



Informed metabolic network analysis implicates disrupted energy metabolism in young adults from low socioeconomic backgrounds

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Social Genomics, UZH Zürich, Switzerland

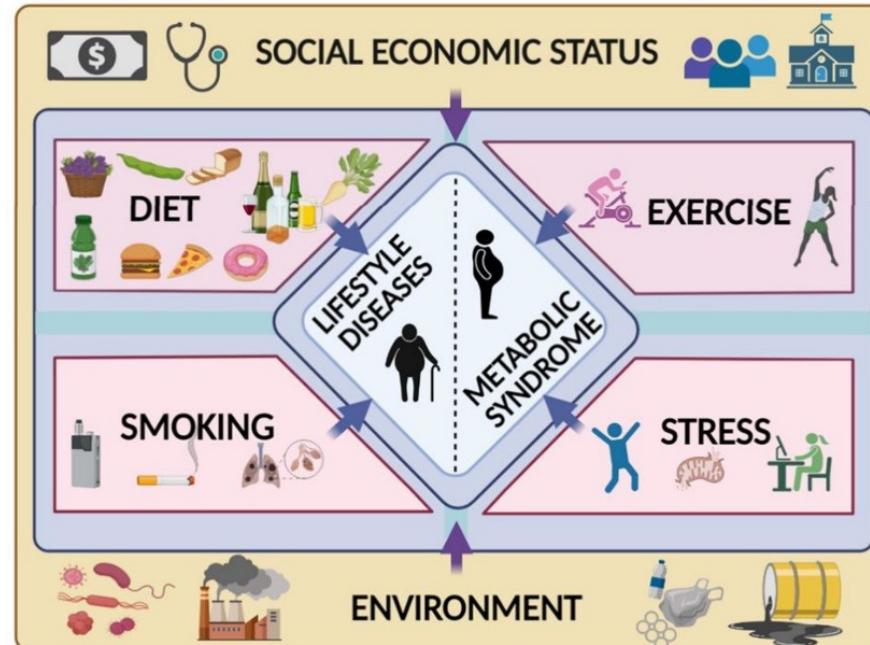
2024 Add Health Users Conference – The Rizzo Center, Chapel Hill, North Carolina



Why?

→ Social stress has a profound and complex impact on metabolism

- Studies in adult populations in various countries have shown elevated risk of metabolic syndrome (MetS) and its remission with lowered socioeconomic status (SES).



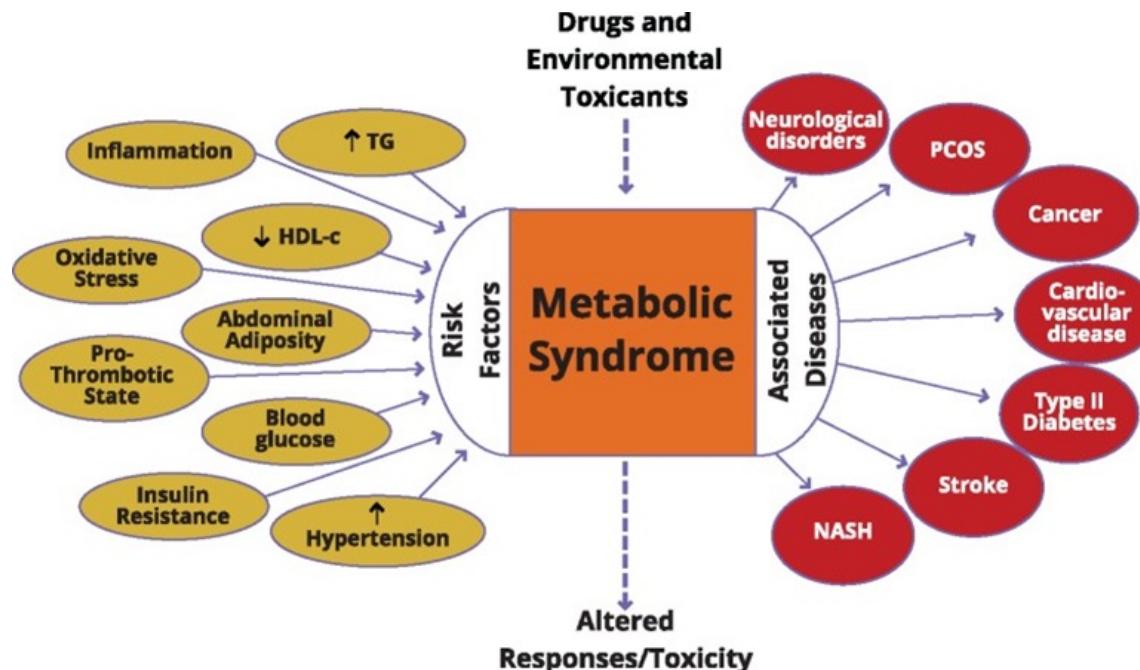
Processes, 9 (11), 2021



Why?

→ Social stress has a profound and complex impact on metabolism

- MetS is a cluster of several physiological and biochemical disorders, including impaired glucose metabolism, elevated blood pressure, dyslipidemia and obesity.

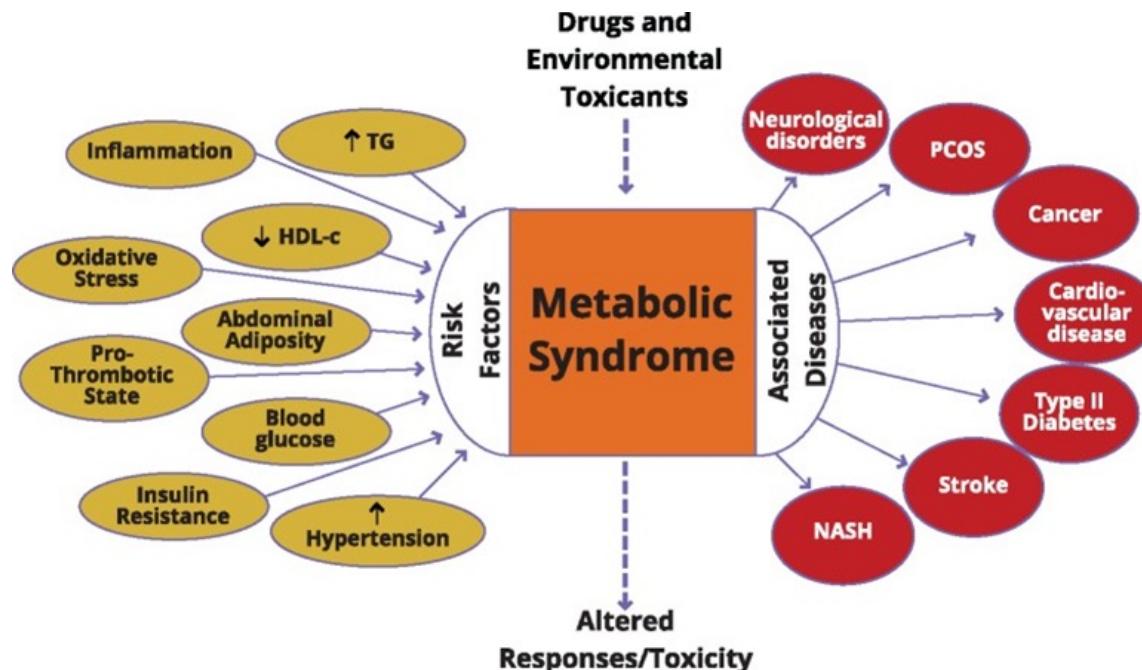




Why?

→ Social stress has a profound and complex impact on metabolism

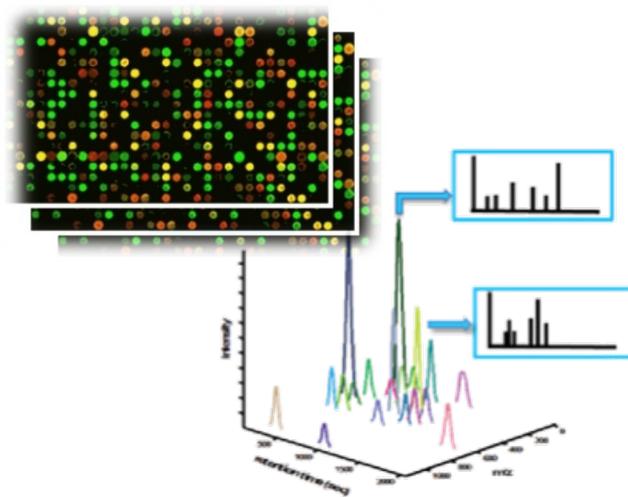
- MetS is responsible for an elevated risk not only of cardiovascular diseases, the leading cause of death worldwide, but also of diabetes and some cancers.



