Human glycosylation disorders: When a little bit isn't enough

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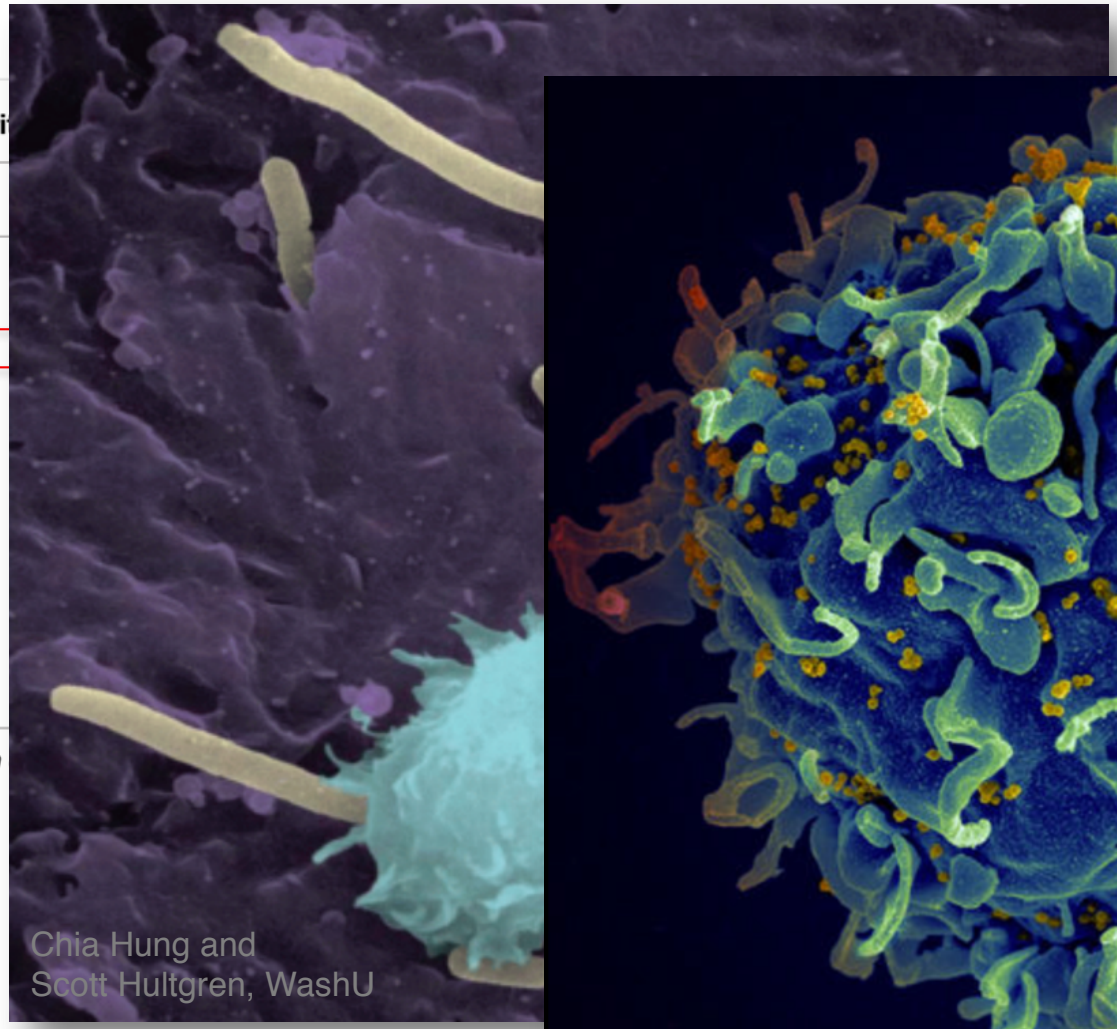
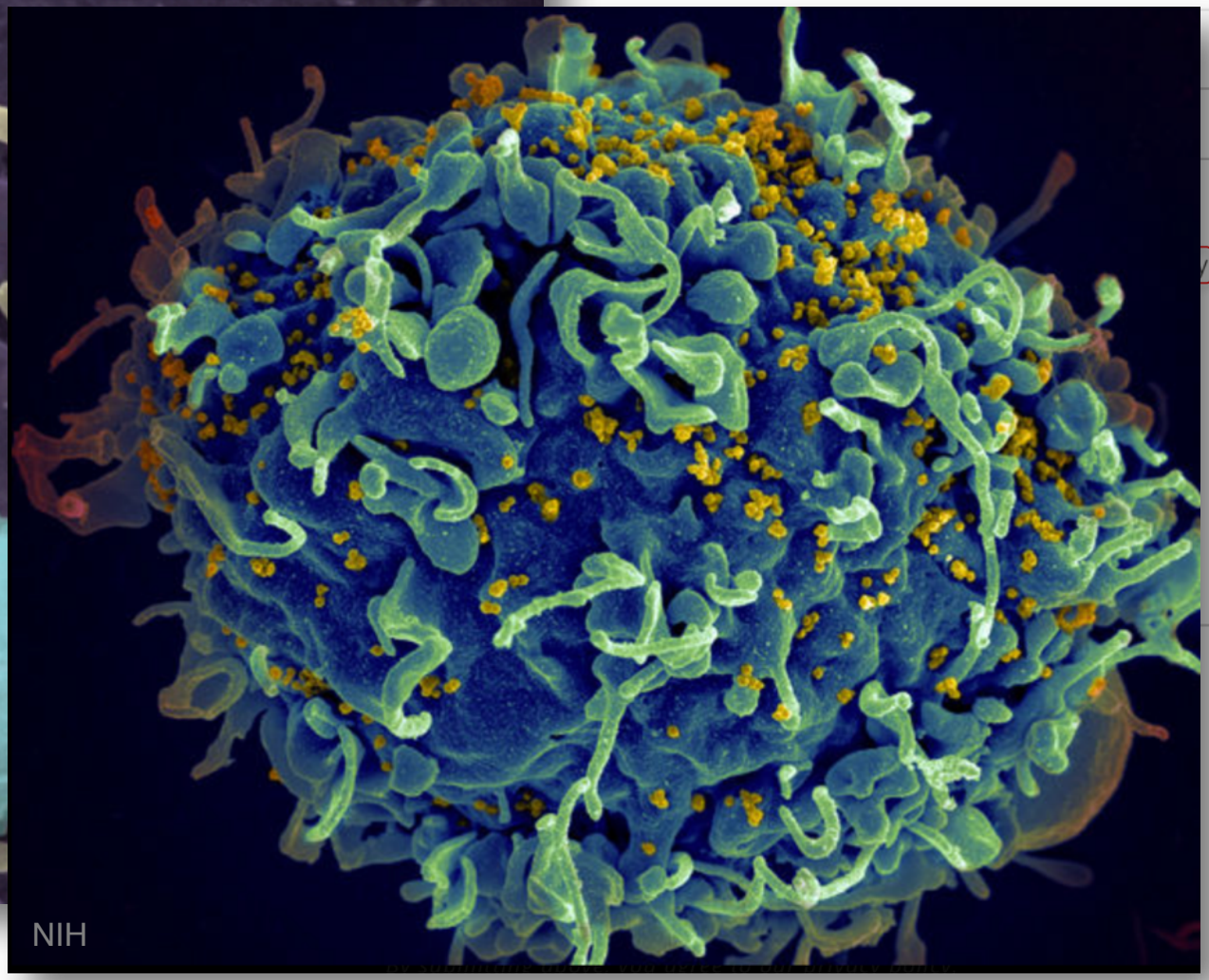
A number of Congenital Disorders of Glycosylation (CDGs) result in altered immunity

