Early-Onset IBD:
Genetic Testing and Clinical Applications

Presenters

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Mayo Clinic

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Disclosures

- **None**

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What is Inflammatory Bowel Disease?

- **Group of disorders characterized by chronic inflammation of the gastrointestinal (GI) tract; prolonged inflammation leads to tissue damage**
  - Crohn Disease
  - Ulcerative Colitis
  - IBD-unspecified
- **Symptoms include diarrhea, abdominal pain, rectal bleeding/bloody stool, weight loss (or failure to thrive), fatigue**

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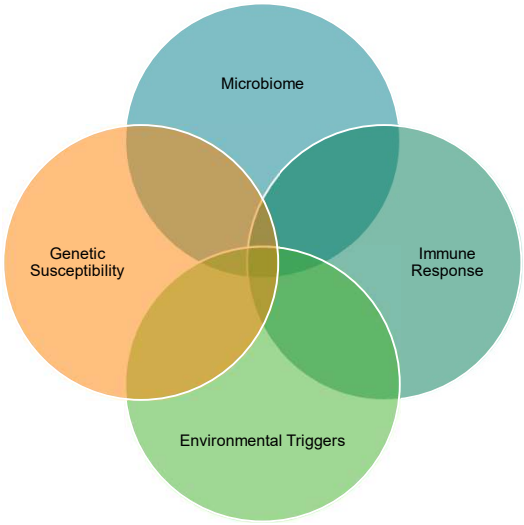
What Causes Inflammatory Bowel Diseases (IBD)?



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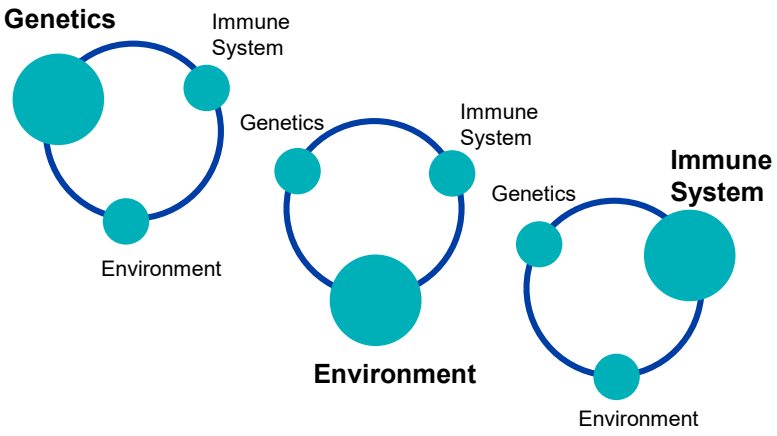
Do All Causes Contribute Equally



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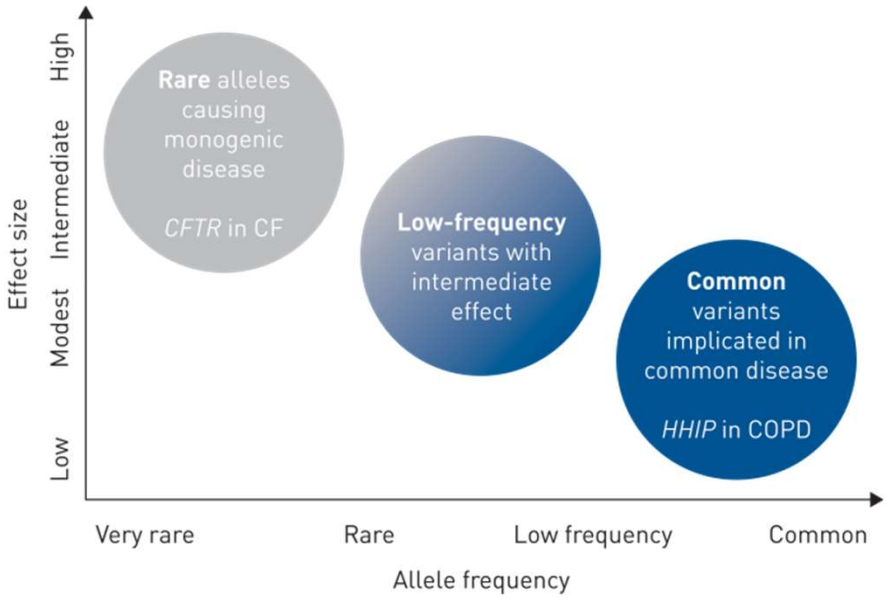

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European Lung *white book*. http://www.erswhitebook.org/chapters/genetic-susceptibility. Accessed May 9, 2019.

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Early-Onset IBD Is Different

- **More severe phenotype**
  - Pancolitis is more common in children with ulcerative colitis (UC)
    - 80–90 % vs. 60 %
  - More aggressive
    - More difficulty in achieving steroid independence
- **Colon-only involvement more common with Crohn's disease (CD)**
  - 2/3 of children with CD vs. 30% of adults
- **Male-to-female ratio in CD**
  - 1.6:1 vs. 1:1 in adults

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Benchimol, et al, Gastroenterology. 2014;147:803–813. Heyman, et al, *J Pediatr.* 2005 Jan;146(1):35-40.
Levine, et al, *Inflamm Bowel Dis.* 2011 Jun;17(6):1314-21.

