CARRIER DETECTION IN X-LINKED HYPOHIDROTIC ECTODERMAL DYSPLASIA AN UPDATE ON MOLECULAR TESTING

Many females in families with X-linked Hypohidrotic Ectodermal Dysplasia (XLHED, sometimes known as CST) are interested in knowing if they are carriers for the genetic disorder. The carrier status of a female is of importance in determining the risk for that female of having a child with the disorder. How can a woman's carrier status be determined?

Evaluation of the family - The first step is an evaluation of the affected family member(s) to confirm the type of Ectodermal Dysplasia in the family. Many other types of Ectodermal Dysplasia exist. This evaluation should also include a detailed family history. If a family has not had such an evaluation in the past, they should contact or ask their doctor to refer them to a Geneticist.

Evaluation of the at-risk female - Once the diagnosis of probable X-linked Hypohidrotic Ectodermal Dysplasia is confirmed, at-risk females should be examined for any clear manifestations of the disorder. Some carrier females have significant features and can be diagnosed as "manifesting" carriers on the basis of a physical examination. However, one must not over-interpret minor physical findings. Some females may be judged "obligate" carriers based on an analysis of their family tree (for example a mother with an affected son and brother). A normal physical examination of an at-risk female does not rule out that she is a carrier.

Laboratory analysis - Assuming that a female is neither a clear "manifesting" carrier, nor an obligate carrier, she would be considered a possible carrier and one can consider molecular testing. At this point, the Geneticist can assist the family in choosing and arranging for the most appropriate test, and interpreting the test results once they are completed. The issues around such testing are complex and it may not result in a simple yes/no answer; a lot depends on whether a definite gene mutation has been identified in an affected male relative.

Choice of tests - There are two basic methods of molecular testing to choose from. Both indirect and direct testing involves sending a blood or DNA sample to the relevant laboratory. The direct test has largely replaced the indirect test. The latter can be used when a mutation is not found on direct testing. Both types of testing can also be used for prenatal diagnosis.

Direct molecular testing (mutation analysis) - This type of test directly examines the gene and tries to detect the change (mutation) responsible for the disorder. The testing is done using a blood sample from an affected individual. This type of testing is usually the only one that can clarify the status of mothers of single affected males and distinguish between sex-linked (X-linked) and autosomal forms where females are fully affected. The mutation in the gene may or may not be found, or a change in the gene could be found whose significance is unknown. If a change in the gene is found in an affected individual, other at-risk family members can then be tested for the same change.

Indirect molecular testing (linkage analysis) - This type of testing requires the sampling and testing of multiple family members. It is most applicable to families with more than one affected individual, but can at times be used in some families with only a single affected male to clarify the carrier status of sisters, aunts or cousins. It usually cannot be used to clarify the carrier status of a mother with a single affected son with certainty, but can help make this more or less likely. The test utilizes genetic markers on the X-chromosome and follows their inheritance in the family. The test does not identify the change (mutation) in the gene, and is thus indirect. Test results are usually expressed as a probability, and post-test genetic counseling is important. In rare instances the test may be uninformative (no answer).

Test interpretation and counseling - It is extremely important that the results of testing be communicated to the family by someone knowledgeable about the Ectodermal Dysplasias and molecular genetic testing. This would be available through the Geneticist. Families do not directly communicate with clinical laboratories as to their test results.

The role of research - Research on Hypohidrotic Ectodermal Dysplasia has been carried out for many years by Geneticists from around the world. Their collective research efforts have culminated in the isolation of the gene responsible for the X-linked disorder, and have identified two genes involved with the autosomal recessive types as well. This research has led to the development of both the indirect and direct molecular tests for XLHED.

Past research participants - In the course of earlier research studies, potentially useful information may have been obtained on participating families. However, these results would require the use of sweat tests: there are two very different types of sweat testing that you may come across. The more common type collects sweat to check its sodium and chloride content – this looks to see if a patient may have Cystic Fibrosis, and is not relevant in ED (although some males affected by ED have recurrent chest infections and CF is considered – but it can be hazardous to try and 'persuade' boys with ED to sweat through heating them up !!) . The other type looks at the pattern of sweating in possible female carriers of XHED – and can still be helpful in deciding if the ED in a family is sex-linked or not, especially where molecular genetic tests have not given clear results.

Reproduced and updated with the kind permission of the National Foundation for Ectodermal Dysplasias

Supporting a normal lifestyle