TABLE 1 | Inheri

Gene
G6PC3
SLC37A4
PGM3
PMM2
ALG1
ALG12
MOGS
SLC35A1
SLC35C1
JAGN1

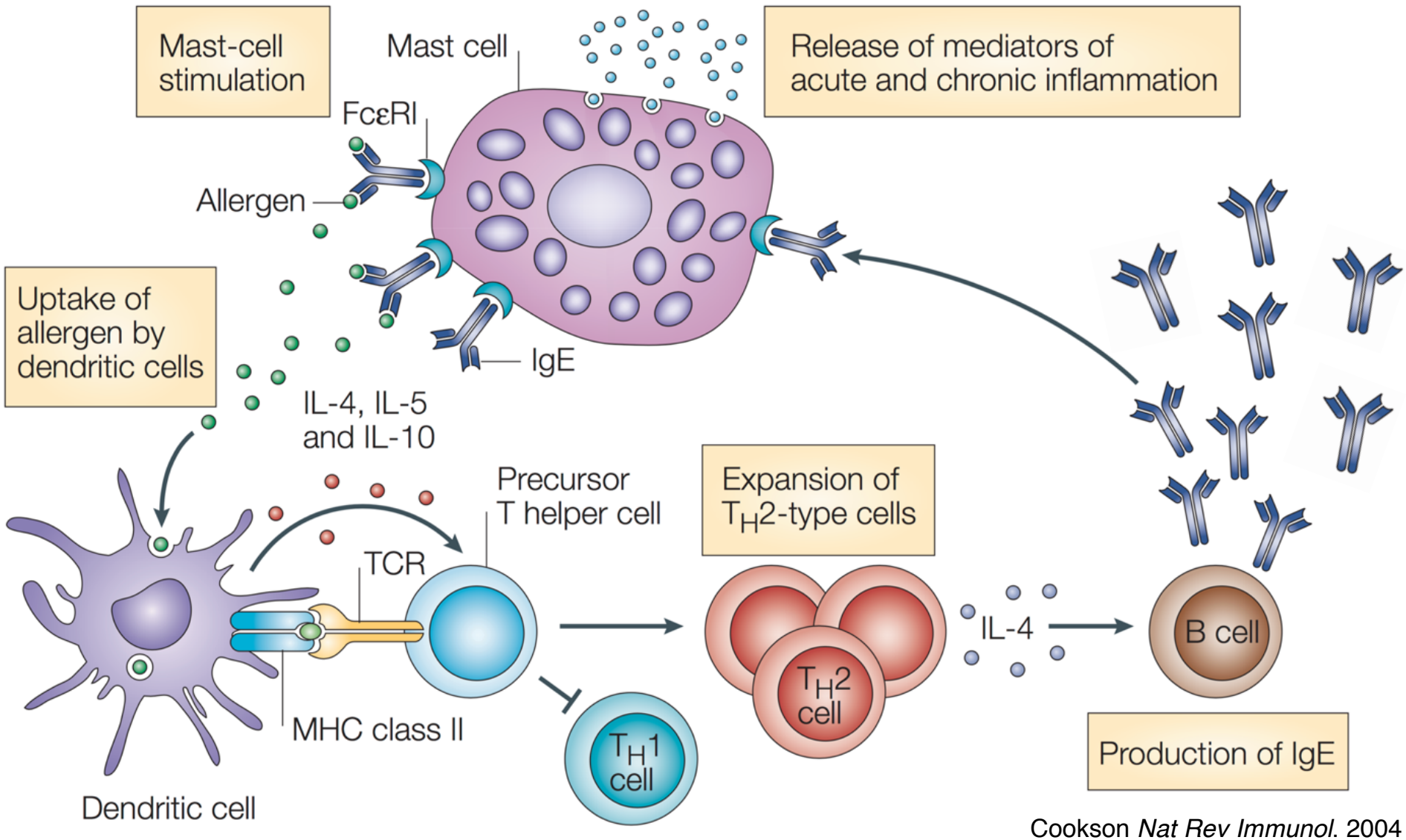
[a] *O-mannosylation*





Lyons et al. *Front Ped*. 2015

A young boy referred to the NIH with a 'hyper-IgE' syndrome



Cookson *Nat Rev Immunol*. 2004

A young boy referred to the NIH with a ‘hyper-IgE’ syndrome

- 12 year old Egyptian male
  - **Elevated IgE** and atopy
    - **atopic dermatitis**, food allergy, asthma, allergic rhinitis
  - Recurrent bacterial infections
    - Recurrent **skin infections**/abscesses
    - recurrent **pneumonia**
    - chronic ear infections
  - Low white blood cells (leukopenia)

Comparison of hyper-IgE conditions

	DOCK8	*STAT3*	Severe atopic dermatitis
IgE	++	+++	+++
Immunoglobulins	low (IgM)/normal/high	low/normal	normal
T_H17	low/normal	absent	normal
Lymphopenia	++	+/-	-
Atopy	+/+++	++	+++
Neurologic Deficits	+/-	-	-
Cutaneous viral infections	+++	+	+
Lymphoma	++	+	-
Vascular Abnormality	+	++	-
Scoliosis	-	+++	+
Retained Primary Teeth	-	+++	+/-

Adapted from Zhang et al. *JACI*. 2014

Some of the conditions with ‘hyper-IgE’

