Novel homozygous *NPC1* mutation diagnosed in a 2 month old with cholestasis by rapid Whole-Genome sequencing

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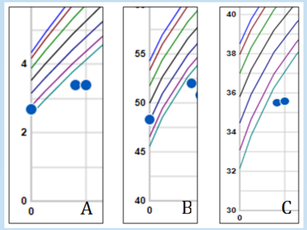
BACKGROUND

- Niemann-Pick Type C disease (NPC) is an autosomal recessive inborn error of intracellular cholesterol trafficking
- Progressive neurologic disorder
- May present with cholestasis in infancy
- Targeted therapy approved in EU
- Promising experimental therapy available

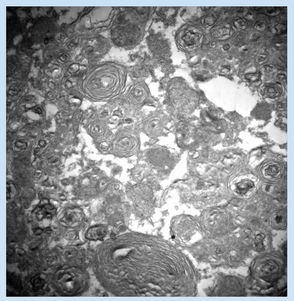
CASE

- Term male
- Non-consanguineous parents
- Admitted at 7 weeks of age for failure to thrive, direct hyperbilirubinemia and elevated hepatic transaminases
- Exam: jaundice, hepatosplenomegay, clinodactyly, hypotonia

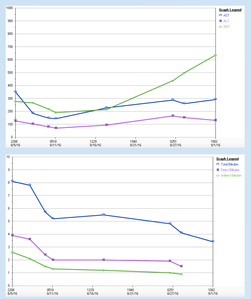


A: Weight (kg) B: Length (cm) C: Head circumference (cm)

DIAGNOSTIC WORKUP

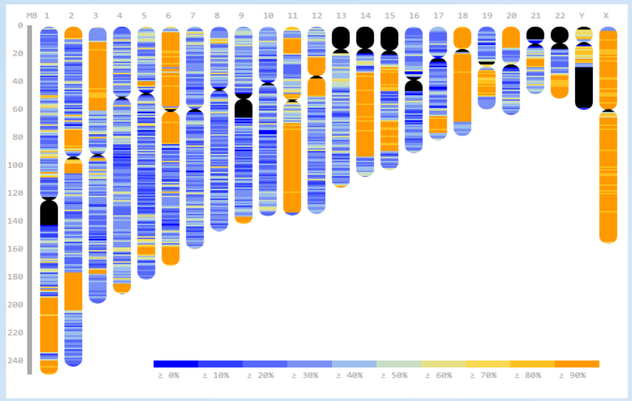


Electron microscopy: numerous concentric lamellar bodies



WGS RESULTS

Gene	Genomic location	HGVS cDNA	HGVS Protein	Zygosity	Variant Interpretation
NPC1	Chr18: 21119857 (on assembly GRCh38	NM_000271.3 c.2713C>T	p.Gln905Ter	Homozygous	Likely Pathogenic



Very Strong	Null variant (nonsense, frameshift, ±1 or 2 splice site position, initiation codon, exon deletion) in gene where LOF known to cause disease
Strong	• Same amino acid change as previously established pathogenic variant • De novo in a patient with the disease and no family history • Functional studies show damaging effect on the gene • Prevalence in affected individuals significantly greater than controls
Moderate	• Located in mutational hot spot/functional domain without benign variation • Absent from controls • For recessive disorders, detected in trans with a pathogenic variant • Protein length changed by in-frame indel in nonrepeat region or stop-loss • Novel missense at amino acid where different missense known to be pathogenic • Assumed de novo, but without confirmation of paternity and maternity
Supporting	• Cosegregation with disease in multiple affected family members in gene known to cause disease • Missense variant in gene with low rate of benign missense variants and where missense variants commonly cause disease • Multiple computational tools call deleterious • Phenotype highly specific for disease with single genetic etiology • Reputable source reports as pathogenic, but unpublished

FAMILY 6011	100023-proband			UNITS	REFERENCE RANGE
Sex	M verified				
Yield: raw/bulk	195.8			Gbp	> 180
% mapped	98.90%			pct	98-100
% duplicates	12.11%			pct	< 15%
Yield	170.4			Gbp	> 130
Insert size: Mean +/- std.dev	352.4 +/- 98.98			bp	300-480
Average and median coverage across genome	51.0			x	> 40
Average coverage over OMIM genes	51.0			x	> 40
# of OMIM genes with coverage at <10X (and list)	254			ENST	< 2% (282)
# of OMIM genes with 100% coverage at >=10X	98.2%			pct	> 98%
# of OMIM genes with 100% coverage at >=20X	96.8%			pct	> 94%
# of OMIM genes with 100% coverage at >=30X	86.9%			pct	> 80%
# of genes with 100% coverage at >=40X	40.0%				
Variation (VCF) metrics					
# of calls Total	4613310				2.5-6.0M
# of PASS calls	4539914				2.5-6.0M
# of calls Total coding	25211				25000-30000
Total # of SNVs	3773668 [81.80%]				
Total # of Indels	839642 [18.20%]				
Hom/Het ratio (in coding regions)	0.84 (0.97)	<-- ROH		ratio	0.5-0.61
Ti/Tv ratio (in coding regions)	2.03 (2.93)			ratio	2-2.2 (2.8-3)
# of het calls (# of hom call)	2565342 (2160093)			units	
In-silico sample swap check	n/a				
Automated upload of VCF to Omicia	PASS				
Inform sign-out of analysis-ready state	PASS				
Detect sample analysis completion state on Omicia	PASS				
Update LIMS	TBD				
Download annotated VCF to RCI	TBD				

CLINICAL COURSE

- Time to diagnosis: 6 days
- Started on Miglustat therapy
- WGS results reported 16 days before clinical testing completed
- Cholestasis resolved

DISCUSSION

- Youngest patient diagnosed with NPC
- Youngest patient to be started on Miglustat
- Rapid WGS allows for timely diagnosis and early targeted therapy
- Early diagnosis prompts debate regarding initiating therapy in such a young child

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