# Genetic modifiers for PMM2-CDG

Giuseppina Andreotti

Institute of Biomolecular Chemistry (ICB)
National Research Council of Italy (CNR)
Pozzuoli-Na

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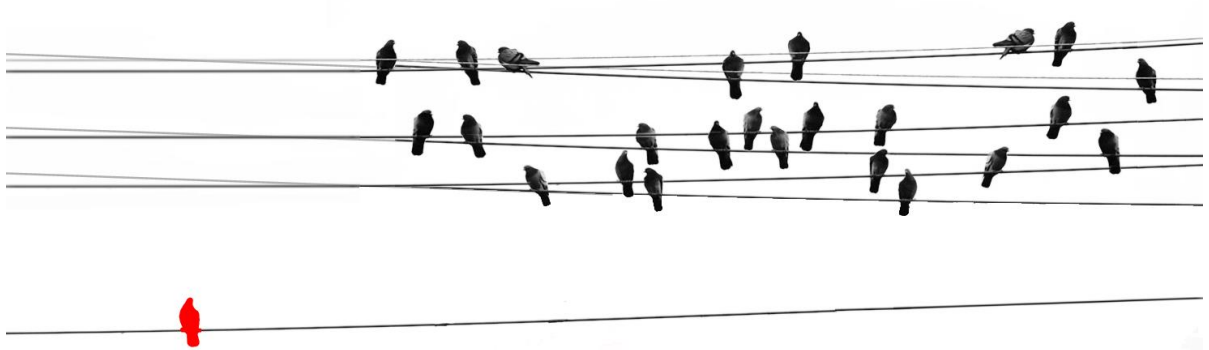
*Molecular Sciences*

MDPI

*Article*

# The Analysis of Variants in the General Population Reveals That *PMM2* Is Extremely Tolerant to Missense Mutations and That Diagnosis of PMM2-CDG Can Benefit from the Identification of Modifiers

Valentina Citro [1], Chiara Cimmaruta [1], Maria Monticelli [1], Guglielmo Riccio [1], Bruno Hay Mele [1,2], Maria Vittoria Cubellis [1,*] and Giuseppina Andreotti [3]