Zhang et al. *NEJM*. 2009

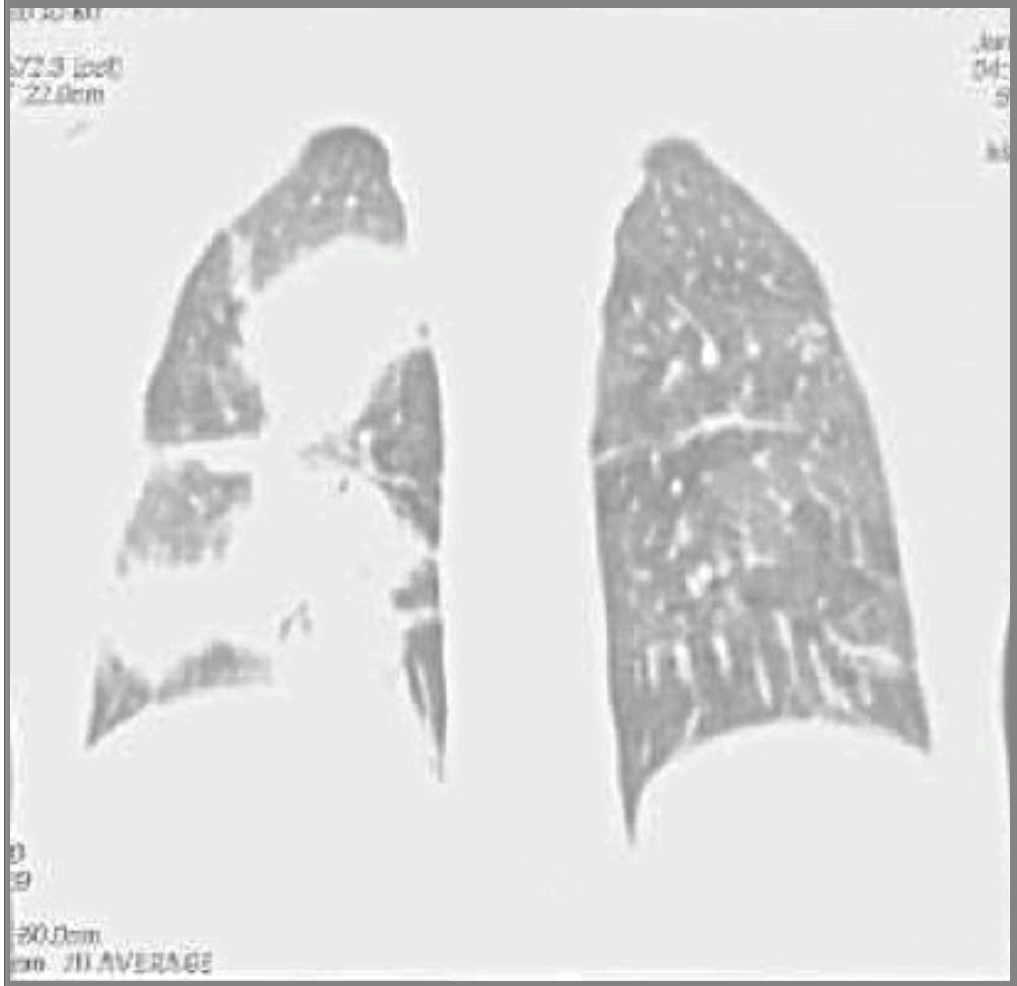
Lyons et al. *Immunol Clin*. 2015

Freeman et al. *Ped Res*. 2009

Birth History

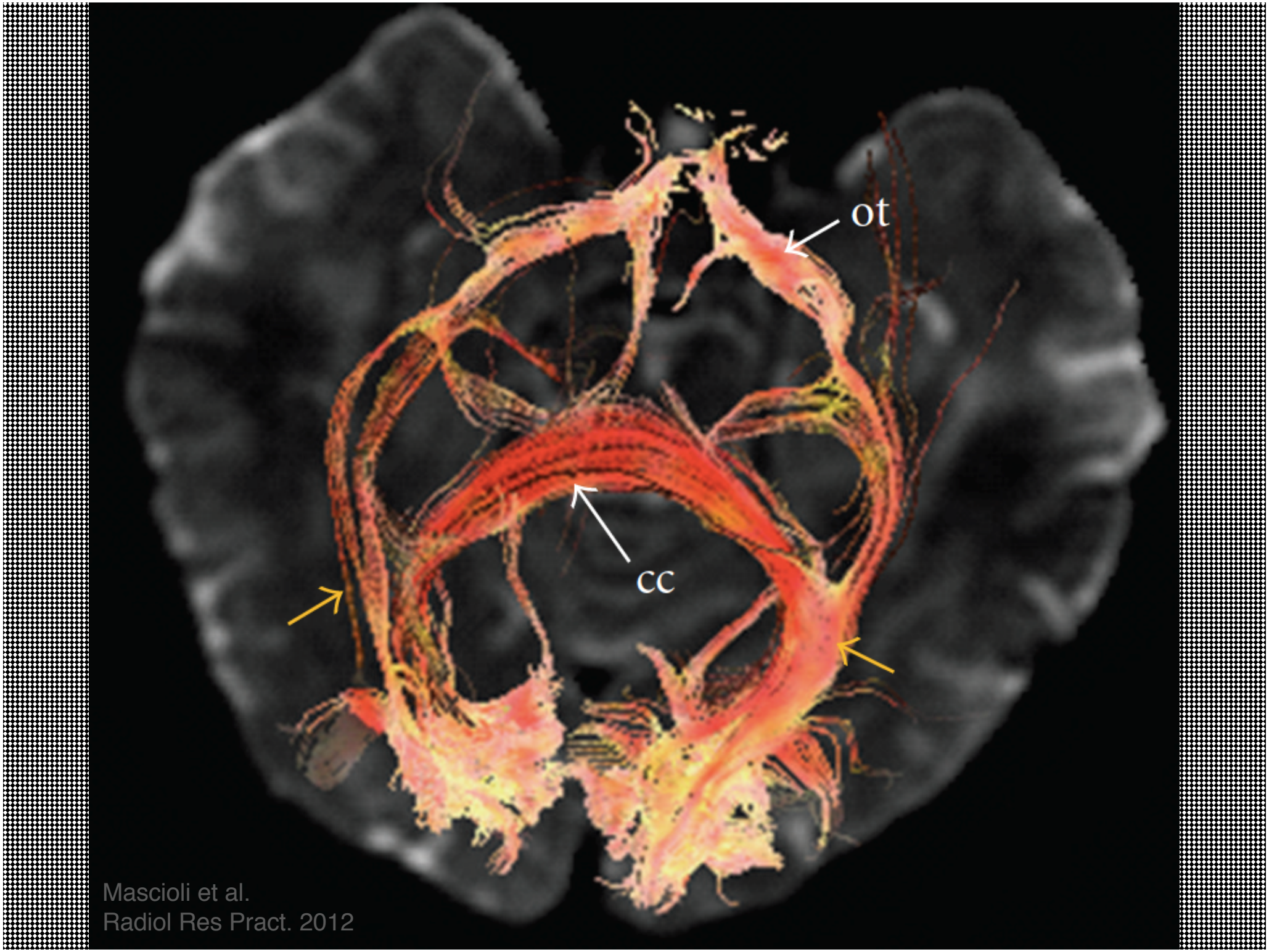
- Egyptian Coptic Christian parents
  - first cousins
- Uncomplicated pregnancy
- Born full term via C-section
- No perinatal or early childhood illnesses

Chest CT from Egypt



Neurologic Abnormalities

- Developmental delay
  - At age 11yo reasoning at 6yo level
  - difficulty with spatial problems
- Discoordination
  - impaired fine motor control and visual tracking
- Speech abnormalities
  - misarticulation, discoordination, slow processing
- History of febrile seizures



Mascioli et al.
Radiol Res Pract. 2012

ARTICLE

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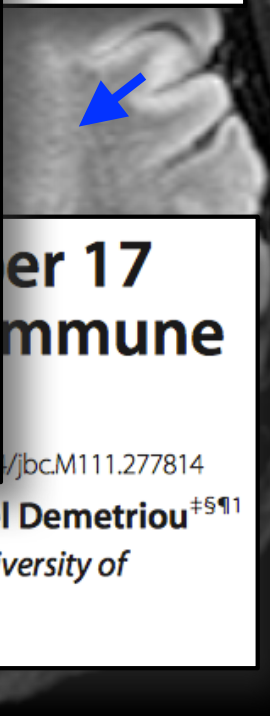
Genetics and the environment converge to dysregulate *N*-glycosylation in multiple sclerosis

Haik Mkhikia … W. Zhou[1],
Christine Bee … Walker[4,5],
Katherine A. … Demetriou[1,2]



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Received for publicat … /jbc.M111.277814

Ani Grigorian[‡§], Lindsey Araujo[¶], Nandita N. Naidu[‖], Dylan J. Place[‡], Biswa Choudhury[‖], and Michael Demetriou[‡§¶1]

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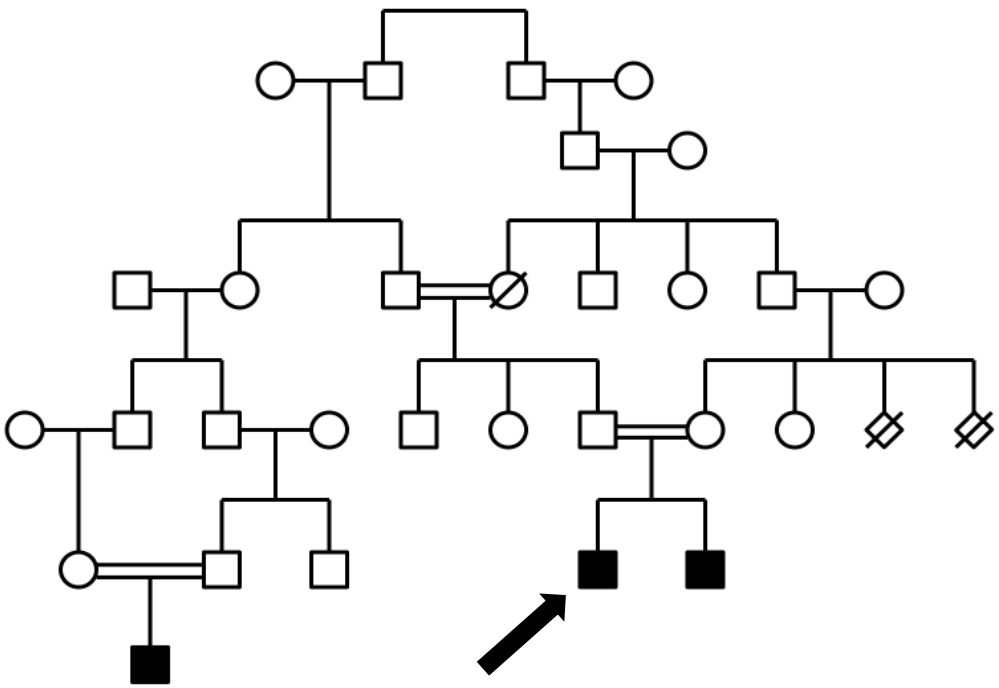
Family History

- 10yo brother
  - Severe allergy, Skin infections, Neurologic difficulties, hemolytic anemia
  - IgE 11405, IgG 2060, IgA 600
  - ANC 1000, ALC 1000
- 9mo M cousin
  - AD, Skin infections, unable to sit unassisted
  - neutropenia



Another family with similar clinical problems

- 5

American Journal of Medical Genetics 125A:145–151 (2004)

Familial Immunodeficiency With Cutaneous Vasculitis, Myoclonus, and Cognitive Impairment

Beverly N. Hay,[1] Julie E. Martin,[2] Barbara Karp,[3] Joie Davis,[1] Dirk Darnell,[2] Beth Solomon,[4] Maria Turner,[5] Steven M. Holland,[2] and Jennifer M. Puck[1*]

