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Supplemental information

Phenotypes of undiagnosed adults

with actionable *OTC* and *GLA* variants

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Table S1. Regeneron Genetics Center author information.

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Table S2. Penn Medicine Biobank author information.

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Contribution: All authors contributed to securing funding, study design and oversight. All authors reviewed the final version of the manuscript.

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Contribution: All authors contributed to the development and validation of clinical phenotypes used to identify study subjects and (when applicable) controls.

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Contribution: A.V., S.S.V. are responsible for the analysis, design, and infrastructure needed to quality control genotype and exome data. Y.B. performs the analysis. T.D. and A.V. provides variant and gene annotations and their functional interpretation of variants.

Fabry Chart Review

Record ID

Variant

MRN

Sex

- Male
 Female

Age

Race

- American Indian or Alaskan Native
 Asian Indian
 Black or African American
 East Asian
 Native Hawaiian or Pacific Islander
 Other
 White

Ethnicity

- Hispanic
 Not Hispanic

Diagnosed with Fabry?

- Yes
 No

Age at diagnosis

Method of Dx

Seeing genetics?

- Yes
 No

Receiving treatment for Fabry?

- Yes
 No

What treatment?

Problem list

Family history

Current medications

Specialists seen

	Yes	No
Ophtho	<input type="radio"/>	<input type="radio"/>
Renal	<input type="radio"/>	<input type="radio"/>
Neuro	<input type="radio"/>	<input type="radio"/>
Cardiology	<input type="radio"/>	<input type="radio"/>
Dermatology	<input type="radio"/>	<input type="radio"/>

Last ophtho A/P

Last renal A/P

Last neuro A/P

Last cardiology A/P

Last derm a/p

Other Specialists seen

Presence of Fabry symptoms

	Yes	No
distal extremity pain/discomfort	<input type="radio"/>	<input type="radio"/>
Neuropathic pain	<input type="radio"/>	<input type="radio"/>
Exercise Intolerance	<input type="radio"/>	<input type="radio"/>
Cold Intolerance	<input type="radio"/>	<input type="radio"/>
Heat Intolerance	<input type="radio"/>	<input type="radio"/>
Hypohydrosis	<input type="radio"/>	<input type="radio"/>
Corneal problems	<input type="radio"/>	<input type="radio"/>
Proteinuria	<input type="radio"/>	<input type="radio"/>

Chronic Kidney disease	<input type="radio"/>	<input type="radio"/>
s/p renal transplant	<input type="radio"/>	<input type="radio"/>
requiring dialysis	<input type="radio"/>	<input type="radio"/>
GI symptoms	<input type="radio"/>	<input type="radio"/>
Angiokeratomas	<input type="radio"/>	<input type="radio"/>
Cardiomyopathy	<input type="radio"/>	<input type="radio"/>
Aortic disease	<input type="radio"/>	<input type="radio"/>
Cardiac valve disease	<input type="radio"/>	<input type="radio"/>
Arrhythmia	<input type="radio"/>	<input type="radio"/>
Heart failure	<input type="radio"/>	<input type="radio"/>
Myocardial infarction	<input type="radio"/>	<input type="radio"/>
s/p stent placement or CABG	<input type="radio"/>	<input type="radio"/>
s/p ICD or pacemaker placement	<input type="radio"/>	<input type="radio"/>
s/p heart transplant or LVAD placement	<input type="radio"/>	<input type="radio"/>
Stroke	<input type="radio"/>	<input type="radio"/>
Vertigo	<input type="radio"/>	<input type="radio"/>
TIA	<input type="radio"/>	<input type="radio"/>
hearing loss	<input type="radio"/>	<input type="radio"/>

Cardiac Testing

- EKG
- Echocardiogram
- Stress Test
- Cardiac MRI
- CTA chest
- Cardiac biopsy
- Troponin
- BNP
- Lipid panel
- Other

Results of last EKG

Results of last echocardiogram

Results of last stress test

Results of last cardiac MRI

Results of last CTA chest

Troponin results

BNP levels (maximum and most recent)

Last lipid panel results

Cardiac Biopsy

Other cardiac results: what test and results

Renal testing

- UA
- Urine protein
- Urine microalbumin
- BMP
- Cystatin C
- Renal Ultrasound
- Renal Biopsy
- Other

UA results

Urine protein/creatinine ratio

Urine microalbumin results

Last serum Cr

Max serum Cr

Current GFR

Cystatin C results

Renal Ultrasound results

Renal Biopsy results

Other renal testing: what and results?

Neurological Testing

- CT Brain
- MRI Brain
- MRA Head/Neck
- Carotid Ultrasound
- EMG/NCV
- Other Ultrasound (I.e. carpal tunnel)
- Other

CT head results

MRI Brain results

MRA head/neck results

Carotid Ultrasound results

EMG/NCV results

Other ultrasound: what ultrasound and results

Other neuro tests: what test and results

Other comments

Otc Deficiency

Record ID

Record ID

Basic Demographic Info

Variant

MRN

Biological sex

- Male
- Female

Age

Race

- American Indian or Alaskan Native
- Asian Indian
- Black or African American
- East Asian
- Native Hawaiian or Pacific Islander
- White
- Other
- Unknown

Ethnicity

- Hispanic
- Not Hispanic
- Unknown

Diagnosed with OTC?

- Yes
- No

Age at diagnosis

Followed by medical genetics?

