About GeneDx

GeneDx was founded in 2000 by two scientists from the National Institutes of Health (NIH) to address the needs of patients diagnosed with rare disorders and the clinicians treating these conditions. Today, GeneDx has grown into a global industry leader in genomics, having provided testing to patients and their families in over 55 countries. Led by its world-renowned clinical genomics program, and an unparalleled comprehensive genetic testing menu, GeneDx has a continued expertise in rare and ultra-rare disorders. Additionally, GeneDx also offers a number of other genetic testing services, including: diagnostic testing for hereditary cancers, cardiac, mitochondrial, and neurological disorders, prenatal diagnostics, and targeted variant testing. At GeneDx, our technical services are backed by our unmatched scientific expertise and our superior customer support. Our growing staff includes more than 35 geneticists and 140 genetic counselors specializing in clinical genetics, molecular genetics, metabolic genetics, and cytogenetics who are just a phone call or email away to assist you with your questions and testing needs. We invite you to visit our website: www.genedx.com to learn more about us.
Retinal Dystrophy

The retinal dystrophies are a clinically and genetically heterogeneous group of eye disorders affecting approximately 1 in 3000 to 1 in 4000 people worldwide. Retinal dystrophies are characterized by degeneration of different cell types within the retina, a thin piece of tissue lining the back of the eye that converts light into electrical signals which are then interpreted by the brain. Retinal cell types involved in retinal dystrophies include the rods (photoreceptors which are distributed throughout the retina and are primarily responsible for vision at low light levels) and cones (photoreceptors which are most concentrated within the fovea, the central area of the retina, and are primarily responsible for color vision, central vision, and visual acuity).

In general, retinal dystrophies are classified according to the types of cells within the retina that are primarily affected, the age of onset of first symptoms, the progression of visual impairment over time, and the presence or absence of other medical features. Specific subtypes of retinal dystrophy include rod-cone dystrophies such as retinitis pigmentosa, cone-rod or cone dystrophies such as achromatopsia, and macular dystrophies such as Stargardt disease.

Clinical Presentation/Course

The timing, progression, and range of symptoms of retinal dystrophy can differ from person to person, depending upon which types of retinal cells are predominantly or initially affected. Symptoms of a retinal dystrophy may include the following:

- Impaired dark adaptation (“night blindness”)
- Difficulties with peripheral vision (“tunnel vision”)
- Difficulties with central vision
- Impaired color vision
- Light sensitivity (photophobia)
- Light flashes or areas of small, blinking lights in the vision (photopsia)

Some types of retinal dystrophy, known as non-syndromic retinal dystrophy, only cause problems with vision. Other types of retinal dystrophy, known as syndromic retinal dystrophy, involve the
Diagnosis

The diagnosis of a retinal dystrophy is made based on a number of factors, including a combination of personal health history, family health history, clinical examination, genetic testing, and ancillary testing, which may include the following:

Electroretinogram (ERG)—measures the electrical activity of light-sensitive cells in the retina (rods, cones, and connecting ganglion cells) in response to a light stimulus

Optical Coherence Tomography (OCT)—cross-sectional imaging study which looks at the structure and tissue of the retina, including the photoreceptors, retinal pigment epithelium, and inner retinal layers

Visual field study—subjective study which helps detect any blind spots in the central or peripheral vision

Retinal photography—photographs which capture an image of the retina to help examine the health of the retina and abnormal vascular or pigmentary changes of this tissue

Physical Examination

In some cases, an individual with retinal dystrophy may have other medical problems, neurological problems, or atypical features that can be identified by physical examination. For example, some genetic syndromes involving retinal dystrophy also cause developmental delay, birth defects, dysmorphic facial features, or other features that can be noted in a physical examination.

Genetic Testing

According to the American Academy of Ophthalmology, genetic testing is an "important component of the assessment of patients with [retinal dystrophies], as genetic testing may be valuable to confirm the diagnosis, provide accurate information to the patient and family members, and potentially to confirm eligibility to participate in clinical trials". Up to 60-80% of individuals with a retinal dystrophy have an identifiable genetic cause. The information obtained from clinical and family histories, physical examination, and ancillary testing can help a clinician determine what type of genetic testing may be appropriate to offer an individual with a known or suspected retinal dystrophy. Genetic testing can improve the timeliness of establishing a diagnosis, can help provide higher accuracy in establishing the clinical course and prognosis for an individual, and can provide a more accurate estimate of disease occurrence or recurrence in families at risk. In some instances, molecular confirmation of a clinical diagnosis of retinal dystrophy may have implications for treatment and management of the specific form of disease.

