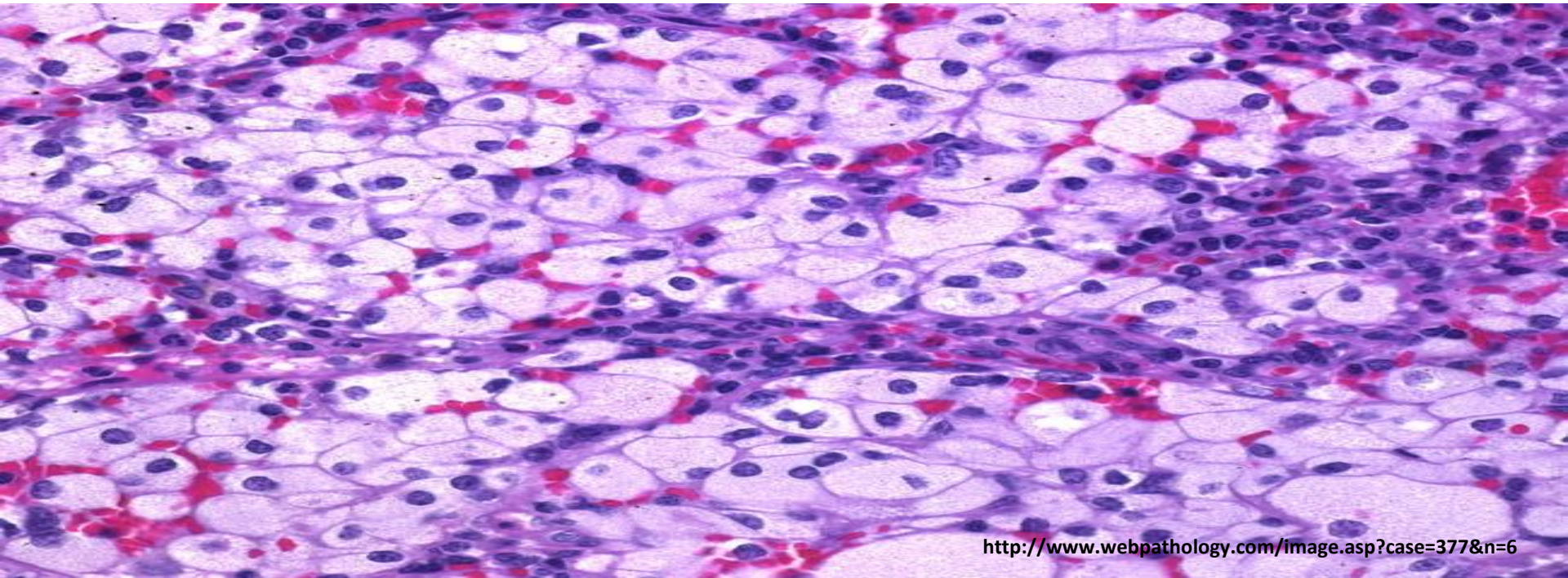
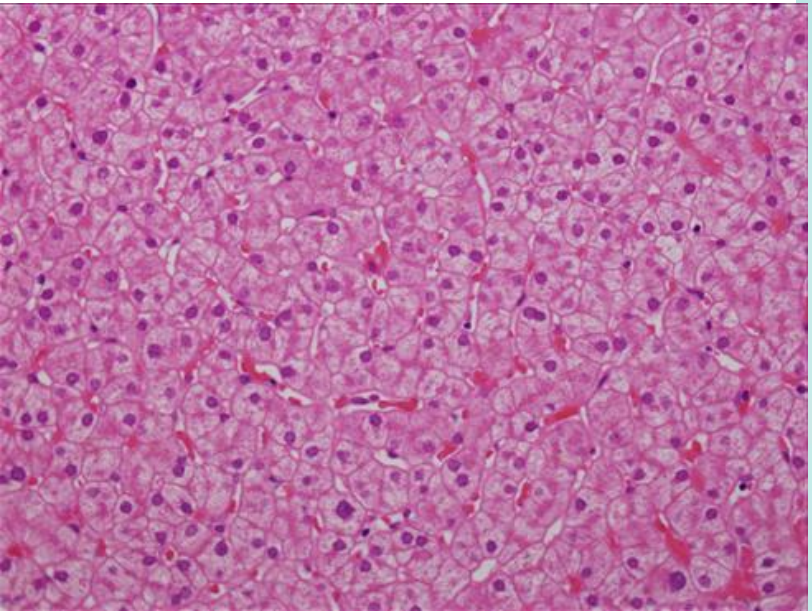
Niemann-Pick and SMPD1

