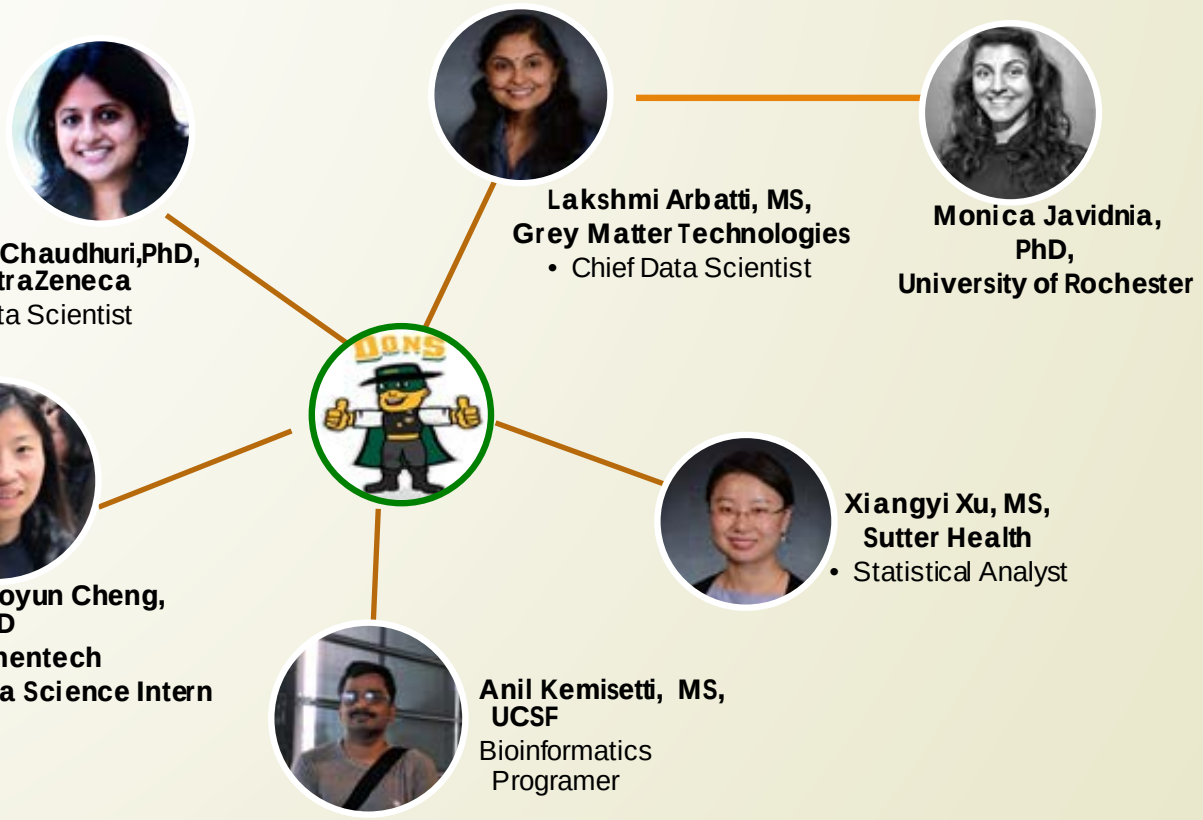
Beyond Undiagnosed

By DONS

June 2019

DONS Team



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Goals

- Help John identify causes.
- Identify possible causes to benefit more people who may be in similar situations.
- Set up workflow replicable.

Hypotheses

- Recurrent themes that we observed in his symptoms point to:
- 1) brain stem area related dysfunction (nausea, difficulty regulating temperature, delayed gastric emptying, vomiting, sweating etc),
- 2) probable collagen disorder,
- 3) probable lysosomal storage disease

Workflow

- As a preparation, fathom medical records, gather physicians and biologists' thoughts, run testing by using IGV (Integrative Genomics Viewer) and CRAVAT VEST-4 (Variant Effect Scoring Tool),CHASM-3.1.
- Listen to John to collect first-hand patient experience, symptoms, and reaction to medications to formulate thoughts.
- 2-way in parallel:
  - Further extract and filter medical records to gather key symptoms and diagnosis.
  - Use Ingenuity Variant Analysis to find suspicious causes based on patient's symptoms sharing.

