

What you should know about genetic testing for mitochondrial disorders



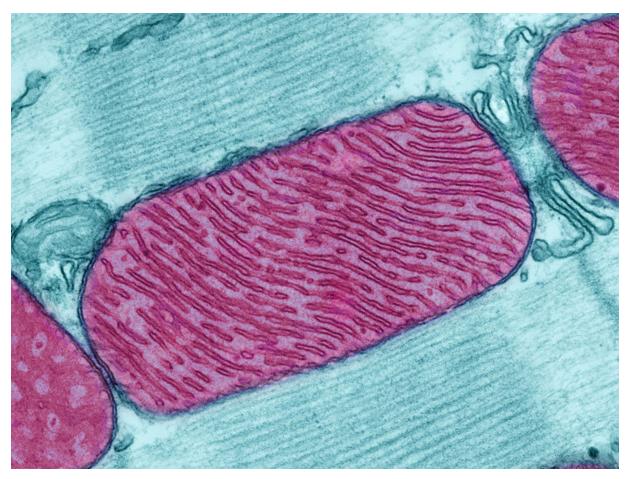


### Disclosures

### I am an employee of GeneDx, Inc., a wholly-owned subsidiary of OPKO Health, Inc.



### What are Mitochondria?

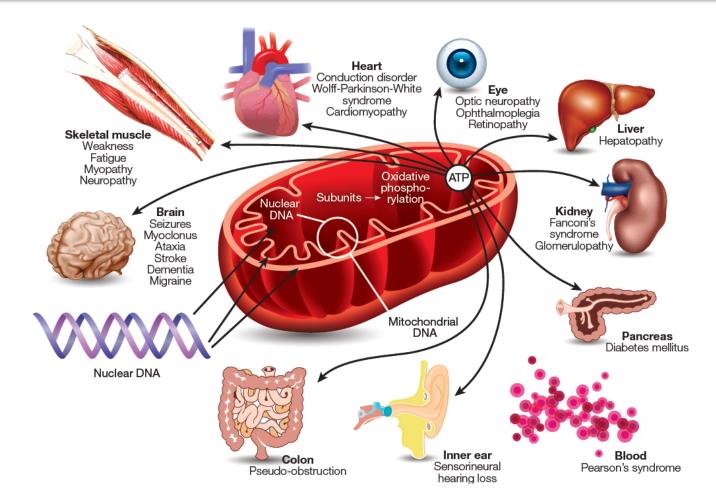


http://www.sciencesource.com/

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### What are symptoms of Mitochondrial Disorders?





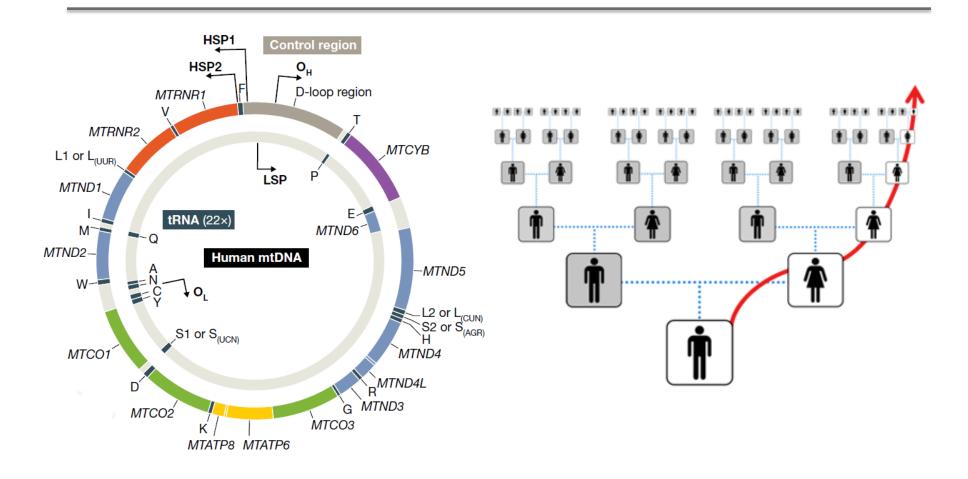


### **Genetics of Mitochondrial Disorders**

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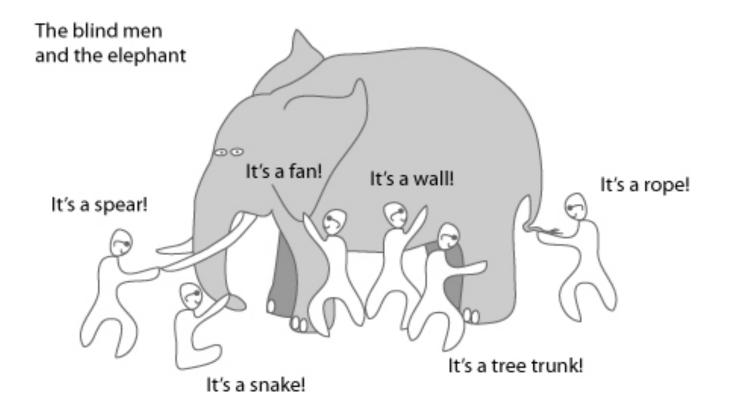
### **Genetics of Mitochondrial Disorders**