Katie Lawler



Niemann-Pick affects lipid metabolism

Normal liver cells



Autosomal recessive

Affects 1 in 250,000 people

http://usatoday30.usatoday.com/news/health/weightloss/2009-10-25-liver-fat_N.htm

Types of Niemann-Pick

Type A

http://npdf.blogspot.com/2012/06/trek-atlas-ingram.html

http://www.umm.edu/imagepages/17215.htm

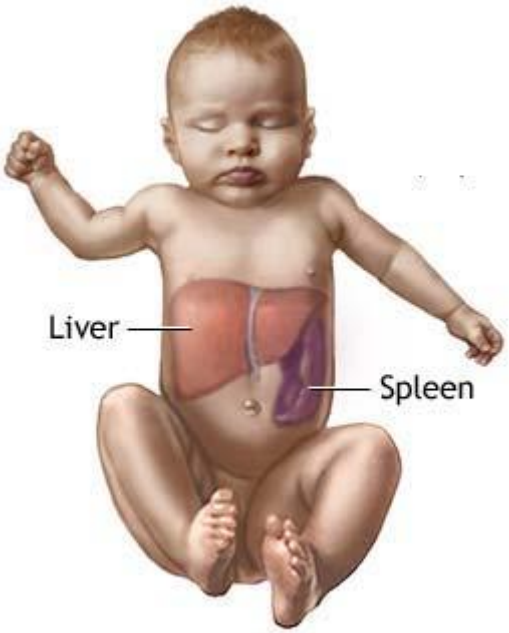
Type B

Enlarged spleen & liver

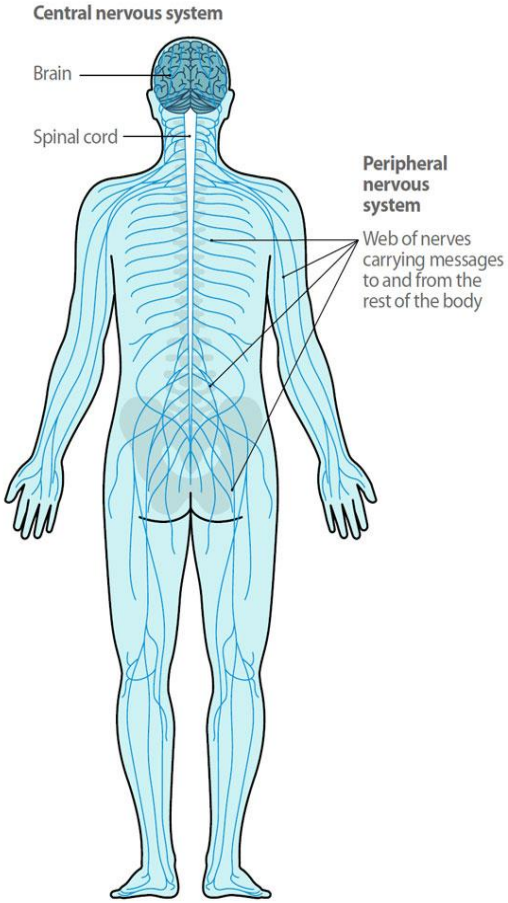
Lung infections

Growth retardation

Sleep inversion



Type C

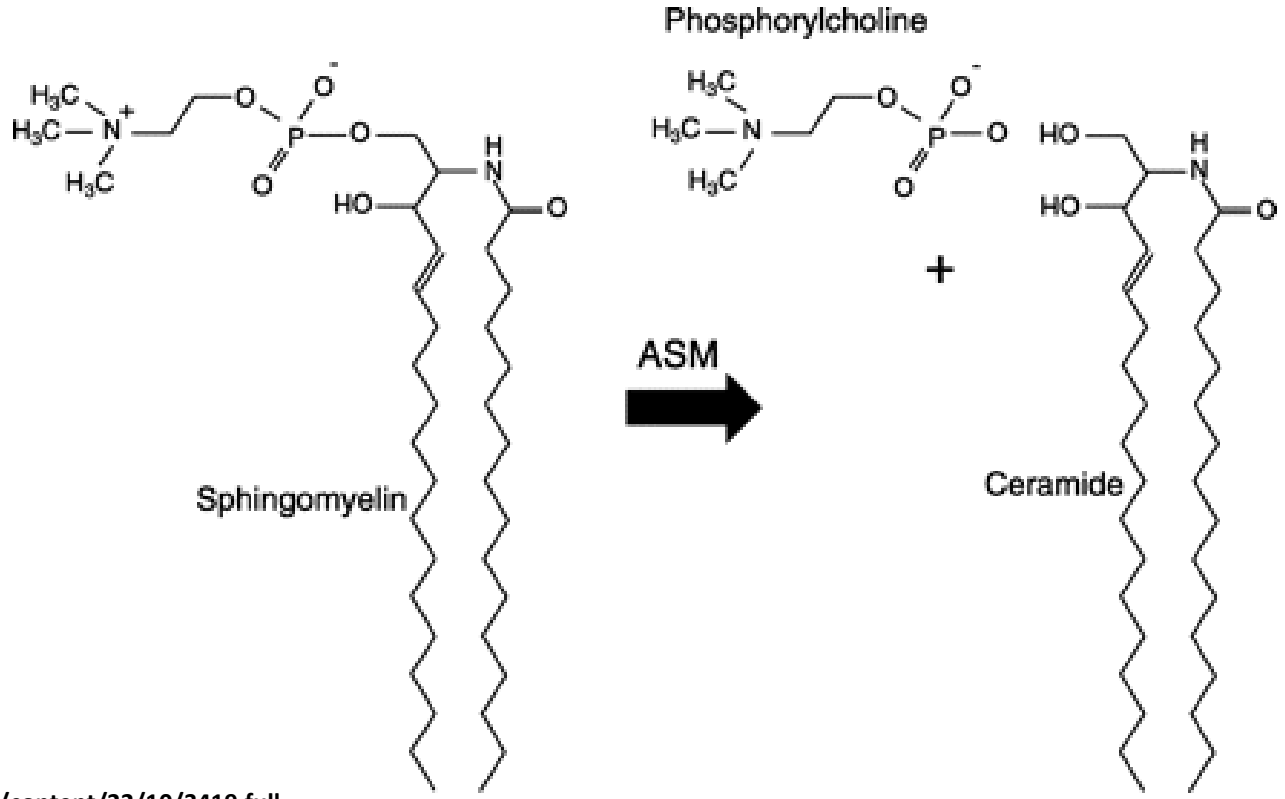


http://www.niemann-pick-c.com/Patient/What-are-the-symptoms-of-Niemann-Pick-type-C-disease

