Genetic Testing for IRDs Workshop

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Disclosures

- Employed at MBKU SCCO
  - Ketchum Health- University Eye Center
  - Low Vision Department
    - Genetic Testing
- Consultant
  - Applied Genetic Technologies Corporation (AGTC)
  - Spark Therapeutics- ID YOUR IRD Speakers' Bureau

CE content for educational purposes only

Online/Digital Resources

- https://sites.google.com/view/genetictestingworkshoputah

SCAN ME

Welcome

SCAN ME

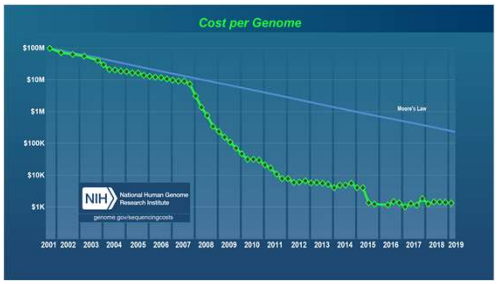
- 2-hour interactive lecture
- Please see provided resources:
  - Multi-gene panel samples
  - Sample genetic testing eligibility forms, requisition form, and consent forms
  - Saliva-sample collection kits
  - Sample genetic test result printouts

GENETIC TESTING INTRO

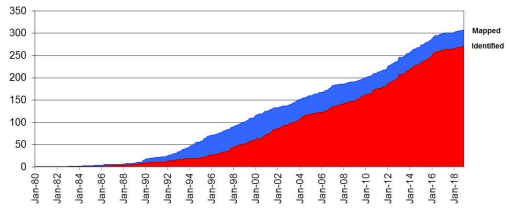
Importance of Genetic Testing for IRDs

- Determine eligibility for gene therapy and clinical trials
- Improve accuracy and specificity of diagnosis
- Improve accuracy of prognosis
- Improve accuracy of genetic counseling, family counseling

Decrease in Cost



Improved Testing



Mapped and Identified Retinal Disease Genes 1980 - 2019

https://sph.uth.edu/retnet/sum-dis.htm

Genetic Testing - 5 Parts

- 1) Clinical determination of genetic eye disease
- 2) Sample collection and testing
- 3) Analysis of results
- 4) Data interpretation within context of clinical findings
- 5) Patient counseling

"Recommendations for Genetic Testing of Inherited Eye Diseases- Report of the American Academy of Ophthalmology Task Force on Genetic Testing"

CLINICAL EVALUATION & CASE HISTORY

Importance of Clinical Assessment

- Genetic testing is not a substitute for clinical evaluation.
- Differential diagnoses are helpful for selecting an appropriate genetic test panel.
- Clinical assessment is needed for genetic test result interpretation and counseling.

Testing Recommendations

- **"Recommendations on Clinical Assessment of Patients with Inherited Retinal Degenerations – 2016"**
- Numbers refer to clinical phenotypes:
  - 1. Rod-cone degenerations
  - 2. Cone-rod degenerations
  - 3. Chorioretinal degenerations
  - 4. Inherited dystrophies that involve the macula

Clinical Evaluation: Inherited Retinal Degenerative Diseases

Assessment	Initial Visit	Follow Up Visit Every 1-2 Years
History • Ocular (including current needs) • Medical (including current medications and history of retinotoxic medication use)	1-4[a]	1-4
Pedigree (family history)	1-4	1-4
Clinical eye examination • Best corrected visual acuity: ETDRS (or equivalent) • Slit-lamp biomicroscopy • Intraocular pressure • Indirect Ophthalmoscopy	1-4	1-4
Imaging • Color fundus photos • Spectral Domain Optical Coherence Tomography • Fundus autofluorescence: Short wavelength with reduced illumination when possible • Infrared autofluorescence (when available)	1-4 1-4 1-4[b] 1, 3, 4	 1-4 1-4[b] 1, 3, 4
Visual fields • Kinetic • Static • Microperimetry (when available)	1-4[c] 1-3[d] 1-4	1-4[c] 1-3[d] 1-4
Electroretinography • Full-field ERG[e] (when appropriate) • Multifocal ERG[f] (when appropriate)	1-4 2,4	1-3 2,4
Genetic Diagnostic Testing	1-4	

https://www.aao.org/clinical-statement/recommendations-on-clinical-assessment-of-patients

AAOphthalmology Clinical Statement

- "…a causative mutation can be identified in up to 60-80% of patients with inherited retinal disorders"

https://www.aao.org/clinical-statement/recommendations-on-clinical-assessment-of-patients

Case History

- Important for eligibility criteria:
  - Ex. any nyctalopia, peripheral field loss, central field loss and age of onset, deterioration of color vision, photophobia
- Include extraocular health history and features

Clinical Pearls

- Fundus autofluorescence imaging can be useful to detect early change in young children with suspected inherited retinal dystrophy.
- Some children may also have high refractive error, but amblyopia is a diagnosis of exclusion.