**PMM2**

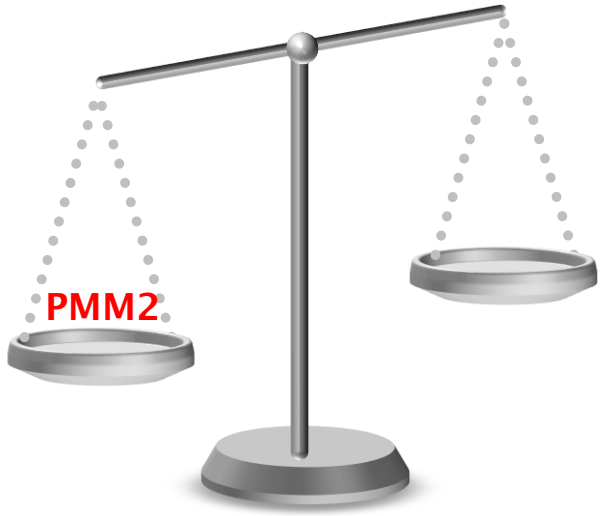
*A gene out of the flock*

# *Let's simplify……*

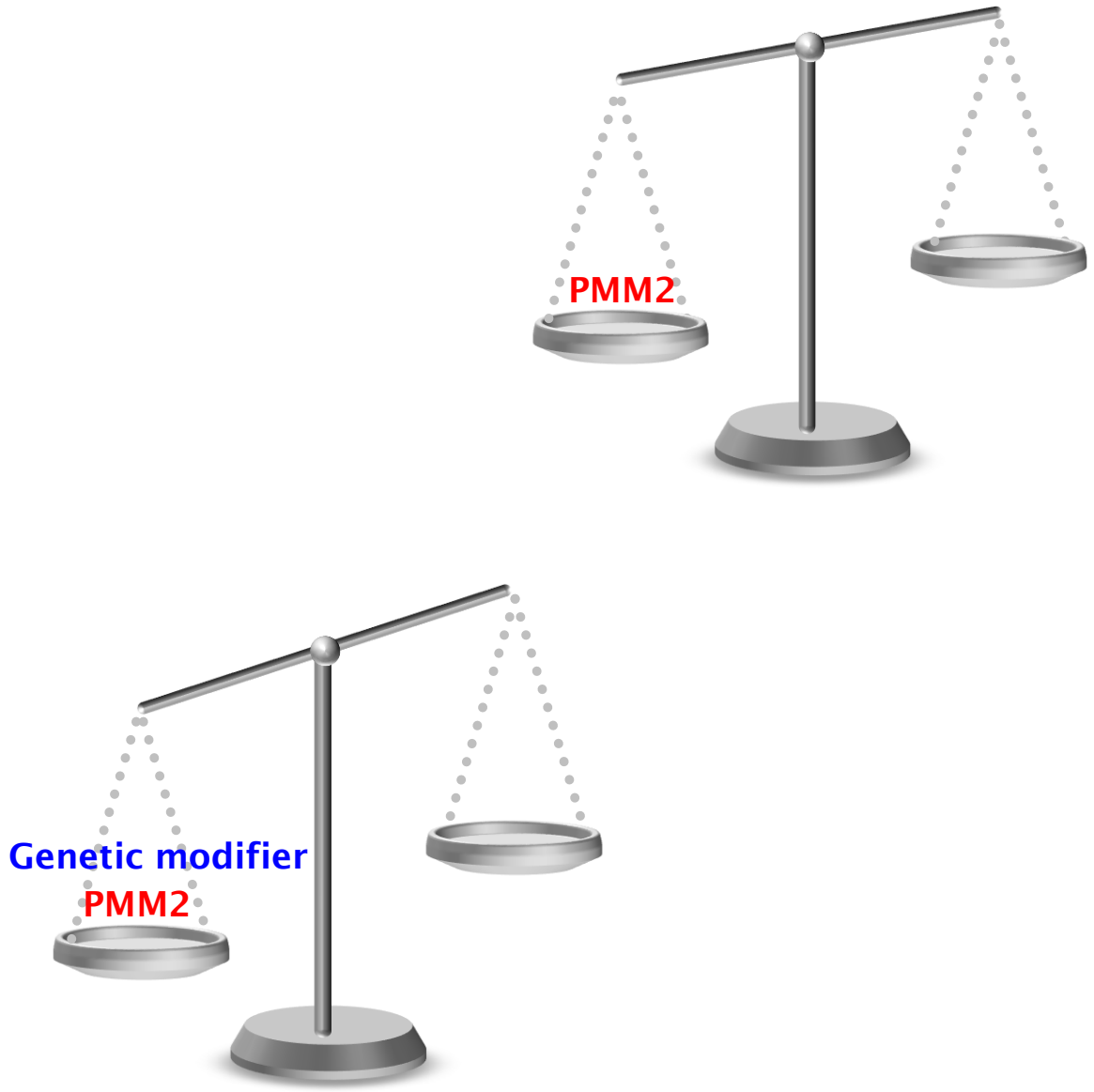
**What are genetic modifiers?**

genes that worsen or improve the clinical picture of a patient

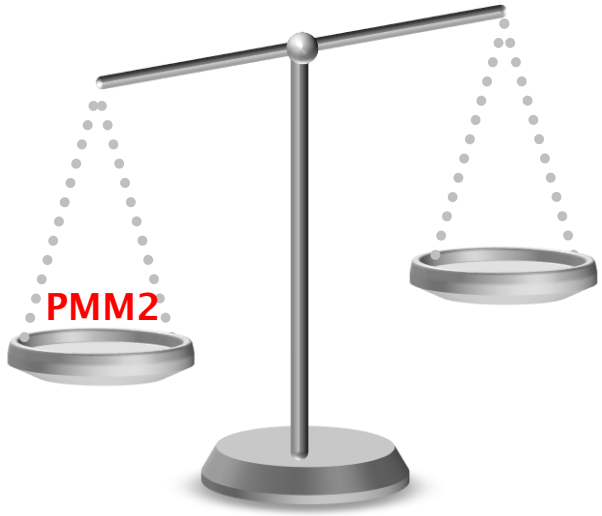
healthy individual



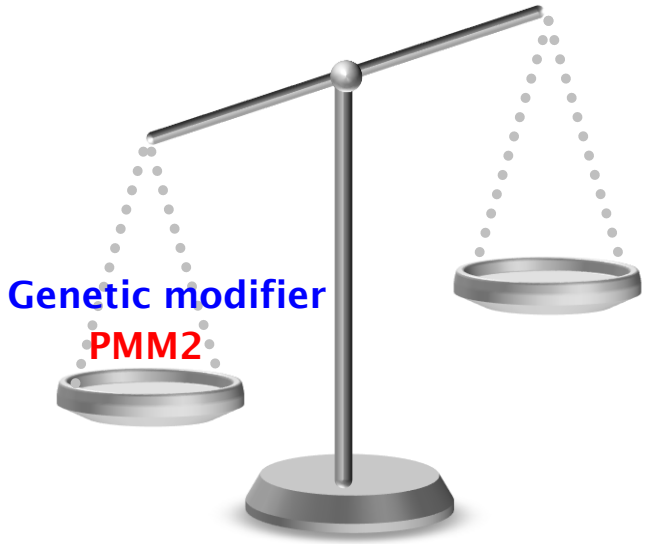

PMM2-CDG patient



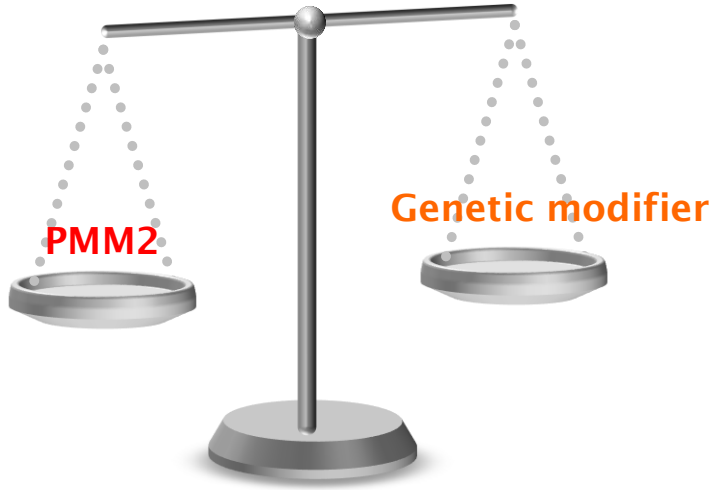

