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 CNAG3 gene account for about 20% of ACHM cases
  - Sixty different genetic variations have been identified in the CNAG3 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, CNAG3, 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 CNAG3. 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 CNGB3 and CNGA3 genes, as well as the GNA T2 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: