LYSOSOMAL STORAGE DISEASES:

Central symptoms and co-morbidities

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DISCLOSURES

- Ozlem Goker-Alpan, M.D. is a consultant, a principal investigator and /or on the speaker bureau, or has received grant support and consultancy fees from the following pharmaceutical companies: Amicus Therapeutics, Genzyme Inc., Takeda, Pfizer/Protalix

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DISEASE SPECTRUM IN LSDS: VARIATION IN ONSET AND SEVERITY

MPS
Attenuated forms with normal cognition or minimal visceral/skeletal involvement

Tay-Sachs
"Late-onset" forms:
- Cerebellar degeneration
- Anterior horn cell involvement
- Psychiatric manifestations in adolescence/adulthood

Gaucher
Symptom onset across lifespan, even within families

Fabry
Females
Cardiac/renal variants

Pompe
Adult-onset mimics LGMD
Lacks cardiomyopathy

Neurodegeneration begins *in utero* with MPS types IVA and VII, Gaucher type 2, GM1 gangliosidosis, Neimann-Pick type C, Farber disease, infantile-free sialic acid storage disease, mucolipidosis type II (non-immune hydrops fetalis)

LGMD = limb-girdle muscular dystrophy

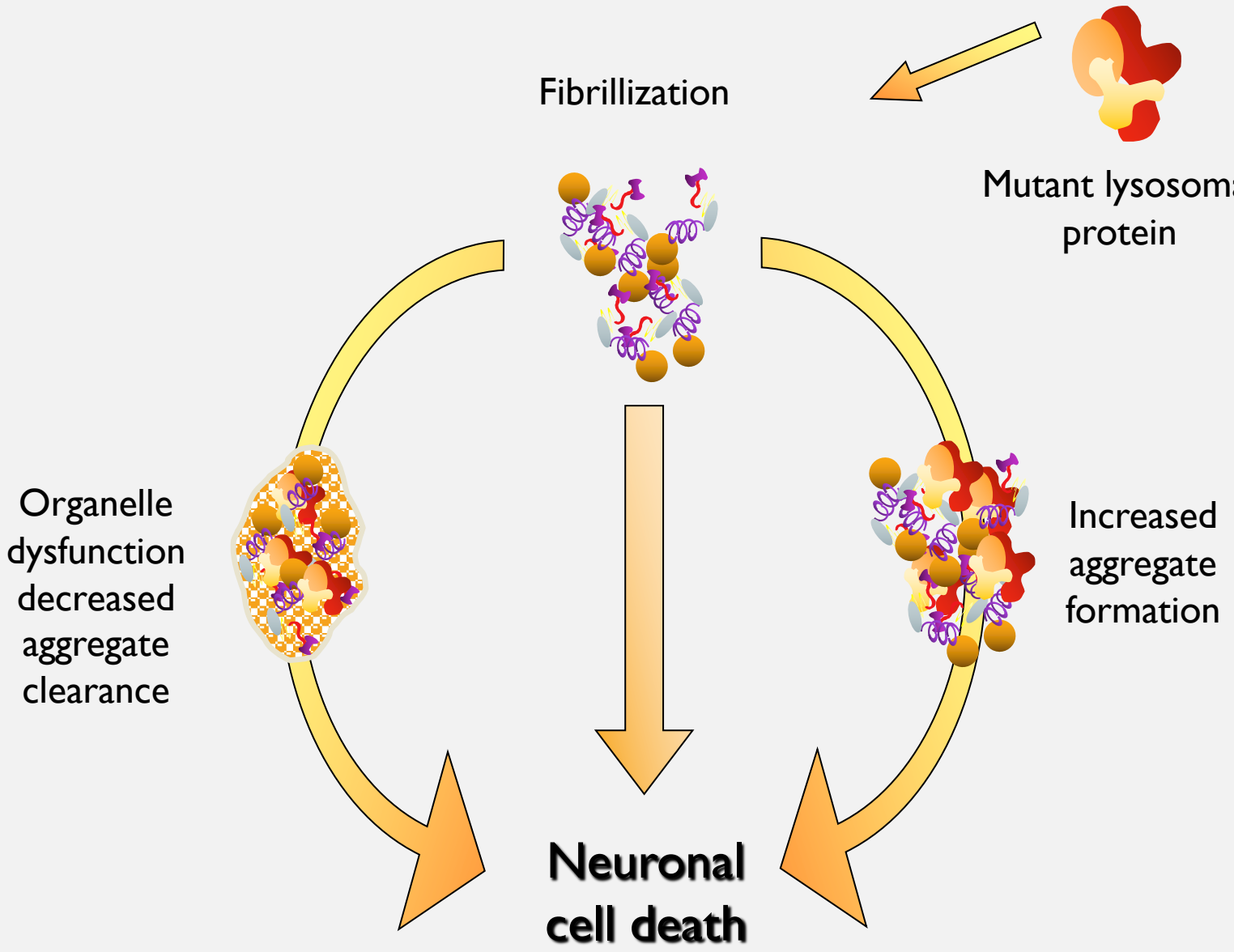
Whybra C, et al. *Orphanet J Rare Dis*. 2012;7:86; Gimovsky AC, et al. *Am J Obstet Gynecol*. 2015;212(3):281–290.

LSDS WITH PSYCHIATRIC MANIFESTATIONS

Lysosomal Disorder	Psychiatric presentations
MPS 3 (A,B,C,D)	Hyperactivity, cognitive decline and aggression
MPS2 (Hunter disease)	Hyperactivity, cognitive decline and aggression
Mannasidosis (alpha and beta)	Hallucinations and psychosis
NPC (C 1 and C2)	ADHD, behavioral changes in children Psychosis in adults
MLD	ADHD, dementia that mimics FTD and psychosis
GM2 gangliosidosis (Tay Sachs and Sandhoff)	Depression, delusions, psychosis Schizophrenia in adults may antedate
Fabry disease	Depression, "brain fog"
Gaucher disease	Depression, hyperactivity, aggression, autism

T. Cox, 2020, Adelwahab, et al, 2017, Goker-Alpan et al, 2008

PROTEIN MISFOLDING DISORDERS ARE ASSOCIATED WITH THE DYSFUNCTION OF PROTEOLYTIC PATHWAYS



Speaker's illustration.

Two major hydrolytic systems- ubiquitin proteasome (UPS) and autophagy-lysosome pathways (ALP) Cellular homeostasis is maintained by clearing damaged, misfolded or aggregated cytosolic proteins.

LYSOSOMAL DISORDERS ARE OVER-REPRESENTED IN PARKINSON DISEASE COHORTS

- Mutations in the glucocerebrosidase gene (***GBA***), which cause Gaucher disease, are also shown as risk factors for Parkinson disease and other synucleionopathies.
- Whole exome sequencing data from 1156 Parkinson's disease cases and 1679 control subjects shows a significant burden of rare, likely damaging lysosomal storage disorder gene variants in association with Parkinson disease risk
- Strong associations at the GBA and SMPD1 loci
- CTSD (Ceroid lipofuscinosis) , SLC17A5 (Sialic acid storage disease), and ASAH1 (Farber disease and SMA-PME) are also implicated as candidate Parkinson disease susceptibility genes.
- The majority of Parkinson disease cases (56%) have at least one putative damaging variant in a lysosomal storage disorder gene, and 21% carry multiple alleles.

