DIAGNOSTIC EXOME SEQUENCING IS SUCCESSFUL IN PROVIDING DIAGNOSES AMONG PATIENTS WITH INTELLECTUAL DISABILITY AND DEVELOPMENTAL DELAY: strong family history correlates with an increased novel genetic etiology detection rate

Heather A. Newman, MS, LCGC
I am a full time, salaried employee at Ambry Genetics. Diagnostic exome sequencing is among the commercially available tests.
At least 2-3% of Americans are diagnosed with intellectual disability (ID) and/or developmental delay (DD).

There can be many causes of ID/DD, some are known but many remain unknown.

AAN, ACMG, and AAP all recommend genetic testing for individuals with ID/DD.

---

Developments Delay (DD)

**CAUSES OF ID/DD**

- Complex inherited conditions resulting from chromosome or single gene changes
- Errors during embryogenesis
- Prenatal and perinatal complications
- Inborn errors of metabolism

**DEVELOPMENTAL DELAY (DD)**

Refers to an important developmental milestone delay in regards to motor, speech and language; cognition; social functioning; and activities of daily living.

Often a temporary diagnosis for children who are unable to undergo standardized IQ evaluation. A good number of children with DD ultimately meet the diagnosis for Intellectual Disability once they reach school age.

**INTELLECTUAL DISABILITY (ID)**

Impairments of general mental abilities that impact adaptive functioning in conceptual, social, and practical domains.

**CONCEPTUAL**:
- Language, reading, writing, math, reasoning, knowledge, and memory.

**SOCIAL**:
- Empathy, social judgment, interpersonal communication skills.

**PRACTICAL**:
- Personal care, job responsibilities, money management, recreation, and organizing school and work tasks.
TIERED GENETIC TESTING STRATEGY

PATIENT WITH UNEXPLAINED INTELLECTUAL DISABILITY (ID/DD)

Does this patient have features of a recognizable genetic syndrome?

YES

SPECIFIC GENETIC TESTING FOR THE SUSPECTED SYNDROME

CHROMOSOMAL MICROARRAY AND FRAGILE X TESTING

Patient’s diagnosis remains unknown

SPECIALIZED PANEL TESTING

NO

WHOLE EXOME SEQUENCING
Each of us has approximately 20,000 genes in our bodies – often referred to as the genome.

We inherit one copy of most of our genes from our mother and another from our father.

Each gene is further divided into two areas: exons and introns.

Exons are the protein coding regions in genes and make up approximately 1-2% of our genomes.

Exome sequencing analyzes the exonic regions of our genomes.

**WHAT IS AN EXOME?**
EXOME SEQUENCING

WHY?

May end “diagnostic odyssey” for patients

High diagnostic rate (~30%)\(^1\)

Cost savings (for patients, insurance companies, and healthcare system)

Impact on medical management and family planning

\(^1\)Farwell KD, et al., Genetics in Medicine, 2014

WHEN?

When a patient’s suspected genetic condition has become a “diagnostic odyssey”

When there are limited or no comprehensive tests available for a patient’s suspected condition

When a patient’s clinical presentation does not correspond with a known genetic disorder or is unclear and or atypical
EXOME SEQUENCING PROCESS FLOW

DNA ISOLATION FROM BLOOD OR SALIVA → HYBRIDIZATION → SEQUENCE ALIGNMENT → VARIANT ANALYSIS

DNA ISOLATION FROM BLOOD OR SALIVA

SANGER CONFIRMATION AND CO-SEGREGATION

MEDICAL REVIEW
EXOME RESULTS

CHARACTERIZED GENETIC ETIOLOGIES:

Positive: Clinically relevant alterations(s) detected
Likely Positive: Alteration(s) with likely clinical relevance detected
Uncertain: Alteration(s) of uncertain clinical relevance detected
Negative: No clinically relevant alteration(s) detected

NOVEL GENETIC ETIOLOGIES:

Uncertain, Candidate: Alteration(s) of potential clinical relevance detected
Uncertain, Suspected Candidate: Alteration(s) of potential clinical relevance detected
Negative: No alteration(s) with potential clinical relevance detected
DESIGN

Retrospective analysis was performed on the first unselected 1200 samples submitted for diagnostic exome sequencing at our laboratory.