PMM2-CDG patient




PMM2-CDG patient




OR



# *Let's simplify……*

**What are genetic modifiers?**

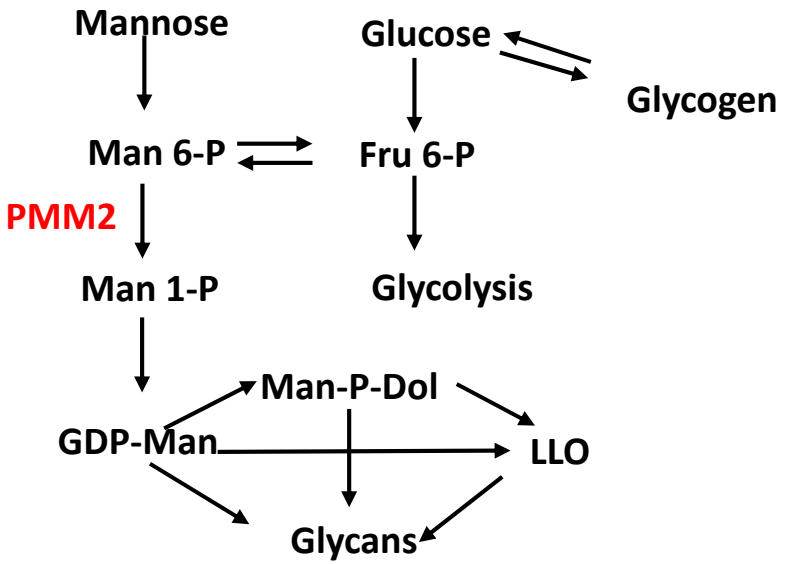
genes that worsen or improve the clinical picture of a patient

**Why are they important?**

deciphering the molecular mechanism(s) of the disease
development of therapeutic approaches
identification of novel target(s) for therapeutic interventions