Talking to John . What did we know : (Part 1)

Gastrointestinal

a. Would vomit up breast milk as a child. Switched to soy formula.
b. Dexamethasone helped with appetite, but experienced negative side effects at higher doses
c. Primarily eats processed foods (e.g., cup of noodles) and as a child, preferred liquids (e.g., broth)
d. Chronic use of laxatives due to gastroparesis/low gut motility
e. Slow reacidification of the stomach
f. Uvula suturing helped with vomiting and nausea, but uvula is still swollen, red
g. MCT and coconut oil lead to abdominal pains and constipation
h. Major abdominal distention and pain following meals

Talking to John . What did we know : (Part 2)

Sleep, vision, olfaction, and hearing are normal

a. Sleep disturbed due to urinary frequency. Also experiences urinary hesitancy and can take 20 minutes to initiate flow. No sexual dysfunction.

Muscle levels are okay, but low body fat is primary concern (major back injury due to low weight)

Fatigues quickly and easily; takes stimulants (e.g., coffee) to counter fatigue

HPV vaccine helped with warts on hands; previously had them frozen off

Symptoms extracted from medical notes using AWS Textract

	A	B	C	D	E	F	
1	Text	Type	Category	Score	BeginOffset	EndOffs	filetype
876	abdominal pain	DX_NAME	MEDICAL_CONDITION	0.905964971	307	321	Undiagnosed_Disease
877	burning	DX_NAME	MEDICAL_CONDITION	0.979380906	326	333	Undiagnosed_Disease
886	metabolic alkalosis	DX_NAME	MEDICAL_CONDITION	0.698283374	948	967	Undiagnosed_Disease
888	frequent urination	DX_NAME	MEDICAL_CONDITION	0.746630013	1271	1289	Undiagnosed_Disease
889	constant	ACUITY	MEDICAL_CONDITION	0.80287689	1294	1302	Undiagnosed_Disease
890	pelvic discomfort	DX_NAME	MEDICAL_CONDITION	0.984199047	1303	1320	Undiagnosed_Disease
892	pain	DX_NAME	MEDICAL_CONDITION	0.949248552	1349	1353	Undiagnosed_Disease
893	burning pain	DX_NAME	MEDICAL_CONDITION	0.368287951	1390	1402	Undiagnosed_Disease
895	frequent	ACUITY	MEDICAL_CONDITION	0.561213255	1487	1495	Undiagnosed_Disease
896	fungal infections	DX_NAME	MEDICAL_CONDITION	0.988404274	1496	1513	Undiagnosed_Disease
898	plantar warts	DX_NAME	MEDICAL_CONDITION	0.586639881	1540	1553	Undiagnosed_Disease
916	homozygous (VUS	DX_NAME	MEDICAL_CONDITION	0.350063235	1859	1874	Undiagnosed_Disease
919	ALDOB	DX_NAME	MEDICAL_CONDITION	0.268204272	1926	1931	Undiagnosed_Disease