Case History

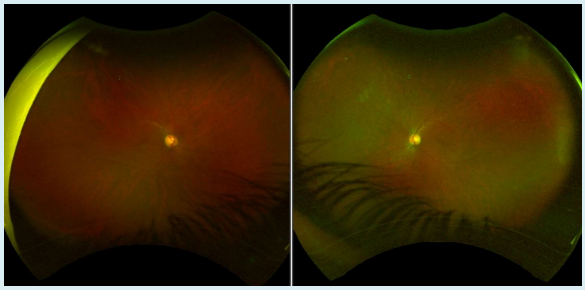
- 44 y/o African American female
- Presented in LV Clinic for DMV Form

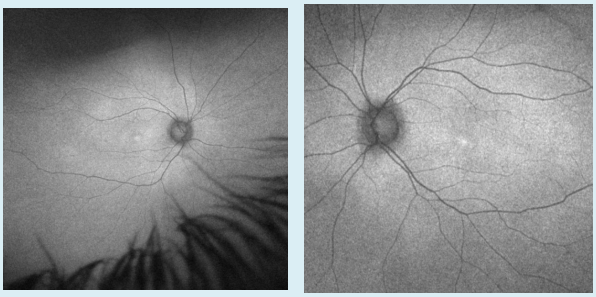
- Longstanding color vision deficiency and decreased VA since childhood
- Light sensitivity
- Wears purple sunglasses

Case History

- Congenital nystagmus
- Cone dystrophy (?)

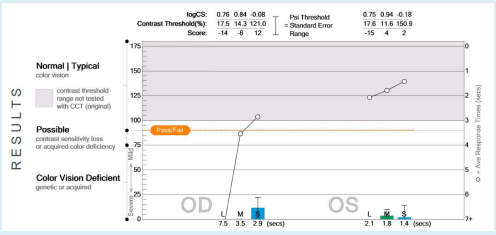
- OD: -6.25-4.00x176 20/100
  OS: -4.00-3.75x012 20/100





Color Vision & Cone Contrast Testing

- HRR: 0/6 OU



TEST PANEL & LAB SELECTION

Lab Testing

- Can test just one or many (300+) genes in one test panel.
- Whole genome testing is not recommended when a retinal dystrophy test panel is more appropriate.
- Saliva-sample, blood-sample, and buccal swab collection kits are available.
  - Saliva-sample is the most commonly used and very convenient.
- Many labs are available. Using a CLIA-approved laboratory is recommended.
- Some commonly used labs are listed.

Lab Testing

- The lab panels available vary slightly. Select a lab panel based on differential diagnoses.
  - Look up the genes associated with the condition.
    - Ex. https://medlineplus.gov/genetics/
  - Check that the lab panel tests those genes listed.

Sample Test Panels

- Blueprint Genetics
  - https://blueprintgenetics.com/tests/panels/ophthalmology/retinal-dystrophy-panel/
  - 351 genes (including RPGR)
- Invitae
  - https://www.invitae.com/en/inherited-retinal-disorders-panel/
  - Recently updated to 330 genes (including RPGR)
- Alternative labs

Example Panel

Panel Content

Genes in the Retinal Dystrophy Panel and their clinical significance

Gene	Associated phenotypes	Inheritance	ClinVar	HGMD
ABCA4	Stargardt disease, Retinitis pigmentosa, Cone rod dystrophy, Retinal dystrophy, early-onset severe, Fundus flavimaculatus	AR	308	1231
ABCC6*	Pseudoxanthoma elasticum	AR	352	377
ABHD12	Polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract	AR	16	20
ACO2	Optic atrophy, Infantile cerebellar-retinal degeneration	AR	16	15
ADAM9	Cone rod dystrophy	AR	6	10

Example Panel

Order test

Primary panel (293 genes)

ABCA4	ABCC6	ABHD12	ACBD5	ACO2	ADAM9	ADAMTS18	ADGRA3
ADGRV1	ADIPOR1	AGBL5	AHI1	AHR	AIPL1	ALMS1	ARHGEF18
ARL13B	ARL2BP	ARL3	ARL6	ARMC9	ARSG	ASRGL1	ATF6
ATOH7	B9D1	BBIP1	BBS1	BBS10	BBS12	BBS2	BBS4
BBS5	BBS7	BBS9	BEST1	C1QTNF5	C8orf37	CA4	CABP4
CACNA1F	CACNA2D4	CAPN5	CC2D2A	CCT2	CDH23	CDH3	CDHR1
CEP164	CEP19	CEP250	CEP290	CEP41	CEP78	CEP83	CERKL
CFAP410	CHM	CIB2	CISD2	CLCC1	CLN2 (TPP1)	CLN3	CLRN1
CLUAP1	CNGA1	CNGA3	CNGB1	CNGB3	CNNM4	COL11A1	COL11A2
COL18A1	COL2A1	COL9A1	COL9A2	COL9A3	CPLANE1	CRB1	CRX
CSPP1	CTNNA1	CWC27	CYP4V2	DHDDS	DHX38	DRAM2	DTHD1
EFEMP1	ELOVL4	EMC1	EXOSC2	EYS	FAM161A	FLVCR1	FRMD7

Sample Test Panels

- Consider differences in…
  - Genes included in the panels
  - Eligibility requirements

Ex. Lab Selection Process

- Your patient has a clinical diagnosis of retinitis pigmentosa. He has a relatively early onset and rapidly progressive field loss.
- After completing a pedigree, you suspect an x-linked inheritance pattern.