**What are the clinical/diagnostic/prognostic implications?**

stratification of patients and selection of a personalized therapy




PMM2-CDG IS A RARE RECESSIVE AUTOSOMIC DISEASE

NO CURE

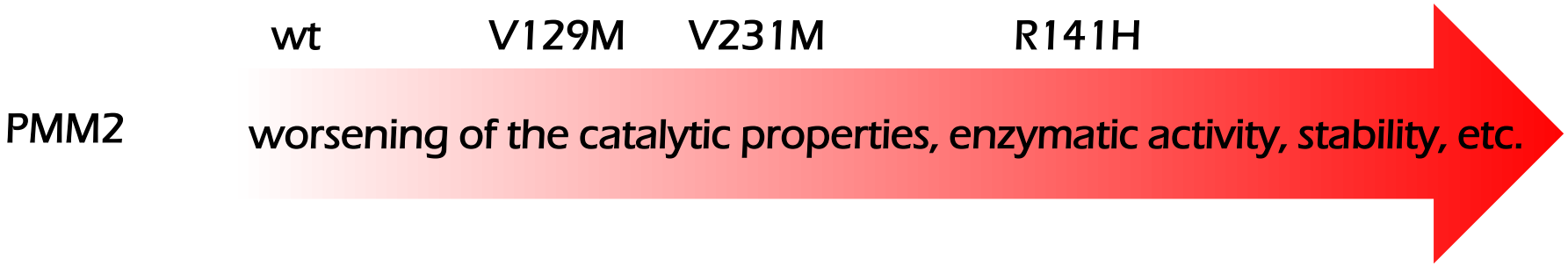
+ 110 MUTATIONS IN HGMD (The Human Gene Mutation Database)

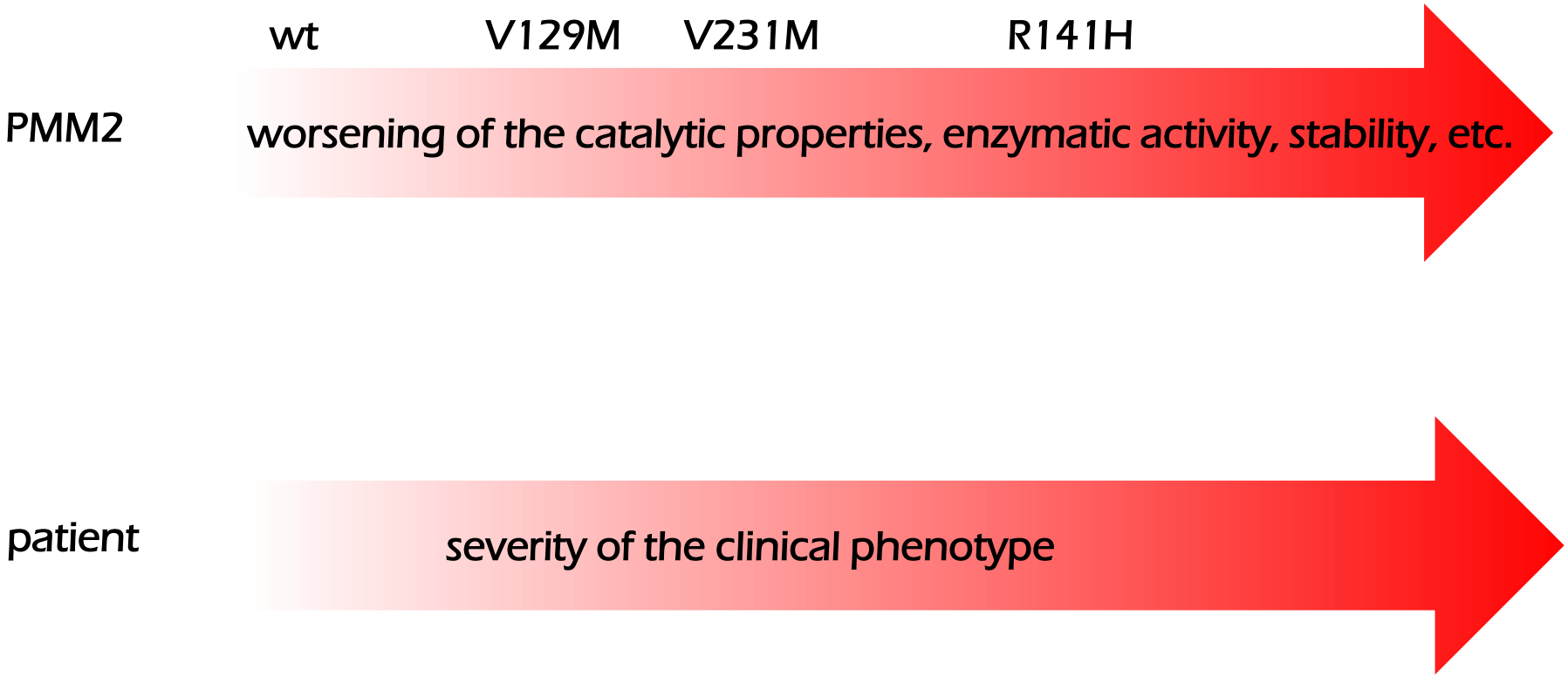
R141H MOST FREQUENT (1/80) F119L SECOND MOST FREQUENT (1/400)