https://www.igenea.com/en/mitochondrial-dna

Chinnery et al. (2015) EMBO Mol Med 7 (12):1503-12 (PMID: 26612854)

# How are Mitochondrial Disorder





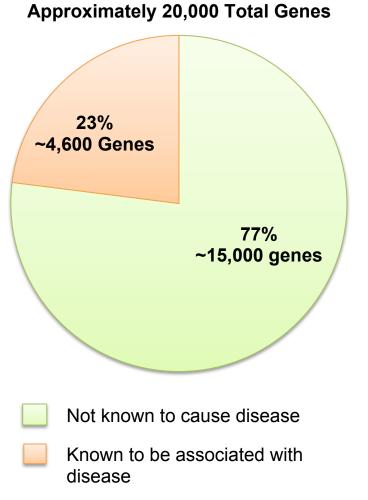
AARS2FHPCCBACAD8GCDHPCK2ACAD9GCSHPDHA1ACAD9GCSHPDHXACADSGLUD1PDHXACADSBHADHPDP1ACAT1HARS2POLGALD42HIBCHPOLG2ALDH2HMGCS2PYCR1ALDH4A1HMGCLRARS2ALDH6A1HSD17B10RMRPAMTHSPD1SARDHATPAF2IDH2SARS2AUHIDH3BSCO1BCAT2ISCUSCO2BCKDHAIVDSDHAF1BCS1LMCCC1SOD2C8of38MCCC2SUCLA2	BCL2 CPT1A DNM1L GCK GK KIF1B PINK1 Mitochondrial outer membrane	K2 DIABLO GATM FFER HTRA2 PPOX MTND4 MTND4 MTND4 MTND4 MTND4 MTND5 MTND6 MTC9 MTC02 MTC03 MTATP6 MTATP8	ABCB7 ACADVL ADCK3 AGK ATP5E C12orf62 COX412 COX6B1 CPT2 CRAT CYC5 CYP11A1 CYP11B1 CYP11B1 CYP11B1 CYP27A1 CYP27B1	DHODH DNAJC19 FASTKD2 GPD2 HADHA HADHB HCCS L2HGDH MMAA MPV17 NDUFA1 NDUFA1 NDUFA10 NDUFA11 NDUFA12 NDUFA13	NDUFB3 NDUFV1 NDUFV1 NDUFV2 NDUFS3 NDUFS4 NDUFS4 NDUFS6 NDUFS7 NDUFS8 OPA1 OPA3 PDS51 SDHA SDHB SDHC	SDH D SLC25A3 SLC25A4 SLC25A12 SLC25A13 SLC25A19 SLC25A20 SLC25A20 SLC25A22 SLC25A38 SPG7 TIMM8A UCP1 UCP2 UCP2 UCP3 UQCRB UQCRD
Cloopf2 MCCE2 SUCLA2 Cloopf2 MCEE SUCLG1 Cl2opf5 ME2 SURF1 C20opf7 MRP516 TACO1 COA5 MRP522 TK2 COX10 MTFMT TMEM70 COX15 MTPAP TRMU CPS1 MUT TSFM D2HGDH NAGS TTC19 DAR52 NDUFAF1 TUFM DBT NDUFAF2 UNG DECR1 NDUFAF2 UNG DECR1 NDUFAF3 XPNPEP3 DGUOK NDUFAF4 YAR52 DLD NUBPL DLAT OAT DMGDH OGDH ETFA OTC ETFFB OXCT1 ETFDH PC FOXRED1 PCCA	9 107 Mitochondri matrix	Mitochondrial inner membrane 81 15 al Submitochondrial location	) 22 Partia locali		AIFM1 AKAP10 AMACR APTX BAX BOLA3 CYB5R3 ETHE1 FXN GDAP1 HK1 GLRX5 HOGA1 MMAB MMADHC PDSS2	HLCS LRPPRC LRRK2 MFN2 MLYCD NFU1 PARK2 PARK7 SACS SPG20 WWOX PNKD PUS1 REEP1 STAR TMEM126A