Ex. Lab Selection Process

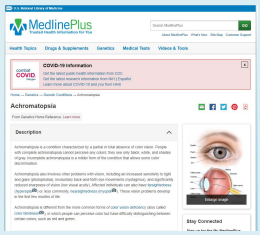
- You search for information about retinitis pigmentosa inheritance patterns and associated genes on MedlinePlus.
- "Together, mutations in the RPGR and RP2 genes account for most cases of X-linked retinitis pigmentosa."
- https://medlineplus.gov/genetics/condition/retinitis-pigmentosa/#synonyms

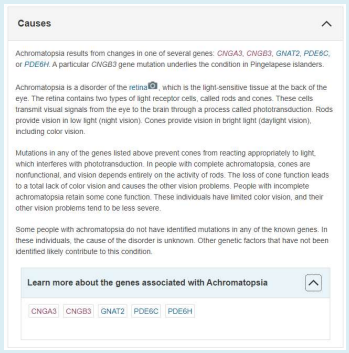
Ex. Lab Selection Process

- You look through both test panels from the labs (Ex. Blueprint Genetics & Invitae)
- You find that both panels currently test *RPGR*.
- The Blueprint panel testing is being sponsored by Foundation Fighting Blindness's My Retina Tracker Program and the Invitae panel testing is being sponsored by Spark Therapeutics, so now you check that your patient meets their eligibility requirements.

Achromatopsia

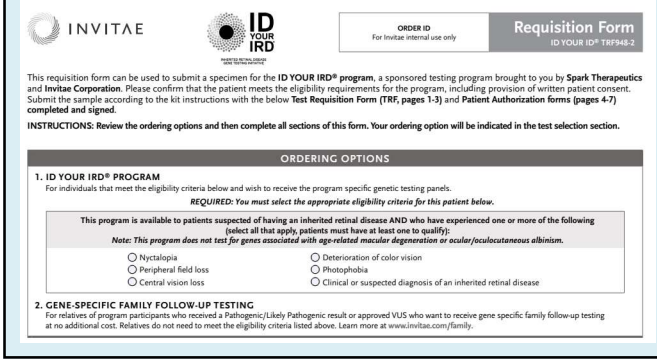
- https://medlineplus.gov/genetics/

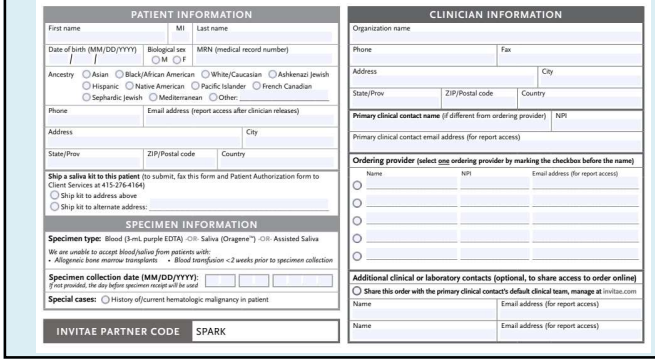


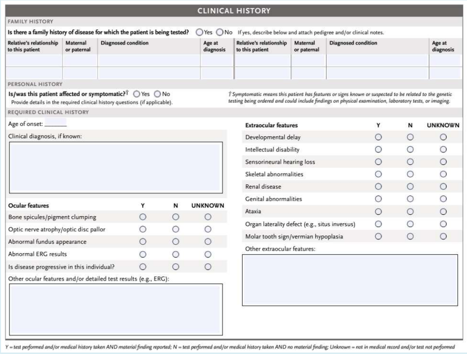


Forms to Complete

- Eligibility Requirements
- Requisition Form
- Consent Form







CLINICAL HISTORY

FAMILY HISTORY

Is there a family history of disease for which the patient is being tested? ◯ Yes ◯ No If yes, describe below and attach pedigree and/or clinical notes.

Relative's relationship to this patient	Maternal or paternal	Diagnosed condition	Age at diagnosis	Relative's relationship to this patient	Maternal or paternal	Diagnosed condition	Age at diagnosis

PERSONAL HISTORY

Is/was this patient affected or symptomatic?† ◯ Yes ◯ No
Provide details in the required clinical history questions (if applicable).

† Symptomatic means this patient has features or signs known or suspected to be related to the genetic testing being ordered and could include findings on physical examination, laboratory tests, or imaging.