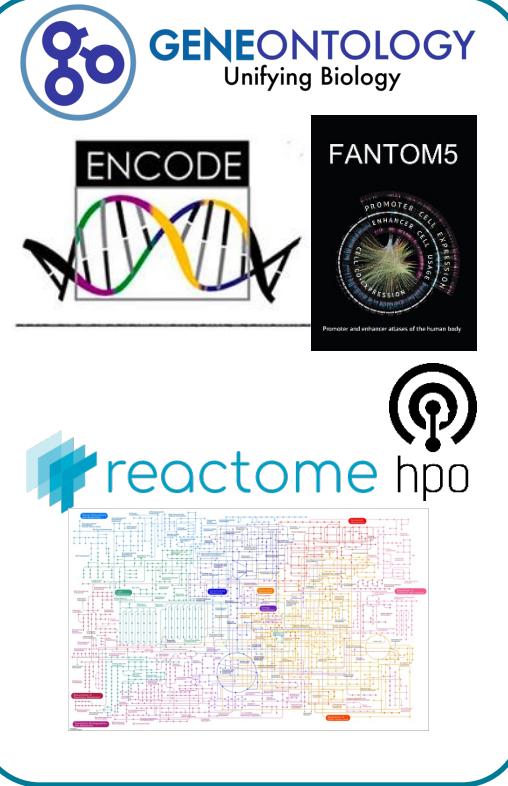
Toxicol. Sci., 162 (1), 2018



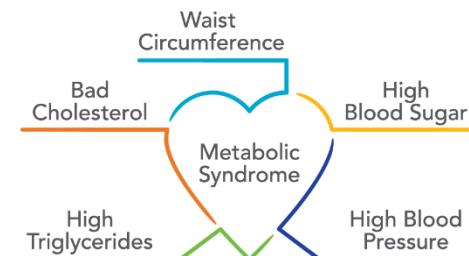
How?



Ontologies and Atlases

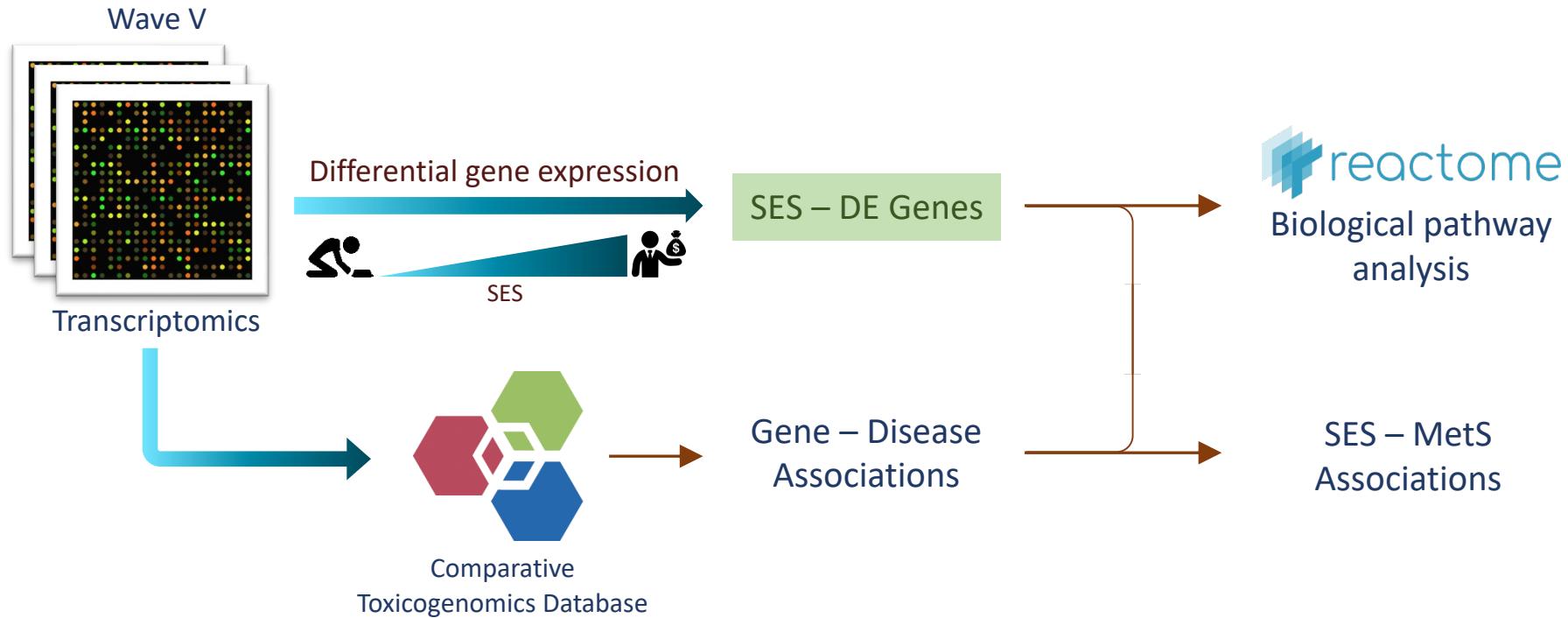


Add Health
The National Longitudinal Study of Adolescent to Adult Health



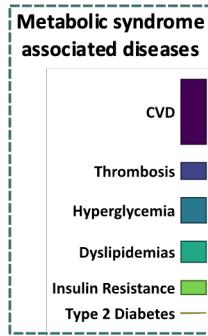
How?