Genetic Heterogeneity

Hundreds of genes have been identified that can cause retinal dystrophy. The inheritance pattern of retinal dystrophy can be autosomal dominant, autosomal recessive, X-linked, or mitochondrial. Variants in a single gene may be associated with different types of retinal dystrophy (clinical heterogeneity), and conversely, variants in different genes can cause the same retinal dystrophy phenotype (genetic heterogeneity). Incomplete penetrance (a phenomenon in which not all individuals carrying a disease-associated genetic variant express the associated condition) and/or variable expressivity (a phenomenon in which features are expressed to a different degree among individuals with the same disease-associated genetic variant) have been reported in many types of retinal dystrophy. In some cases, individuals with retinal dystrophy may harbor a de novo variant not inherited from either parent. Due to the heterogeneous nature of retinal dystrophies, it can often be challenging to determine the specific form of retinal dystrophy or predict the disease-causing gene based on clinical and family histories, physical examination, or ancillary testing alone. Moreover, new genes associated with retinal dystrophy are being discovered regularly.

Recent studies have demonstrated that exome sequencing may provide a diagnostic yield comparable to that of previously available gene panels. A trio approach, where the affected proband and both parents are included when performing genetic testing for retinal dystrophy to clarify the inheritance of variants, may help with interpretation of the clinical significance of variants.
Clinical Indications

1. Diagnostic testing in an individual with a retinal dystrophy
   a. Confirm a clinical diagnosis of a specific genetic syndrome or type of retinal dystrophy
   b. Distinguish between syndromic and non-syndromic forms of retinal dystrophy
   c. Provide information about prognosis
2. Assistance with selection of optimal treatment options or determination of eligibility for clinical trial enrollment
3. Predictive testing for asymptomatic family members of a proband with a known pathogenic variant associated with a retinal dystrophy
   a. Enable clinical monitoring, follow-up, and optimal treatment when symptoms develop in an individual with a positive result
   b. Reduce anxiety and forego clinical monitoring if result is negative
4. Prenatal diagnosis in at-risk pregnancies for known, pathogenic variants
5. Genetic counseling, recurrence risk determination, and family planning
Retinal Dystrophy Xpanded panel

Test Overview

Frequently updated gene list which includes recently identified and emerging genetic causes of retinal dystrophy

Includes analysis for the recurrent c.2991+1655A>G variant in the CEP290 gene associated with Leber’s Congenital Amaurosis and for the deep intronic variants of ABCA4 previously reported in the literature in association with Stargardt disease (see below).

<table>
<thead>
<tr>
<th>ABCA4 intronic variants evaluated by Retinal Dystrophy Xpanded Panel</th>
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<tbody>
<tr>
<td>5196+1216C&gt;A</td>
</tr>
<tr>
<td>5196+1056A&gt;G</td>
</tr>
<tr>
<td>3050+370C&gt;T</td>
</tr>
<tr>
<td>4539+2001G&gt;A</td>
</tr>
<tr>
<td>2160+584A&gt;G</td>
</tr>
</tbody>
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The ORF15 region of the RPGR gene associated with X-linked retinitis pigmentosa is included. However, this region has inherent sequence properties that yield suboptimal data and pathogenic variants in this region may not be reliably detected.

- Utilizes a trio approach to genetic testing. Proband and parents are sequenced and analyzed concurrently
- Facilitates identification and interpretation of pathogenic variants based on inheritance, especially de novo variants
- Single report including inheritance information allowing for more accurate variant interpretation. Turn around time of approximately 6 weeks.

Test Sensitivity

The sensitivity of this test is expected to be comparable to trio-based whole exome sequencing since it uses a trio approach to test a comprehensive list of genes known to be associated with retinal dystrophy.

Previous exome sequencing studies evaluating individuals with retinal dystrophy have demonstrated a diagnostic rate of 49-71%.