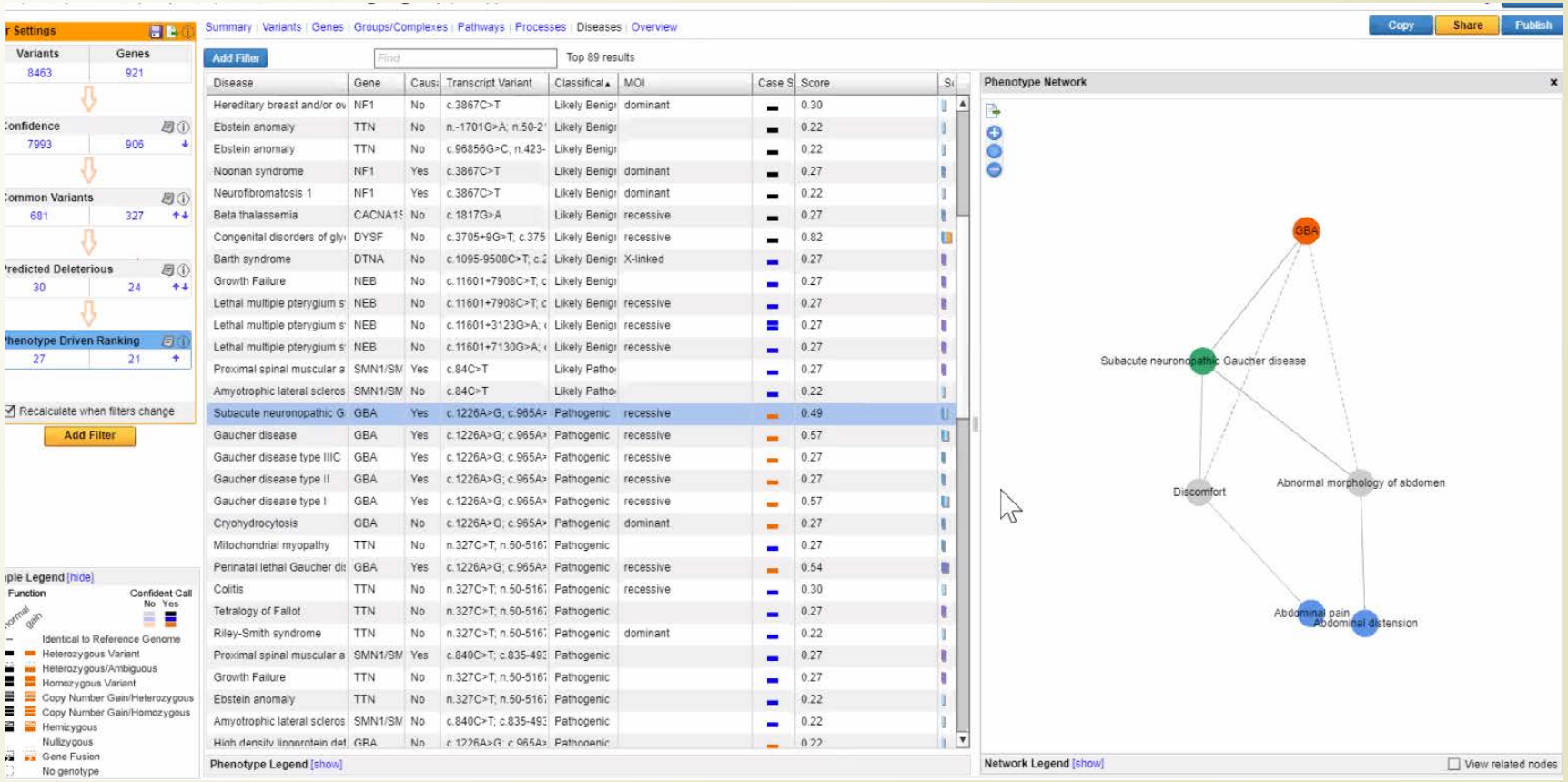
Phenotype Driven Analysis (QIAGEN-IVA)

Panel:

Cardial-neural

Filters:

- Abdominal distension
- Abdominal pain
- Weight and growth Stagnation
- Hyperhidrosis



CRAVAT

Referen c bas	Alternat e bas	Sampl e	HUGO symb	Sequenc e onto	Protein sequ cha	ClinVar	COSMIC ID	COSMIC variant count (tissue)	Number of samples w variant	dbSNP	ESP6500 AF (averag	GeneCards summary (from http://www.genecards.org)	PubMed article co	P sea
T	C	SQ9192	GBA	MS	N409S	Pathogenic/Likely pathogenic, risk factor			1	rs76763715	0.00139568	This gene encodes a lysosomal membrane protei	24	http:

Sample ID	HUGO symbol	Sequence ontology	Protein sequence change	CHASM p-value	CHASM FDR	ClinVar	COSMIC ID	COSMIC variant count (tissue)	Number of samples with variant	dbSNP	ESP6500 AF (average)	GeneCards summary (from http://www.genecards.org)	PubMed article count	PubMed search term	gr
SQ9309_LS805	GBA	MS	N409S	0.4372	1.00	Pathogenic/Likely pathogenic, risk factor			1	rs76763715	0.00139568	This gene encodes a lysosomal	24	http://www.ncbi	0
SQ9309_LS805	GYG1	MS	D102H	0.0472	1.00	Pathogenic/Likely pathoge	COSM3736309	skin(1)	1	rs143137713	0.00104372	This gene encodes a member o	0		0
SQ9309_LS805	ALDOB	MS	A150P	0.6342	1.00	Pathogenic			1	rs1800546	0.00272696	Fructose-1,6-bisphosphate ald	6	http://www.ncbi	0