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Classification of Pediatric IBD

Age of Onset

- Younger than 17
- Younger than 10
- Younger than 6
- Younger than 2
- First 28 days of life

Group/Classification

- Montreal A1/Paris A1b
- Paris A1a
- VEOIBD
- Infantile IBD
- Neonatal IBD

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Levine A, et al. *Inflamm Bowel Dis.* 2011;1314-1321.
Uhlig H, et al. *Gastroenterology.* 2014;147:990-1007.

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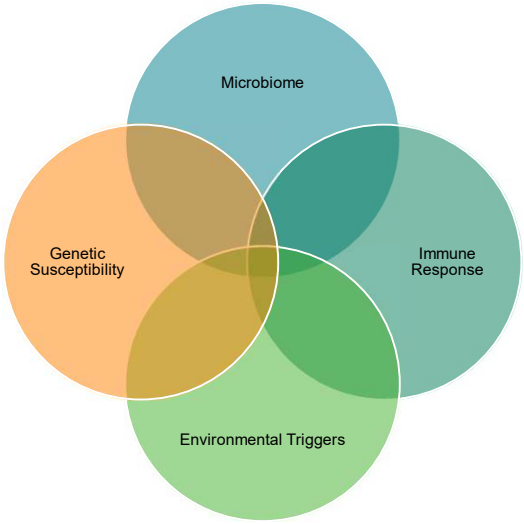
What Causes Inflammatory Bowel Diseases (IBD)?



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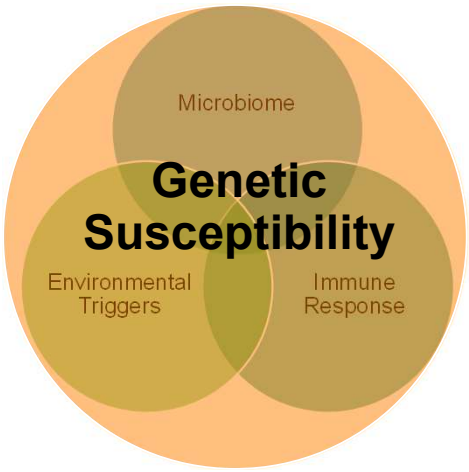
What Causes Very Early-Onset IBD in Children?



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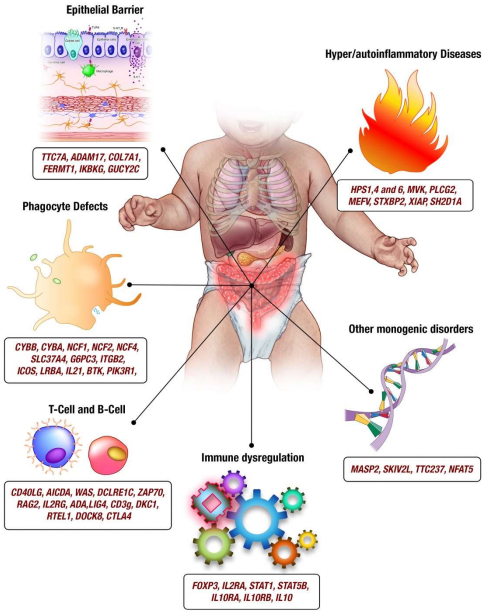

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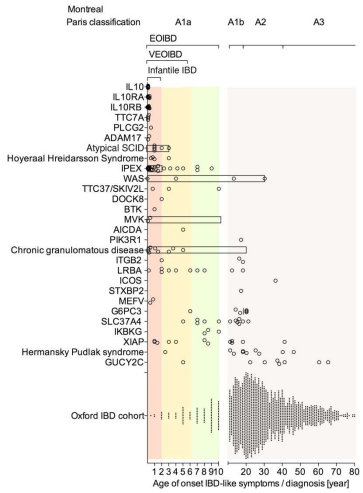
How Does This Apply to Adult Patients?

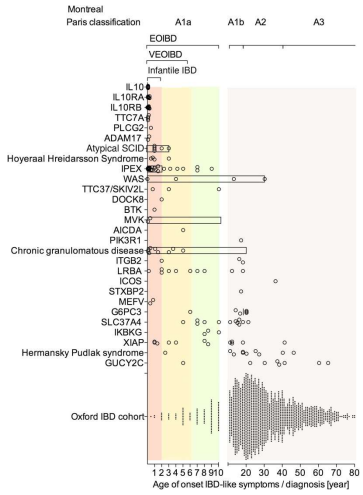


Uhlig H, et al. *Gastroenterology.* 2014;147:990-1007.

12

How Does This Apply to Adult Patients?

- These kids grow up
- Variable penetrance
- Variation in age of onset
- Familial



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Uhlig H, et al. *Gastroenterology.* 2014;147:990-1007.