Compared positive rates in individuals whose primary was ID/DD vs. those whose was something different.

Compared positive rates in individuals with strong, mild, and no/unknown family histories.

DEFINITIONS:

- **STRONG FAMILY HISTORY:** at least one relative with a similar phenotype as the proband
- **MILD FAMILY HISTORY:** at least one relative with intellectual disability and or developmental delay
PRIMARY INDICATIONS FOR TESTING

- ID/DD: 67% (n=1200)
- Not ID/DD: 33%

NON ID/DD PRIMARY INDICATIONS

- Various Single Organ Systems: 48% (n=391)
- Multiple Congenital Anomalies: 19%
- Neuromuscular/Neuropathy: 15%
- Cancer: 7%
- Seizures: 4%
- Neurodevelopmental: 4%
- Ataxia/Spasticity: 3%
- Neurodevelopmental: 4%
- Cancer: 7%
- Seizures: 4%
- Neurodevelopmental: 4%
- Ataxia/Spasticity: 3%
RESULTS

PRIMARY INDICATIONS

- ID/DD: 67%
- Not ID/DD: 33%

n=1200

POSITIVE RATE OF EXOME SEQUENCING

- Characterized Genetic Etiologies: 30%
- Novel Genetic Etiologies: 23%

- Primary Indication ID/DD
- Primary Indication not ID/DD

- Characterized Genetic Etiologies: 7%
- Novel Genetic Etiologies: 4%
RESULTS

UNCERTAIN AND NEGATIVE RESULTS IN EXOME SEQUENCING

PRIMARY INDICATIONS

- ID/DD
- Not ID/DD

n=1200

% of positive findings

- Uncertain: 10% (67%)
- Negative: 54% (64%)

Primary Indication

- Primary Indication ID/DD
- Primary Indication not ID/DD
RESULTS

PRIMARY INDICATIONS

FAMILY HISTORY AND POSITIVE RATE OF EXOME SEQUENCING

% of positive findings

Strong: 25% (Characterized), 13% (Novel)
Mild: 29% (Characterized), 3% (Novel)
None/Unknown: 31% (Characterized), 7% (Novel)

- De novo rate 2%
- 52/53 inherited AR or XL

ID/DD: 67%
Not ID/DD: 33%
n=1200

p-value 9E-2

Characterized
Novel
RESULTS

PRIMARY INDICATIONS

POSITIVE RATE OF EXOME SEQUENCING

% of positive findings

Characterized Genetic Etiologies

ID/DD

Not ID/DD

n=1200

33%

28%

33%

Characterized Genetic Etiologies

Novel Genetic Etiologies

Males

Females

6%

7%

67%

33%
CONCLUSIONS

Exome sequencing can provide a positive result in up to 30% and 7% of individuals with primary indications of ID/DD in characterized and novel genetic etiologies, respectively

- This is significantly higher than the positive rates of 23% and 4% in individuals without ID/DD in characterized and novel genetic etiologies, respectively.

Negative exome sequencing results are less common in individuals with primary indications of ID/DD vs. in individuals with different primary indications

- 54% vs. 64%

Strong family history of ID/DD is a positive predictor of informative novel genetic etiology detection

- Diagnostic rate in novel genetic etiologies in individuals with strong family history was four times greater than in individuals with mild family history

The total positive rates in females with intellectual disability and or developmental delay was greater than that of males in both characterized and novel genetic etiologies
In future studies we plan to:

Analyze the positive rate in exome sequencing depending on the patient’s:
- age
- ethnicity
- inheritance pattern(s)
QUESTIONS?

Let’s find the answer.