1. Is SES associated with MetS in Add Health subjects?



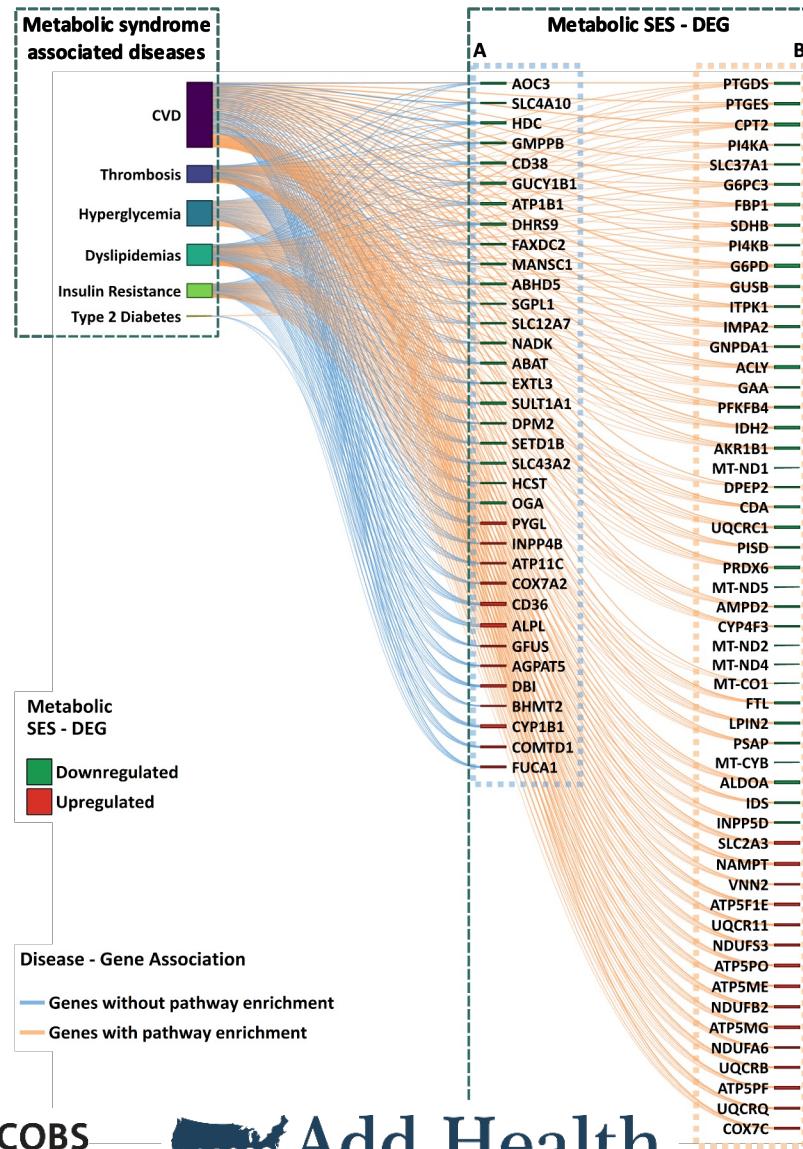


Young adult SES disparity is associated to MetS

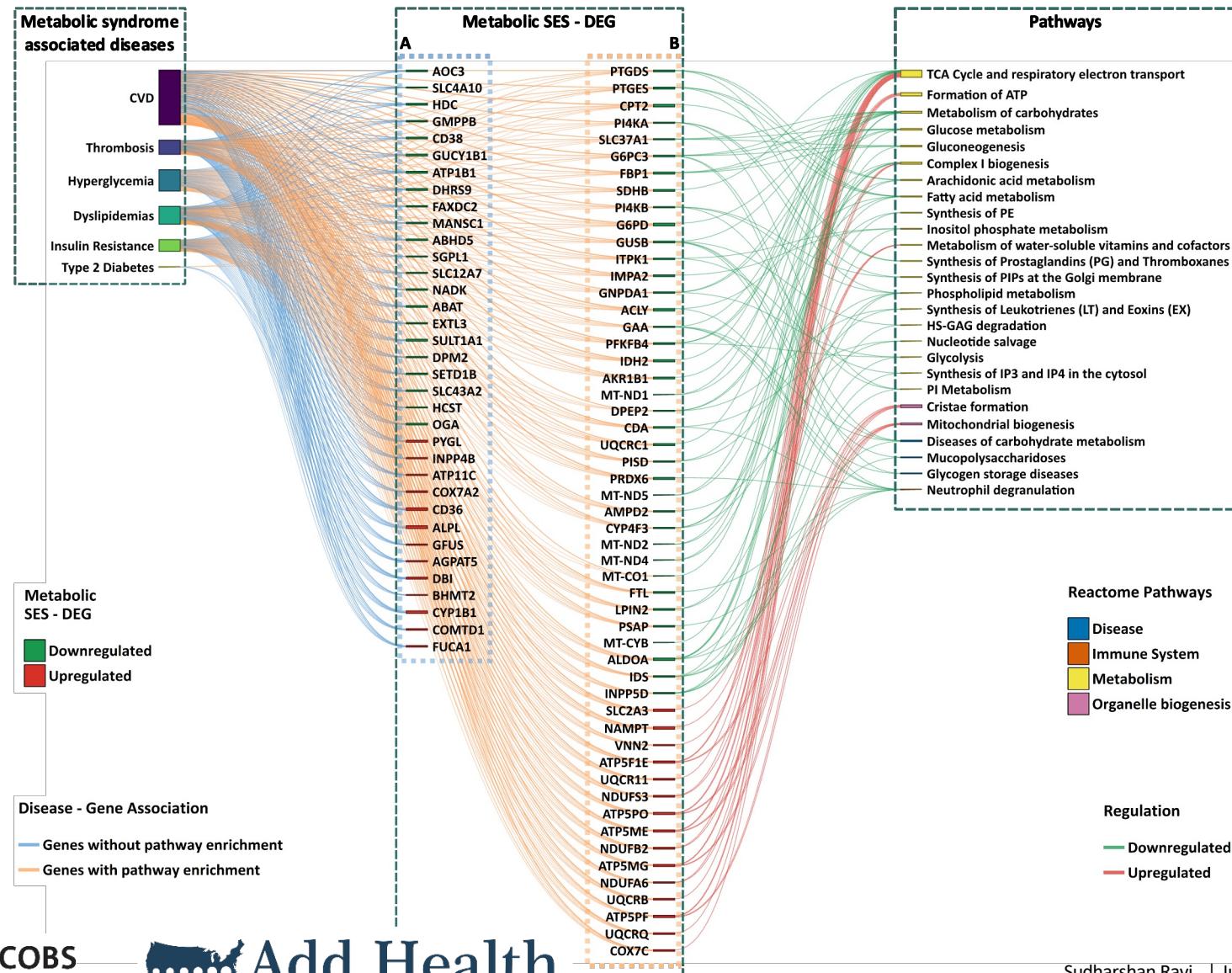




Young adult SES disparity is associated to MetS

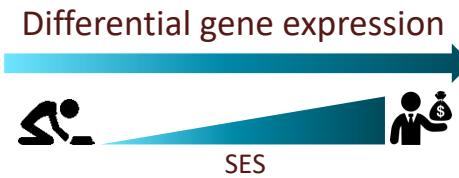
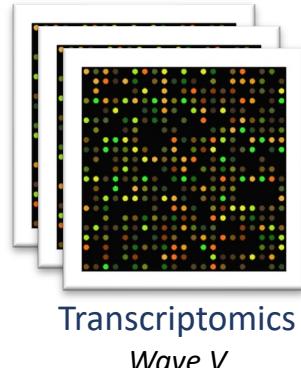


Young adult SES disparity is associated to MetS

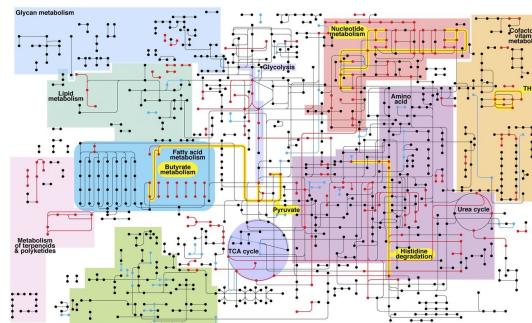


How?

2. How does SES impact metabolism?



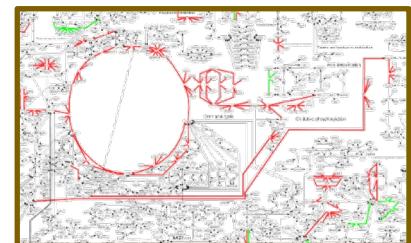
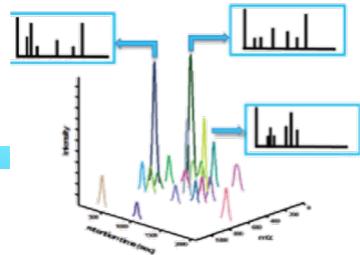
SES – DE Genes



Human Genome scale
metabolic network (GSMN)