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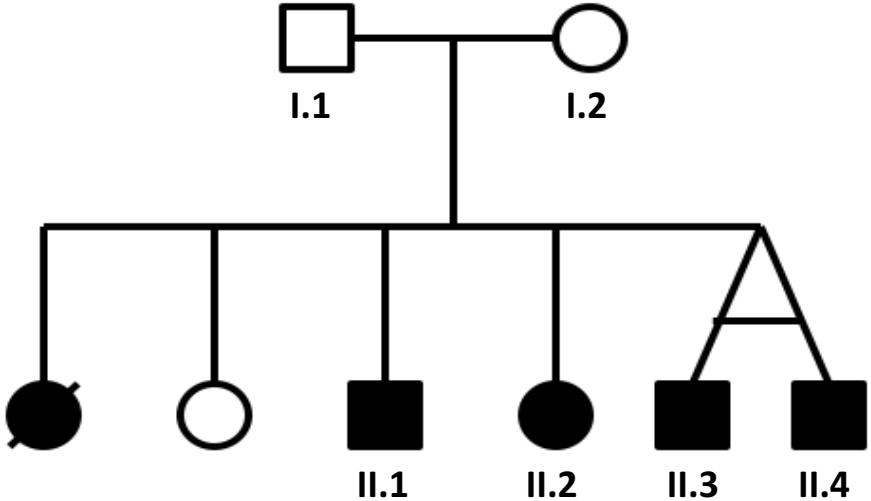
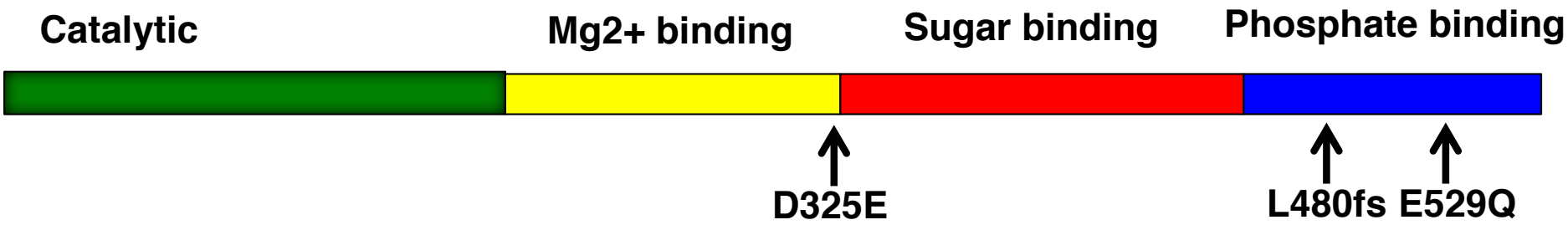
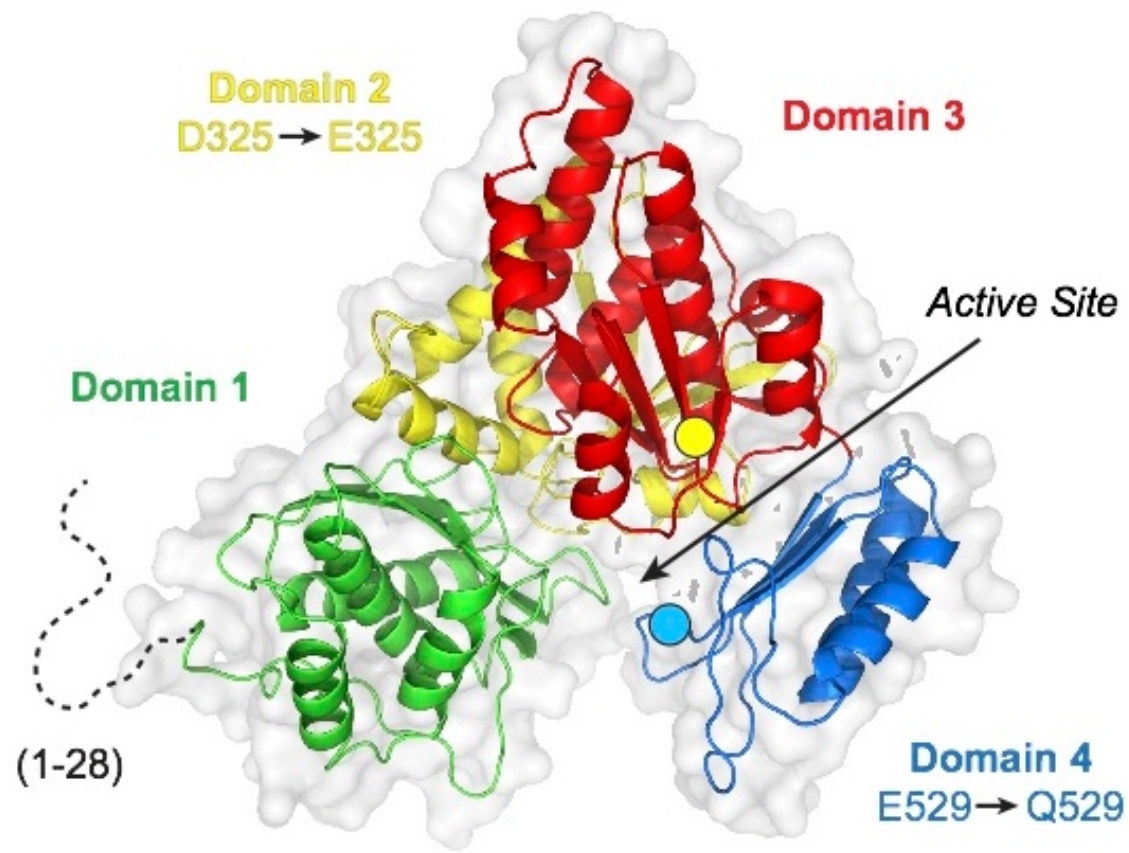
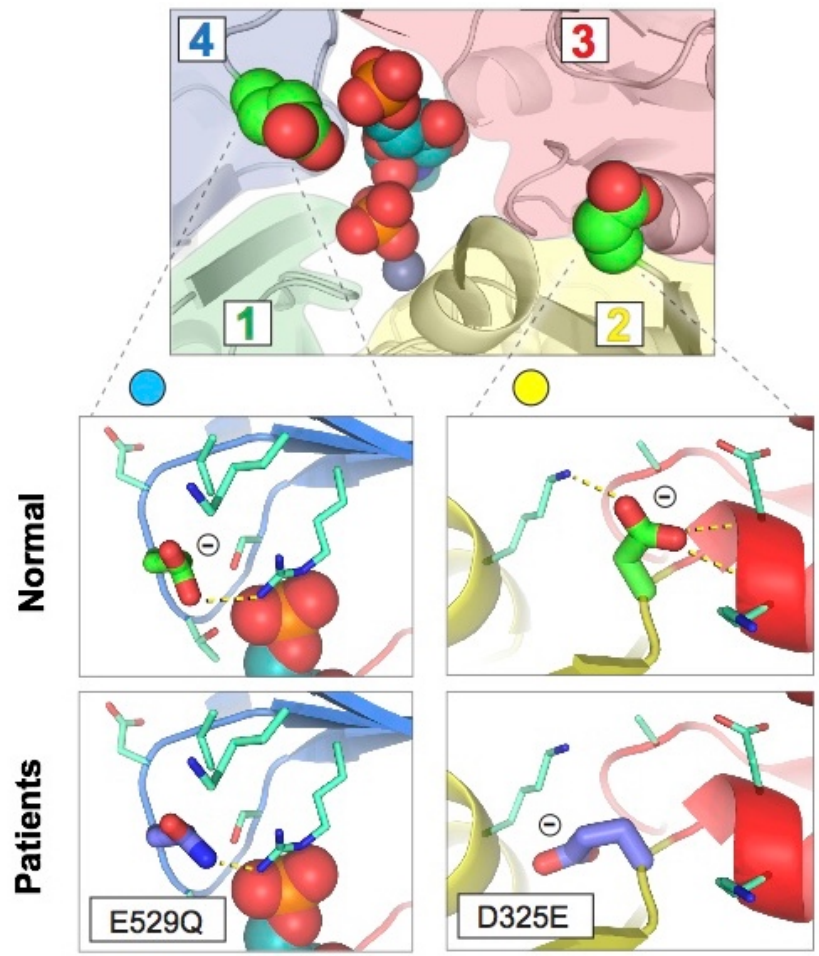
[4]*W.G. Magnuson Center, Rehabilitation Medicine Department, Speech Pathology Section, National Institutes of Health, Bethesda, Maryland*
[5]*National Cancer Institute, National Institutes of Health, Bethesda, Maryland*



PGM3 deficiency







Zhang et al. *J. Allergy Clin. Immunol*. 2014

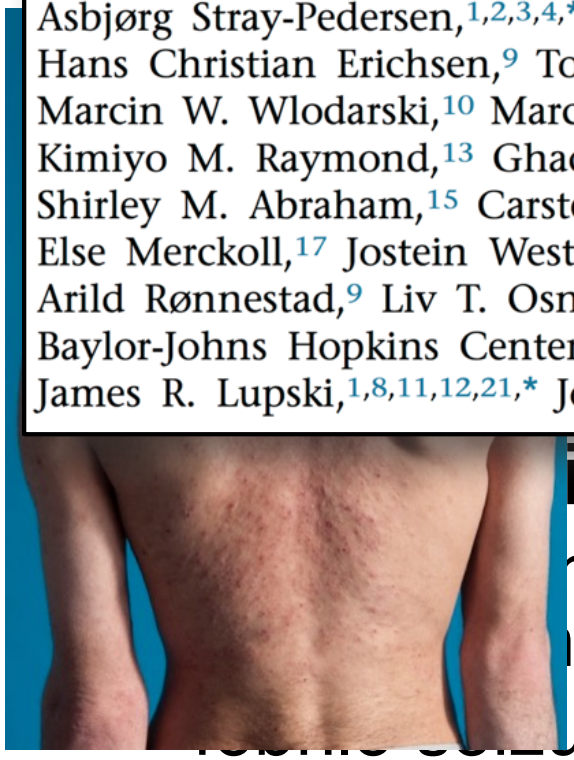
The clinical phenotype of PGM3 deficiency