le	HUGO symbol	Sequenc	Protein	CHASM	CHASM	ClinVar	COSMIC	COSMIC	Number	dbSNP	ESP6500	GeneCards summary (from http://www.genecards.org)	PubMed	PubMed	gnomAD	gnomAD	gnomAD	gnomAD	gnomAD	gn
04_LS	GBA	MS	N409S	0.3072	1	Pathogenic/Likely pathogenic, risk			1	rs76763715	0.001396	This gene encodes a lysosomal membrane protein that cleaves the	24	http://www	0.002248	0.000167	0.000872	0.027192		0
04_LS	GYG1	MS	D102H	0.0542	1	Pathogenic	COSM3736	skin(1)	1	rs14313771	0.001044	This gene encodes a member of the glycogenin family. Glycogenin	0		0.001025	0.000125	0.00122			3
04_LS	HTT	ID	QQ18_			Pathogenic	COSM5001	upper_aero	1	rs3740769	0.307359	Huntingtin is a disease gene linked to Huntington's disease, a neu	64	http://www.ncbi.nlm.nih.gov/pubmed?term=HTT[TIAB]+AND+cancer[MH]						
04_LS	HTT	II	Q18QQ			Pathogenic	COSM5960	thyroid(3);	1		0.307359	Huntingtin is a disease gene linked to Huntington's disease, a neu	64	http://www.ncbi.nlm.nih.gov/pubmed?term=HTT[TIAB]+AND+cancer[MH]						
04_LS	KLKB1	MS	S143N	0.3504	1	Pathogenic	COSM3760	large_intes	1	rs3733402	0.621562	Plasma prekallikrein is a glycoprotein that participates in the surfa	4	http://www	0.545419	0.737611	0.630375	0.438325	0.669813	0
04_LS	FGFR4	MS	G388R	0.7522	1	Pathogenic			1	rs351855	0.214624	The protein encoded by this gene is a member of the fibroblast gr	132	http://www	0.320905	0.128659	0.420218	0.320439	0.45	
04_LS	ALDOB	MS	A150P	0.2592	1	Pathogenic			1	rs1800546	0.002727	Fructose-1,6-bisphosphate aldolase (EC 4.1.2.13) is a tetrameric g	6	http://www	0.003059	0.000791	0.001598	0.001774		
04_LS	MBL2	MS	R52C	0.8152	1	Pathogenic			1	rs5030737	0.040552	This gene encodes the soluble mannose-binding lectin or mannos	40	http://www	0.055	0.011238	0.025917	0.102741	0.000106	0
04_LS	CDKN1C	ID	PAPAP206P			Pathogenic			1	rs7591347	0	This gene is imprinted, with preferential expression of the matern	74	http://www.ncbi.nlm.nih.gov/pubmed?term=CDKN1C[TIAB]+AND+cancer[						
04_LS	SAA1	MS	A70V	0.4916	1	Pathogenic	COSM1471	upper_aero	1	rs1136743	0	This gene encodes a member of the serum amyloid A family of apo	27	http://www	0.490997	0.508098	0.419646	0.365436	0.253253	0
04_LS	PTPRJ	MS	Q276P	0.5472	1	Pathogenic	COSM1127	large_intes	1	rs1566734	0.140766	The protein encoded by this gene is a member of the protein tyros	25	http://www	0.165065	0.119022	0.095804	0.235648	0.275615	0
04_LS	ATN1	ID	QQQQQQQ488_			Pathogenic	COSM4317	upper_aero	1		0	Dentatorubral pallidoluysian atrophy (DRPLA) is a rare neurodeger	3	http://www.ncbi.nlm.nih.gov/pubmed?term=ATN1[TIAB]+AND+cancer[MH						
04_LS	GJB2	FD	G12V*			Pathogenic			1	rs8033893	0.00586	This gene encodes a member of the gap junction protein family. Th	9	http://www	0.006258	0.001166	0.004707	0.003646		0
04_LS	TGM1	MS	R286Q	0.8608	1	Pathogenic/Likely pathogenic			1	rs1219187	0	The protein encoded by this gene is a membrane protein that cata	1	http://www	2.03E-05	6.53E-05			5.80E-05	
04_LS	IL4R	MS	I75V	0.2696	1	Pathogenic	COSM1749	thyroid(2);	1	rs1805010	0.473101	This gene encodes the alpha chain of the interleukin-4 receptor, a	35	http://www	0.446891	0.496206	0.453356	0.396844	0.510715	0
04_LS	CACNA1A	ID	QQQQQQ2326_			Pathogenic	COSM5619	haematopo	1	rs7651698	0.44153	Voltage-dependent calcium channels mediate the entry of calcium	8	http://www	0.019559	0.014331	0.005121	0.009082	0.004557	0
04_LS	APOE	MS	C130R	0.3504	1	Pathogenic	COSM3749	large_intes	1	rs429358	0.153099	Chylomicron remnants and very low density lipoprotein (VLDL) rem	275	http://www	0.142539	0.216551	0.104069	0.115518	0.088538	0
04_LS	CST3	MS	A25T	0.217	1	Pathogenic	COSM3749	large_intes	1	rs1064039	0.179436	The cystatin superfamily encompasses proteins that contain multi	3	http://www	0.202127	0.218914	0.09438	0.163061	0.1313	0

Correlation with Medical Literature-1

Gaucher Disease May Rarely Include GI Symptoms, Case Report Highlights

JANUARY 24, 2019 BY ANA PENA IN NEWS.