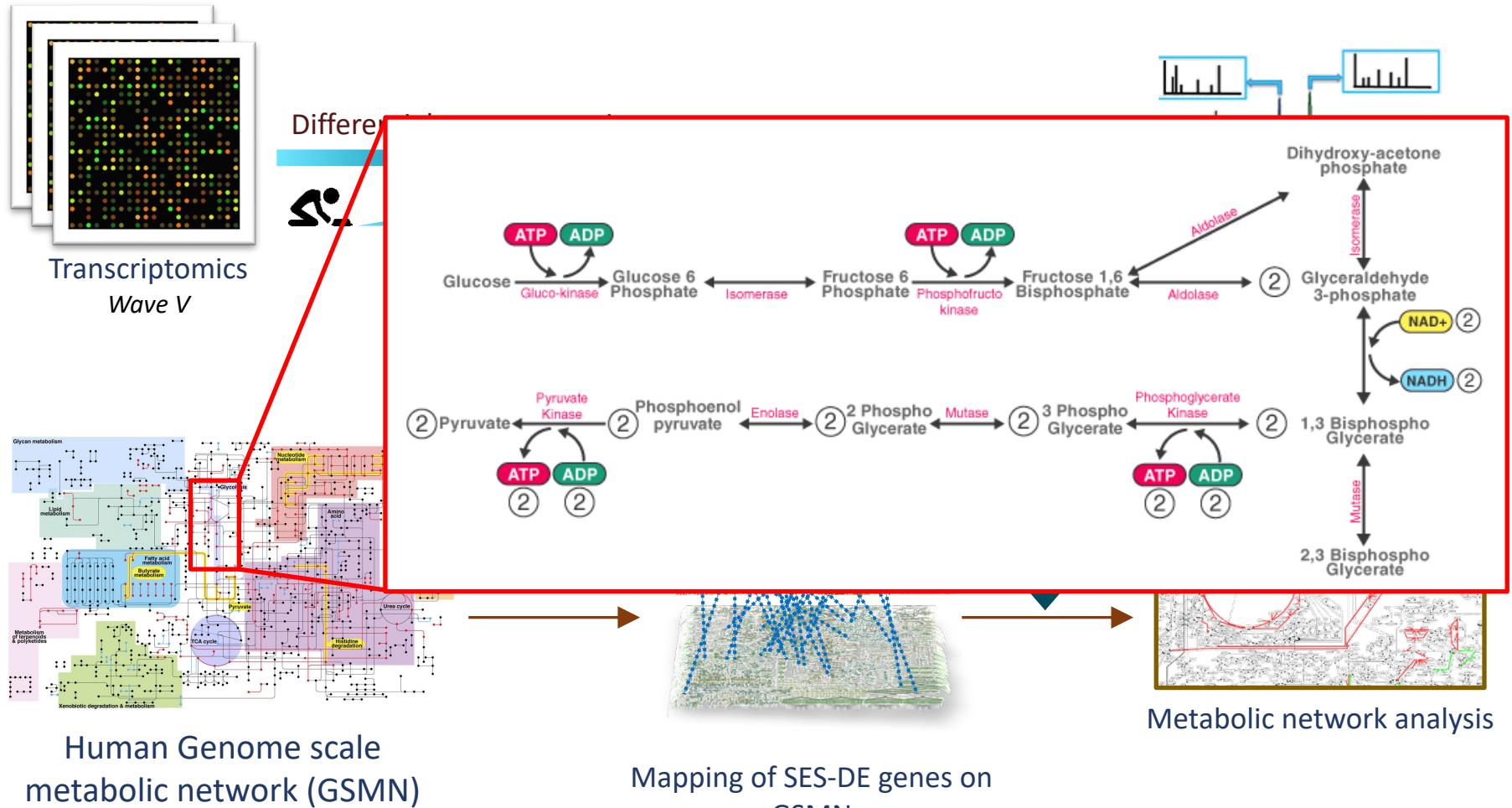


Mapping of SES-DE genes on
GSMN



How?

2. How does SES impact metabolism?

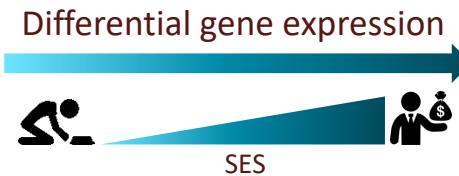
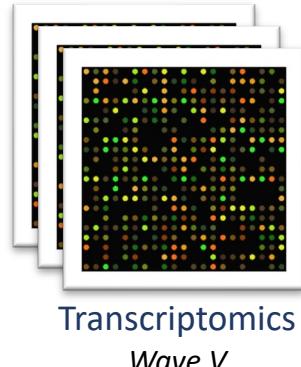


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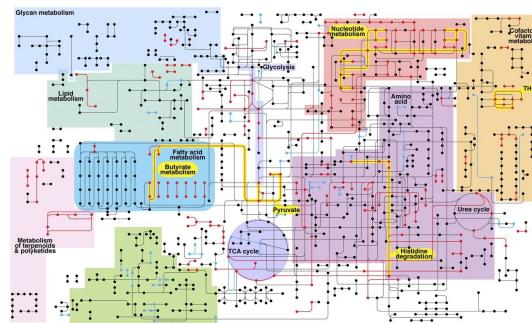
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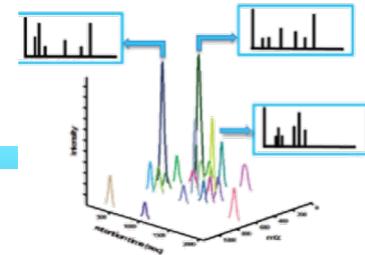
SES – DE Genes



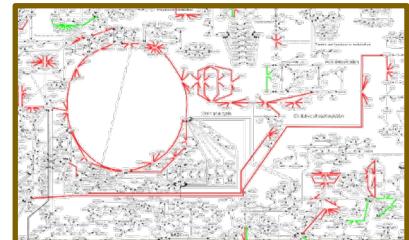
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Mapping of SES-DE genes on
GSMN



Metabolite Assays
Wave V Biomarker
Data

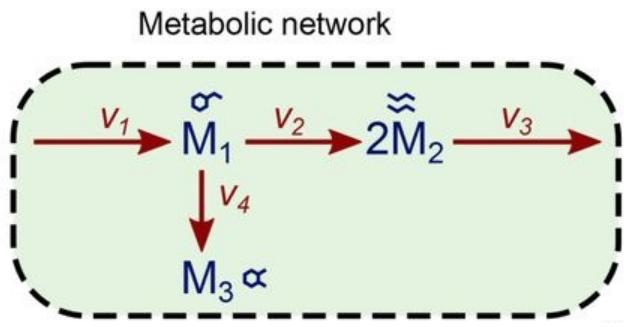


Metabolic network analysis



What are these predictions?

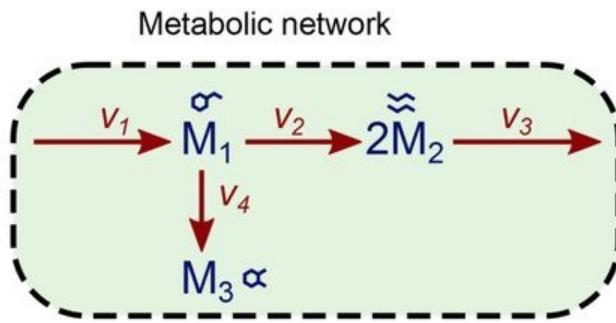
Structure





What are these predictions?

Structure



1. Construct model

Stoichiometry Matrix

$$\mathbf{S} = \begin{pmatrix} 1 & -1 & 0 & -1 \\ 0 & 2 & -2 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix} \begin{array}{l} \text{Reaction} \\ \hline 1 & 2 & 3 & 4 \end{array} \begin{array}{l} M_1 \\ M_2 \\ M_3 \end{array}$$

Metabolite

$\overset{\circ}{\rightarrow} M_1 \rightarrow 2M_2 \overset{\approx}{\rightarrow}$

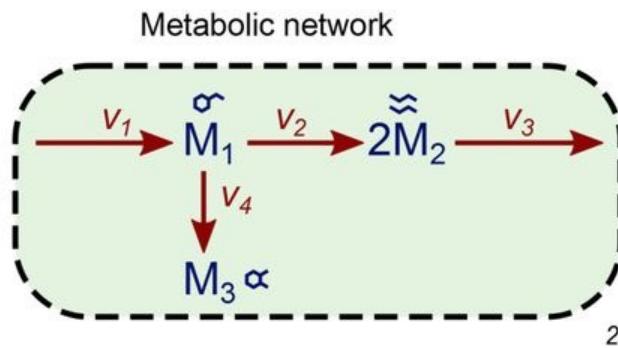
Rates Vector

$$\vec{v} = \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \end{pmatrix}$$



What are these predictions?

Structure



1. Construct model

2. Compute model
at steady state

$$\frac{dM}{dt} = S \cdot \vec{v} = 0$$

Stoichiometry Matrix

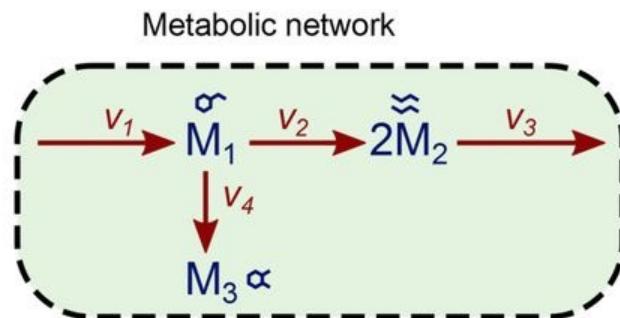
	Reaction	1	2	3	4	
Metabolite		1	-1	0	-1	M_1
		0	2	-2	0	M_2
		0	0	0	1	M_3

Rates Vector

$$\vec{v} = \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \end{pmatrix}$$

What are these predictions?