- Allergy

REPORT

PGM3 Mutations Cause a Congenital Disorder of Glycosylation with Severe Immunodeficiency and Skeletal Dysplasia

Asbjørg Stray-Pedersen,[1,2,3,4,*] Paul H. Backe,[5,6,7] Hanne S. Sorte,[4] Lars Mørkrid,[6,7] Niti Y. Chokshi,[3,8] Hans Christian Erichsen,[9] Tomasz Gambin,[1] Katja B.P. Elgstøen,[6] Magnar Bjørås,[5,7] Marcin W. Wlodarski,[10] Marcus Krüger,[10] Shalini N. Jhangiani,[1,11] Donna M. Muzny,[1,11] Ankita Patel,[12] Kimiyo M. Raymond,[13] Ghadir S. Sasa,[8,14] Robert A. Krance,[8,14] Caridad A. Martinez,[8,14] Shirley M. Abraham,[15] Carsten Speckmann,[10] Stephan Ehl,[10] Patricia Hall,[16] Lisa R. Forbes,[2,3,8] Else Merckoll,[17] Jostein Westvik,[17] Gen Nishimura,[18] Cecilie F. Rustad,[4] Tore G. Abrahamsen,[7,9] Arild Rønnestad,[9] Liv T. Osnes,[19] Torstein Egeland,[7,19] Olaug K. Rødningen,[4] Christine R. Beck,[1] Baylor-Johns Hopkins Center for Mendelian Genomics, Eric A. Boerwinkle,[1,11,20] Richard A. Gibbs,[1,11] James R. Lupski,[1,8,11,12,21,*] Jordan S. Orange,[2,3,8,21] Ekkehart Lausch,[10,21] and I. Celine Hanson[3,8,21]



ive impairment

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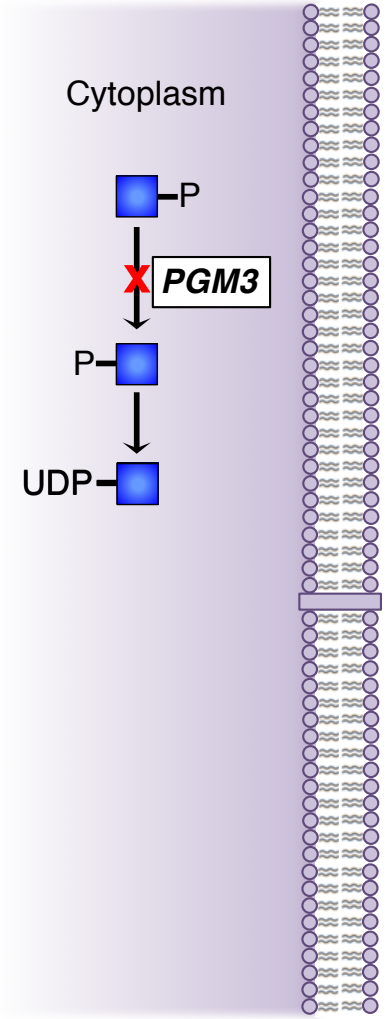
PGM3 deficiency results in severe atopy and is associated with reduced UDP-■(GlcNAc) pools

Zhang et al. *JACI*. 2014



Allergic diseases in *PGM3* def.

- Atopic dermatitis
- Allergic rhinosinusitis/conjunctivitis
- Asthma
- Food allergy (IgE-mediated and Eosinophilic)
- Allergic fungal mastoiditis
- Allergic bronchopulmonary aspergillosis (ABPA)
- Food-protein induced enteropathic syndrome (FPIES)
- Drug allergy (IgE and cell-mediated)

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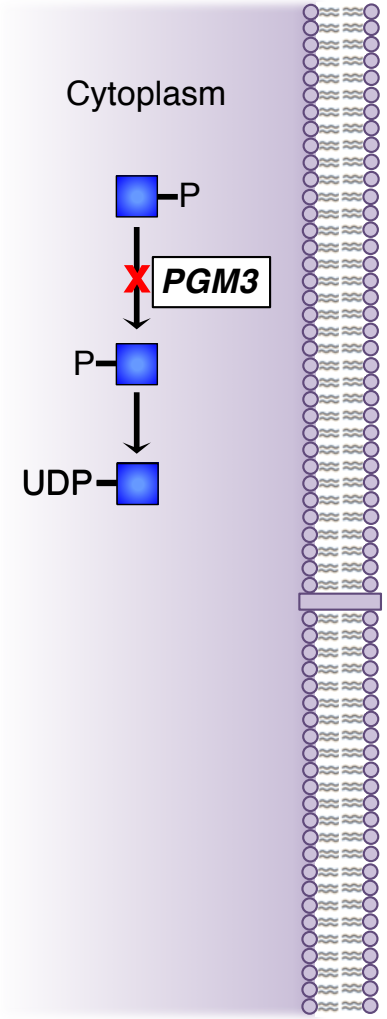

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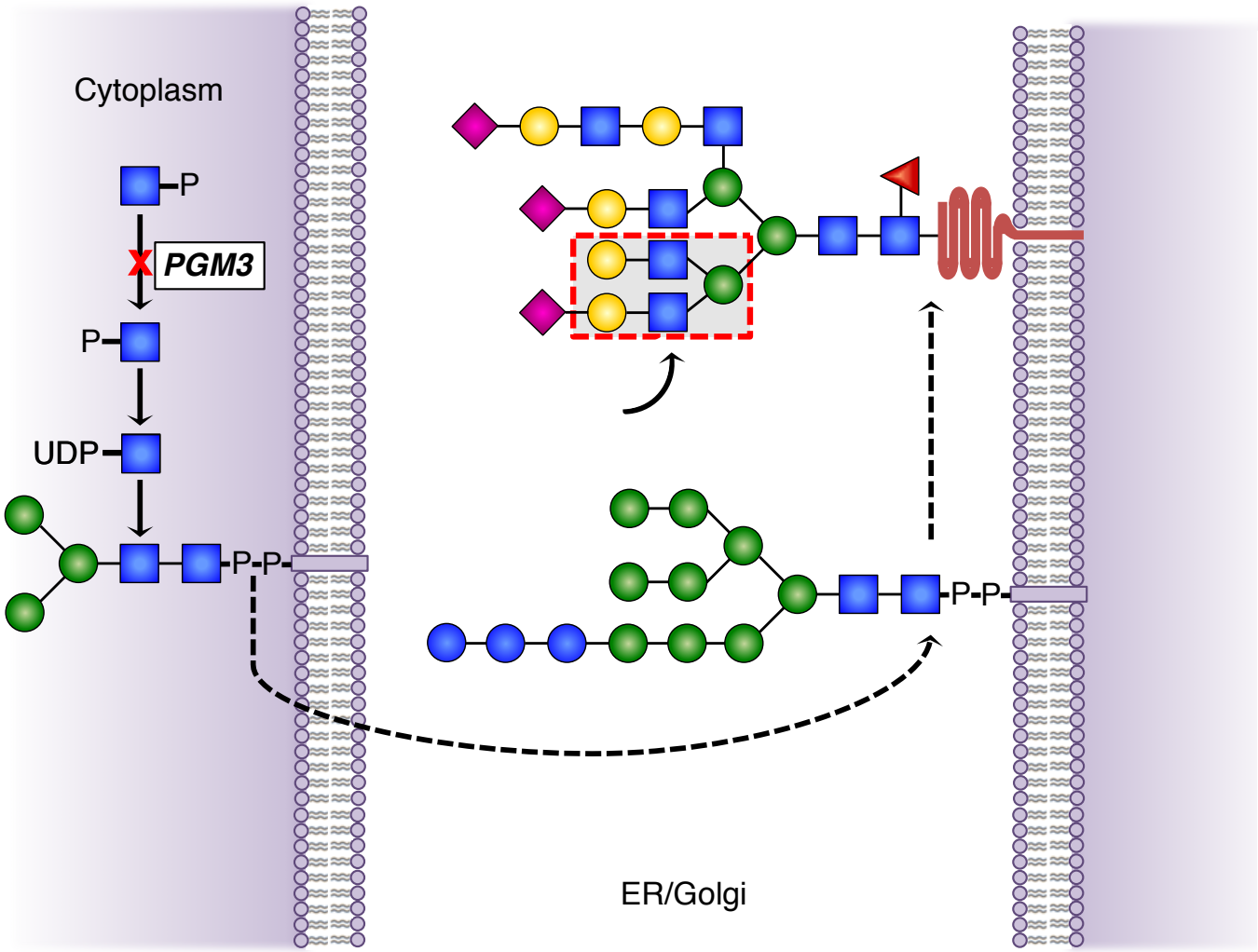
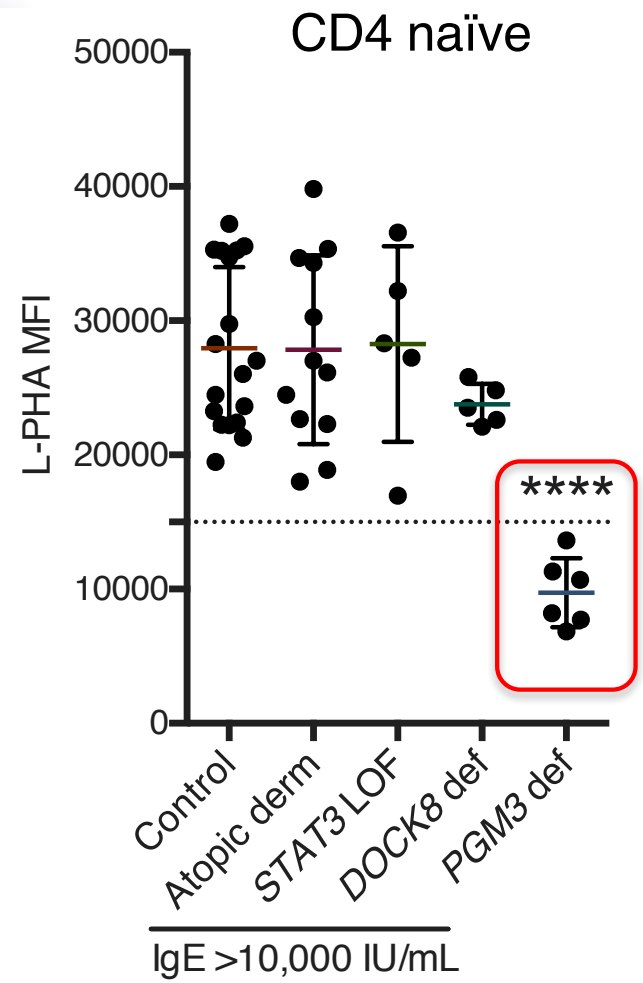
N-glycan complexity is dependent upon UDP-■(GlcNAc) pools