COMPOSITE HETEROZYGOSITY: F119L/R141H, V129M/R141H, V231M/R141H...

HOMOZYGOSITY: F119L/F119L,....., R141H/R141H NEVER OBSERVED

- **People carrying only one mutated allele are asymptomatic**
- **Affected people have PMM2 residual activity**
- **Complete loss of PMM2 activity is not compatible with life**
- **Possible therapy designed to enhance protein stability?**


wt
V129M
V231M
R141H
PMM2
worsening of the catalytic properties, enzymatic activity, stability, etc.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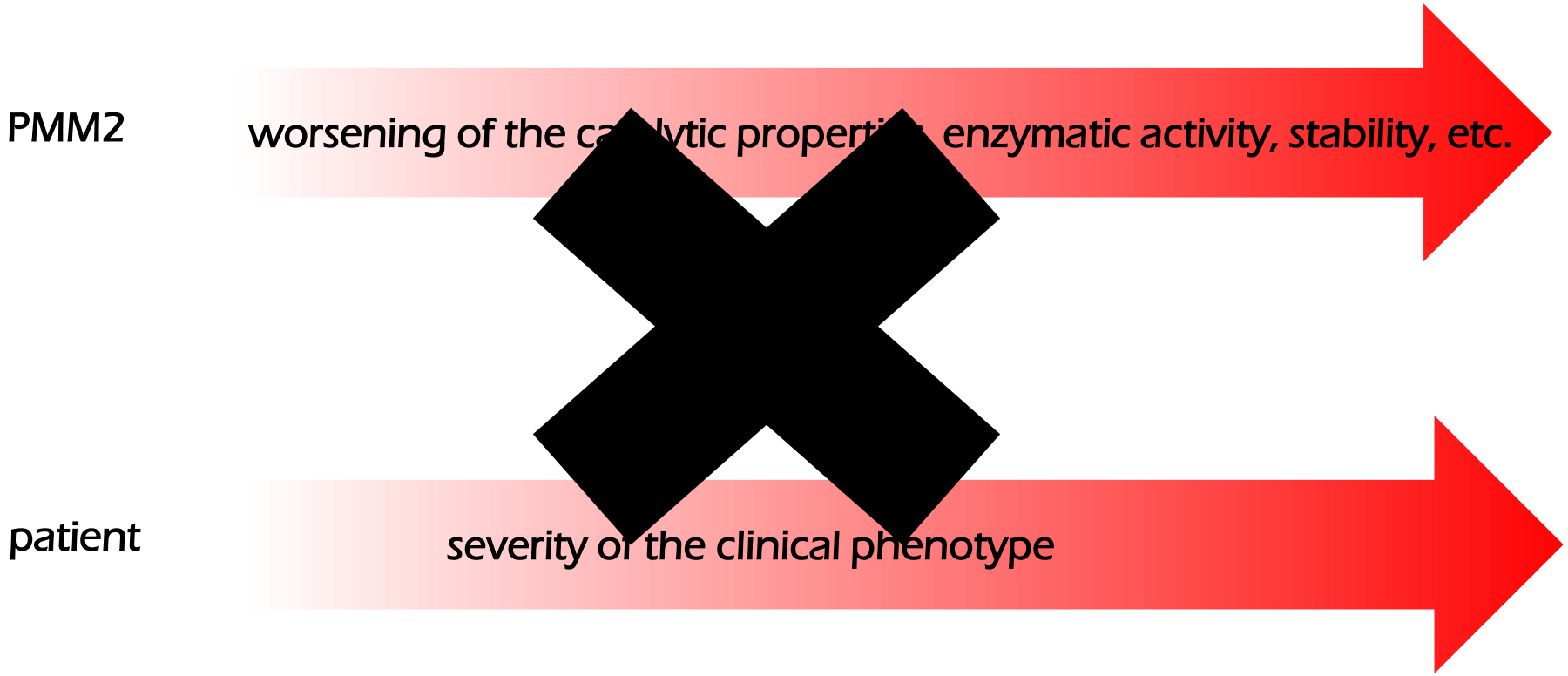
patient
severity of the clinical phenotype