REQUIRED CLINICAL HISTORY

Age of onset: ______

Clinical diagnosis, if known:

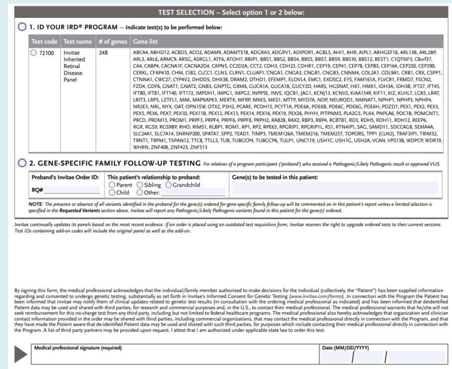
Ocular features	Y	N	UNKNOWN
Bone spicules/pigment clumping	◯	◯	◯
Optic nerve atrophy/optic disc pallor	◯	◯	◯
Abnormal fundus appearance	◯	◯	◯
Abnormal ERG results	◯	◯	◯
Is disease progressive in this individual?	◯	◯	◯

Other ocular features and/or detailed test results (e.g., ERG):

Extraocular features	Y	N	UNKNOWN
Developmental delay	◯	◯	◯
Intellectual disability	◯	◯	◯
Sensorineural hearing loss	◯	◯	◯
Skeletal abnormalities	◯	◯	◯
Renal disease	◯	◯	◯
Genital abnormalities	◯	◯	◯
Ataxia	◯	◯	◯
Organ laterality defect (e.g., situs inversus)	◯	◯	◯
Molar tooth sign/vermian hypoplasia	◯	◯	◯

Other extraocular features:

Y = test performed and/or medical history taken AND material finding reported; N = test performed and/or medical history taken AND no material finding; Unknown = not in medical record and/or test not performed



TEST SELECTION – Select option 1 or 2 below:

◯ 1. ID YOUR IRD® PROGRAM – Indicate test(s) to be performed below:

Test code	Test name	# of genes	Gene list
◯ 72100	Invitae Inherited Retinal Disease Panel	248	ABCA4, ABHD12, ACBD5, ACO2, ADAM9, ADAMTS18, ADGRA3, ADGRV1, ADIPOR1, AGBL5, AHI1, AHR, AIPL1, ARHGEF18, ARL13B, ARL2BP, ARL3, ARL6, ARMC9, ARSG, ASRGL1, ATF6, ATOH7, BBIP1, BBS1, BBS2, BBS4, BBS5, BBS7, BBS9, BBS10, BBS12, BEST1, C1QTNF5, C8orf37, CA4, CABP4, CACNA1F, CACNA2D4, CAPN5, CC2D2A, CCT2, CDH3, CDH23, CDHR1, CEP19, CEP41, CEP78, CEP83, CEP164, CEP250, CEP290, CERKL, CFAP410, CHM, CIB2, CLCC1, CLN3, CLRN1, CLUAP1, CNGA1, CNGA3, CNGB1, CNGB3, CNNM4, COL2A1, COL9A1, CRB1, CRX, CSPP1, CTNNA1, CWC27, CYP4V2, DHDDS, DHX38, DRAM2, DTHD1, EFEMP1, ELOVL4, EMC1, EXOSC2, EYS, FAM161A, FLVCR1, FRMD7, FSCN2, FZD4, GDF6, GNAT1, GNAT2, GNB3, GNPTG, GRM6, GUCA1A, GUCA1B, GUCY2D, HARS, HGSNAT, HK1, HMX1, IDH3A, IDH3B, IFT27, IFT43, IFT80, IFT81, IFT140, IFT172, IMPDH1, IMPG1, IMPG2, INPP5E, INVS, IQCB1, JAG1, KCNJ13, KCNV2, KIAA1549, KIF11, KIZ, KLHL7, LCA5, LRAT, LRIT3, LRP5, LZTFL1, MAK, MAPKAPK3, MERTK, MFRP, MKKS, MKS1, MTTP, MYO7A, NDP, NEUROD1, NMNAT1, NPHP1, NPHP3, NPHP4, NR2E3, NRL, NYX, OAT, OPN1SW, OTX2, P3H2, PCARE, PCDH15, PCYT1A, PDE6A, PDE6B, PDE6C, PDE6G, PDE6H, PDZD7, PEX1, PEX2, PEX3, PEX5, PEX6, PEX7, PEX10, PEX11B, PEX12, PEX13, PEX14, PEX16, PEX19, PEX26, PHYH, PITPNM3, PLA2G5, PLK4, PNPLA6, POC1B, POMGNT1, PRCD, PRDM13, PROM1, PRPF3, PRPF4, PRPF6, PRPF8, PRPH2, RAB28, RAX2, RBP3, RBP4, RCBTB1, RD3, RDH5, RDH11, RDH12, REEP6, RGR, RGS9, RGS9BP, RHO, RIMS1, RLBP1, ROM1, RP1, RP2, RPE65, RPGRIP1, RPGRIP1L, RS1, RTN4IP1, SAG, SAMD11, SDCCAG8, SEMA4A, SLC24A1, SLC7A14, SNRNP200, SPATA7, SPP2, TEAD1, TIMP3, TMEM126A, TMEM216, TMEM237, TOPORS, TPP1 (CLN2), TRAF3IP1, TRIM32, TRNT1, TRPM1, TSPAN12, TTC8, TTLL5, TUB, TUBGCP4, TUBGCP6, TULP1, UNC119, USH1C, USH1G, USH2A, VCAN, VPS13B, WDPCP, WDR19, WHRN, ZNF408, ZNF423, ZNF513