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FOXP3

- **IPEX**
  - Immunodeficiency
  - Polyendocrinopathy
  - Enteropathy
  - X-linked

The immunological and genetic basis of immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome

Khalid Bin Dhuban[a] and Ciriaco A. Piccirillo[b]

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Curr Opin Allergy Clin Immunol. 2015;15:525–532.

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Representative Case

- 24-year-old male
- Disseminated varicella age 5 PICU
- Severe Crohn ileocolitis
- Immunoglobulin deficiencies (IVIG)
- Periodic fevers

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Whole Exome Sequencing

FOXP3 gene variant: p.P339A classified as likely pathogenic.

Heterozygous pathogenic variant in *MEFV* gene, p.E148Q associated with periodic fever (FMF; familial Mediterranean fever). Patient has reported episodes of unexplained fever.

Also, had heterozygous variants (VUS) in *SLC37A4* and *TTC37* genes.

SLC37A4 gene mutations are associated with glycogen storage diseases 1b and 1c.

TTC37 gene mutations are associated with trichohepatoenteric syndrome (THE).

Both the above are autosomal recessive conditions.

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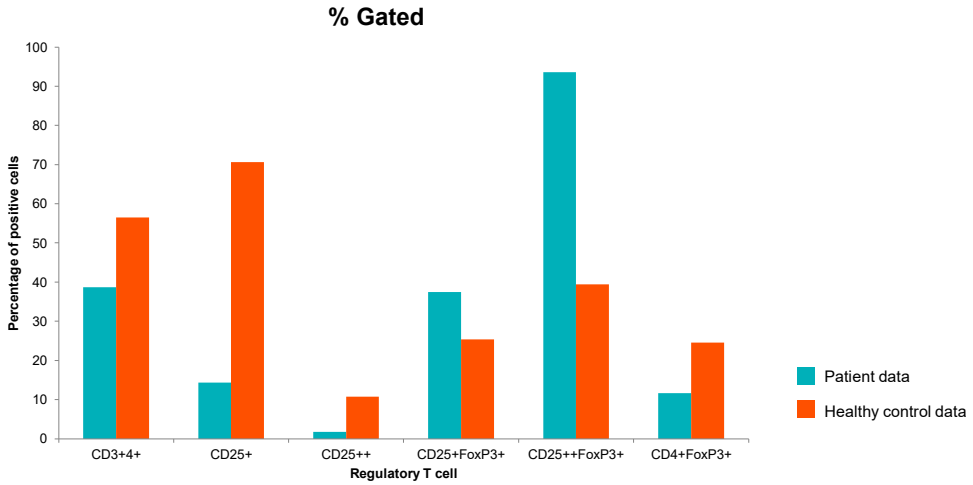
Patient Data Compared to Healthy Control
Percent Positive Cells for Each Subset Listed on X Axis



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Laboratory of Roshini Abraham, Ph.D.

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How Did This Change the Patient's Care?

- Sirolimus
- Referral for bone marrow transplantation

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Journal of Crohn's and Colitis, 2018, 1104–1112
doi:10.1093/ecco-jcc/jjy068
Advance Access publication May 18, 2018
Original Article

Original Article

Diagnostic Yield of Next-generation Sequencing in Very Early-onset Inflammatory Bowel Diseases: A Multicentre Study

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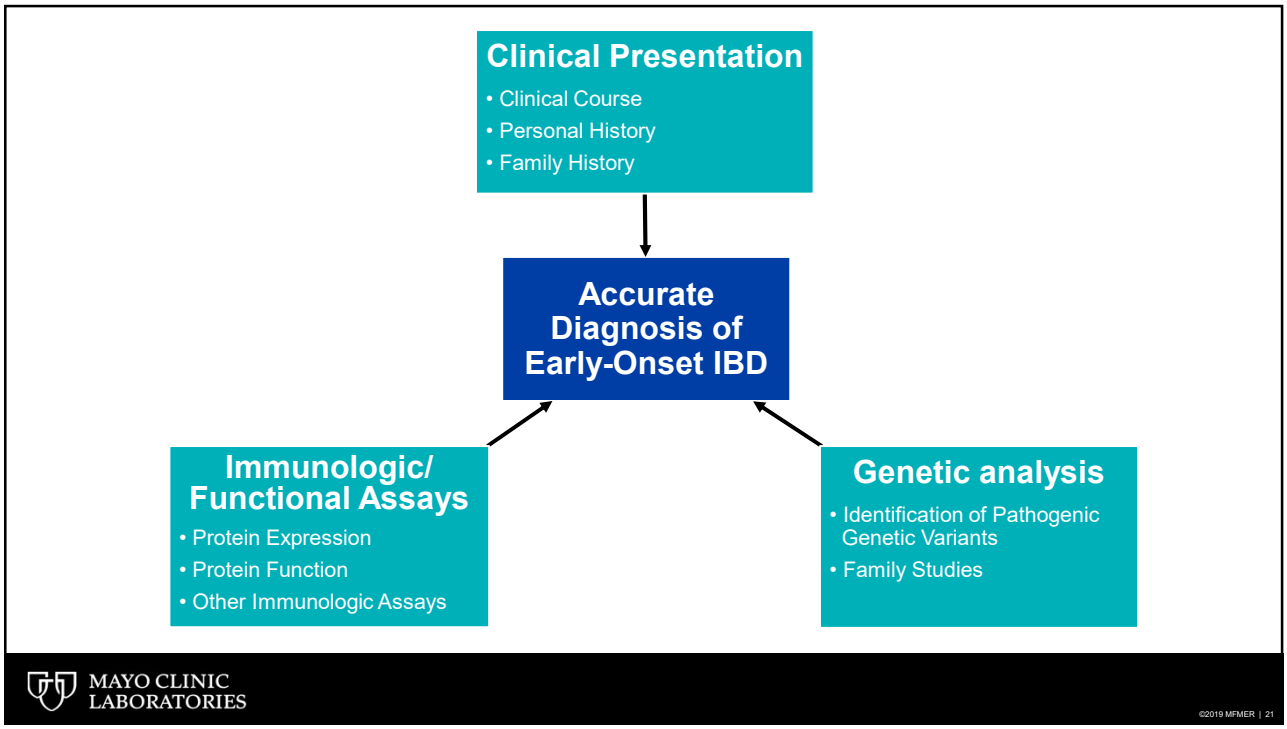
"In a routine clinical setting, TNGS is the method to prefer as it is cost- and time-effective while providing optimal coverage of the genes of interest."