Structure



1. Construct model

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at steady state

Stochiometry Matrix

$$\mathbf{S} = \begin{pmatrix} 1 & -1 & 0 & -1 \\ 0 & 2 & -2 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}$$

Reaction

M₁ M₂ M₃

Metabolite

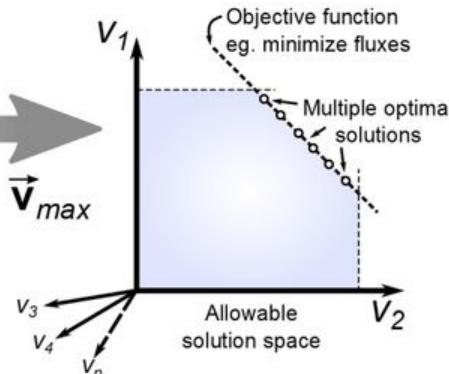
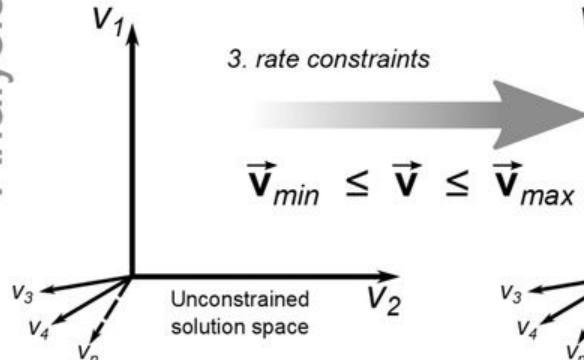
$\stackrel{\circ}{\rightarrow} M_1 \longrightarrow \stackrel{\approx}{2M_2}$

Rates Vector

$$\vec{v} = \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \end{pmatrix}$$

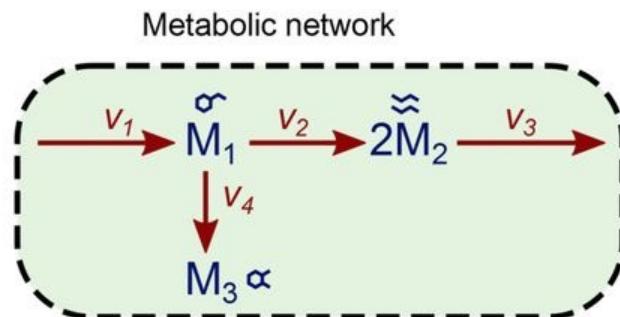
$$\frac{dM}{dt} = \mathbf{S} \cdot \vec{v} = 0$$

Analysis



What are these predictions?

Structure



1. Construct model

2. Compute model at steady state

Stochiometry Matrix

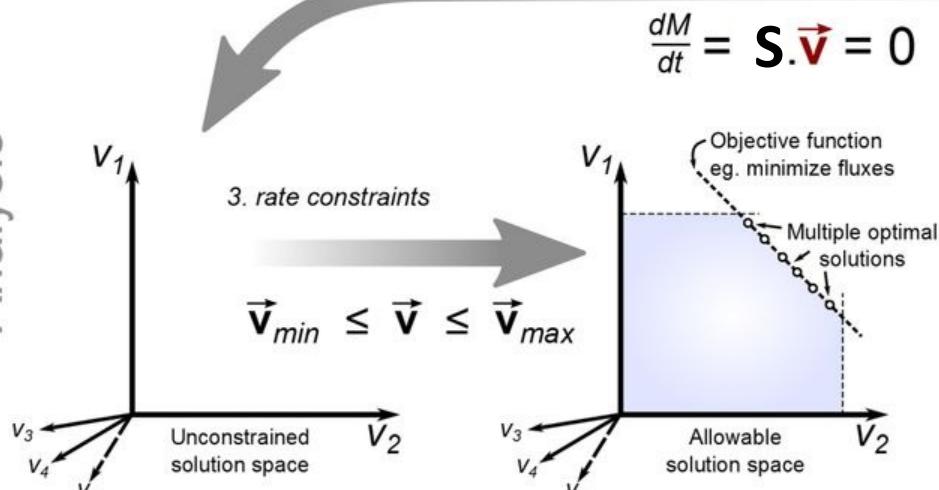
Reaction				M_1	M_2	M_3
1	2	3	4			
1	-1	0	-1	1	0	0
0	2	-2	0	0	0	1
0	0	0	1			

$\textcircled{1} M_1 \rightarrow 2\textcircled{2} M_2$

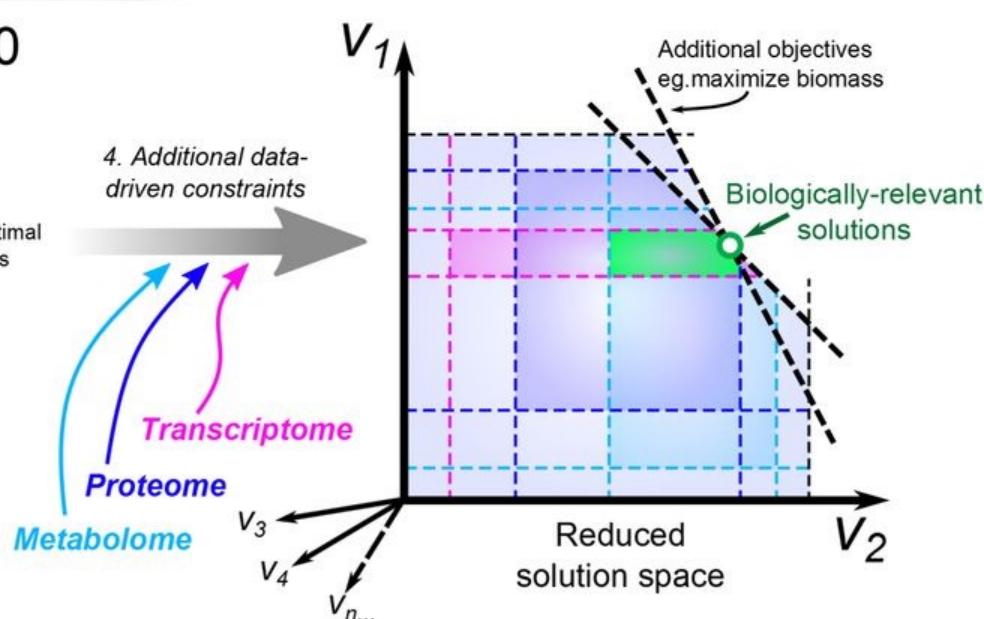
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$$\vec{v} = \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \end{pmatrix}$$

Analysis

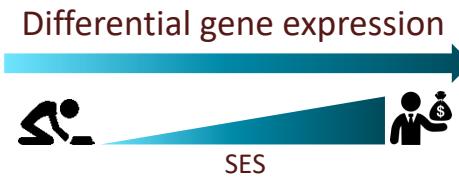
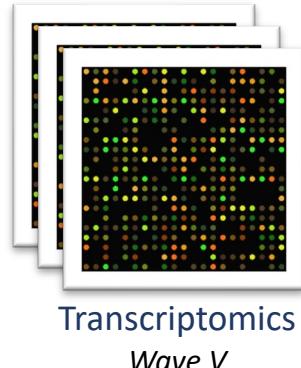


4. Additional data-driven constraints

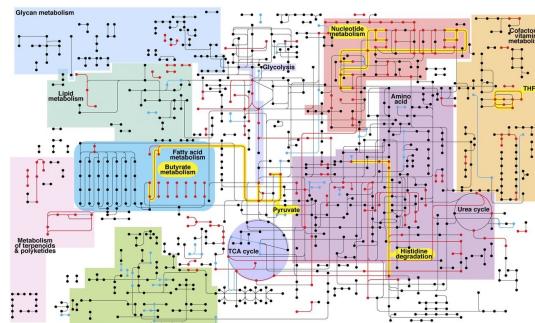


How?