Table 1 LSD genes and variants in the IPDGC cohort

Disease	Gene	Variants[a]
Aspartylglucosaminuria	*AGA*	13 (10)
Metachromatic leukodystrophy	*ARSA*	5 (5)
Maroteaux-Lamy disease	*ARSB*	11 (10)
Farber Lipogranulomatosis	*ASAH1*	20 (17)
Kufor-Rakeb syndrome	*ATP13A2*	24 (18)
Neuronal ceroid lipofuscinosis (CLN3)	*CLN3*	18 (17)
Neuronal ceroid lipofuscinosis (CLN5)	*CLN5*	-
Neuronal ceroid lipofuscinosis (CLN6)	*CLN6*	10 (7)
Neuronal ceroid lipofuscinosis (CLN8)	*CLN8*	9 (4)
Cystinosis	*CTNS*	13 (12)
Galactosialidosis	*CTSA*	14 (11)
Neuronal ceroid lipofuscinosis (CLN10)	*CTSD*	7 (4)
Neuronal ceroid lipofuscinosis (CLN13)	*CTSF*	11 (9)
Pycnodysostosis	*CTSK*	6 (5)
Neuronal ceroid lipofuscinosis (CLN4B)	*DNAJC5*	5 (5)
Fucosidosis	*FUCA1*	15 (12)
Pompe disease	*GAA*	15 (10)
Krabbe disease	*GALC*	36 (30)
Morquio A disease	*GALNS*	22 (14)
Gaucher disease	*GBA*	39 (32)
Fabry disease	*GLA*	9 (7)
GM1-gangliosidosis/Morquio B	*GLB1*	8 (4)
GM2-gangliosidosis	*GM2A*	1 (1)
I-Cell disease	*GNPTAB*	39 (31)
Sanfilippo D syndrome	*GNS*	20 (11)
Neuronal ceroid lipofuscinosis (CLN11)	*GRN*	19 (12)
Sly disease	*GUSB*	17 (10)
Tay-Sachs disease	*HEXA*	20 (18)
Sandhoff disease	*HEXB*	8 (6)
Sanfilippo C syndrome	*HGSNAT*	18 (15)
Mucopolysaccharidosis type IX	*HYAL1*	13 (9)
Hunter syndrome	*IDS*	9 (8)
Hurler syndrome	*IDUA*	8 (4)
Neuronal ceroid lipofuscinosis (CLN14)	*KCTD7*	4 (3)
Danon disease	*LAMP2*	9 (7)
Wolman disease	*LIPA*	14 (10)
Alpha-mannosidosis	*MAN2B1*	12 (11)
Beta-mannosidosis	*MANBA*	18 (15)
Mucolipidosis type IV	*MCOLN1*	19 (14)
Neuronal ceroid lipofuscinosis (CLN7)	*MFSD8*	18 (14)
Schindler disease/Kanzaki disease	*NAGA*	9 (8)
Sanfilippo B syndrome	*NAGLU*	10 (9)
Sialidosis	*NEU1*	-
Niemann-Pick disease type C1	*NPC1*	43 (35)
Niemann-Pick disease type C2	*NPC2*	2 (2)
Neuronal ceroid lipofuscinosis (CLN1)	*PPT1*	9 (7)
Sphingolipid-activator deficiency	*PSAP*	22 (16)
Action mycolonus-renal failure syndrome	*SCARB2*	10 (7)
Sanfilippo A syndrome	*SGSH*	10 (8)
Salla disease	*SLC17A5*	18 (17)
Niemann-Pick disease type A/B	*SMPD1*	25 (21)
GM3-gangliosidosis	*ST3GAL5*	11 (11)
Multiple sulfatase deficiency	*SUMF1*	-
Neuronal ceroid lipofuscinosis (CLN2)	*TPP1*	15 (13)

[a]The number of variants (MAF < 3%) in each LSD gene is shown for the IPDGC discovery cohort, including total number of non-synonymous variants and likely damaging variants based on CADD (in parentheses). Of the 54 LSD genes considered, no exonic variants in *CLN5* or *NEU1* passed quality control filters (see 'Materials and methods' section), and no non-synonymous variants were identified in *SUMF1*.

Robak and Jensen et al, , Brain 2017, 3191-203

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