Normal role of SMPD1

Production of acid sphingomyelinase

SMPD1=ASM

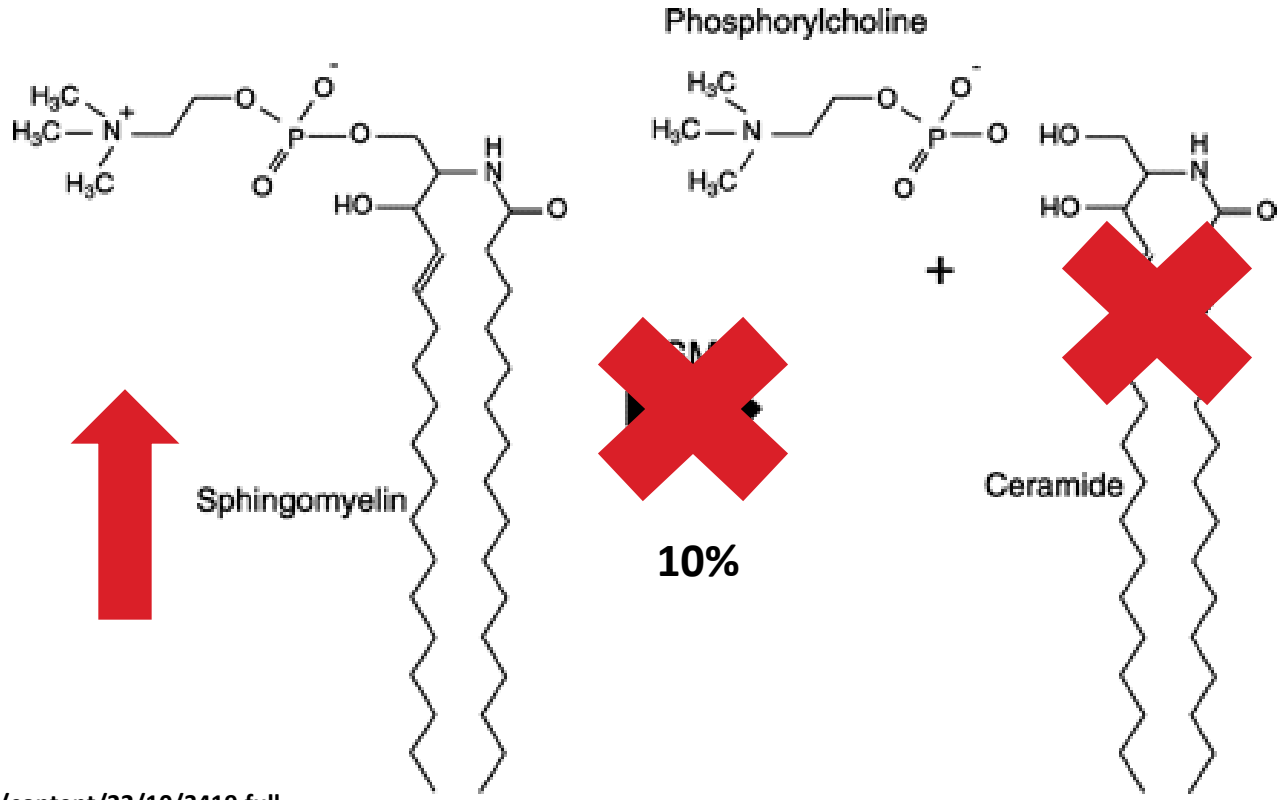


http://www.fasebj.org/content/22/10/3419.full

SMPD1 in Niemann-Pick disease

Production of acid sphingomyelinase

SMPD1=ASM



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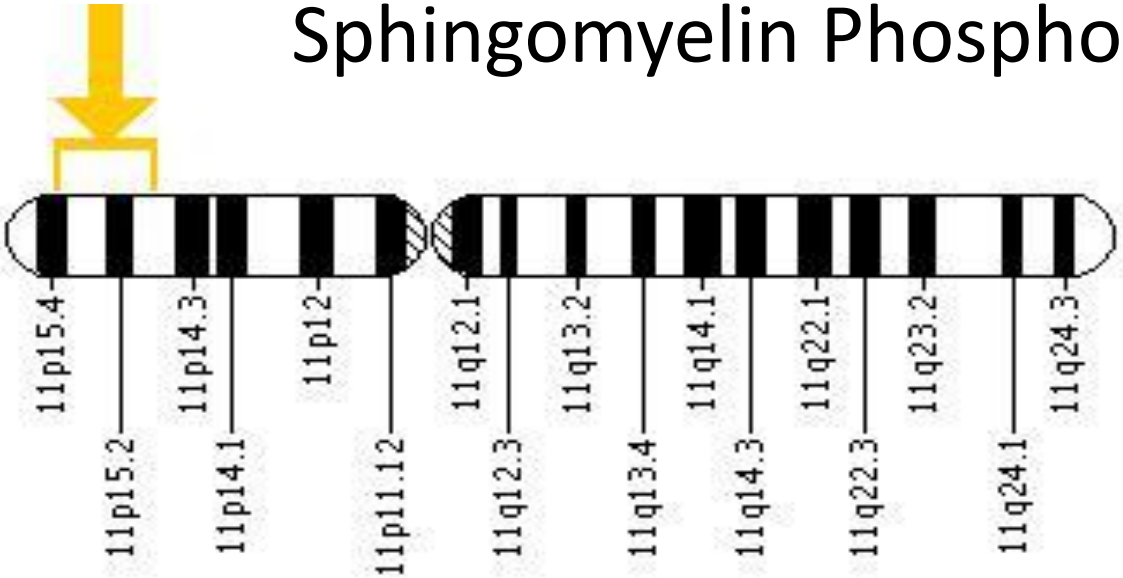
SMPD1 is on chromosome 11