◯ 2. GENE-SPECIFIC FAMILY FOLLOW-UP TESTING *For relatives of a program participant ('proband') who received a Pathogenic/Likely Pathogenic result or approved VUS.*

Proband's Invitae Order ID:	This patient's relationship to proband:	Gene(s) to be tested in this patient:
RQ# ______	◯ Parent ◯ Sibling ◯ Grandchild ◯ Child ◯ Other: ______	

***NOTE**: The presence or absence of all variants identified in the proband for the gene(s) ordered for gene-specific family follow-up will be commented on in this patient's report unless a limited selection is specified in the **Requested Variants** section above. Invitae will report any Pathogenic/Likely Pathogenic variants found in this patient for the gene(s) ordered.*

Invitae continually updates its panels based on the most recent evidence. If an order is placed using an outdated test requisition form, Invitae reserves the right to upgrade ordered tests to their current versions. Test IDs containing add-on codes will include the original panel as well as the add-on.

By signing this form, the medical professional acknowledges that the individual/family member authorized to make decisions for the individual (collectively, the "Patient") has been supplied information regarding and consented to undergo genetic testing, substantially as set forth in Invitae's Informed Consent for Genetic Testing (www.invitae.com/forms). In connection with the Program the Patient has been informed that Invitae may notify them of clinical updates related to genetic test results (in consultation with the ordering medical professional as indicated) and has been informed that deidentified Patient data may be used and shared with third parties, for research and commercial purposes and, in the U.S., to contact their medical professional. The medical professional warrants that he/she will not seek reimbursement for this no-charge test from any third party, including but not limited to federal healthcare programs. The medical professional also hereby acknowledges that organization and clinician contact information provided in the order may be shared with third parties, including commercial organizations, that may contact the medical professional directly in connection with the Program, and that they have made the Patient aware that de-identified Patient data may be used and shared with such third parties, for purposes which include contacting their medical professional directly in connection with the Program. A list of third party partners may be provided upon request. I attest that I am authorized under applicable state law to order this test.

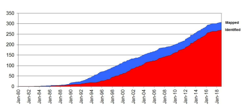
Medical professional signature (required)	Date (MM/DD/YYYY)
	/ /

Clinical Pearls

- Know or use resources to look up the genetics of the diagnosis or differential diagnoses before collecting the saliva sample. Make sure to select an appropriate panel and lab.
- Genetic testing does not replace the clinical exam. The clinical exam is necessary for differential diagnoses and genetic test program eligibility.

Clinical Pearls

- If your patient has had negative genetic test results in the past, consider how long ago the test was conducted and what genes were tested. If the test panel was insufficient and more appropriate test panels are now available, consider retesting.



COMMONLY ASKED PATIENT QUESTIONS – Q&A

Genetic Testing Q&A

- How much does genetic testing cost?
  - The lab testing might be free if the patient meets the eligibility requirements.
  - There may be cost associated with office visits.
- How long will it take to get the results?
  - Could be as short as 2 weeks; could be longer depending on the lab and testing.
- Do you need a blood sample?
  - Saliva sample is sufficient in most cases.

Genetic Testing Q&A

- Will this tell me what eye condition I have?
  - Not always. Genetic testing does not replace a clinical exam. Depending on the eye condition, genetic testing panel, and current knowledge on the condition, the possibility of positive or negative genetic test results varies.
- I did genetic testing a long time ago. Is this the same?
  - Consider retesting if genetic test was inconclusive in the distant past.
- Can children be tested?
  - Yes. Keep in mind ethical considerations. For conditions with possible treatment, earlier testing is recommended when earlier treatment provides better outcomes.

Gene Therapy Q&A

- Will I qualify for gene therapy?
  - Most likely not right now since gene therapy is only available for RPE65 mutation, but if you have RP or LCA there is a small possibility.
- Will I qualify for a gene therapy clinical trial?
  - Possibly. Can determine after receiving the genetic testing results.