Additional Testing Options

Additional testing options are available, including targeted variant testing for a previously identified pathogenic or likely pathogenic variant. Appropriate test selection depends on the specific clinical history of a patient, including family and personal health histories as well as familial test results.
Sample Submission

Genetic testing can be performed on blood, oral rinse, buccal swabs or extracted DNA samples. GeneDx test kits are available to ordering providers, and include sample collection items (such as mouthwash, collection tubes), the necessary sample submission paperwork, and a self-addressed return shipping label.

Additionally, all test requisition forms are available for download from the GeneDx website: www.genedx.com/forms.

Please note that all testing must be performed under the guidance of a healthcare provider. For more information on the sample submission process, please visit our website: www.genedx.com/supplies or email us at: zebras@genedx.com

Genetic Testing Process

Patient Identification

Discussion of personal and family history

Explanation of genetic testing options

Sample Submission

At the laboratory, genetic testing for most genes includes next-generation sequencing and/or exon array analysis

Genetic Testing

Contains information on the results of the genetic test and available medical management options

Genetic Test Results

The final report is sent to the ordering healthcare provider

Post-Test Discussion

Healthcare provider discusses the test results, medical management options, and implications for family members with the patient
Genetic Test Results

Nearly all test results fall into one of four categories:

1. Positive (pathogenic variant(s) identified)
2. Likely pathogenic variant(s) identified
3. Variant(s) of uncertain significance (VUS) identified
4. Negative (no variants of clinical significance identified)

GeneDx test reports contain detailed information about a specific genetic result and, if available, medical management options. Genetic counseling is recommended prior to genetic testing to understand the benefits and limitations of testing and after genetic testing to discuss the implications of the genetic test results. Genetic counseling services across the country can be found at www.nsgc.org

Positive Result

A positive result indicates a pathogenic (disease-causing) genetic variant (change) was identified in a specific disease gene. This finding confirms an underlying genetic cause for the patient’s symptoms and provides a diagnosis of a specific genetic disorder or indicates an increased risk for developing a genetic disorder. Knowledge of the specific pathogenic variant(s) provides valuable information to the patients, their healthcare providers and family members because it helps to determine the recurrence risk and to develop an appropriate medical management plan. A medical management plan may include lifestyle modifications, ongoing screening, preventative medications and measures, and/or surgical/medical device interventions. Furthermore, a positive genetic test result allows targeted testing of at-risk relatives to determine if any of them carry the pathogenic variant(s) as well as to address the recurrence risk of the disorder in future offspring.
Likely Pathogenic Result
A likely pathogenic result indicates the presence of genetic variant(s) in a specific disease gene for which there is significant, but not conclusive, evidence that the variant(s) are disease-causing. This finding strongly suggests an underlying genetic cause of the patient’s disorder or indicates an increased risk for developing a genetic disorder. With this type of result, medical management options and testing of family members are often similar as described above for a positive result.

Variant of Uncertain Significance (VUS)
A variant of uncertain significance (VUS) result indicates an inconclusive outcome of a genetic test. A VUS is a change in a gene for which the association with disease cannot be clearly established. The available information for the variant is either insufficient or conflicting, and it cannot be determined at this time whether the variant is associated with a specific genetic disorder or if the variant is a unrelated (benign) variant unrelated to the patient’s disorder.

In the case of a VUS test result, all medical management recommendations should be based on clinical symptoms, and past personal and family history. Predictive genetic testing of family members for a VUS is not indicated. Nevertheless, in some circumstances, it can be useful to test other family members through our Variant Testing Program to gain more evidence about the variant itself and its possible association with disease. Over time, additional clinical evidence may be collected about certain VUS, which could ultimately lead to the reclassification of the variant and test result.

Negative Result
A negative result indicates that the genetic test did not identify reportable, medically relevant variant(s) in any of the genes tested. Therefore, the cause for the patient’s disorder or family history remains unknown. Although the patient’s disorder may be caused by non-genetic factors, a negative genetic test result does not completely rule out an underlying genetic cause. For example, the patient’s disorder may be due to unidentified genetic changes in gene regions or genes not included in the initial test.

Depending on the patient’s personal and family health history, additional genetic testing may be indicated for the patient or another family member. A genetic specialist or other healthcare providers can determine if further genetic testing is appropriate.

In case of a negative genetic test result, all medical management recommendations should be based on clinical symptoms in addition to past personal and family history. Predictive genetic testing of family members is not available.