Sphingomyelin Phosphodiesterase 1

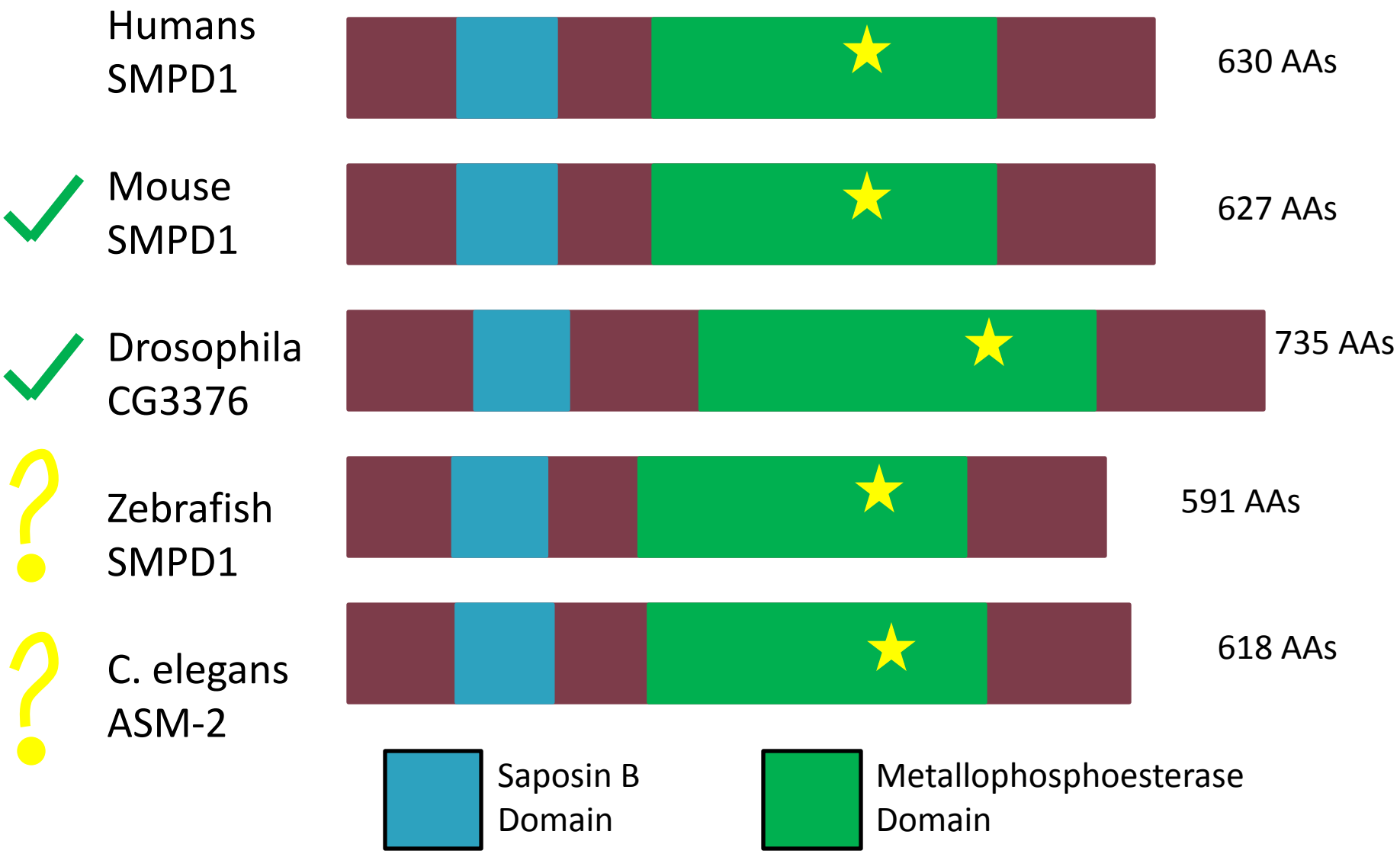


http://ghr.nlm.nih.gov/gene/SMPD1

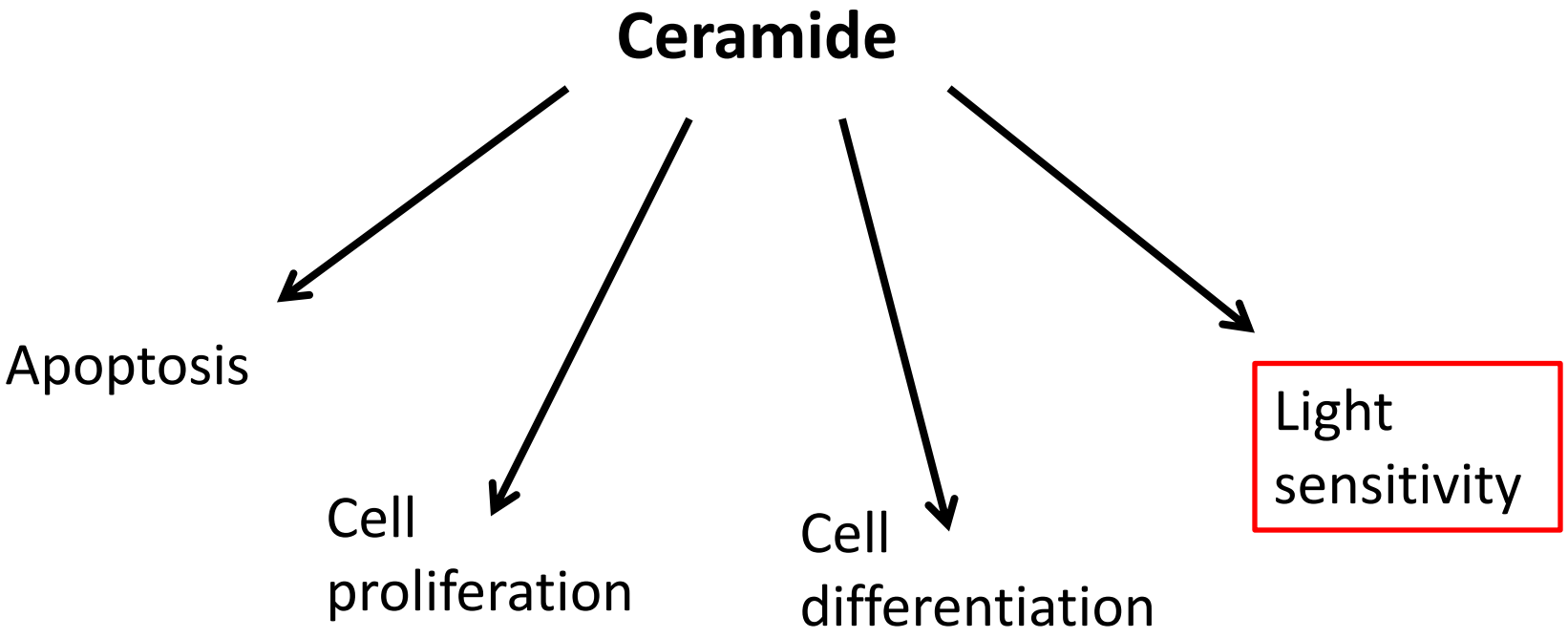
Saposin B Domain

Metallophosphoesterase Domain

SMPD domain well conserved