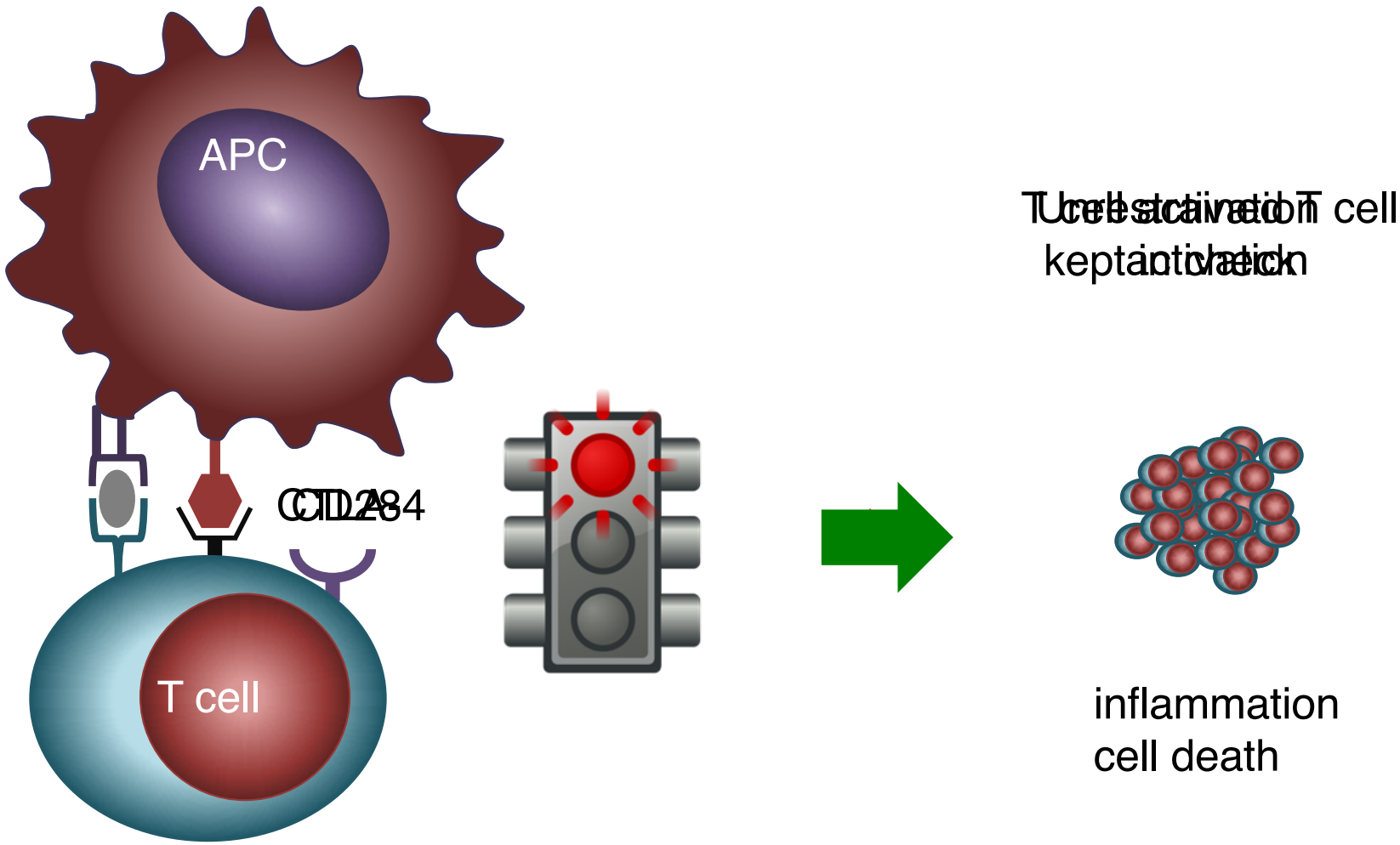




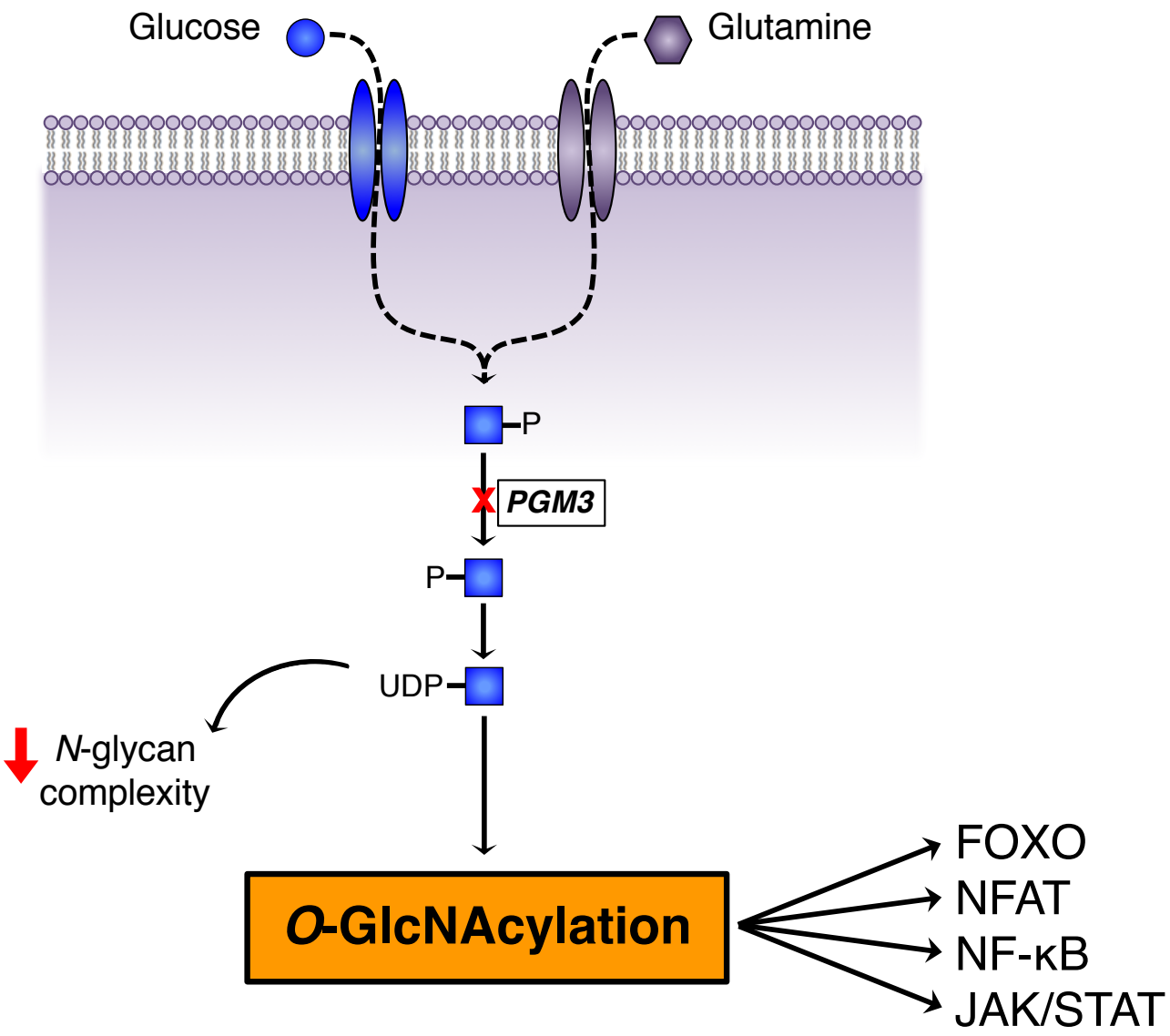
adapted from Lyons et al. *Front Ped.* 2015