PMM2
worsening of the catalytic properties, enzymatic activity, stability, etc.
patient
severity of the clinical phenotype

# *ExAC*

Exome Aggregation Consortium **more than 60 000 individuals**

- number of observed and expected mutations per gene

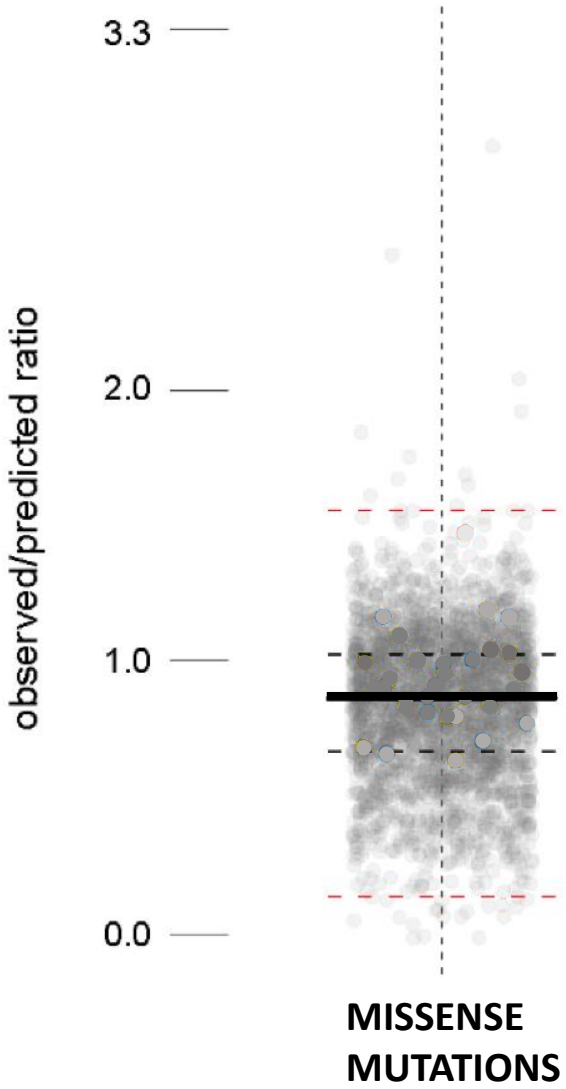
*We selected* → genes that were annotated in UniProt database with the keyword "disease"

*We subtracted* → genes that are associated with autosomal dominant diseases

3125 instances

$$\frac{\text{number of observed mutations}}{\text{number of expected mutations}}$$

