Whole Genome Sequencing for Rare Disorders: The Future is Here

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About

Christine is the Chief Director of Clinical Genomics at Variantyx. She is particularly familiar with the complexities of interpretation of genetic data for patients with rare inherited disorders given the many cases she has worked on over the years, first at Athena Diagnostics and later at Courtagen Life Sciences. Christine brings that experience to Variantyx where she now oversees clinical genomic interpretations for the laboratory, developing the standards for identifying and reporting relevant, causal variants.

Christine holds a PhD in Human Genetics from the Medical College of Virginia with fellowship training at Boston University in clinical molecular genetics. She is a diplomate of the American Board of Medical Genetics and Genomics and a Fellow of the American College of Medical Genetics and Genomics. She additionally maintains a part-time appointment as Clinical Laboratory Director of C2i Genomics.
The following personal financial relationships with commercial interests relevant to this presentation existed during the past 12 months:

Christine Stanley is employed by two diagnostic testing companies: Variantyx and C2i Genomics. Both labs offer NGS-based genome, exome and gene level tests.
Overview

How genomes provide a data platform for comprehensive testing

Why complex disorders require a unifying single test

How genomes provides answers for symptoms of mitochondrial disease
Genomes provide a data platform
Genetic tests begin with fragmented genomes
Typical exomes and gene panels sequence only a subset of the data by mechanically pulling the pieces out.

Genomes use it all.
DATA: ONCE IT’S GONE, IT’S GONE
Genomes sequence everything

**EXOME/PANEL**
1-2% of all DNA
Data holes

**GENOME**
98% of all DNA, has no holes

SAME SCALE
Genome data used to **develop and validate** detection of small sequence changes, repeat expansions and structural variants.
Variantyx uses a single sample to identify the many changes that cause complex disease.
Genetics diseases are caused by a complex variety of changes:

- Small sequence changes
- Structural variants
- Mitochondrial variants
- Tandem repeat expansions
Variantyx unifies different tests into one test.
A typical patient with rare disease:

- Takes 7+ years to be diagnosed
- Visits 8 physicians
- Spends an average of $28,000
Mitochondria are “powerhouses of the cell”

Mitochondrial diseases are long-term disorders that occur when the mitochondria fail to produce enough energy for the body to function properly.
Organs requiring large amounts of energy are usually affected

**Brain**
- Developmental delays, dementia, migraines, autistic features, seizure, stroke, atypical cerebral palsy, learning disabilities

**Muscles**
- Poor growth, Muscle weakness, muscle pain, low muscle tone, exercise intolerance

**Heart**
- Heart defects, blockage, cardiomyopathy

**Lungs**
- Respiratory (breathing) problems
Other clinical symptoms associated with mitochondrial disease:

**Eyes**
- Vision loss, ptosis, optic atrophy, strabismus, ophthalmoplegia, retinitis pigmentosa

**Ears**
- Hearing loss

**Liver**
- Low blood sugar, liver failure

**Kidneys**
- Renal tube failure

**Gastrointestinal disorders**
- Swallowing difficulties, diarrhea or constipation, unexplained vomiting, reflux.

**Pancreas**
- Diabetes, pancreatic failure, parathyroid failure

**Other**
- Thyroid problems, movement disorders and Lactic acidosis (a buildup of lactate).
Clinical cases demonstrate how genome sequencing provides answers.
Abnormal gait, foot dystonia

Tremor, upper extremities ataxia

Anxiety

27 year old female

4 year diagnostic odyssey

CMA: negative mitochondrial analysis: negative

DNA analysis of 9 genes: negative + VUSs

WES VUS only

FMR1 SCA1,2,3,6,7 FXN: negative
**POLR3-related leukodystrophy**
Pathogenic small sequence change and pathogenic deletion in *POLR3A*
Premature birth (34 weeks)
Suspected ataxic Cerebral Palsy
Dystonia, stiffness
Seizures
Developmental delay
Current: frequent falls, mild dysphagia, fatigue, dystonia
23 year old female
Encephalopathy due to defective mitochondrial and peroxisomal fission-1 (EMPF1)

De novo deletion in DNM1L gene
60 year old female

- Age 55: left eye deviated inward followed by 3 strabismus surgeries
- Progressive ophthalmoplegia
- Severe ptosis
- Gait ataxia
- Hyporeflexia of lower limbs
Loss of function variant in *HSPB1* gene suggesting Charcot-Marie-Tooth disease axonal type 2F

Mitochondrial disease is now known to occur at any age, although the adult disease may be more difficult to diagnosis because it can be more varied, subtle, and have a narrower spectrum of laboratory findings compared to mitochondrial disease that begins in childhood.
4 year old female

3 year diagnostic odyssey

Normal at birth

Neuropathy, status epilepticus, hypotonia, global developmental delay

9 months: Muscle biopsy - mild neurogenic atrophy and type 2 atrophy

2 years: abnormal MRI

6 months: Lab workup - normal MRI - normal

CMA - normal
WES - normal
Mitochondrial panel - normal

Comprehensive Neuropathies Panel - negative.

Comprehensive Neuromuscular Disorders Panel - 5 VUS reported
**TBCK-related intellectual disability syndrome**

A likely pathogenic, maternally inherited splice site variant and non maternally inherited, likely pathogenic heterozygous deletion of exon 24 of the *TBCK* gene.
23 year old male

- Hypophosphatemic rickets
- Nystagmus, partial optic atrophy
- Ataxia and oculomotor apraxia
- MRI: atrophic cerebellum
Positive for two different genetic disorders

- Compound heterozygous in SPG7 gene, causing Spastic Paraplegia, type 7
- *De novo* hemizygous for PHEX gene causing hypophosphatemic rickets
28 year old female

22 year diagnostic odyssey

Bilateral ophthalmoplegia

Facial weakness, left ptosis

Muscle fatigue

BLE myalgia

Lab - normal

Age 22: Mitochondrial lab screen: negative

CT/MRI/NCS/EMG - normal
This variant was recently reported in a patient who presented with myasthenia gravis type symptoms (fatigable ptosis, increased jitter on single fiber EMG, and a thymic mass) who was subsequently diagnosed with a mitochondrial myopathy.

The m.5728 T > C variant was absent in the proband's blood and detected in 41% heteroplasmy in muscle tissue (PMID: 31026515).
Variantyx uniquely identifies difficult to detect causal variants in a wide variety of genetic disorders using genomes.
Genomic Unity® costs are comparable to exome costs

Three payment methods are available

Institutional billing
Insurance billing
Direct patient pay
Genomic Unity® provides the ability to rerun analyses

Because the entire genome has been sequenced, patient data can be re-analyzed without re-sequencing as

- Their health situation changes
- Variants are reclassified
- New variant-disease associations are published or submitted to variant databases
- New gene-disease associations are published
- Variant calling algorithms are refined
Thank you!

Learn more about WGS and Genomic Unity® testing at www.variantyx.com.

For questions, email us at info@variantyx.com

Or call us at 617-209-2090