Koopman et al. (2012) N. Engl. J. Med. 366 (12):1132-41 (PMID:

22435372)

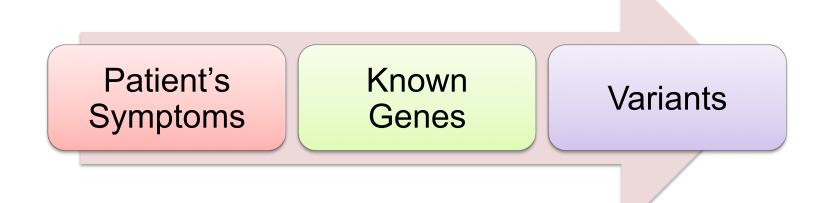
### Genetic Testing for Mitochondria Disorders - Whole Exome Sequencing

- What is Whole
  Exome Sequencing
  - Sequencing of the protein-coding regions of the human genome
  - Only genetic changes that seem like they're related to the patient's symptoms are reported





### Analysis of Genetic Testing





### Variant Interpretation Guidelines

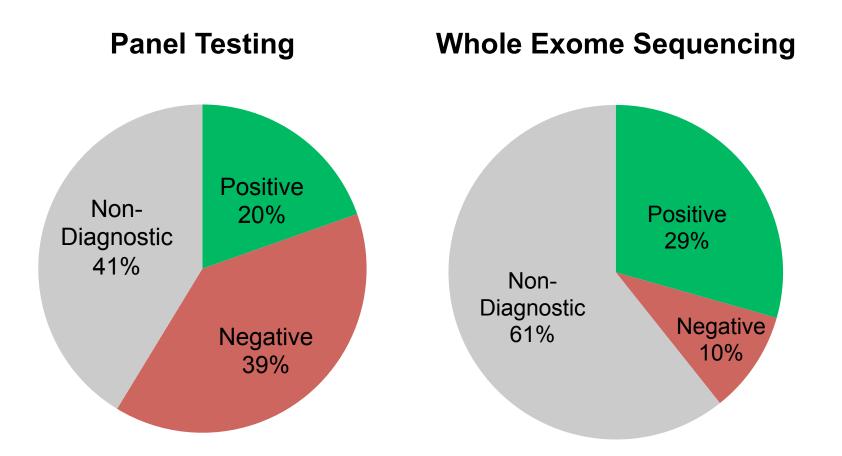


Which Test is Best for Mitochondria Disorders?

- There is no single best test for <u>all</u> patients who are suspected of having a mitochondrial disorder
  - It depends on specific symptoms that individual person has



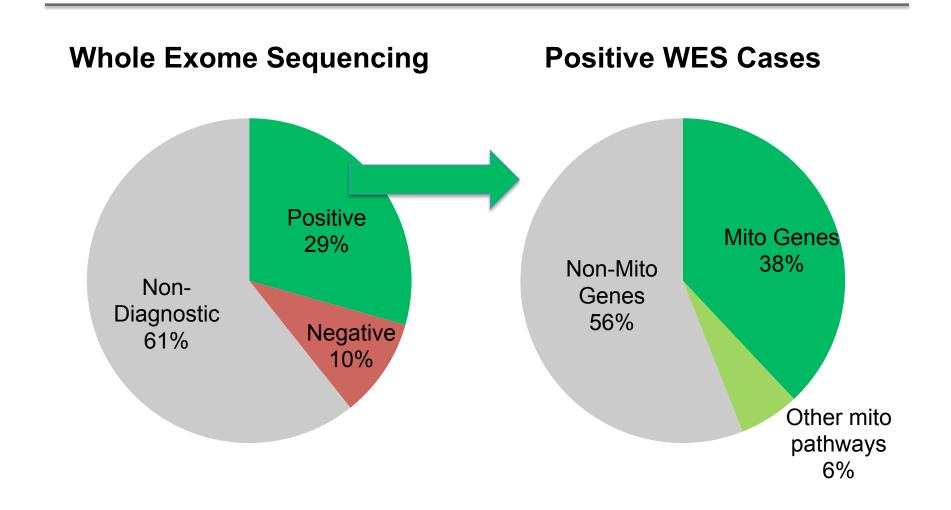
### Panel testing vs. Whole Exome Sequencing



Bai R et al. WES and WMGS for Molecular Diagnosis of Mitochondrial Disorders: Lessons from 865 Cases [Abstract #119 and platform presentation]. Presented at the 2015 UMDF Symposium, June 18, 2015, Washington DC;