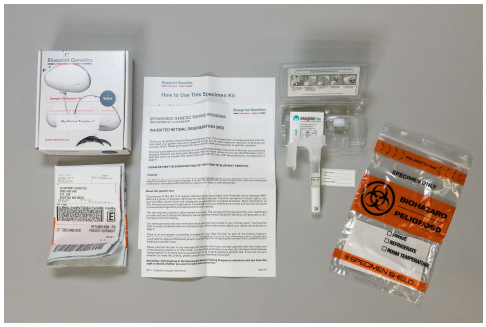
Clinical Pearls

- Take into account how likely a positive genetic test will be depending on the patient's diagnosis or differential diagnoses and the genes on the test panels. Manage patient expectations of genetic testing.
- Manage patient expectations on eligibility for gene therapy or clinical trials.

Achromatopsia

- Chance of getting a positive test result is high
- CNGA3 and CNGB3 account for a large majority of cases

GENETIC TESTING – SALIVA SAMPLE COLLECTION

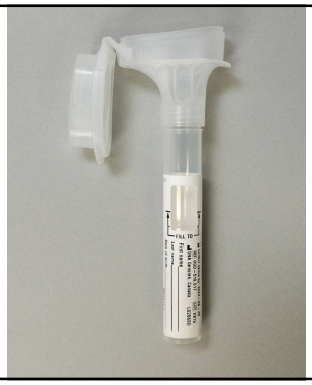


Clinical tips for successful sample collection:

- Can't eat, drink, or smoke immediately before testing
- Can't use saliva sample testing if:
  - Blood transfusion <2 weeks prior
  - History of allogeneic bone marrow transplant
- **Don't forget to completely & legibly label the tube**
  - **Full name, date of birth, specimen collection date**

Clinical tips for successful sample collection:

- Saliva Sample: there must be enough saliva to reach the marked line (and bubbles don't count), seal the tube, gently shake the tube.
- If the patient is having difficulty producing saliva, you can prompt them to think of sour things.



Tips for mailing:

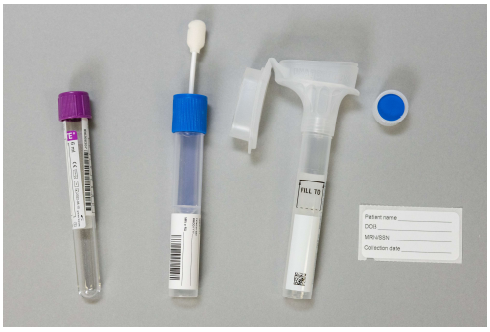
- Proper sealing and packaging of specimen tube, inclusion of requisition form if appropriate.
- Mail as soon as possible, priority mail to lab.
- Do not leave specimen out in the heat.

Tips for clinical setup:

- Have sample kits on hand.
- Be cognizant of your pickup times.
- Cannot charge the patient for the genetic testing if using sponsored programs.

Tips for clinical setup:

- Reserve time for paperwork.
- Designate a primary clinical contact.
- Make sure genetic test results are secure and that staff maintain confidentiality of results.
- Reserve time for follow-up discussions with the patient.



GENETIC TEST RESULTS

AAOphthalmology Clinical Statement

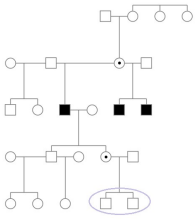
- "…a causative mutation can be identified in up to **60-80%** of patients with inherited retinal disorders"
- Likelihood of positive result can depend on the condition

Result Interpretation

- Not all genes are tested. Not all tests will deliver satisfactory results.
- **Positive result-** found pathogenic mutation in the gene(s) tested
- **Negative result-** did not find mutation in the gene(s) tested
- **Inconclusive results**
  - Variants of Uncertain Significance

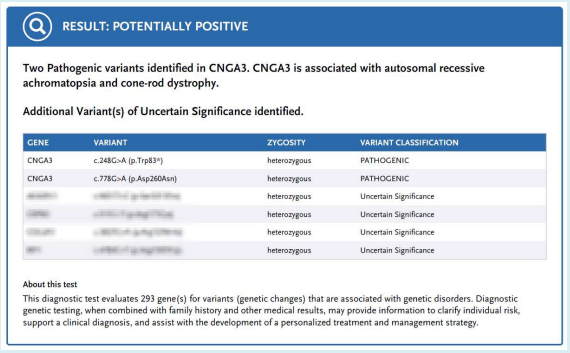
Result Interpretation

- Sometimes additional family member testing is indicated.



Online Portals

- Clinician and patient access to results
- Can be used to view updated lab results (ex. VUS reclassification)
- Provide patient with access to copy of results



RESULT: POTENTIALLY POSITIVE

Two Pathogenic variants identified in CNGA3. CNGA3 is associated with autosomal recessive achromatopsia and cone-rod dystrophy.