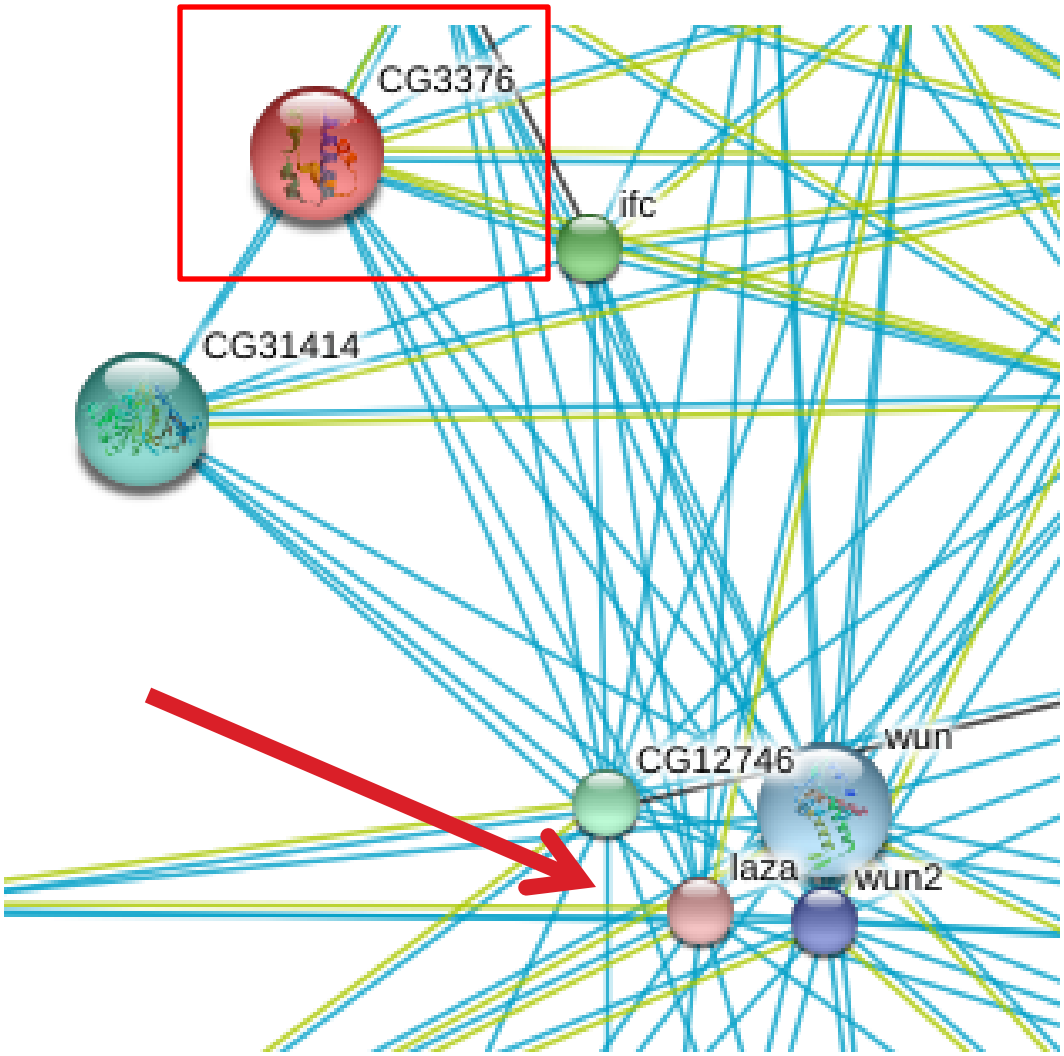
Lack of ceramide inhibits downstream signaling



Lazaro responds to light intensity

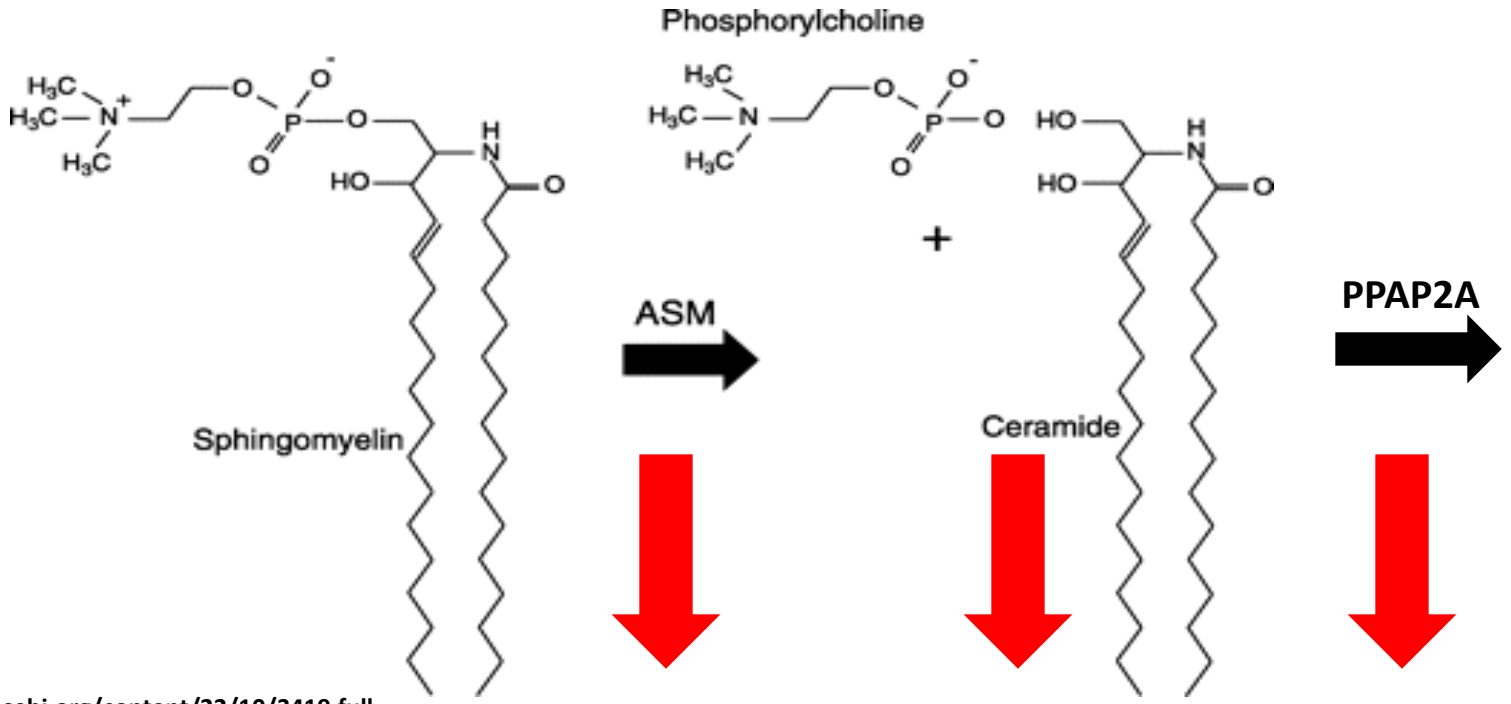
Shares family with wunen

Wunen homolog = PPAP2A



Q1: Where are SMPD1 and PPAP2A expressed in cells?

