POSITIVE RESULTS GUIDE: RPE65

This document is not part of the Invitae® clinical report and does not represent medical advice. These are general guidelines that are not specific to your result and may not represent all relevant international recommendations. You can use this guide to talk to your healthcare provider about your test results, clinical history, and the most current guidelines. This guide may not be appropriate for results that are suspected to be blood-limited, possibly mosaic, or suggestive of a larger imbalance of genetic material. We recognize that individuals have diverse gender and sexual identities. In this guide, the terms female, male, women, and men refer to sex assigned at birth.

What is a positive RPE65 result?

A positive test result means that a genetic change (variant) was found in the RPE65 gene. A positive RPE65 variant is considered "pathogenic" or "likely pathogenic" because it is associated with retinal dystrophy with choroidal involvement.

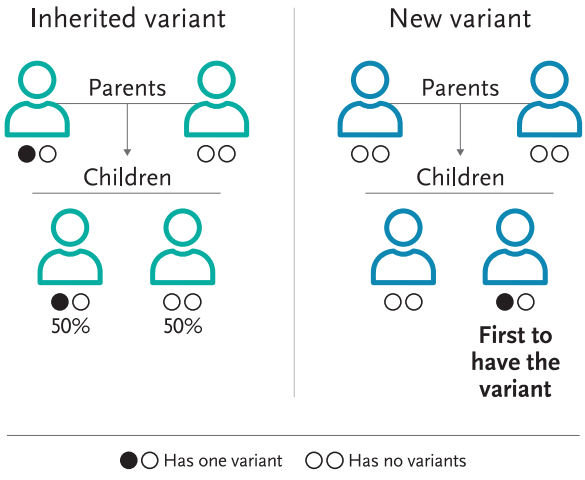
What does this mean?

Individuals with a RPE65 variant have an increased chance to develop retinal dystrophy with choroidal involvement. Retinal dystrophy with choroidal involvement is an inherited eye disorder that causes damage to the light-sensitive layer in the back of the eye (retina) and a nearby network of blood vessels (the choroid). Individuals with this condition may experience loss of side (peripheral) vision and/or difficulty seeing in low light (night blindness) starting in adulthood and symptoms can slowly worsen over time. Symptoms, severity, and age of onset can vary. Some individuals may never develop symptoms. Individuals may have different conditions or symptoms depending on whether they inherit one or two variants in RPE65. Some people inherit two RPE65 variants, which may cause Leber congenital amaurosis (LCA) and retinitis pigmentosa (RP). See the table later in this guide for more information and possible next steps.

What does this mean for family members?

Relatives should be informed about these results. It is recommended that family members talk with their own healthcare provider about a plan for genetic testing and/or health screening. Genetic testing is a personal choice and some individuals may choose not to have genetic testing. Laws protecting employment and health insurance may apply to individuals undergoing genetic testing (for example, the Genetic Information Nondiscrimination Act in the United States).

Will family members have the same variant(s)?
The image shows where a RPE65 variant may have come from. Any individual can inherit and pass on a RPE65 variant, regardless of sex.



RPE65 variants are usually inherited from a parent. Siblings, children, and other relatives may also have this RPE65 variant. Being the first person in the family to have a new RPE65 variant is rare.

For individuals who are planning a family, reproductive options may be available to help lower the chance of passing on a variant to children.

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Create a plan with a healthcare provider

These options are a guide for an individual and their healthcare provider. They are meant to be used along with an individual's genetic test results and other health information as part of a discussion to make a personalized care plan. Available options should be considered on an individual basis. A positive test result on its own cannot predict how a condition may affect an individual. This guide may not be appropriate for results that are suspected to be blood-limited, possibly mosaic, or suggestive of a larger imbalance of genetic material.

Options to consider

TOPIC	OPTION	MORE INFORMATION
Retinal dystrophy with choroidal involvement	• For individuals with a positive RPE65 result, evaluation by an ophthalmologist and/or retinal specialist is recommended. (1) • Follow-up evaluation should occur every 1-2 years. (1)	• The diagnosis of retinal dystrophy with choroidal involvement is not based on a genetic test alone. Assessment may involve medical history, clinical eye exam, imaging, visual field testing, and/or electroretinography (ERG). (1) • Clinical findings and symptoms can resemble and may be initially diagnosed as different inherited eye disorders (choroideremia or adult-onset maculopathy). (2,3) • Treatments to prevent or slow down progression of vision loss caused by this autosomal dominant RPE65 variants are not yet available. Rather, existing targeted therapy is directed at autosomal recessive Leber congenital amaurosis (LCA) and retinitis pigmentosa (RP) associated with different RPE65 variants.
Supportive care	• Discuss additional daily living needs and/or planning for the future.	• Supportive care for daily living may include identifying helpful resources at school or work, training to use assistive devices or technologies, and more.
RPE65-releated research	• Consider options for clinical trials and/or other research. • To find current information about available clinical trials, visit ClinicalTrials.gov	• There are many factors when considering participation in research studies, including time, location, and whether or not an individual meets the specific requirements to be in a study.
Family planning	• Discuss reproductive risks. (4) • Individuals with a RPE65 variant have a 50% chance to pass on the variant to a child.	• Preconception and prenatal reproductive options are available and could be discussed in more detail with a reproductive specialist.
	• Individuals with certain RPE65 variants may also have an increased chance to have a child with autosomal recessive Leber congenital amaurosis (LCA) or retinitis pigmentosa (RP), if their reproductive partner also has a RPE65 variant.	• Autosomal recessive LCA and RP are characterized by earlier onset and more severe vision impairment than retinal dystrophy related to a single RPE65 variant.
	• An individual's reproductive partner can consider genetic testing to help determine the risk of a child inheriting two RPE65 variants and having autosomal recessive LCA or RP. (4)	• If an individual's reproductive partner also has a RPE65 variant, there would be a 25% chance to have a child with autosomal recessive LCA or RP.

These options include recommendations from The American Academy of Ophthalmology Recommendations on Clinical Assessment of Patients with Inherited Retinal Degenerations" (www.aao.org) (1), PMID: 27307694 (2), PMID: 40985799 (3), and PMID: 28225426 (4). More information about genetics and disease continues to be available, so please always refer to the current guidelines and recommendations when considering surveillance and treatment options. Information on this document may not include all relevant international recommendations and acts as a supplement to the report. This information is not meant to replace a discussion with an individual's healthcare provider and should not be considered or interpreted as medical advice. Additional resources

provided within this document do not indicate or imply any endorsement by Labcorp with respect to any third party or any website or the products or services offered by any third party.

Resources

Genetic counseling can help individuals understand their genetic test results and options for next steps. Reviewing test results with a genetic counselor or other healthcare provider is recommended. Local or telehealth genetic counselors can be identified using the Find a Genetic Counselor search tool at nsgc.org (US and Canada). Individuals with a test result can contact a genetic counselor, and/or join the Invitae Patient Insights Network (PIN) (pin.invitae.com), an online platform where individuals can share information about their health and experiences to help advance research and drug development.

Connect with advocacy groups and other resources:

Please note that the websites and/or third party groups listed below are not endorsed or supported by Labcorp.

- Foundation Fighting Blindness: www.fightingblindness.org
- National Eye Institute: www.nei.nih.gov
- Hope in Focus (LCA): www.hopeinfocus.org
- National Organization for Rare Disorders (LCA): www.rarediseases.org

Notes for personalized assessment