Exome Aggregation Consortium (ExAC)
more than 60,000 individuals



Exome Aggregation Consortium (ExAC)
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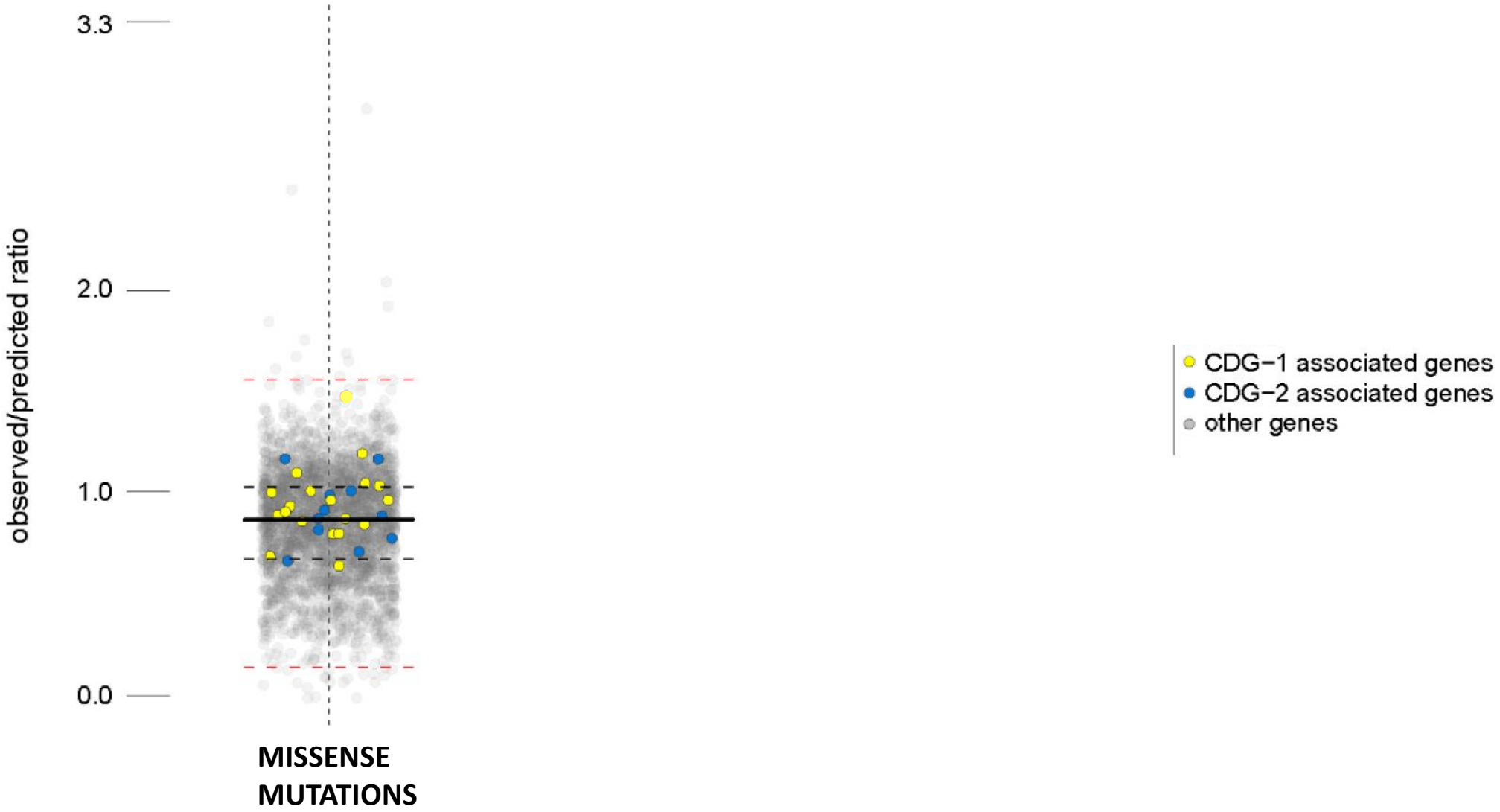

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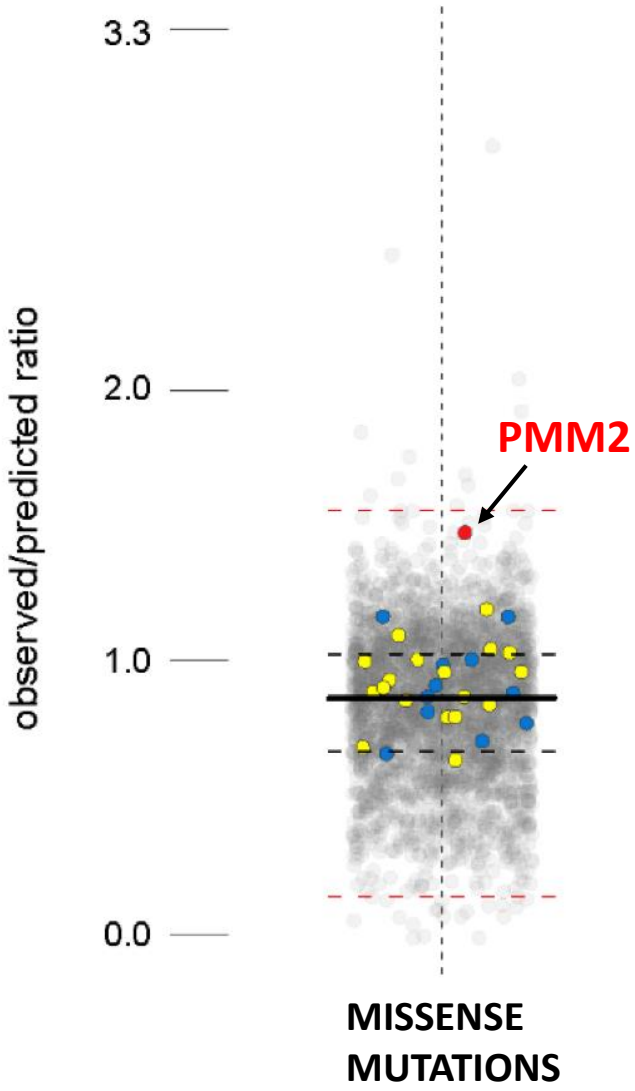


