

Clinical Utility of Whole Exome Sequencing in the Diagnosis of a Child

David Dimmock

Human and Molecular Genetics Center &
Department of Pediatrics

Medical College of Wisconsin

Genetics Center,

Children's Hospital of Wisconsin

The following relationship(s) exist related to this presentation: No relationships to disclose.

Exome/Genome Sequencing

- To date has focused on:
 - Celebrity individuals
 - Familial disease
 - Collections of individuals with a well defined syndrome
- For true clinical utility the technology must be applicable to a simplex case

Clinical Case

- Male who presented at 15 months with poor weight gain and a perianal abscess.
- Symptoms progressed over a few months to an aggressive, refractory inflammatory bowel disease.
- Pathological studies revealed focal granulation tissue with chronic active granulomatous inflammation, consistent with a severe Crohn's disease.

Clinical Course

- In spite of aggressive medical and immunomodulatory therapy the disease progressed with:
 - mucosal inflammation
 - strictures
 - enterocutaneous fistulae
 - poor cutaneous wound healing
- ultimately requiring a total colectomy.

Immunological work-up

- anti-neutrophil antibody
- abnormal chemotaxis of neutrophils
- decreased NK cytotoxicity, but no evidence of HLH
- memory skewing of CD4 cells
- inverted CD4 to CD8 ratio

Diagnosis?

- Several forms of immune dysfunction have been associated with inflammatory bowel disease
- May respond to immune reconstitution or require alternate treatment plan dependent on the underlying cause
- Immune reconstitution is a risky procedure

3 options

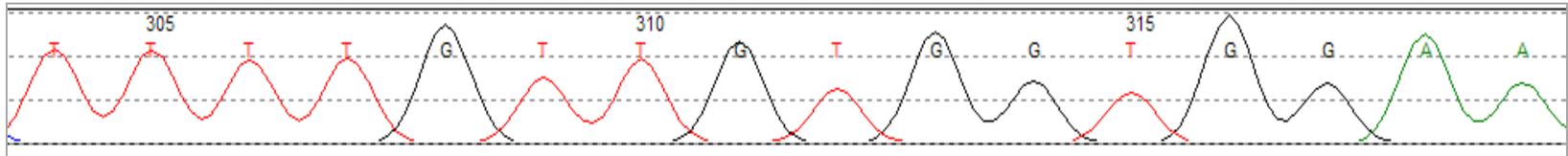
- Continue current treatment
- Blindly attempt alternate risky therapies
- See if we could obtain information to make a more informed choice

Variant analysis summary

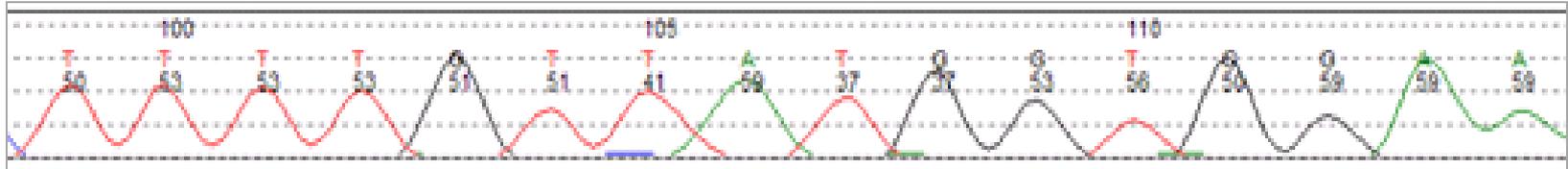
High Confidence variants	16,124
Genic variants	16,012
Protein coding	15,272
Non-synonymous	7,157
Two variants in gene predicted to be damaging	67
-Altering highly conserved amino acids	19
-Not known to contain many missense mutations	5
Novel (dbSNP129) Non-synonymous	878
Homozygous or hemizygous	70
-Predicted to be damaging	17
-Novel (against dbSNP 130)	8
-Altering highly conserved amino acid	4
-Not found in reference genome sequences	2
-Not known to contain many missense mutations	1

Sanger validation

Normal reference



Child



The child is hemizygous (single X chromosome copy in a male) for the variant.

Follow-Up

- Mutation independently confirmed
- Because of risk of lymphoproliferative disorder decision made to perform BMT
- Almost total remission of bowel disease following immune reconstitution

- We demonstrated that Genomic sequencing is a useful advance in DNA diagnostic testing that can inform clinical decision making.

Others could benefit

- After initial success significant interest in applying technology to other cases

Ethical Concern

- When sequencing a whole genome, not all disease associated variants will be pertinent to the question at hand
- Although, this is a problem occasionally encountered with clinical array CGH it is expected that this will be seen with increased frequency when performing WGS

- Resources to analyze data and obtain consent are limited

Case Selection- Principals

- Equity of access
- Reserved for individuals in whom
 - the likelihood of success is high
 - reasonable clinical testing has not achieved answer
 - molecular diagnosis has the potential to advance clinical decision making

Two Step Process

- Phase 1 - Nomination
- Phase 2 – Review group

Phase 1 -Nomination

- Two physicians with expertise in disease area determine:
 - Standard clinical assessments have been utilized
 - WGS is clinically warranted in the context of management of the patient and their family
 - Patient/Family is interested in considering WGS
- Referred to:
 - Genetics to initiate consent process
 - Review group

Review group - Members

- Chair –Hospitals Chief Medical Officer
- Three physicians with expertise in the area of interest not directly involved in the case
- Chair of hospital ethics committee
- Medical College ethicist
- Geneticist
- Genomics expert
- Genetic counselor

Review group - Process

- Nominating Physician presents case
- Review group determine:
 - What disease information is related to the clinical question
 - Ensure appropriate clinical consent is obtained
 - Ensure appropriate research protocol and consent are in place if information will be used for research

Confirmatory testing

- We require all DNA testing in our laboratory to be confirmed on a second extraction, preferably by a second technique
- WGS not considered definitive/medically actionable until confirmed

Consent for Data return - Pediatrics

- Ethical opinion:
- “the return of any or all of this [genomic] information was morally permissible and that such a decision as to what should be returned should remain at the discretion of informed parental choice.”

Categorical model for choice

- Decided that parents should preemptively be asked what data they would like returned.
- This is part of the consent process
- Consent by Genetic Counselor and one of two named Clinical Geneticists
- Typical face to face time 6-9 hours with additional telephone calls

Categories

Information actionable in the child in childhood

- “ if such results are discovered there is a duty of care to confirm and act upon these results. There is no opt out if such results are discovered”
- There is no obligation on the physicians/testing Lab to actively analyze the data to discover such abnormalities as this is not the focus of the test.

actionable disease with adult onset

- Examples would include BRCA1/2,
Hypercholesterolemia

non-actionable disease with onset in adulthood

- Examples: Parkinson, Huntington's