Hypothesis: If low levels of SMPD1 → then low levels of PPAP2A.



http://www.fasebj.org/content/22/10/3419.full

If low levels SMPD1 → then low levels PPAP2A

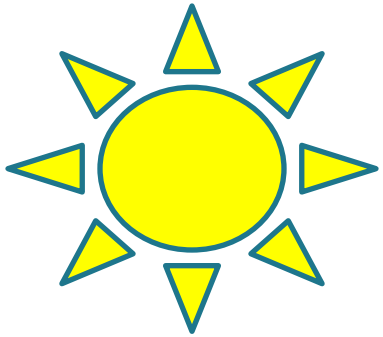
Mice	Liver				Lungs				Retinal			
	Healthy		Mutant		Healthy		Mutant		Healthy		Mutant	
1												
2												
3												
4												
5												

SMPD1

PPAP2A

Q2: How does light affect SMPD1 and PPAP2A levels?

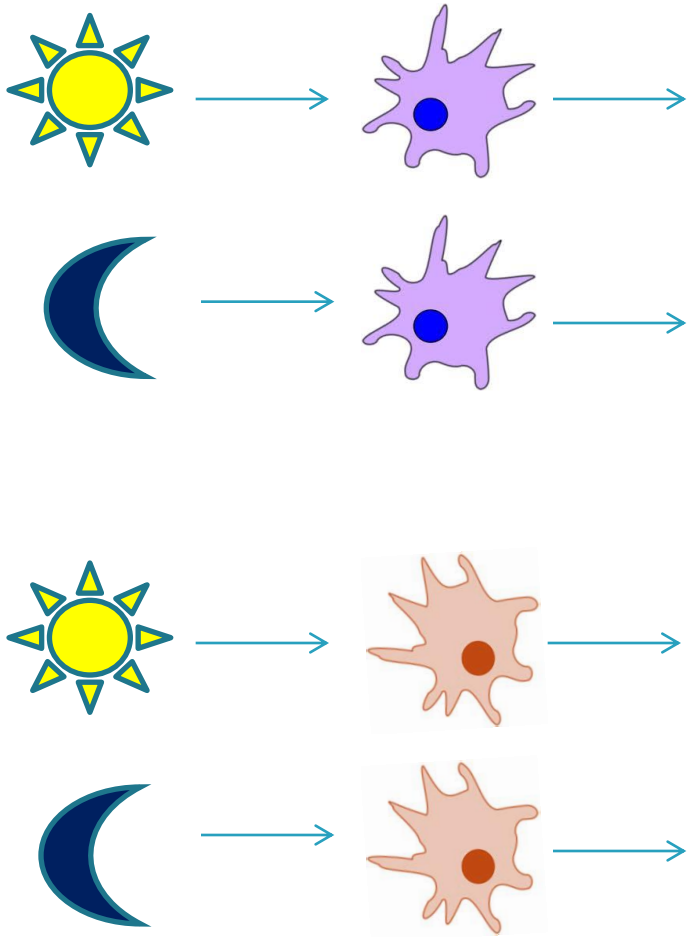
Hypothesis: Levels of SMPD1 and PPAP2A will be higher in light versus dark environments.