2. How does SES impact metabolism?



SES – DE Genes

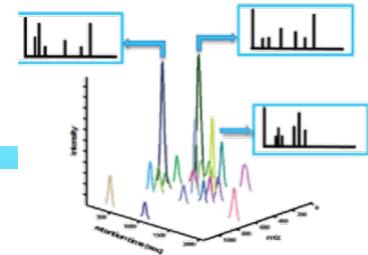


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metabolic network (GSMN)

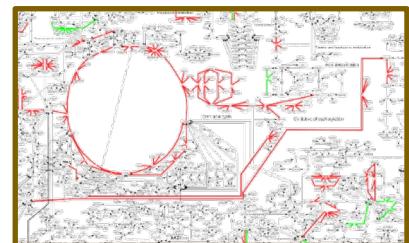


Mapping of SES-DE genes on
GSMN

Differential concentration

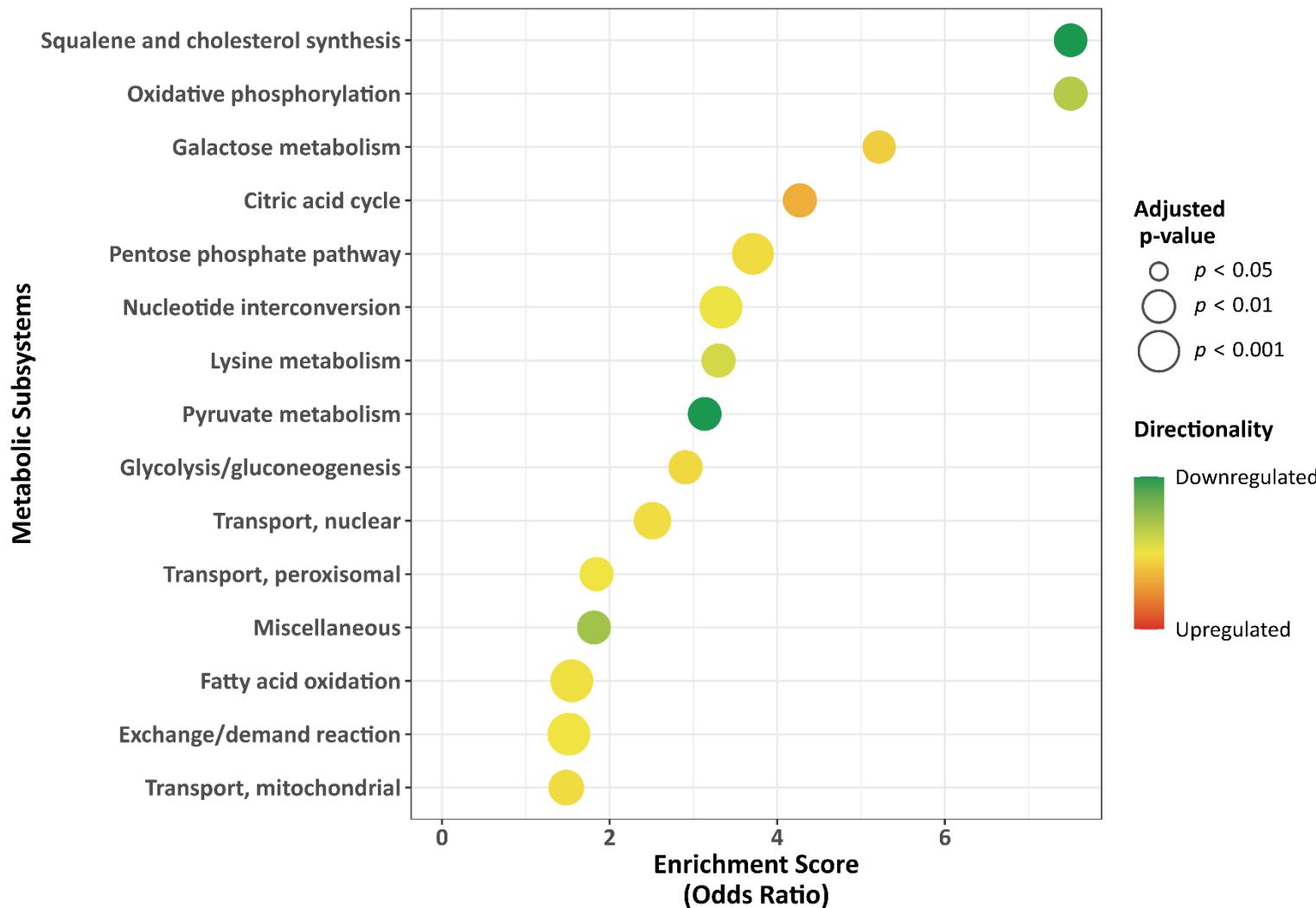


Metabolite Assays
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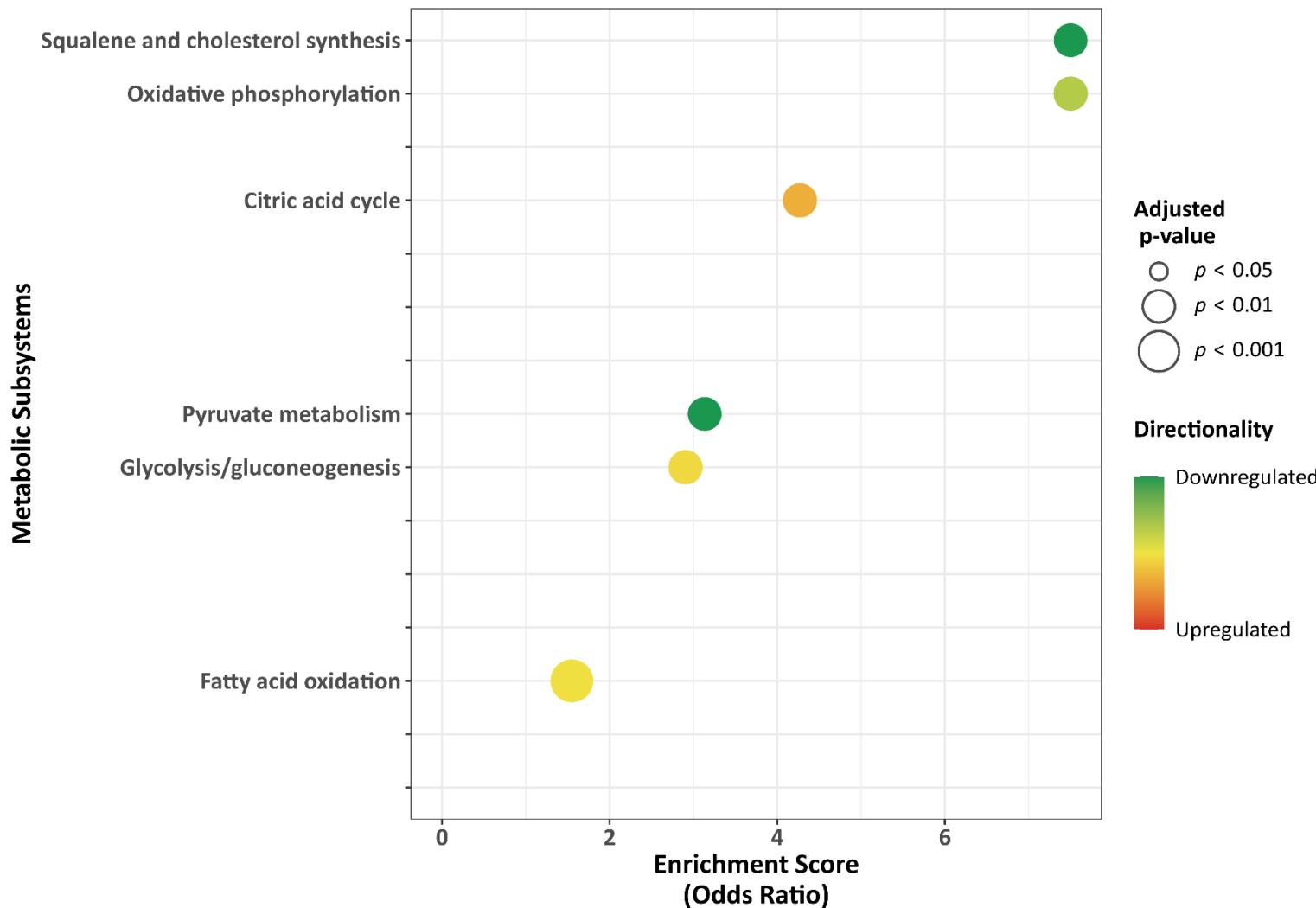