****P<0.0001 Carlson et al. *JACI* 2016

Driving inflammation without brakes



Reduced UDP-■(GlcNAc) impairs *O*-GlcNAcylation homeostasis in *PGM3* deficiency



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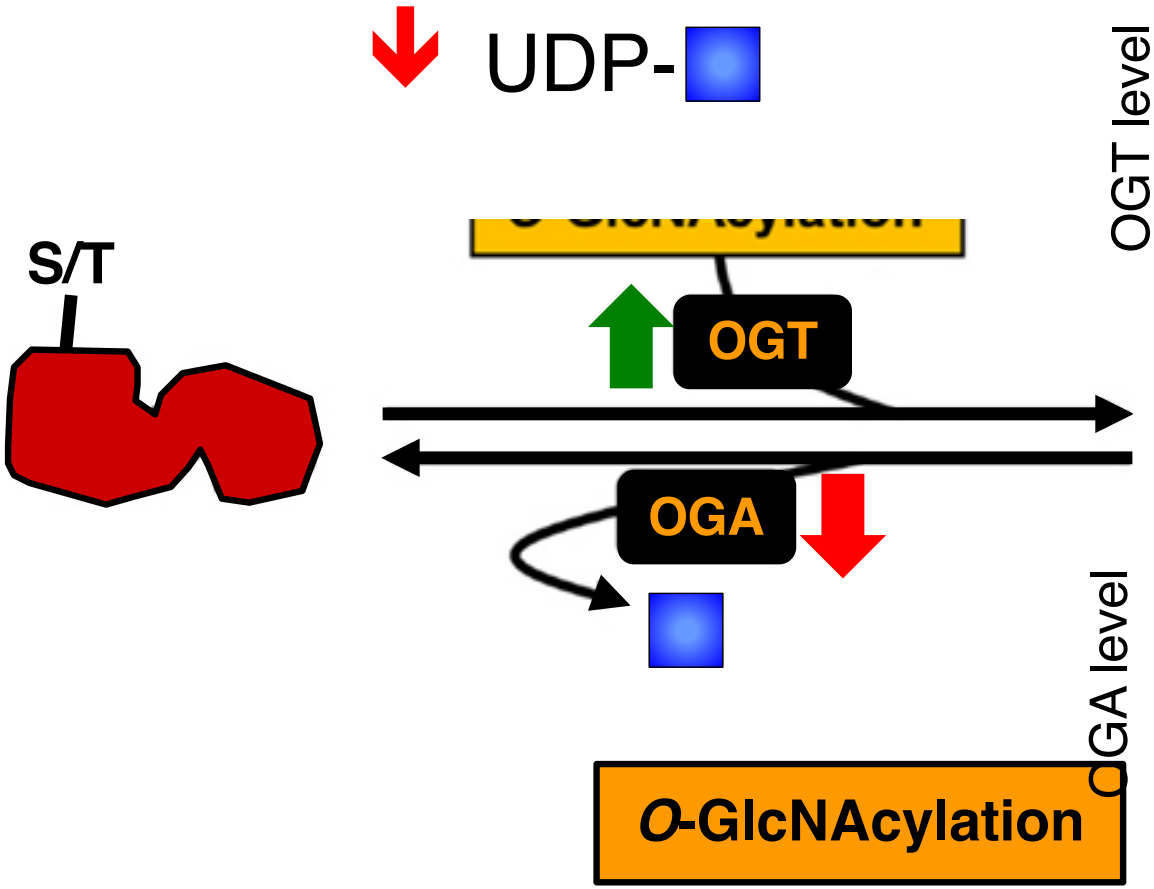
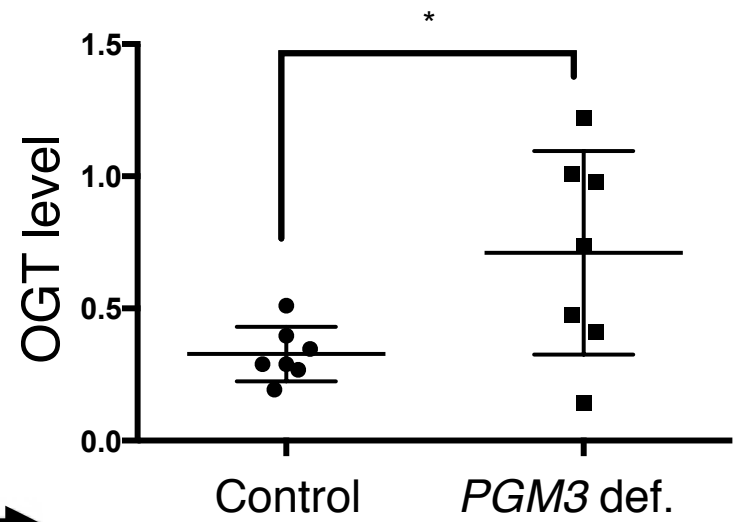
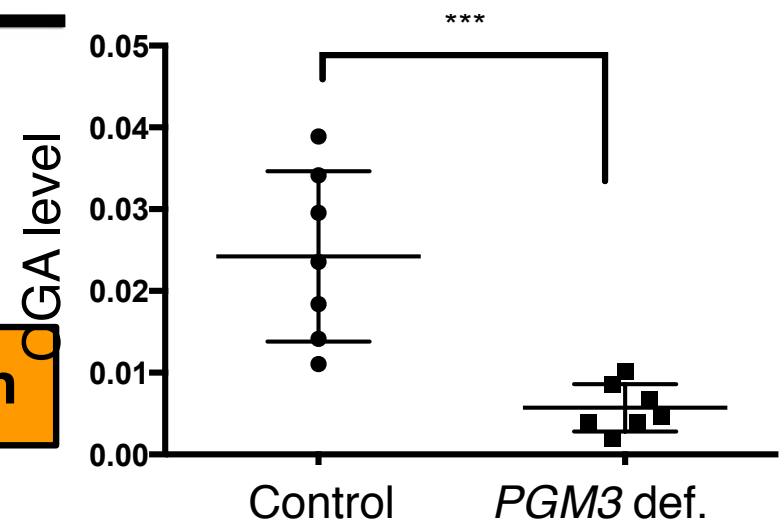