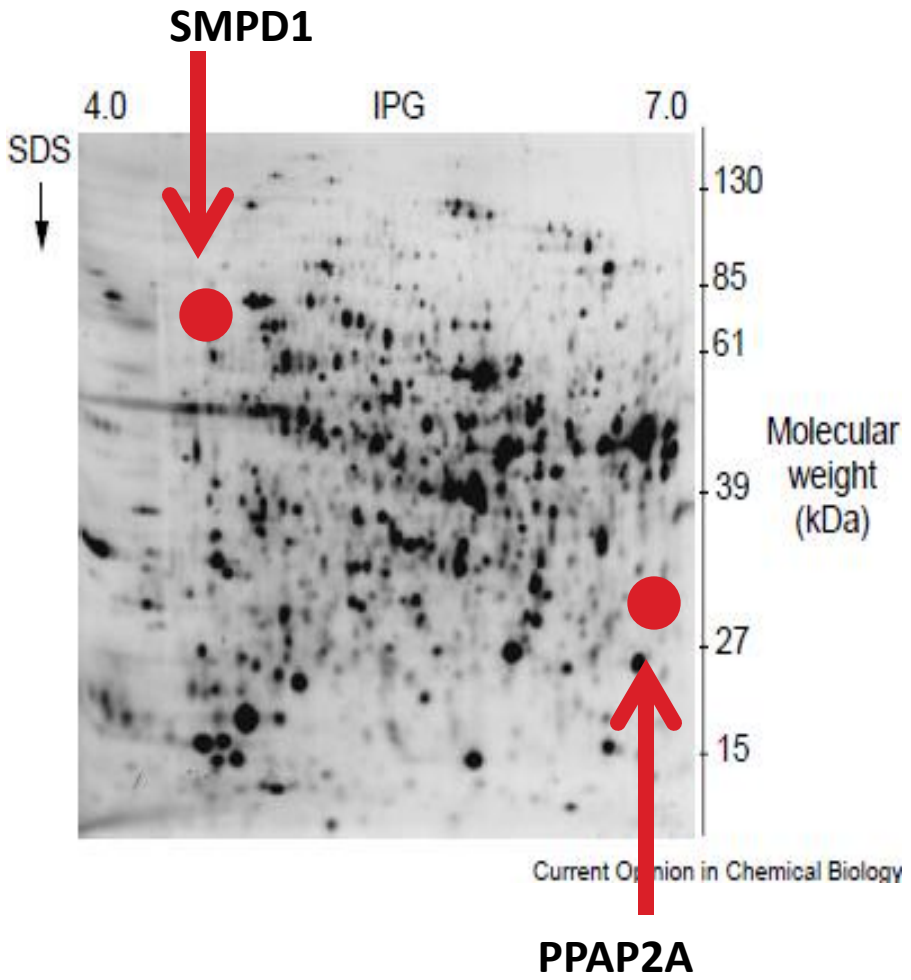


Levels of SMPD1 & PPAP2A higher in light environments

Normal Mice

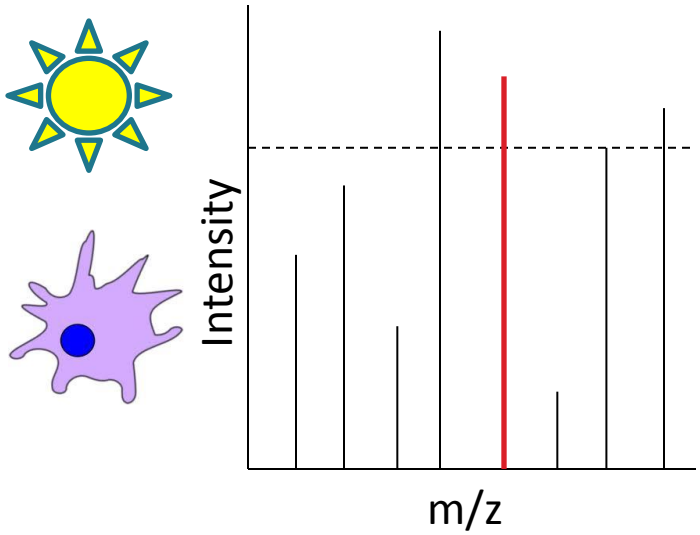
SMPD1 Mutant Mice

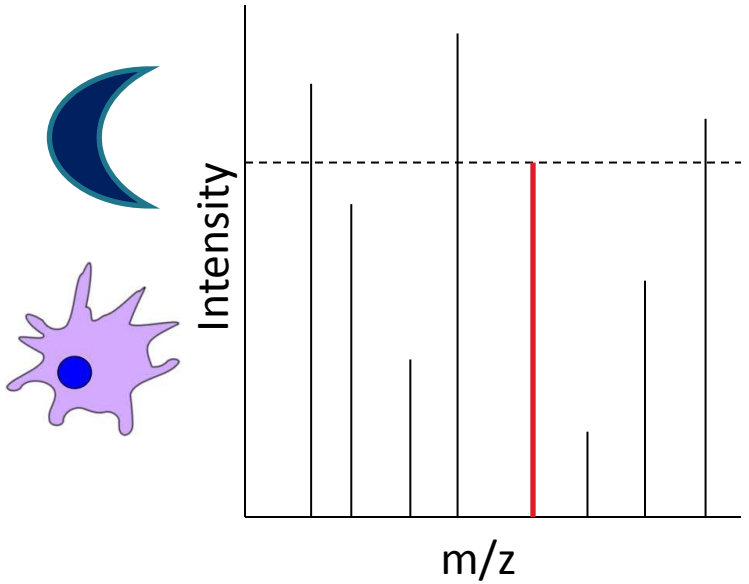


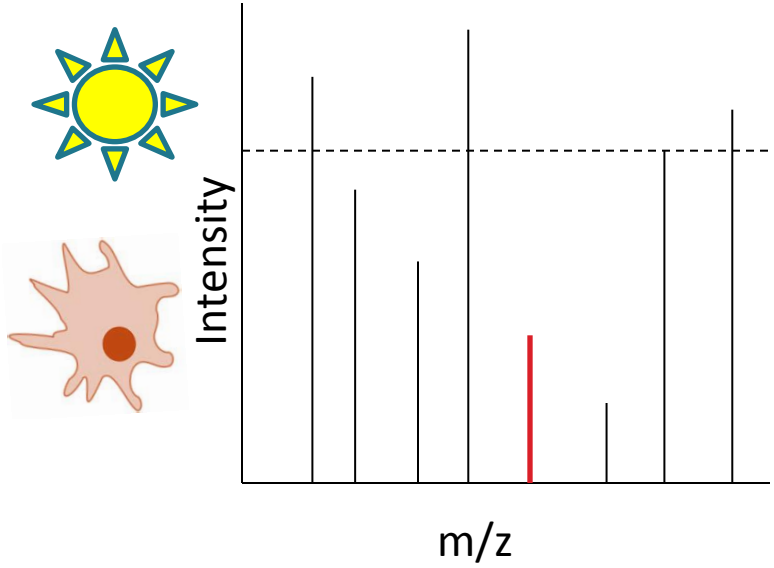


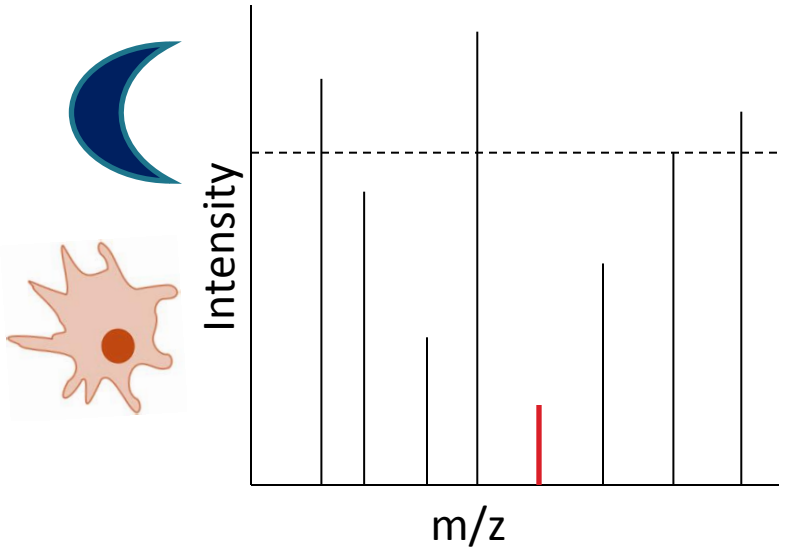
http://gen677.weebly.com/uploads/8/6/5/7/865764/fey2dgelreview2001.pdf

Varying intensities of PPAP2A









Levels of SMPD1 & PPAP2A higher in light environments

				
	SMPD1	**PPAP2A**	**SMPD1**	**PPAP2A**
Healthy Control	High	High	Average	Average
SMPD1 Mutant	Low	Low	Really low	Really low

Next step……drug therapy

Add PPAP2A into cells

Phenotypic change?

http://www.thejanedough.com/morning-sickness-drug/sleeping-baby/

Future Research

Lung infections in gills (zebrafish)?

