivity, they do not test for, or report, alpha subunits since their DQ testing is done by Bonfils. Based on the limited data I have accumulated so far, DQ2 and DQ8 also seem to carry a risk of mastocytic enterocolitis.

What if you do not have DQ2 or DQ8?

According to data accumulated, but as of February 2008, not yet published by Dr. Ken Fine, unless you are DQ4/DQ4 you are still at risk for being sensitive to or intolerant of gluten. According to Fine's [fecal gliadin antibody](#) data all DQ types except for DQ4 carry a risk of gluten sensitivity. My clinical experience supports this claim. The presence of one copy of DQ1, DQ3, DQ5, DQ6, DQ7, or DQ9, even with one DQ4, is associated with a risk for elevated [stool](#) gliadin antibody and symptoms of gluten sensitivity that responds to a gluten free diet.

What if your genetic testing was done by Enterolab, Quest, Bonfils or a hospital that utilized Bonfils, and it indicated that you were DQ2 and DQ8 negative?

Since Bonfils does not test for the alpha subunit and they perform the testing for Enterolab and Quest, you may not be completely negative for DQ2 or DQ8. You do not have the beta subunits associated with the highest risk for celiac disease. For example, you could be “half-DQ2” positive and still be genetically at risk for the [autoimmune](#) form of gluten sensitivity that we know as celiac disease, along with all of its risks.

What if you have not yet had celiac DQ genetic testing?

I recommend that everyone have the testing. I realize that most insurance companies and doctors, including some celiac experts, would disagree with me. However, the value of DQ testing is that it can provide a great deal of information about your risk, especially if you have testing done for both alpha and beta subunits. I recommend that you have testing done by Kimball Genetics, LabCorp or Prometheus if you have not yet had genetic testing done. If your insurance or budget does not allow for this more expensive testing, but does cover testing by Quest or Bonfils or you can afford the \$159 that Enterolab charges, then I still recommend that you get DQ testing using one of these laboratories. You just need to be aware of the limitations of the results as I have reviewed them here.

What are the advantages of DQ testing through Kimball Genetics?

Kimball can perform testing on either blood or mouth swab samples. The tests can be ordered without a doctor’s order. You can purchase testing on mouth swab sample for \$345. The advantages of Kimball’s tests include alpha and beta subunit testing and full DQ typing to determine if you carry the other gluten sensitive DQ patterns besides DQ2 and DQ8.

What about LabCorp?

LabCorp also provides both alpha and beta subunit testing and they report the other DQ types. They only provide testing on blood samples, a doctor must order the testing, and preauthorization is required.

Do health insurance companies cover celiac DQ genetic testing?

Many but not all health insurance companies cover HLA DQ testing and almost all require preauthorization. The ICD9 diagnostic codes that typically are honored are V18.5 genetic predisposition for [gastrointestinal](#) disease; V84.8, genetic predisposition for other diseases; and 579.0, celiac disease.

Why are the genetics so difficult to understand and why are so many doctors either unaware of the testing or reluctant to order the tests?

I write and speak about DQ genetic testing frequently, and try to get testing for as many of my patients as possible. However, many insurance companies will not cover the cost of these tests. Most primary care doctors and even some GI doctors are completely unaware of the existence of a genetic test for celiac disease. The testing is difficult to understand and the reporting by some labs is very confusing and even misleading.

I realize that understanding the DQ genetics is difficult for the average layperson. Most scientists and doctors don’t understand this information, so don’t despair if you are having difficulty following this or understanding your results, and don’t be surprised if your doctor does not understand them either. However, you do not need to completely understand the complexities of HLA typing to locate your DQ types and determine your risk of celiac disease, non-celiac gluten sensitivity, etc.

Then what do you need to know or remember about celiac DQ genetics?

Hopefully, you now understand enough to know that you should consider having celiac DQ testing, if possible, especially if you have symptoms, laboratory tests, or an [intestinal biopsy](#) that is suggestive of

celiac disease. You should also know that the testing can be done on blood or mouth swabs, and many insurance companies will cover the testing but most require pre-authorization. You should also be aware that the testing is available without a doctor's order, if you are willing to pay for it, and that some tests are better than others. I also hope you understand that the tests can help you determine your risk for celiac disease or if you are at risk for non-celiac gluten sensitivity. You should also know that your results, especially when combined with those of one or more family members, may help you determine, to some degree, the risks for your parents and your children. You should also know what laboratories offer testing, what test codes your doctor should use to order the tests, and that the absence of DQ2 or DQ8 does not exclude risk of gluten sensitivity or intolerance. Depending on what laboratory conducts your DQ testing, your results also may fail to exclude your risk of celiac disease.

What if I am still confused or I don't know how to interpret my genetic results or my previous evaluation for celiac disease?

If you are still confused by your test results or want more a personalized review of your results, symptoms or diagnostic tests I recommend that you see a physician who is an expert in celiac disease and understands these tests. I also offer on-line consultation for a reasonable fee through a secure consultation site, www.medem.com. You simply register (registration is free) for secure on-line communication and request a consultation. The consultation fee is \$50, and some insurance companies will cover on-line communication. I also see many patients from outside of Colorado Springs for consultation if you are willing to travel here.