Metabolic network analysis

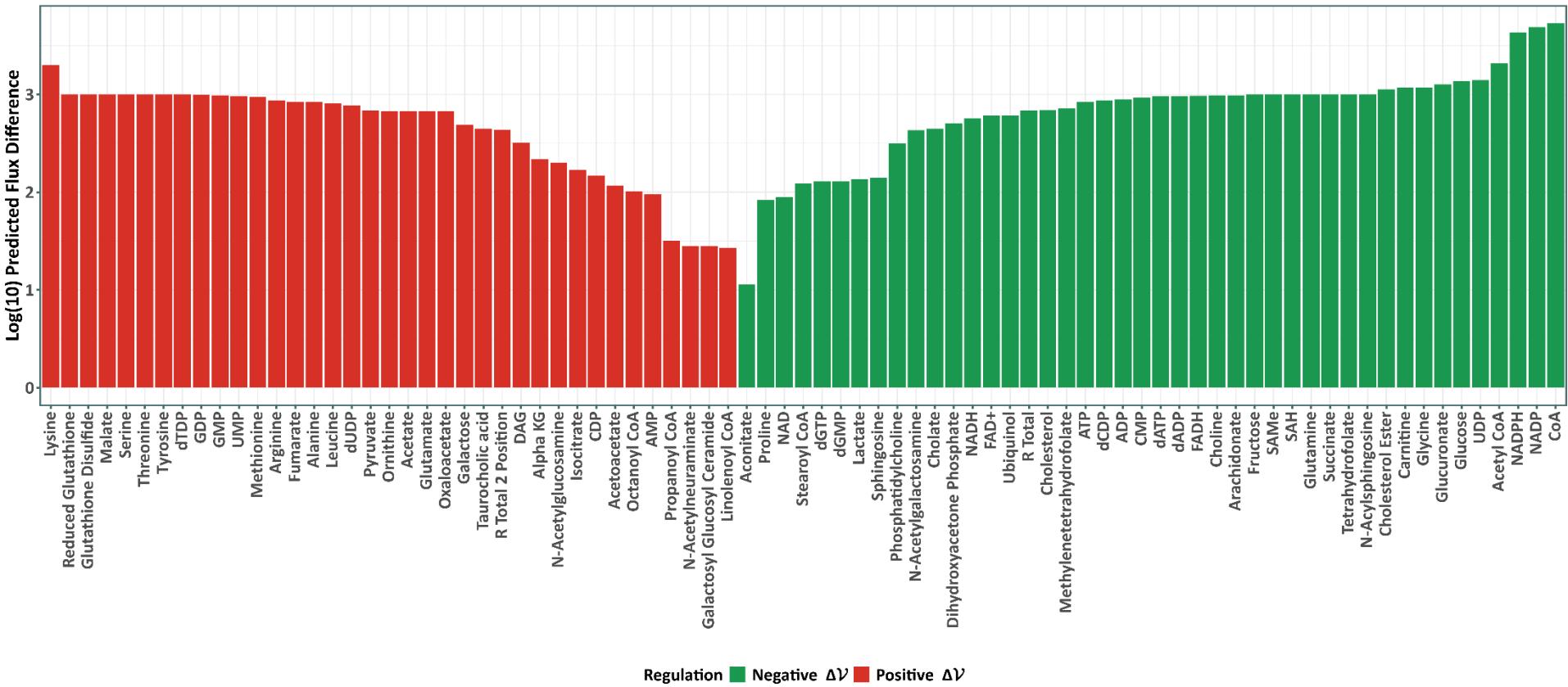
SES disparity dampens cellular energy generation