It is not always a complicated answer

A new path forward: Hussein - Insights (mayocliniclabs.com)



21

Early Onset Monogenic Inflammatory Bowel Disease Gene Panel (EOIBD)

- **Designed to detect variants in genes associated with monogenic inflammatory bowel disease (IBD) or IBD-like conditions**
  - Designed for patients with early-onset or very early-onset disease
- **May allow for:**
  - A more specific treatment plan
  - Predictive testing of at-risk family members

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Early Onset Monogenic Inflammatory Bowel Disease Gene Panel (EOIBD)

- Next-generation sequencing (NGS) panel with supplemental Sanger sequencing
- Recently updated from 51 genes to **107 genes**
- Specimen types: blood, skin biopsy, cultured fibroblasts

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EOIBD (107 genes)

ADA	*ADAM17*	*AICDA*	*AIRE*	*ALPI*	*ANKZF1*	*ARPC1B*	*ASAH1*	*BACH2*	*BTK*
CARMIL2	*CASP8*	*CD3G*	*CD40LG*	*CD55*	*COL7A1*	*CTLA4*	*CYBA*	*CYBB*	*CYBC1*
DCLRE1C	*DEF6*	*DGAT1*	*DKC1*	*DOCK8*	*DUOX2*	*EPCAM*	*FCHO1*	*FERMT1*	*FOXP3*
G6PC1	*G6PC3*	*GUCY2C*	*HPS1*	*HPS3*	*HPS4*	*HPS6*	*ICOS*	*IFIH1*	*IKBKG*
IL10	*IL10RA*	*IL10RB*	*IL21*	*IL21R*	*IL2RA*	*IL2RB*	*IL2RG*	*IL7R*	*ITCH*
ITGB2	*JAK1*	*LCT*	*LIG4*	*LRBA*	*MALT1*	*MEFV*	*MVK*	*MYO5B*	*NCF1*
NCF2	*NCF4*	*NEUROG3*	*NFKBIA*	*NLRC4*	*PAX1*	*PCSK1*	*PIK3CD*	*PIK3R1*	*PLCG2*
PLVAP	*POLA1*	*RAG1*	*RAG2*	*RIPK1*	*RTEL1*	*SH2D1A*	*SI*	*SKIV2L*	*SLC10A2*
SLC26A3	*SLC37A4*	*SLC39A4*	*SLC51B*	*SLC5A1*	*SLC9A3*	*SPINT2*	*STAT1*	*STAT3*	*STAT5B*
STIM1	*STX3*	*STXBP2*	*TGFB1*	*TGFBR1*	*TGFBR2*	*TLR3*	*TNFAIP3*	*TRIM22*	*TRNT1*
TTC37	*TTC7A*	*UNC45A*	*WAS*	*WIPF1*	*XIAP*	*ZAP70*	*ZBTB24*		

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How were the 107 genes selected?

- **Literature Review**
  - Emerging field; may be able to design a panel ranging from ~20 up to 160 genes depending on selection criteria
    - Laboratories may include only immunodeficiency genes, include/exclude genes for differential diagnosis (e.g. congenital diarrhea), include/exclude emerging genes that are more of academic interest and not yet well-established; polygenic risk loci
    - Our approach: immune genes as well as those in differential diagnosis; limited ”emerging” genes; excluded polygenic risk loci

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Who should you test?