Additional Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
CNGA3	c.248G>A (p.Trp83*)	heterozygous	PATHOGENIC
CNGA3	c.778C>A (p.Asp260Asn)	heterozygous	PATHOGENIC
[redacted]	[redacted]	heterozygous	Uncertain Significance
[redacted]	[redacted]	heterozygous	Uncertain Significance
[redacted]	[redacted]	heterozygous	Uncertain Significance
[redacted]	[redacted]	heterozygous	Uncertain Significance

About this test

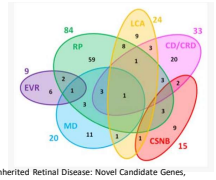
This diagnostic test evaluates 293 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

INTERPRETATION OF GENETIC TEST RESULTS IN CLINICAL CONTEXT

Results Interpretation

- Gene with mutation may be associated with several different eye conditions
- Clinical exam is still important for diagnosis
- Other factors must still be taken into account
  - Patient ocular findings
  - Patient medical history
  - Patient family history

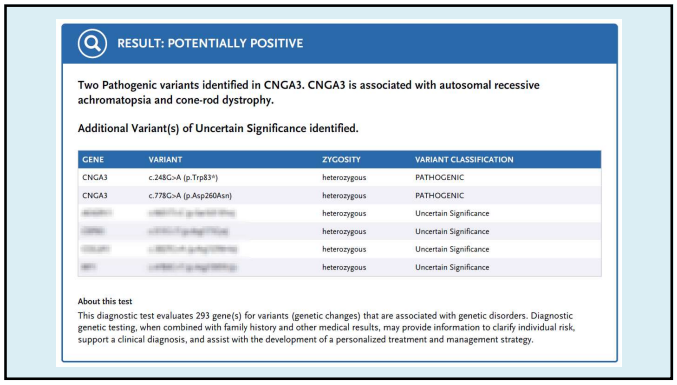
- Some IRDs are associated with many different genes
- Some genes are associated with many different IRDs



Cremers FPM, Boon CJF, Bujakowska K, Zeitz C. Special Issue Introduction: Inherited Retinal Disease: Novel Candidate Genes, Genotype–Phenotype Correlations, and Inheritance Models. *Genes*. 2018; 9(4):215. https://doi.org/10.3390/genes9040215

Resources for more information about specific genes:

- National Institutes of Health (NIH) - Medline Plus Genetics (previously Genetics Home Reference) - https://medlineplus.gov/genetics/
- Useful quick resource to search Causes (& Genes Associated) & Inheritance Pattern.



RESULT: POTENTIALLY POSITIVE

Two Pathogenic variants identified in CNGA3. CNGA3 is associated with autosomal recessive achromatopsia and cone-rod dystrophy.

Additional Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
CNGA3	c.248G>A (p.Trp83*)	heterozygous	PATHOGENIC
CNGA3	c.778G>A (p.Asp260Asn)	heterozygous	PATHOGENIC
[redacted]	[redacted]	heterozygous	Uncertain Significance
[redacted]	[redacted]	heterozygous	Uncertain Significance
[redacted]	[redacted]	heterozygous	Uncertain Significance
[redacted]	[redacted]	heterozygous	Uncertain Significance

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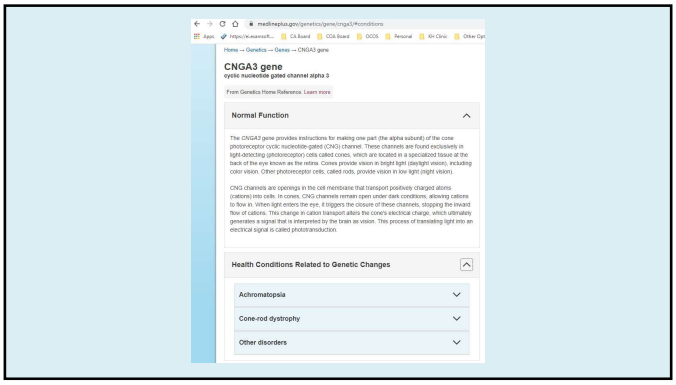


CNGA3 gene

cyclic nucleotide gated channel alpha 3

From Genetics Home Reference. Learn more

Normal Function

The CNGA3 gene provides instructions for making one part (the alpha subunit) of the cone photoreceptor cyclic nucleotide-gated (CNG) channel. These channels are found exclusively in light-detecting (photoreceptor) cells called cones, which are located in a specialized tissue at the back of the eye known as the retina. Cones provide vision in bright light (daylight vision), including color vision. Other photoreceptor cells, called rods, provide vision in low light (night vision).

CNG channels are openings in the cell membrane that transport positively charged atoms (cations) into cells. In cones, CNG channels remain open under dark conditions, allowing cations to flow in. When light enters the eye, it triggers the closure of these channels, stopping the inward flow of cations. This change in cation transport alters the cone's electrical charge, which ultimately generates a signal that is interpreted by the brain as vision. This process of translating light into an electrical signal is called phototransduction.