- Yes
- No

Problem list

Current medications

Family History

Family history

Family history suggestive of OTC deficiency

	Yes	No
Known OTC deficiency	<input type="radio"/>	<input type="radio"/>
Urea cycle disorders	<input type="radio"/>	<input type="radio"/>
Unexplained newborn male death	<input type="radio"/>	<input type="radio"/>
Cerebral palsy NOS	<input type="radio"/>	<input type="radio"/>
Migraines / Headaches	<input type="radio"/>	<input type="radio"/>
Psychiatric conditions	<input type="radio"/>	<input type="radio"/>
Recurrent vomiting	<input type="radio"/>	<input type="radio"/>
Other decompensation during hospitalization / stress	<input type="radio"/>	<input type="radio"/>

Pregnancy History

Ever pregnant? Yes No

Living children. List as (#M, #F)

Other pregnancy history suggestive of OTC deficiency

	Yes	No
Spontaneous abortion	<input type="radio"/>	<input type="radio"/>
Had newborn male child who died	<input type="radio"/>	<input type="radio"/>
Had male child with sepsis in first week of life	<input type="radio"/>	<input type="radio"/>
Had male child with failure to thrive in first week of life	<input type="radio"/>	<input type="radio"/>
Had male child with somnolence in first week of life	<input type="radio"/>	<input type="radio"/>
Had a male child with unexplained tachypnea in first week of life	<input type="radio"/>	<input type="radio"/>
elective abortion	<input type="radio"/>	<input type="radio"/>

Other pregnancy history

Specialists seen

	Yes	No
Psychiatry	<input type="radio"/>	<input type="radio"/>
Neurology	<input type="radio"/>	<input type="radio"/>
OB/GYN	<input type="radio"/>	<input type="radio"/>
GI	<input type="radio"/>	<input type="radio"/>
Nutrition	<input type="radio"/>	<input type="radio"/>

Last Neurology A/P

Last Psychiatry A/P

Last OB/GYN A/P

Last GI A/P

Last Nutrition A/P

Presence of OTC deficiency symptoms

	Yes	No
Delirium	<input type="radio"/>	<input type="radio"/>
Encephalopathy or Altered Mental Status	<input type="radio"/>	<input type="radio"/>
Psychosis or erratic behavior NOS	<input type="radio"/>	<input type="radio"/>
Anxiety/Depression	<input type="radio"/>	<input type="radio"/>
Recurrent vomiting	<input type="radio"/>	<input type="radio"/>
Headaches / Migraine headaches	<input type="radio"/>	<input type="radio"/>
Seizure	<input type="radio"/>	<input type="radio"/>
Allergy to protein / protein intolerance	<input type="radio"/>	<input type="radio"/>
HCC	<input type="radio"/>	<input type="radio"/>
Reye-like syndrome	<input type="radio"/>	<input type="radio"/>
Executive function deficits	<input type="radio"/>	<input type="radio"/>
Mild cognitive impairment	<input type="radio"/>	<input type="radio"/>

Self-restriction of protein / Vegetarian diet / Avoidance of milk, red meat, eggs, high-protein foods (list specific food restrictions)

Headache description (From most recent PCP A/P Problem list)

Presence of OTC deficiency symptoms during precipitating events or catabolic stress

	Altered Mental Status	Vomiting	Headache
Pregnancy and/or Delivery	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Systemic corticosteroid administration	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Infection	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Trauma (e.g. motor vehicle collision)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cancer therapy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Meat/protein ingestion	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Labs/Imaging

Neurologic testing EEG
 Head CT
 Head MRI
 Other neuropsych testing

Results of any abnormal EEG

Head CT Results

Head MRI Results

What other neuropsych testing and results

Other imaging Abdominal US
 CT A/P
 Other Liver imaging

Results of last abdominal U/S

Results of last CT A/P (Liver Findings and Impression)

Other liver imaging: what test and results

Other Labs

- Ammonia (serum)
- Blood gas
- LFTs
- PT/PTT
- Urine studies

Serum ammonia levels with dates

ABG showing respiratory alkalosis?

- Yes
- No

Last AST/ALT

Last PT/PTT

Elevated urine orotic acid

Other comments

Table S5. Table of participant demographics.

	<i>OTC</i> PLPV	<i>GLA</i> PLPV
Total	3	3
Female, n (%)	3 (100)	1 (33.3)
Age, Mean \pm SD	51 (11.8)	54.3 (17.6)
Race/Ethnicity, n (%)		
Asian	0 (0)	0 (0)
Black	1 (33.3)	0 (0)
Other	0 (0)	0 (0)
White, Hispanic	0 (0)	0 (0)
White, Non-Hispanic	2 (66.7)	3 (100)

Table S6. American College of Medical Genetics variant classification criteria for *GLA* and *OTC* variants found in biobank participants.

Gene	DNA	Protein	Classification	Classification Criteria				Allelic fraction
				Very Strong	Strong	Moderate	Supporting	
<i>GLA</i>	c.335G>A	p.Arg112His	Pathogenic		PS3, PS4	PM2, PM5	PP1, PP3	1.00 (male)
<i>GLA</i>	c.647A>G	p.Tyr216Cys	Likely Pathogenic		PS4	PM3	PP1, PP3	1.00 (male)
<i>GLA</i>	c.868A>C	p.Met290Leu	Likely Pathogenic		PS4	PM2	PM2, PP1, PP4	0.56 (female)
<i>OTC</i>	c.118C>T	p.Arg40Cys	Likely pathogenic		PS3	PM2, PM5	PP!	0.50 (female)
<i>OTC</i>	c.274C>T	p.Arg92*	Pathogenic	PVS1	PS3	PM2	PP3	0.48 (female)
<i>OTC</i>	c.583G>A	p.Gly195Arg	Pathogenic		PS3	PM2, PM5	PP3, PP5	0.65 (female)