- **Pediatric Porto Group of European Society of Paediatric Gastroenterology, Hepatology and Nutrition; British Society of Gastroenterology and British Society of Paediatric Gastroenterology, Hepatology and Nutrition:**
  - Genetic sequencing is ‘recommended’ for every child with IBD onset <2 yo
  - ‘Suggested’ for children <6yo, particularly if other clinical features are present

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J Pediatr Gastroenterol Nutr. 2021;72(3):456-473

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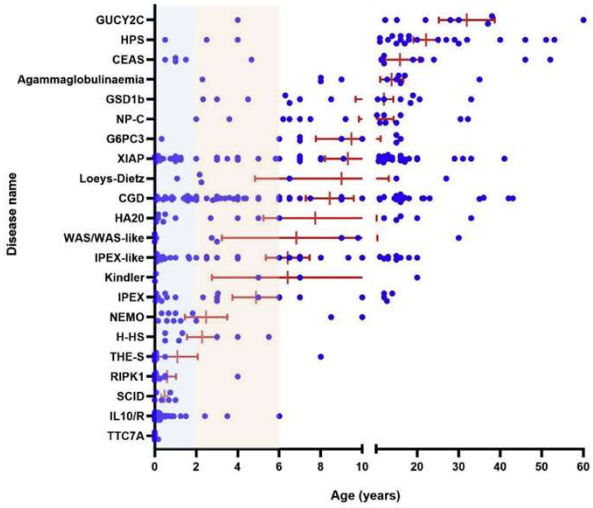
Clinical Gastroenterology and Hepatology 2022;20:e653–e663

ELECTRONIC SYSTEMATIC REVIEWS AND META-ANALYSES

Siddharth Singh, Section Editor

A Systematic Review of Monogenic Inflammatory Bowel Disease



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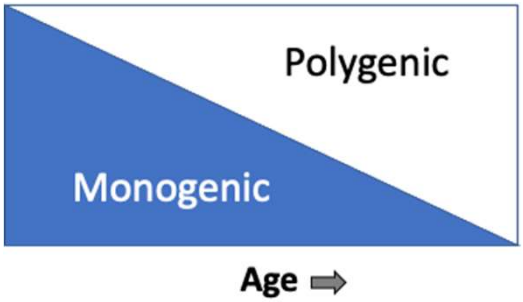
Who should you test?

- **6.3-7.9% of patients with very early onset IBD have a monogenic cause**
  - This may significantly change treatment
- **Among patients with monogenic IBD:**
  - >60% developed IBD before age 6 years
  - 17% developed IBD between ages 10-17.9 years
  - 10.9% developed IBD after age 18



- ***Although monogenic IBD is more common in young children, nearly one third of all patients were diagnosed after 6 years of age and more than 10% as adults.***

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Clin Gastroenterol Hepatol 2022;20(4):e653-e663
Clin Immunol 2022;240:109047
J Crohns Colitis 2022;16(9):1380-1396

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A Behind-the-Scenes Look at the Lab

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Genetic Testing at Mayo Clinic Laboratories

- **Sample arrives in lab**
  - Patient information sheet is reviewed (if provided) to ensure appropriate testing
  - Genetic counselors will contact ordering provider if a misorder is suspected
- **DNA is extracted and sample is run on our targeted panel**
  - NGS with Sanger sequencing to fill in gaps in coverage and for homologous genes

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	Targeted Panels	Exomes	Genomes
Number of Genes	<500	4,000–20,000	>20,000 plus intergenic
Inclusion of Genes for Disease of Interest	Yes (gaps in coverage typically filled)	Possibly (may miss key genes)	Generally yes (not optimized for specific disease)
Inclusion of Important Non-Coding Regions	Often included in test design	Typically not	Yes
Pros	Higher sensitivity for specific phenotypes due to test design	Useful for non-specific/overlapping phenotypes and gene discovery	Useful for non-specific/overlapping phenotype and gene discovery
Cons	Limited by what is on the panel	May have lower sensitivity due to lack of supplemental analysis	May have lower sensitivity due to lack of supplemental analysis
Cost	$	$$	$$$

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NGS: Depth of Coverage (Read Depth)

- How many times each base has been sequenced/read
- NGS has relatively high error rate
- Each base needs to be read many times to make a confident base call (i.e., >30x)

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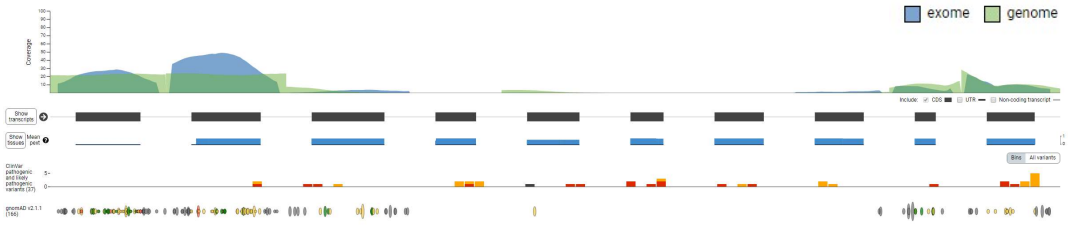
Exome/Genome Sequencing Does Not Include All Genes

IKBKG

- X-linked ectodermal immunodeficiency
- Crohn's disease-like enterocolitis; increased epithelial apoptosis
- Skin lesions



https://gnomad.broadinstitute.org/gene/ENSG00000073009

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IKBKG inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase gamma. gnomAD browser. https://gnomad.broadinstitute.org/gene/ENSG00000073009. Accessed May 7, /2019.