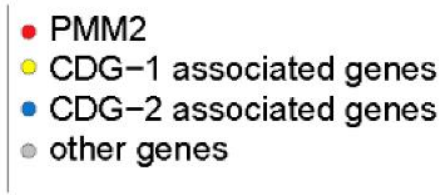


*the ratio between the number of observed and predicted missense mutations for PMM2 is abnormally high*

# Reduced mannomutase activity has a beneficial role under certain conditions

Biochimie 83 (2001) 791–799

S0300908401012925/FLA

## Balancing N-linked glycosylation to avoid disease

Hudson H. Freeze*, Vibeke Westphal

*The Burnham Institute, 10901 North Torrey Pines Road, La Jolla, CA 92037, USA*

(Received 18 April 2001; accepted 6 May 2001)

# ALG6-CDG/α1,3-glucosyltransferase

# variant F304S worsen PMM2_CDG phenotype

Hum Mol Genet. 2002 Mar 1;11(5):599-604.

**A frequent mild mutation in ALG6 may exacerbate the clinical severity of patients with congenital disorder of glycosylation Ia (CDG-Ia) caused by phosphomannomutase deficiency.**

Westphal V[1], Kjaergaard S, Schollen E, Martens K, Grunewald S, Schwartz M, Matthijs G, Freeze HH.

Gene. 2013 Dec 1;531(2):506-9. doi: 10.1016/j.gene.2013.07.083. Epub 2013 Aug 26.

**PMM2-CDG: phenotype and genotype in four affected family members.**

Bortot B[1], Cosentini D, Faletra F, Biffi S, De Martino E, Carrozzi M, Severini GM.

# ExAC

Exome Aggregation Consortium

***more than 60 000 individuals***

**Table 2.** Frequent deleterious variants in type I disorders of glycosylation other than PMM2-glycosylation (CDG).

| Gene | Mutation | Allele Frequency |
|---|---|---|
| *ALG6* | p.Leu453Val | 0.012 |
| *ALG3* | p.Val362Ile | 0.001 |
| *MPDU1* | p.Ala229Thr | 0.154 |
| | p.Gly225Ser | 0.010 |
| *ALG12* | p.Ile393Val | 0.112 |
| *ALG8* | p.Arg268Gln | 0.014 |
| *ALG2* | p.Pro56Leu | 0.001 |
| *ALG1* | p.Thr64Asn | 0.003 |
| | p.Ala3Asp | 0.001 |
| *ALG9* | p.Ser255Leu | 0.003 |
| *RFT1* | p.Ala185Thr | 0.017 |
| | p.Ser16Cys | 0.001 |
| *SRD5A3* | p.His309Asp | 0.004 |
| *DDOST* | p.Arg315Gln | 0.003 |
| | p.Thr400Ile | 0.001 |

**mutations that are relatively frequent in the general population**

# ExAC

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**Institute of Biomolecular Chemistry-CNR**
***chemistry, biochemistry***

**G. Andreotti,** ***researcher***
**L. Liguori,** ***PhD student***
**M.T. Allocca,** ***PhD student***


**Department of Biology-Univ. of Naples Federico II**
***cellular biology, bioinformatic***

**M.V. Cubellis,** ***professor***
**M. Monticelli,** ***PhD student***
**V. Citro,** ***post-doc***


# *Thanks!*