When an individual tests negative for a familial pathogenic variant that was previously identified in another affected family member, this is considered a ‘true’ negative test result. In most cases, this means that the individual has no greater risk for developing the specific genetic disorder that runs in the family than anyone in the general population.

Medical Management
Specific interventions or low vision accommodations may be recommended for individuals who are diagnosed with a retinal dystrophy. While other neuroimaging or medical testing is not routinely recommended for individuals with retinal dystrophy, additional evaluations may be warranted depending on whether genetic testing uncovers a specific diagnosis in which there are other associated clinical features (e.g. developmental delay, hearing loss, or abnormalities of other organ systems). Identifying an underlying genetic etiology can be informative in guiding selection of more targeted medical surveillance and management options.

There are also genes on the Retinal Dystrophy Xpanded panel such as ABCA4, RPE65, and RS1 where clinical trials are currently underway to evaluate the feasibility and efficacy of gene therapy interventions to limit or reverse disease progression (www.clinicaltrials.gov).
Implications for Family Members

Regardless of the result, patients should share their test report with their blood relatives, who can then discuss the results with their healthcare providers. Sharing a copy of the test result with family members and healthcare providers will help to determine if additional testing is necessary and will ensure that the proper test is ordered for relatives, if indicated.

For positive or likely pathogenic test results in autosomal dominant conditions, first-degree relatives (including parents, siblings, and children) have a 50% chance to have the same variant. The risk for other family members to carry the variant depends on how closely related they are to the person with a positive or likely pathogenic test result. It is important to remember that for some of these genes, not all people who inherit a pathogenic or likely pathogenic variant will experience visual impairment due to reduced penetrance.

In cases where the gene is associated with an autosomal recessive condition, an individual inherits two pathogenic variants, one from each parent. Full siblings of the individual with retinal dystrophy have a 25% chance to inherit both pathogenic variants and be at risk to develop a retinal dystrophy.

Genetic Counseling

Prior to genetic testing, patients should speak with their healthcare provider and/or a genetics specialist about their personal and family health history. Healthcare providers should discuss the benefits and limitations of testing, as well as possible test results. These conversations help to determine if the patient is an appropriate candidate for testing, facilitate the ordering of appropriate test(s) and ensure that the patient has agreed to the proposed genetic testing (written informed consent).

If a pathogenic variant(s) has already been identified in a family member, testing of the specific variant(s) is appropriate. If no pathogenic variant(s) is known in a family with a specific genetic disorder, an affected family member with the highest likelihood of a positive test outcome (an individual manifesting associated clinical symptoms) is ideally the best person for initial testing within a family.
Once a patient makes the decision to undergo genetic testing, post-test genetic counseling is recommended to understand the implications of the results, including a discussion of the appropriate medical management based on both the test results and the patient’s medical and family history. Genetic counseling services across the country can be found at www.nsgc.org

Insurance Coverage and Cost for Genetic Testing

GeneDx accepts all commercial insurance plans and is a Medicare provider. Additionally, GeneDx is a participating provider with several Medicaid plans. If a patient does not have health insurance coverage or cannot afford to pay the cost of testing, GeneDx offers a financial assistance program to assist with access to medically necessary genetic testing.

For more information on the paperwork that is required by some insurance carriers, as well as additional details on patient billing and our financial assistance program, please visit our website: www.genedx.com/billing

Genetic Information and Nondiscrimination Act

The Genetic Information Nondiscrimination Act of 2008, also referred to as GINA, is a federal law that protects Americans from discrimination by health insurance companies and employers based on their genetic information. However, this law does not cover life insurance, disability insurance, or long-term care insurance. GINA’s employment protections do not extend to individuals in the U.S. military, federal employees, Veterans Health Administration and Indian Health Service. Some of these organizations may have internal policies to address genetic discrimination. For more information, please visit: http://genome.gov/10002328

Resources

American Foundation for the Blind: www.afb.org
Foundation Fighting Blindness: www.blindness.org
GeneReviews, a database of genetic diseases: www.genereviews.org
National Society of Genetic Counselors, to help you find a counselor near you: www.nsgc.org

References

6. Audo et al. (2012) Orphanet Journal Of Rare Diseases 7 :8 (PMID: 22277662)