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Targeted NGS vs Exome Coverage

Exome

- Most ES platforms cover only 85–90% of exons
- 50% of exons are <30x average coverage in 60,000 samples from ExAC*
- 60% of low-coverage reads in ES occur in highly repetitive stretches of DNA**
- Thus, exome sequencing can miss critically important regions/variants

Targeted panels

- Coverage issues are usually easy to overcome
- Regions that still have poor coverage after boosting can be analyzed by supplementary methods

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*Exome Aggregation Consortium. ExAC Browser. 2016. http://exac.broadinstitute.org.
**Wang, et al. *Scientific Reports*. 2017;7:885.

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Genetic Testing at Mayo Clinic Laboratories

- Sample arrives in lab
- DNA is extracted and sample is run on our targeted panel
- Data is analyzed
  - A team of expert genetic counselors and laboratory directors reviews each case
  - Use the American College of Medical Genetics and Genomics/ Association for Molecular Pathology (ACMG/AMP) criteria for variant classification

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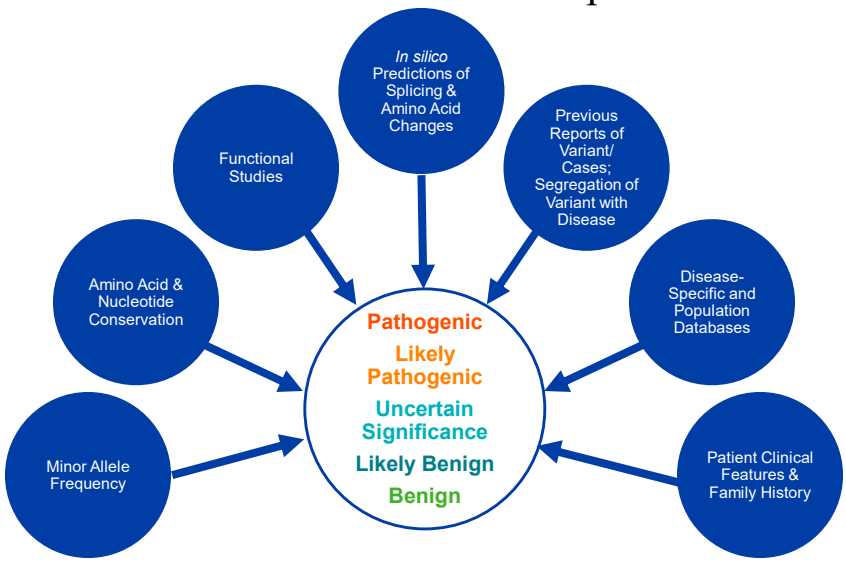
Classification of Variants and Results Interpretation



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Genetic Variant Classification and Interpretation

- Genetic testing is probabilistic in nature
  - Variants are classified along a continuum of estimated likelihood that a variant causes disease based on the weight of current evidence
- Variant classification and interpretation is the most challenging portion of genetic testing
  - Although guidelines with specific criteria are used, professional judgement is required
  - Is a detected variant the cause of the patient's phenotype?
- A variant's classification may change over time as more evidence becomes available

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Genetic Test Results Should Be Used in the Context of the Patient's Clinical Presentation

Pathogenic	•Variant has met criteria such that provider may use molecular testing information in clinical decision-making •Use in conjunction with other clinical information when possible
Likely Pathogenic	•Sufficient evidence that the provider may use molecular testing information in clinical decision-making when combined with other evidence of the disease in question •Additional follow-up testing is recommended to support decision-making
Uncertain Significance	•Should not be used in clinical decision-making •Efforts to resolve the classification as pathogenic or benign should be undertaken •Additional monitoring of the patient for the disorder in question should be considered
Likely Benign	•Sufficient evidence that the provider may conclude the variant is not the cause of the patient's disorder when combined with other information •Typically not reported clinically
Benign	•Sufficient evidence that the provider may conclude the variant is not the cause of the patient's disorder •Typically not reported clinically

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Limitations of Mayo Clinic's Inflammatory Bowel Disease Primary Immunodeficiency Panel (IBDGP)

- **Unlikely to be helpful for patients who present in late adolescence or adulthood, particularly those who respond to conventional therapy**
  - Patients less likely to have a monogenic cause of IBD
- **Detection of copy number variation is not included in the current version (update expected soon)**
- **If chronic granulomatous disease (CGD) is suspected, consider adding dihydrorhodamine flow test (DHR)**
  - Variants in *NCF1* ($p47^{phox}$) account for 25% of CGD in the Western world and a higher percentage elsewhere
  - *NCF1* has a common GT deletion that is difficult to detect by NGS and is not included in our panel

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Future Directions/Challenges

- **Today we are able to test for monogenic forms of IBD**
- **Polygenic risk testing may be available in the future**
  - Currently there are challenges, including whether they are appropriate/applicable across ancestral backgrounds
- **Beginning to identify more potential "risk" variants/alleles**
  - Difficult today to classify these variants, but as literature emerges, will need a system for classification/reporting

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Benefits of Performing Genetic Testing for Early Onset IBD through Mayo Clinic Laboratories

