The John and Marcia Carver Nonprofit Genetic Testing Laboratory

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Clinical genetic testing for Achromatopsia: *Information for Patients and Families*

Introduction: If you (or someone you love) have received a diagnosis of Achromatopsia, you need to know you have options. You need to know that despite the label of "rare inherited eye disease," one in which it is estimated that there are fewer than 1 in 30,000 people affected, there are reasons to be optimistic.

Achromatopsia (ACHM) is an inherited eye condition present from birth. It is most often characterized by poor visual acuity, nystagmus, significant to extreme sensitivity to light and absent or severely reduced color vision (color blindness). Color blindness can be so complete that many affected individuals have no comprehension of the concept of color, while others with less severe symptoms may be able to discern very saturated colors under certain lighting.

A confirmed diagnosis is needed for proper management of the condition. While there are observable features and several tests that can contribute to the diagnosis of ACHM, a molecular genetic test that successfully isolates the specific genetic cause of the condition is the most definitive.

What exactly is a molecular genetic test?: A molecular genetic test is a laboratory procedure in which a person's DNA is extracted (in this case from a blood sample) and analyzed. Tests have been designed to specifically search for the disease-causing variations currently known to be associated with autosomal recessive achromatopsia (meaning each parent contributed one non-functional copy of the gene to their affected child). While not all disease-causing variations have yet been identified, statistically speaking the chances are good that such a variation will be found in one of the three main genes known to date. To date, we know that genetic variations:

- in the *CNGB3* gene account for approximately 50% of all ACMH patients
- in the *CNGA3* gene account for about 20% of ACHM cases
- in the *GNAT2* gene are responsible for approximately 2% of ACHM cases

Why should I (or my child) consider a genetic test?: Determining whether or not a genetic test is a good idea for you or your family is a very personal decision and should only be made after a thoughtful, careful consultation with a referring physician and/or a genetic counselor. You'll want to consider the following:
a genetically confirmed diagnosis, when possible

- will help alleviate a misdiagnosis and the uncertainty of the "unknown"
- may help to indicate treatment strategies (in consultation with an ophthalmologist)
- may help with family planning decisions (genetic counseling is advised)
- research is ongoing; only with a confirmation of a specific disease-causing variation will a patient know if he is ever eligible for future clinical trials

How does one arrange for a genetic test at the Carver Lab?: *Once* the decision has been made to proceed with genetic testing, arranging for a clinical genetic test is as simple as arranging for a blood test. Your physician will need to order the test on your behalf. This will need to be accomplished via our online test ordering and tracking system. Visit www.carverlab.org and follow the link to "Request a Genetic Test". There your physician will be able to download instructions for sending a blood sample to the Carver Lab. Whenever possible, we request blood samples from both parents in addition to the affected patient's sample.

What should I (we) expect?: The estimated turnaround time is between 8-14 weeks, depending on the testing being performed. Testing may include some or all of the following:

Tier 1 - The "first tier" clinical genetic test will include automated DNA sequencing (reading) of portions of the *CNGB3* and *CNGA3* genes known to harbor disease-causing variations. We estimate a 50% chance of finding a disease-causing variation at a cost of less than $200.

Phase testing is a very important component of genetic testing for autosomal recessive diseases. When one or more plausible disease-causing variation(s) are identified in an affected individual, the parents' DNA will be screened for the specific variation(s) in question. Screening of the parent's DNA for autosomal recessive disorders is considered part of the proband's test and there is no additional charge.

Clinical Test Price and Turn-around Time:

Tier 1 - CNGB3, CNGA3, and OPN1LW (LCR) gene analysis
Cost: $181 (nonprofit), parental samples included
CPT codes: 83890, 83898, 83904; Turn-around time: 8-10 weeks;
Carrier testing for additional family members (other than parents) $75

Will insurance cover the cost of testing for ACHM?: The Carver Lab is dedicated to providing affordable, nonprofit testing. Payment by check or credit card is expected at the time a test is ordered. Genetic testing is a relatively new form of medical testing. While it is encouraging that insurance companies are starting to pay for genetic testing at an increased rate, it is not covered by all companies. Therefore, it is the patient's responsibility to contact his/her insurance company prior to testing to confirm, something the physician and/or genetic counselor may be able to assist with. It will be helpful if you provide the CPT (Current Procedural Terminology) codes listed above as they will help define the method of testing. You will receive a detailed invoice from the Carver Lab that will include all of the information needed for you to submit for reimbursement from your insurance company.

Completed Test Results: Upon completion of clinical genetic testing for ACHM, a final report of the results will be forwarded to the referring physician. It is recommended you arrange for a consultation with your physician and/or a genetic counselor to discuss test results. There are a variety of reasons for why we recommend the involvement of a physician for genetic testing, including 1) the accuracy of the genetic test is dependent to a significant degree on the accuracy of the clinical diagnosis; 2) the sensitivity of the genetic test is greatly increased by an accurate clinical diagnosis; 3) genetic test results can be complicated and need to be carefully explained to patients and family members; 4) patients with inherited disorders of the eye can develop additional or related eye problems that are treatable in some cases.

It is important to understand that a "negative" test result does not necessarily mean that the diagnosis of ACHM is incorrect. Individuals who have a negative result after tier one and/or tier two testing can be enrolled in ongoing research projects. One component of the research will focus on broadening clinical testing for ACHM by incorporating more parts of the *CNGA3* and *CNGB3* genes, as well as the *GNAT2* gene. DNA samples will also be included in research projects to identify novel gene(s) and/or variations associated with ACHM. For more information contact CarverLab@uiowa.edu.

For reporting purposes, we use a system that combines known functional and association information about genetic variations to estimate their pathogenic probability (EPP). EPP divides variations into four categories with increasing pathogenic potential: 0) very unlikely to be disease-causing 1) unlikely to be disease-causing 2) possible disease-causing 3) probable disease-causing. Details about the calculation of these values can be obtained at www.carverlab.org or Stone, Trans. Am. Ophth. Soc., 101:437-484, 2003.

References:

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2. Eksandh, L., S. Kohl, and B. Wissinger, *Clinical features of achromatopsia in Swedish patients with defined genotypes.* Ophthalmic Genet, 2002. 23(2): p. 109-20.
3. Wissinger, B., et al., *CNGA3 mutations in hereditary cone photoreceptor disorders*. Am J Hum Genet, 2001. 69(4): p. 722-37.
4. Nishiguchi, K.M., et al., *Cone cGMP-gated channel mutations and clinical findings in patients with achromatopsia, macular degeneration, and other hereditary cone diseases*. Hum Mutat, 2005. 25(3): p. 248-58.