The John and Marcia Carver Nonprofit Genetic Testing Laboratory

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Clinical Genetic Testing for Achromatopsia

Disease Characteristics of ACHM: Characteristics typically associated with Achromatopsia (ACHM) include: poor visual acuity, nystagmus, significant to severe light sensitivity, and complete or severely reduced color vision. ACHM is present from birth. Considered a rare inherited eye disease, it is estimated that there are fewer than 1 in 30,000 people living with ACHM. It is inherited in an autosomal recessive pattern.

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.

Molecular Genetics of ACHM: While not all disease-causing mutations have yet been identified, statistically speaking, to date we know that genetic variations:

- in the *CNGB3* gene account for approximately 50% of all ACHM patients
  - The specific genetic variation, Thr383 del1aC, is the single most common cause of ACHM (34%)
  - An additional 36 different genetic variations have also been identified in 10 of the 18 *CNGB3* exons
- in the *CNGA3* gene account for about 20% of ACHM cases
  - Sixty different genetic variations have been identified in the *CNGA3* gene
  - Seventy-eight percent of them occur in exon 8
- in the *GNAT2* gene are responsible for approximately 2% of ACHM cases

Some patients who are suspected to have ACHM are later found to have an "incomplete" form of the disease known as blue-cone monochromacy (BCM). The genes known to be responsible for BCM are *OPN1LW* and *OPN1MW*.

- Deletions in the 5' flanking region of *OPN1LW*, cause an estimated 31% of BCM
- There are three reported point mutations associated with BCM
  - Cys203Arg causes an estimated 42% of BCM. (This variation is most prevalent in *OPN1MW*, but has also been detected in *OPN1LW*.)
  - Together Arg247TER in *OPN1LW* and Pro307Leu in *OPN1MW* account for <3% of BCM

Clinical Genetic Testing: *Clinical Test Price and Turn-around Time*
Tier 1 - CNGB3, CNGA3, and OPN1LW (LCR) mutation analysis

Tier 1 testing includes automated DNA sequencing of exon 10 of *CNGB3*, which harbors the genetic variation Thr383 del1aC, and exon 8 of *CNGA3*. This assay will identify at least one disease-causing variation in 50% of ACHM patients. Tier one will also include sequence based identification of a second disease-causing allele. When one plausible disease-causing variation is identified, the patients' DNA will be sequenced through the remainder of that gene in an effort to identify the second disease-causing allele.

When one or more plausible disease-causing variations are identified in the proband, 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.

Sample specifications: *Lavender (EDTA) top tube 3 mls per tube (1 per Child)*
6 mls per tube (Adult) (2 tubes for adults)
Cost: *$181 (nonprofit)*
CPT codes: *83890, 83898, 83904*
Turn-around Time: *12-14 weeks*
Carrier testing for additional family members (other than parents): $75

Completed Test Results

Upon completion of clinical genetic testing for ACHM, a final results report will be forwarded to the referring physician as a matter of protocol.

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.

Exclusionary Findings

In infants with no visual responses and an ophthalmoscopically normal or near-normal retina, the diagnosis of Leber congenital amaurosis is more likely than ACHM and molecular testing for that disease should be pursued first.

In patients with clearly progressive photoreceptor dysfunction and/or ophthalmoscopic evidence of photoreceptor cell death (e.g., bone-spicule-like pigmentation) a diagnosis of cone dystrophy, cone-rod dystrophy or retinitis pigmentosa would be more likely than ACHM and should be pursued first.

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:

1. Kohl, S., et al., *CNGB3 mutations account for 50% of all cases with autosomal recessive achromatopsia*. Eur J Hum Genet, 2005. 13(3): p. 302-8.
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.