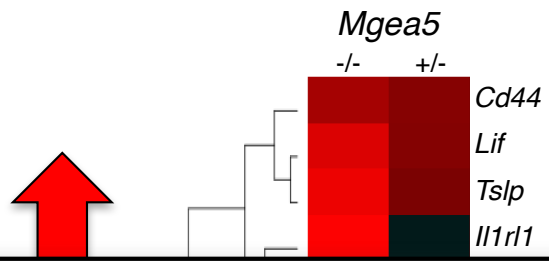


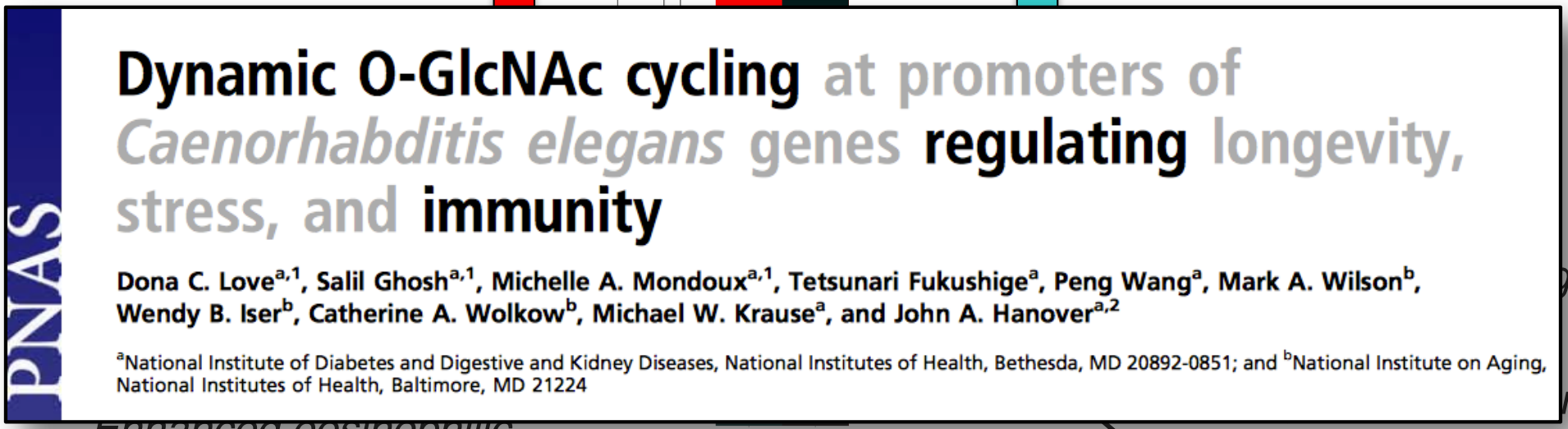


adapted from Chaiyawat et al. *Front Endocrinol*. 2014

Unpublished data; *P<0.05, ***P<0.001

OGA deficient embryonic fibroblasts display an intrinsic atopic transcriptional profile





PNAS

Dynamic O-GlcNAc cycling at promoters of *Caenorhabditis elegans* genes **regulating** longevity, stress, and **immunity**

Dona C. Love[a,1], Salil Ghosh[a,1], Michelle A. Mondoux[a,1], Tetsunari Fukushige[a], Peng Wang[a], Mark A. Wilson[b], Wendy B. Iser[b], Catherine A. Wolkow[b], Michael W. Krause[a], and John A. Hanover[a,2]

[a]National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892-0851; and [b]National Institute on Aging, National Institutes of Health, Baltimore, MD 21224

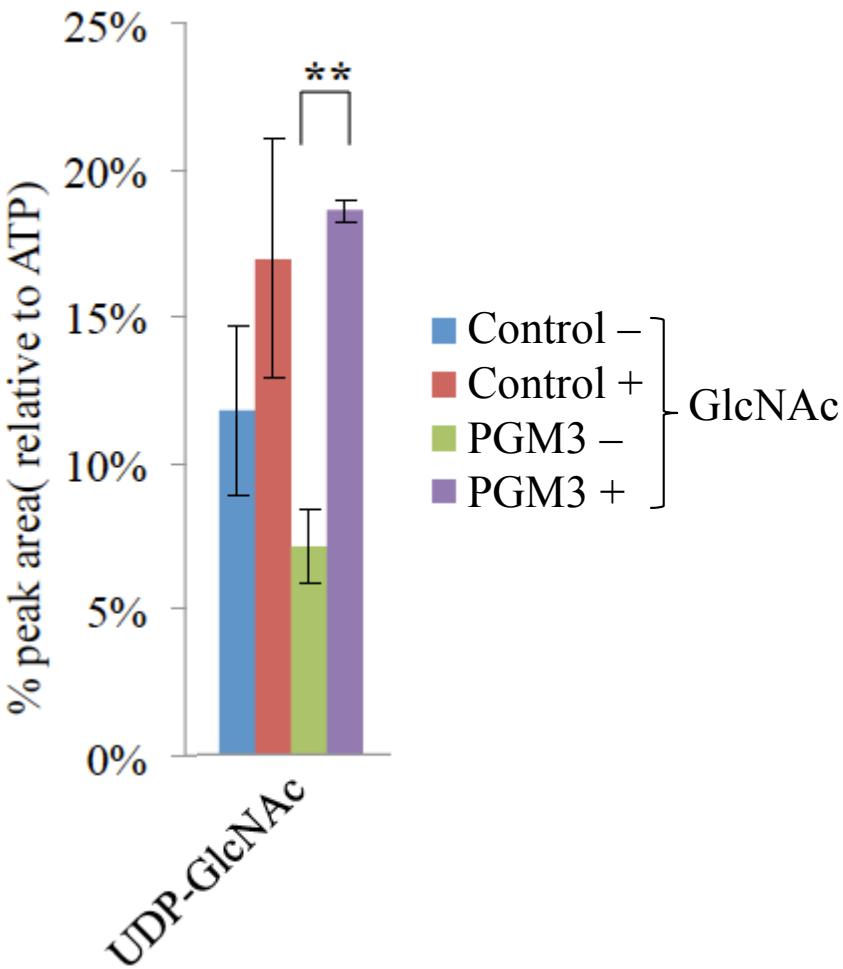
Enhanced eosinophilic inflammation

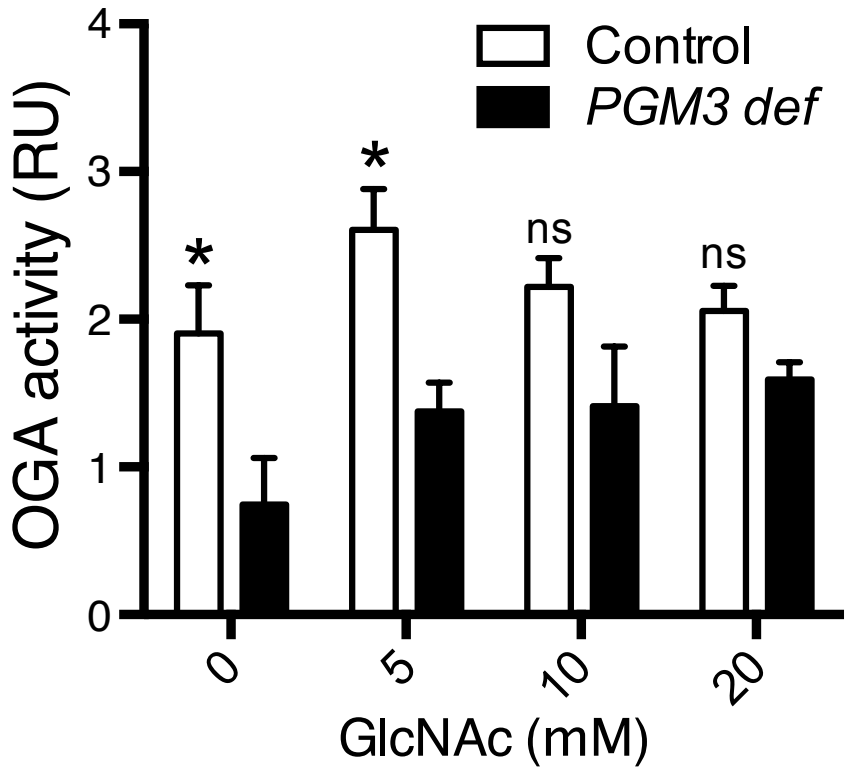
Th17 suppression

Increased atopy and Th17 associated autoimmunity

Unpublished data

Exogenous GlcNAc can restore UDP-GlcNAc pools and normalize OGA activity *in vitro*





Zhang et al. *JACI*. 2014

*P<0.05, Unpublished data

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Tom DiMaggio

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Dirk Darnell

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Ming Zhao
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Glen Nardone

Sanford Burnham
Hudson Freeze
Mie Ichikawa

NIAID Clinical Genomics Program

Support
NIAID DIR

National Institute of Allergy and Infectious Diseases

Comparison of hyper-IgE syndromes and congenital disorders of glycosylation

	PGM3	*DOCK8*	*STAT3*	Severe atopic dermatitis	CDGs
IgE	+++	++	+++	+++	NR
Immunoglobulins	high	low (IgM)/normal/high	low/normal	normal	low/normal
Peripheral T_H17	increased	low/normal	absent	normal	NR
T Lymphopenia	++	++	+/-	-	+/-
Atopy	+++	+/+++	++	+++	-
Neurologic Deficits	+++	+/-	-	-	+++
EBV viremia	++	++	+	-	-
Cutaneous viral infections	++	+++	+	+	-
Lymphoma	++	++	+	-	-
Vascular Abnormality	+/-	+	++	-	-
Bronchiectasis	++	++	+++	-	-
Scoliosis	++	-	+++	+	++
Retained Primary Teeth	-	-	+++	+/-	-