RNAi screen lipid metabolism genes (C. elegans)

Relationship between NPC1 and SMPD1?

References

Jones, I., He, X., Katouzian, F., Darroch, P., & Schuchman, E. (2008). Characterization of Common SMPD1 Mutations causing Types A and B Niemann-Pick Disease and Generation of Mutation-Specific Mouse Models. Molecular Genetics and Metabolism, 95(3), 152. doi: 10.1016/j.ymgme.2008.08.004

Smith, E., & Schuchman, E. (2008). The unexpected role of acid sphingomyelinase in cell death and the pathophysiology of common diseases. The FASEB Journal, 22(10), 3419. doi: 10.1096/fj.08-108043

Zhang, H., Wang, Y., Gong, Z., Li, X., Qiu, W., Han, L., Ye, J. (2013). Identification of a distinct mutation spectrum in the SMPD1 gene of Chinese patients with acid sphingomyelinase-deficient Niemann-Pick disease. Orphanet Journel of Rare Diseases, 8(15). doi: 10.1186/1750-1172-8-15

Fey, S., & Larsen, P. (2001). 2D or not 2D. Current Opinion in Chemical Biology, 5(1), 26.

Brown, P., & Botstein, D. (1999). Exploring the new world of the genome with DNA microarrays. Nature America Inc.

http://ghr.nlm.nih.gov/gene/SMPD1

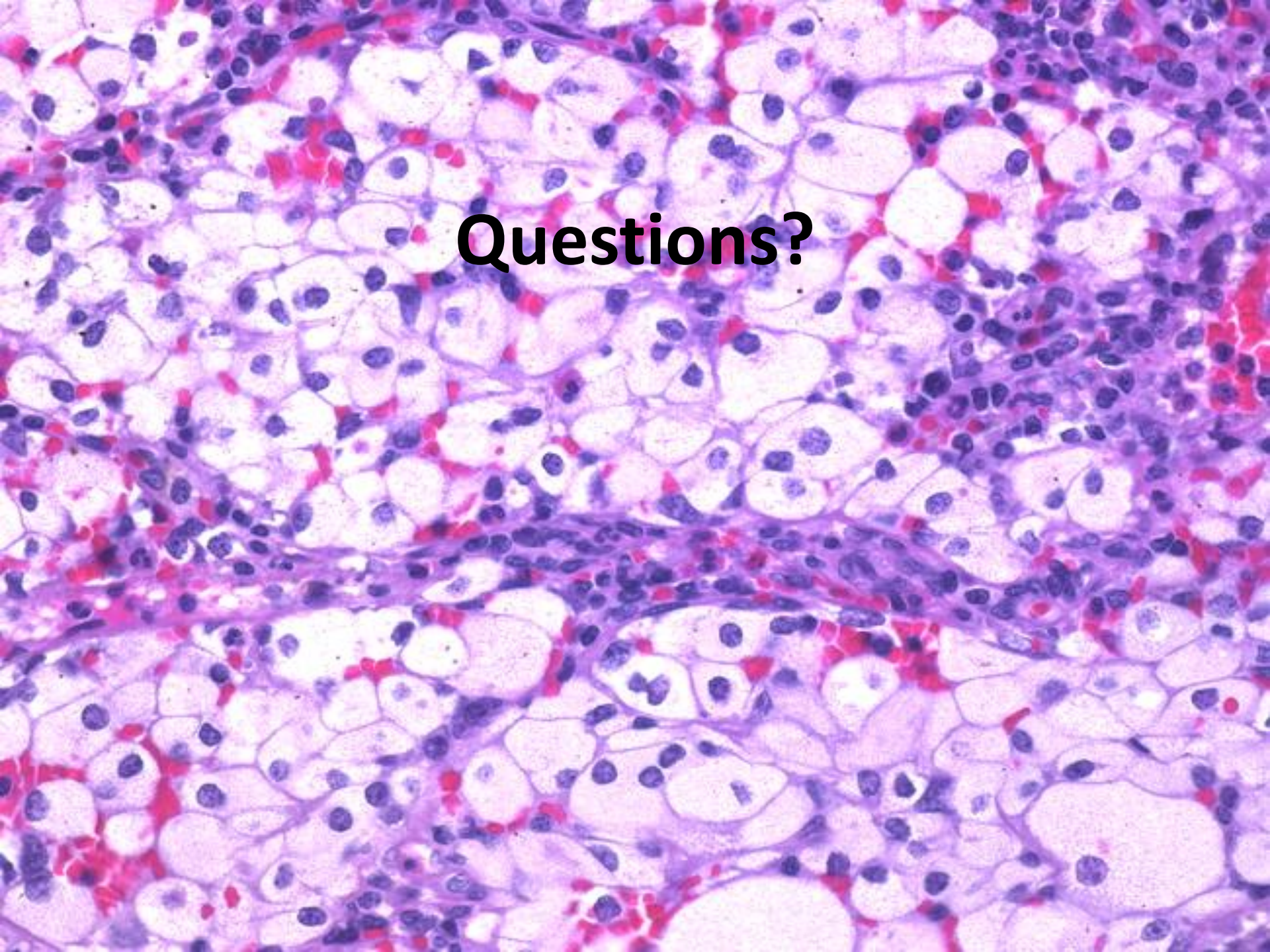
http://ghr.nlm.nih.gov/condition/niemann-pick-disease

http://www.phosphosite.org/proteinAction.do;jsessionid=42CBF10E7131847DE1720F6046DD3C84?id=25705062&showAllSites=true

http://www.nnpdf.org/npdisease_01.html

http://www.phosphosite.org/proteinAction.do?id=18321&showAllSites=true

Databases: Pfam, SMART, String


Questions?