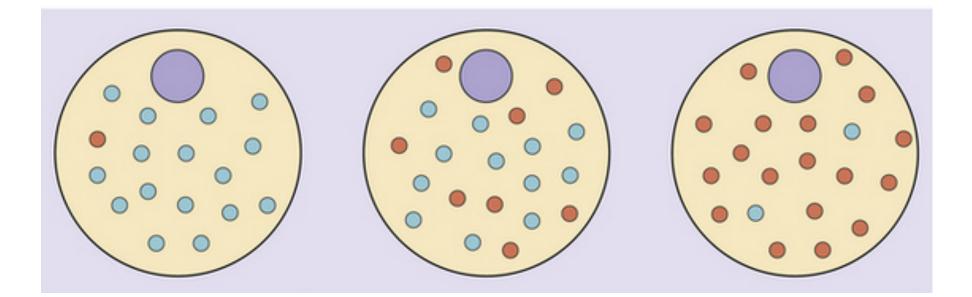
### Whole Exome Sequencing Results



3/2016 GeneDx internal data



## Special Considerations with for Mitochondrial Genome Testing



Low Heteroplasmy

Intermediate Heteroplasmy

High Heteroplasmy

https://clinicalgate.com/mitochondrial-encephalopathies/



### Mitochondrial Genome Heteroplasmy

- The proportion of mitochondrial genomes that have a variant
- Percentage can vary from tissue to tissue
- Percentage can vary with age
- Threshold effect
  - Variant must be present at a high enough level in a particular tissue in order to cause clinical symptoms

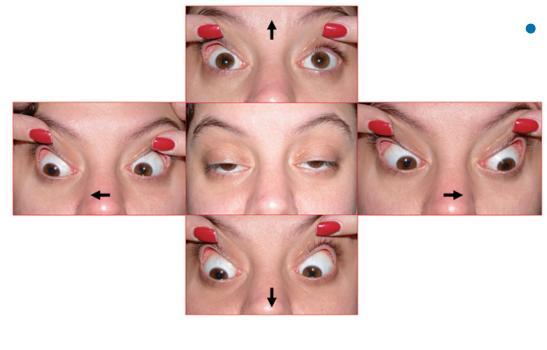
– Threshold percentage can vary by variant

Sample Type and Mitochondrial Generations

- Sample type
  - Heteroplasmy can vary from tissue to tissue
  - Best to send sample from an affected tissue
    - Most frequently this is muscle or liver
    - Very important for patients with specific symptoms



### Chronic Progressive External Ophthalmoplegia



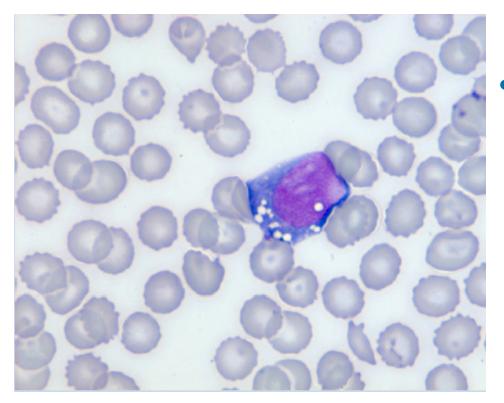
CPEO is a symptom that is highly specific for a mitochondrial disorder

 Approximately 50% of these patients harbor a large mtDNA deletion that is confined to muscle

http://www.reviewofophthalmology.com/article/how-to-spot-dangerous-ptosisthe-sequel



## **Pearson Syndrome**



- Infantile onset sideroblastic anemia and pancreas dysfunction
  - Also associated

ant in

blood.

Tumino et al. (2011) Am. J. Med. Genet. A 155A (12):3063-6 (PMID: 22012855)



### Other sample types for Mitochondrial Genome Testing

- Oral rinse and buccal swabs
  - Similar to blood heteroplasmy for most patients
- Skin cells
  - Most skin cells are cultured and some mitochondrial genome variants are selected against when cultured making them more difficult to detect
- Urine epithelial cells
  - Similar to muscle heteroplasmy
  - However, DNA quality from urine is extremely poor, so it frequently does not yield results
- Hair follicles
  - Poor DNA quality
  - Heteroplasmy can vary greatly from follicle to follicle



### Limitations of Genetic Testing

The scientific knowledge available about the function of all genes in the human genome is incomplete at this time

Testing may identify the presence of a variant in an affected individual, but we will not recognize it as the cause of their disease due to insufficient knowledge about the gene and its function

Not all types of genetic testing can detect all types of genetic variants known to cause disease (such as repeat expansions, variants not present in exons)

For mitochondrial genome variants, as heteroplasmy levels can vary from tissue to tissue, some variants may not be detected in the sample type submitted but still be present in other tissues



### Acknowledgements

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