- **Expert curation and interpretation of each variant identified**
  - Genetic counselors and laboratory directors are only a phone call (or email) away and happy to discuss appropriateness of testing and/or results with ordering providers
- **Testing for family members is available when a clinically significant variant is identified (test ID: FMTT)**
- **In addition to genetic testing, many functional tests are available through Mayo Clinic Laboratories**
  - Helpful to confirm diagnosis and/or obtain additional information when a variant of unknown significance (VUS) is identified
- **Easy-to-read report with detailed information on findings**

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1-800-533-1710

IBDGP

Inflammatory Bowel Disease Primary Immunodeficiency (PID) Panel

Patient ID	Patient Name		Birth Date	Gender	Age
SA00536198	TESTINGRNV, IBDGP ABNORMAL		2013-12-31	F	5
Order Number	**Client Order Number**	**Ordering Physician**	**Report Notes**		
SA00536198	SA00536198	CLIENT,CLIENT			
Account Information		**Collected**			
C7028846 DLMP Rochester		20 Mar 2019 00:00			

Result Summary

MCR

Pathogenic Variant(s) Detected

Result

MCR

ADA	ADAM17	AICDA	BTK	CD3G	CD40LG	CTLA4	CYBA	CYBB
DCLRE1C	DKC1	DOCK8	FOXP3	G6PC3	ICOS	IKBKG	IL10	IL10RA
IL10RB	IL21	IL21R	IL2RA	IL2RG	ITGB2	LIG4	**LRBA**	MEFV MVK
NCF2	NCF4	NLRC4	PIK3CD	PIK3R1	PLCG2	RAC1	RAG2	RTEL1
SH2D1A	SKIV2L	SLC37A4	STAT1	STAT3	STIM1	STXBP2	TNFRSF13	TTC37
TTC7A	WAS	WIPF1	XIAP	ZAP70				

The following variant was detected:

Gene (Transcript): LRBA (NM_006726.4)
Genomic position: Chr4(GRCh37):g.151792597dup
cDNA change: c.2267dupC
Amino acid change: p.Glu757Argfs*14
The patient is homozygous for this variant.
Classification: Pathogenic

The results for the remaining genes on this panel are negative.

MCR

Performing Site Legend

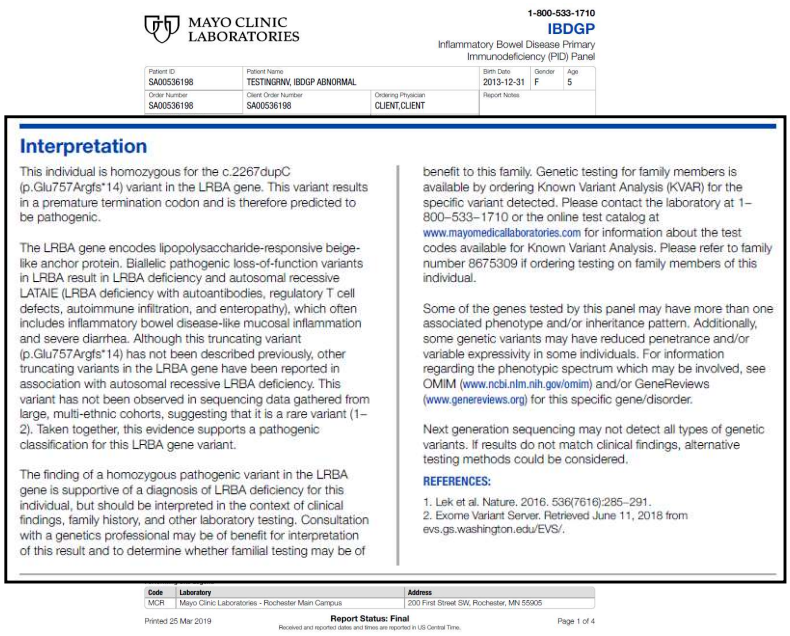
Code	Laboratory	Address
MCR	Mayo Clinic Laboratories - Rochester Main Campus	200 First Street SW, Rochester, MN 55905

Printed 25 Mar 2019

Report Status: Final

Received and reported dates and times are reported in US Central Time.

Page 1 of 4



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1-800-533-1710

IBDGP

Inflammatory Bowel Disease Primary Immunodeficiency (PID) Panel

Patient ID	Patient Name		Birth Date	Gender	Age
SA00536198	TESTINGRNV, IBDGP ABNORMAL		2013-12-31	F	5
Order Number	**Client Order Number**	**Ordering Physician**	**Report Notes**		
SA00536198	SA00536198	CLIENT,CLIENT			

Interpretation

This individual is homozygous for the c.2267dupC (p.Glu757Argfs*14) variant in the LRBA gene. This variant results in a premature termination codon and is therefore predicted to be pathogenic.