The case of a young women with Gaucher disease type 3, which affected her small bowel, calls attention to the possibility, although rare, that certain gastrointestinal (GI) symptoms can be a sign of Gaucher disease, a case report shows.

The patient presented with bowel obstruction and gastrointestinal bleeding, likely caused by the deposition of Gaucher cells and the development of a mass in her bowel.

The case report, "Small Bowel Mucosal Involvement and Mesenteric Mass Formation in a Young Female with Type 3 Gaucher Disease. A Case Report," was published in the *Journal of Gastrointestinal and Liver Diseases*.

Gaucher disease is a condition caused by a deficiency in the glucocerebrosidase enzyme, which normally degrades a fat molecule called glucocerebroside. In Gaucher patients, this fat molecule accumulates in certain cells and causes some organs to function abnormally.

The condition mostly affects the spleen, liver, bone, and lungs, but other organs are sometimes also involved. In this case, researchers are reporting on a 24-year-old female who developed symptoms in her GI tract.

The patient had been diagnosed at 1 year old with Gaucher type 3, and had been receiving therapy with Cerezyme (imiglucerase) and albumin infusions, and Vimpat (lacosamide) and levetiracetam to control seizures.

She was admitted to the hospital due to pneumonia in February 2017, complaining of several GI symptoms. A computed tomography (CT) scan revealed enlargement of the liver and spleen, a

Correlation with Medical Literature-2

Akinesia is a disease symptom that causes a person to lose the ability to move their muscles on their own. Sometimes a person's body feels as if it is "frozen" in time.

Doctors commonly associate akinesia with Parkinson's disease, which causes someone to lose control of their movements. However, there are other medical causes connected with akinesia.

Babies in the womb can experience akinesia, which in turn impacts their development. Movement is an important part of fetal development, and akinesia can affect growth and maturation in the womb.

Fast facts on akinesia:

- Akinesia is a condition that can occur at any age.
- It is sometimes referred to as "freezing."
- In Parkinson's disease, akinesia is usually a symptom of later stages.

Correlation with patient metabolite levels

”The lysosomal enzyme glucocerebrosidase, encoded by the glucocerebrosidase gene, is involved in the breakdown of glucocerebroside into glucose and ceramide. ”

Siebert M, Sidransky E, Westbroek W. Glucocerebrosidase is shaking up the synucleinopathies. Brain. 2014 Feb 14;137(5):1304-22.

A	B	C	D	E	F	G	H	
		Min	Max	mean	SD		John's Values	Class
acm322	411	0.032	5.877	0.573	0.639		0.8163	ceramide
acm343	411	0.049	3.398	0.530	0.478		0.6682	ceramide
acm342	411	0.028	3.831	0.508	0.489		1.0359	ceramide
acm363	411	0.030	3.899	0.493	0.507		0.4778	ceramide
acm362	411	0.022	6.016	0.517	0.586		1.0676	ceramide
acm383	411	0.078	3.280	0.539	0.384		0.5580	ceramide
acm382	411	0.038	4.560	0.561	0.532		0.6026	ceramide
acm403	411	0.023	3.276	0.434	0.424		0.5055	ceramide
acm402	411	0.025	6.140	0.665	0.647		3.9438	ceramide
acm413	411	0.045	2.361	0.512	0.365		0.5879	ceramide
acm412	411	0.059	3.311	0.691	0.539		0.6980	ceramide
acm424	411	0.014	2.282	0.364	0.337		0.5104	ceramide
acm423	411	0.015	2.333	0.339	0.327		0.5426	ceramide
acm422	411	0.029	4.932	0.812	0.664		0.8782	ceramide

Next Steps...

- **A blood test is used to make the diagnosis of Gaucher disease.**
  - The enzyme assay test measures the activity of the glucocerebrosidase enzyme in certain white blood cells. Having less than 15% of normal enzyme activity is diagnostic for Gaucher disease. Genetic analysis is also done to establish the specific type of mutations in the GBA1 gene.
- **Other medications**
  - drugs that block the production of the sphingolipids that accumulate in cells and cause symptoms. These drugs are known as glucosylceramide synthase inhibitors and are taken by mouth. Two drugs in this class are miglustat (Zavesca) and eliglustat (Cerdelga).

Acknowledgement

- John “JCM”
- SVAI

Thank You!