SES disparity dampens cellular energy generation

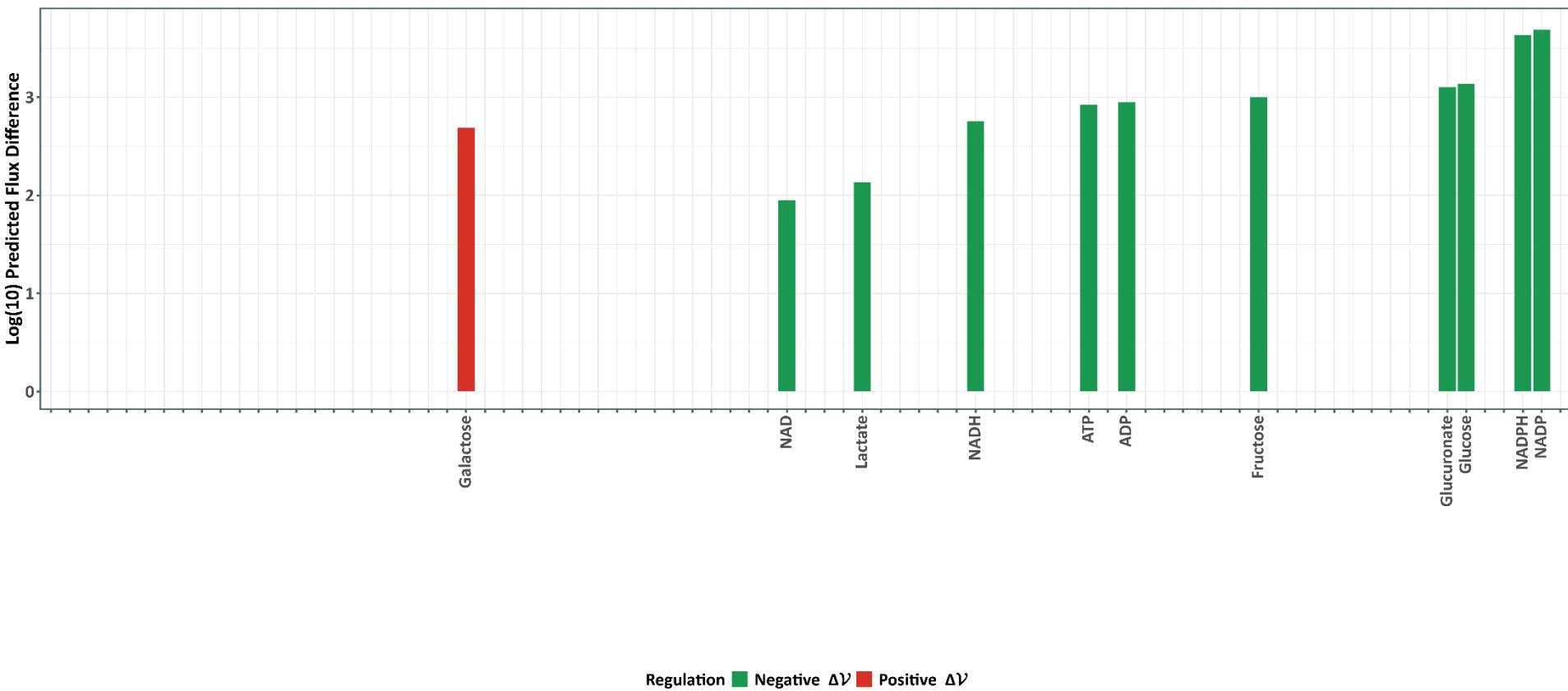


SES disparity dampens cellular energy generation



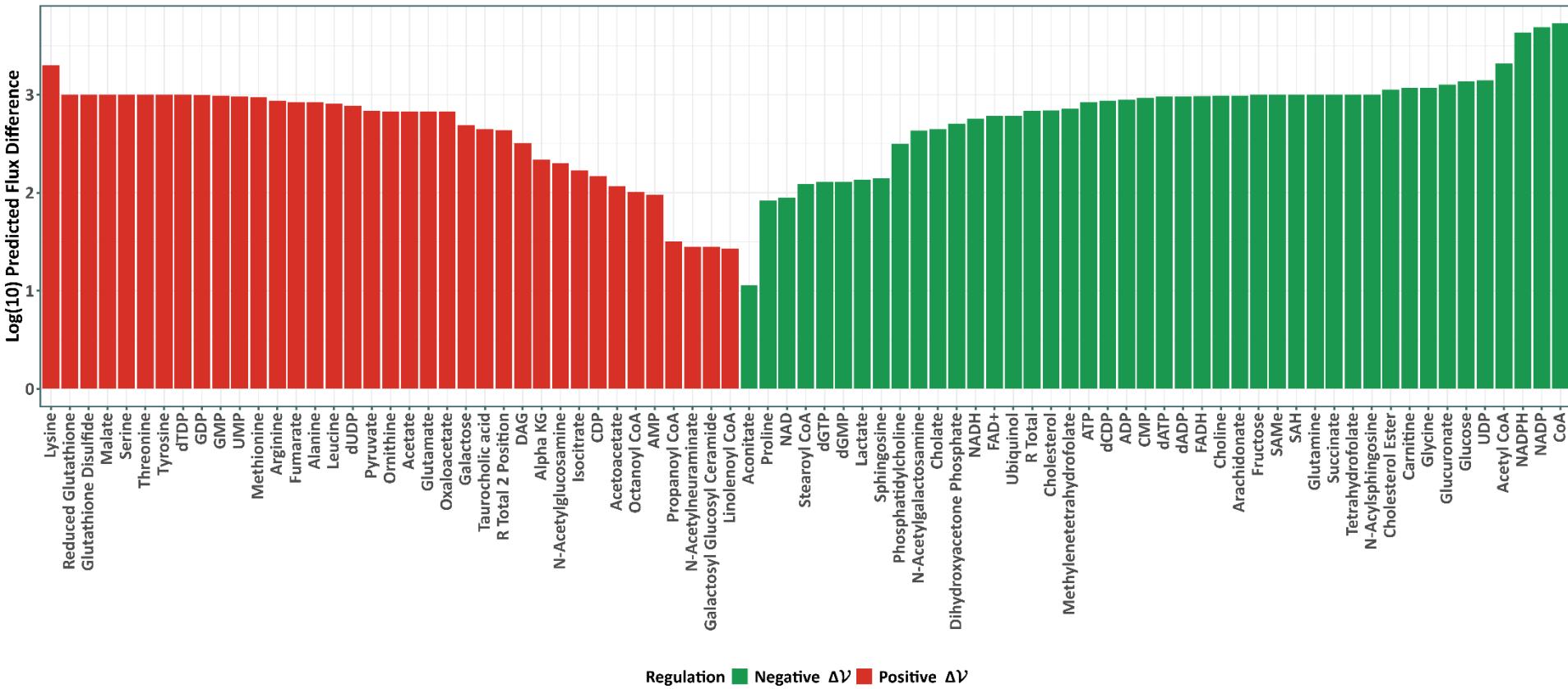


SES disparity dampens cellular energy generation



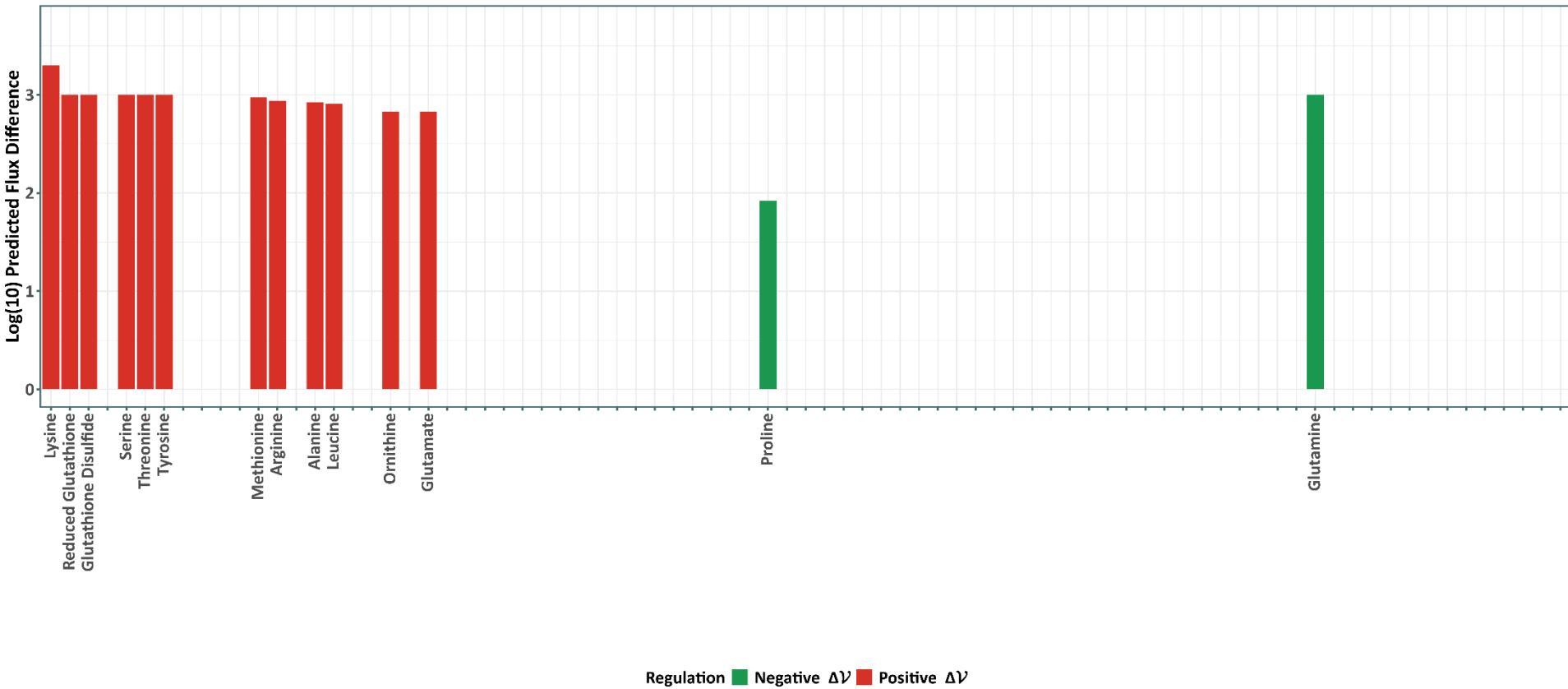


SES disparity elevates biomarkers of oxidative stress





SES disparity elevates biomarkers of oxidative stress





Summary

Is SES associated with MetS in Add Health subjects?

- Socioeconomic disparities in young adults in Add Health study show significant changes in expression of metabolic genes.
- These metabolic genes are significantly over-represented in pathways involving cellular energy generation and fatty acid metabolism.
- Furthermore, these genes are also linked with a cluster of metabolic conditions that characterize metabolic syndrome.



Summary

Is SES associated with MetS in Add Health subjects?

- Socioeconomic disparities in young adults in Add Health study show significant changes in expression of metabolic genes.
- These metabolic genes are significantly over-represented in pathways involving cellular energy generation and fatty acid metabolism.
- Furthermore, these genes are also linked with a cluster of metabolic conditions that characterize metabolic syndrome.

How does SES impact metabolism and potentially cause metabolic syndrome?

- Informed metabolic network analysis reveals an attenuated cellular energy generation and increased oxidative stress with low socioeconomic status.
- Diseases associated with metabolic syndrome are characterized by identical dysregulations in metabolic health.
- Combined with significant association of differentially expressed genes with metabolic syndrome, the evidence strongly supports the pivotal role of early metabolic events in predisposing individuals with low socioeconomic status to metabolic syndrome.



Thank you for your attention



Social Genomics Group, UZH Zürich

Collaborators

- Prof. Dr. Steve W Cole, UCLA, USA
- Dr. Brandt Levitt, UNC, USA
- Dr. Justin Chumbley, MSD, Switzerland
- Prof. Dr. Rudiyanto Gunawan, University at Buffalo, USA

Questions?

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🏡 ravisudharsh.github.io

The Many Ways to Spell "Postdoc"

"postdoc"	The lazy way
"Post-doc"	The grammatically correct way
"PostDoc"	The German way?
"Postdoc Student"	The Confused Admin way
"Post Doctor"	Chinese standard
"Postdoctoral Fellow/Scholar"	"Look at me, I'm Ivy League"
"Postdoctoral Researcher/ Associate"	"I'm not sure this is better but throw me a bone, will you" way