The LRBA gene encodes lipopolysaccharide-responsive beige-like anchor protein. Biallelic pathogenic loss-of-function variants in LRBA result in LRBA deficiency and autosomal recessive LATAIE (LRBA deficiency with autoantibodies, regulatory T cell defects, autoimmune infiltration, and enteropathy), which often includes inflammatory bowel disease-like mucosal inflammation and severe diarrhea. Although this truncating variant (p.Glu757Argfs*14) has not been described previously, other truncating variants in the LRBA gene have been reported in association with autosomal recessive LRBA deficiency. This variant has not been observed in sequencing data gathered from large, multi-ethnic cohorts, suggesting that it is a rare variant (1–2). Taken together, this evidence supports a pathogenic classification for this LRBA gene variant.

The finding of a homozygous pathogenic variant in the LRBA gene is supportive of a diagnosis of LRBA deficiency for this individual, but should be interpreted in the context of clinical findings, family history, and other laboratory testing. Consultation with a genetics professional may be of benefit for interpretation of this result and to determine whether familial testing may be of benefit to this family. Genetic testing for family members is available by ordering Known Variant Analysis (KVAR) for the specific variant detected. Please contact the laboratory at 1–800–533–1710 or the online test catalog at www.mayomedicallaboratories.com for information about the test codes available for Known Variant Analysis. Please refer to family number 8675309 if ordering testing on family members of this individual.

Some of the genes tested by this panel may have more than one associated phenotype and/or inheritance pattern. Additionally, some genetic variants may have reduced penetrance and/or variable expressivity in some individuals. For information regarding the phenotypic spectrum which may be involved, see OMIM (www.ncbi.nlm.nih.gov/omim) and/or GeneReviews (www.genereviews.org) for this specific gene/disorder.

Next generation sequencing may not detect all types of genetic variants. If results do not match clinical findings, alternative testing methods could be considered.

REFERENCES:

1. Lek et al. Nature. 2016. 536(7616):285–291.
2. Exome Variant Server. Retrieved June 11, 2018 from evs.gs.washington.edu/EVS/.

Code	Laboratory	Address
MCR	Mayo Clinic Laboratories - Rochester Main Campus	200 First Street SW, Rochester, MN 55905

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Report Status: Final

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Page 1 of 4

43

Benefits of Performing Genetic Testing for Early-Onset IBD through Mayo Clinic Laboratories

- We recognize that there is a patient behind every sample that comes into our laboratory
- We offer high-quality testing to help you care for your patients

44

Early Onset Monogenic Inflammatory Bowel Disease Gene Panel (EOIBD)

- Next-generation sequencing (NGS) panel with supplemental Sanger sequencing
- Recently updated from 51 genes to **107 genes**
- Specimen types: blood, skin biopsy, cultured fibroblasts

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45

EOIBD (107 genes)

ADA	*ADAM17*	*AICDA*	*AIRE*	*ALPI*	*ANKZF1*	*ARPC1B*	*ASAH1*	*BACH2*	*BTK*
CARMIL2	*CASP8*	*CD3G*	*CD40LG*	*CD55*	*COL7A1*	*CTLA4*	*CYBA*	*CYBB*	*CYBC1*
DCLRE1C	*DEF6*	*DGAT1*	*DKC1*	*DOCK8*	*DUOX2*	*EPCAM*	*FCH01*	*FERMT1*	*FOXP3*
G6PC1	*G6PC3*	*GUCY2C*	*HPS1*	*HPS3*	*HPS4*	*HPS6*	*ICOS*	*IFIH1*	*IKBKG*
IL10	*IL10RA*	*IL10RB*	*IL21*	*IL21R*	*IL2RA*	*IL2RB*	*IL2RG*	*IL7R*	*ITCH*
ITGB2	*JAK1*	*LCT*	*LIG4*	*LRBA*	*MALT1*	*MEFV*	*MVK*	*MYO5B*	*NCF2*
NCF4	*NEUROG3*	*NFKBIA*	*NLRC4*	*PAX1*	*PCSK1*	*PIK3CD*	*PIK3R1*	*PLCG2*	*PLVAP*
POLA1	*RAG1*	*RAG2*	*RIPK1*	*RTEL1*	*SH2D1A*	*SI*	*SKIV2L*	*SLC10A2*	*SLC26A3*
SLC37A4	*SLC39A4*	*SLC51B*	*SLC5A1*	*SLC9A3*	*SPINT2*	*STAT1*	*STAT3*	*STAT5B*	*STIM1*
STX3	*STXBP2*	*TGFB1*	*TGFBR1*	*TGFBR2*	*TLR3*	*TNFAIP3*	*TRIM22*	*TRNT1*	*TTC37*
TTC7A	*UNC45A*	*WAS*	*WIPF1*	*XIAP*	*ZAP70*	*ZBTB24*			

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46

How were the 107 genes selected?

- **Literature Review**
  - Emerging field; may be able to design a panel ranging from ~20 up to 160 genes depending on selection criteria
    - Laboratories may include only immunodeficiency genes, include/exclude genes for differential diagnosis (e.g. congenital diarrhea), include/exclude emerging genes that are more of academic interest and not yet well-established; polygenic risk loci
    - Our approach: immune genes as well as those in differential diagnosis; limited ”emerging” genes; excluded polygenic risk loci

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47

Thank You!

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48

Questions?

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49