Health Conditions Related to Genetic Changes

Achromatopsia

Cone-rod dystrophy

Other disorders

COUNSELING & ADDITIONAL MANAGEMENT

Genetic Counseling

- **Genetic Counseling** is recommended
  - Family counseling
  - Inheritance patterns
- Additional family member testing is indicated in some cases

Genetic Counseling

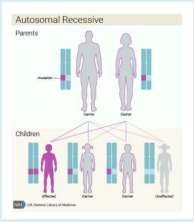
- Referral options
  - Foundation Fighting Blindness & IDYourIRD programs
  - National Society of Genetic Counselors
    - https://www.nsgc.org/

Clinical Pearl

- Even if patients have completed genetic counseling, they may still have questions for you about their specific eye condition, vision, and prognosis. Schedule a follow-up appointment.

Counseling

- Autosomal Recessive
  - Sons are carriers, but unlikely for their children to have achromatopsia
- Good prognosis, stable condition
  - Unlikely cone-rod

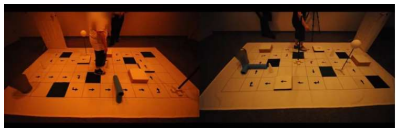


Determine Gene Therapy Eligibility

- *voretigene neparvovec-rzyl*
- FDA approved for biallelic RPE65 mutation-associated retinitis pigmentosa & Leber congenital amaurosis

voretigene neparvovec-rzyl

- Result
  - Improvement in multi-luminance mobility testing (MLMT) score



https://luxturnahcp.com/efficacy/clinical-trial-results/

voretigene neparvovec-rzyl

- Improved functional vision
- Statistically significant improvement in light sensitivity
- Statistically significant improvement in VF
- Non-statistically significant improvement in VA

https://luxturnahcp.com/efficacy/additional-endpoints/

Determine Clinical Trial Eligibility

- Ongoing research includes:
  - Choroideremia
  - Stargardt disease (ABCA4)
  - Leber's hereditary optic neuropathy
  - Retinitis pigmentosa (RPE65/ PDE6B)
  - X-linked retinitis pigmentosa (RPGR)
  - Achromatopsia (CNGA3, CNGB3)
  - Leber Congenital Amaurosis 10 (CEP290)
  - Usher Syndrome (USH2A)
  - And more…

Clinical Trial Resources:

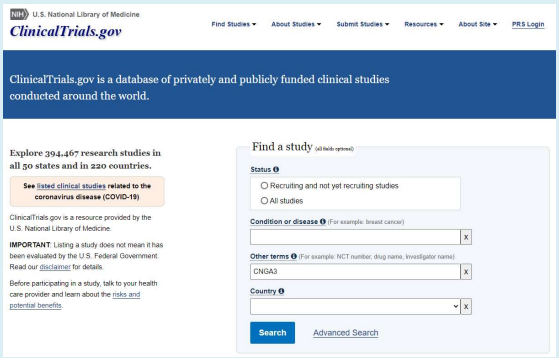
- **NIH- U.S. National Library of Medicine - https://clinicaltrials.gov/**
- World Health Organization Clinical Trials Search Portal - https://apps.who.int/trialsearch/

Clinical Trial Referral Tips:

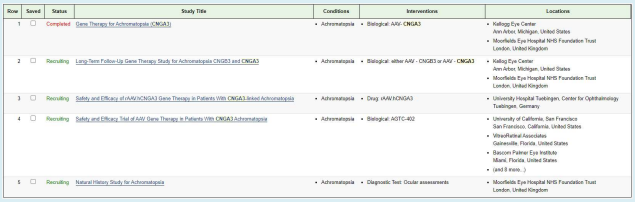
- Check the Inclusion and Exclusion criteria
- Check Recruitment Status

Other Patient Tips:

- Provide patient with copy of results
  - Results can be overwhelming for patients. Consider highlighting the important and relevant findings.
- Patient registries
  - Ex. MyRetinaTracker
  - Patients can join to be informed of updates for clinical trials.
- Natural history studies



Clinical Trials



Other Management

- Low vision follow-ups
  - Trialed red tint
  - Resources
- ~~Additional testing~~
- ~~Family member testing~~
- ~~Support groups~~
- ~~Additional genetic counseling~~

Patient Management

- Continuous process.
- Specific genotype directed care is evolving.
- Patients who do not qualify for any treatments now might qualify for them in the near future.
- If patients do not currently qualify for clinical trials, inform them of importance of regular follow-up.

Importance of Early Testing & Referrals

- Earlier treatment can lead to better outcomes.
- Earlier identification of syndromic conditions can lead to earlier monitoring and management of systemic conditions.

ADDITIONAL CASES

Conclusions

- Increase public and patient awareness
- Increase access to genetic testing and gene therapy
- Importance of early testing & referrals
- Importance of continued ocular health & low vision management

Recommended Reading

- "Recommendations for Genetic Testing of Inherited Eye Diseases- Report of the American Academy of Ophthalmology Task Force on Genetic Testing"
  - https://www.aao.org/clinical-statement/recommendations-genetic-testing-of-inherited-eye-d
- "Recommendations on Clinical Assessment of Patients with Inherited Retinal Degenerations – 2016"
  - https://www.aao.org/clinical-statement/recommendations-on-clinical-assessment-of-patients

Q&A

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