

# The Human Trisome Project: From Data to Discovery

Matthew Galbraith  
Linda Crnic Institute for Down Syndrome

Data Science for Developing Scholars in  
Down Syndrome Research (DS3) 2025

# Acknowledgements



**LINDA CRNIC INSTITUTE  
HUMAN TRISOME PROJECT™**  
GLOBAL DOWN SYNDROME FOUNDATION

## All Human Trisome Project participants

### Crnic Institute team

Joaquin Espinosa

Kelly Sullivan

Angela Rachubinski

Experimental Models Program team

Clinical and Translational Sciences Program team

Data Sciences Program team

### Many collaborators at the University of Colorado



School of Medicine

UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS



**INCLUDE**  
INvestigation of Co-occurring  
conditions across the Lifespan  
to Understand Down syndromE



Eunice Kennedy Shriver National Institute  
of Child Health and Human Development



National Heart, Lung,  
and Blood Institute



National Institute of  
Allergy and  
Infectious Diseases



National Institute of  
Arthritis and Musculoskeletal  
and Skin Diseases



National Center  
for Advancing  
Translational Sciences



National Institute  
on Aging

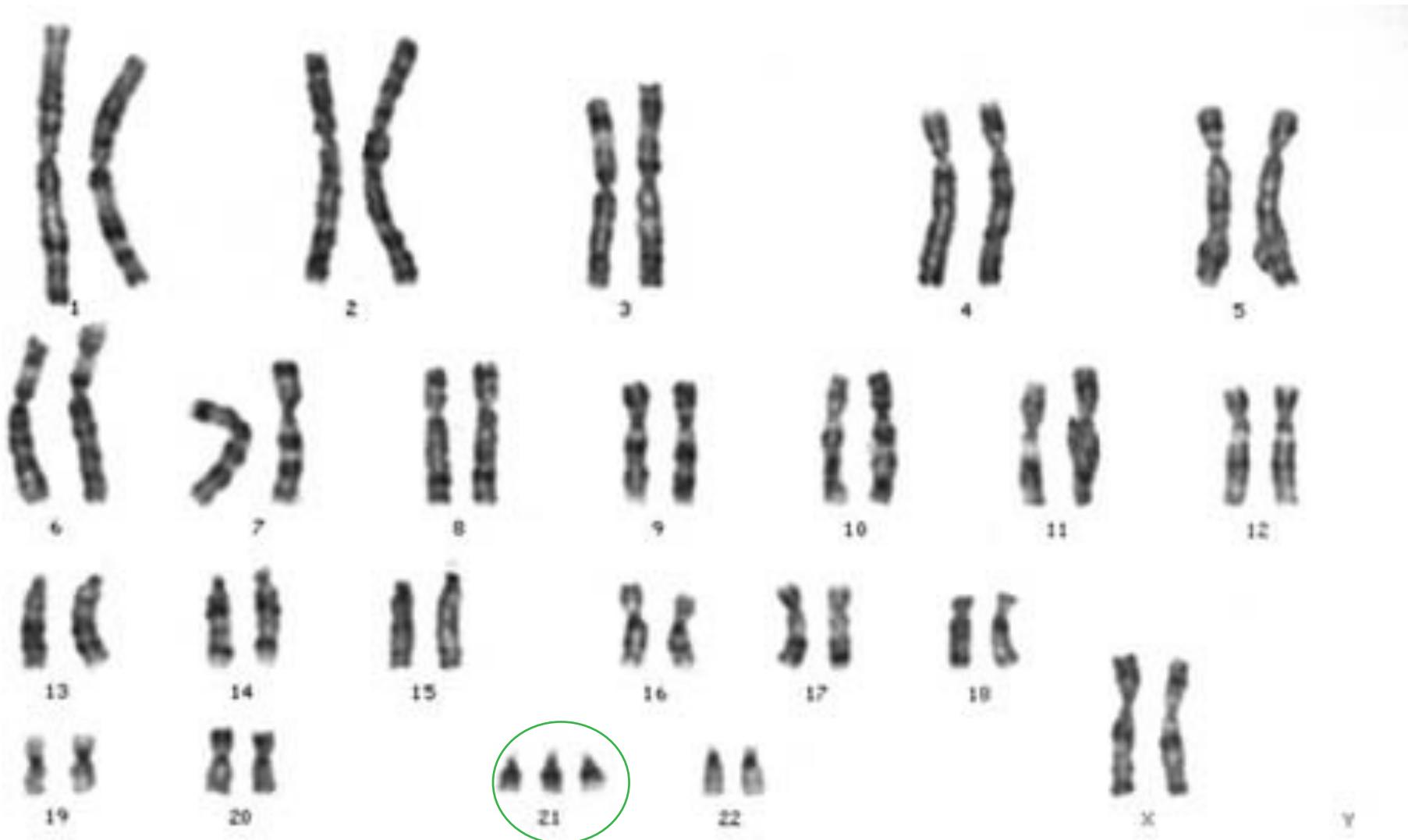


**GLOBAL**  
DOWN SYNDROME  
FOUNDATION®

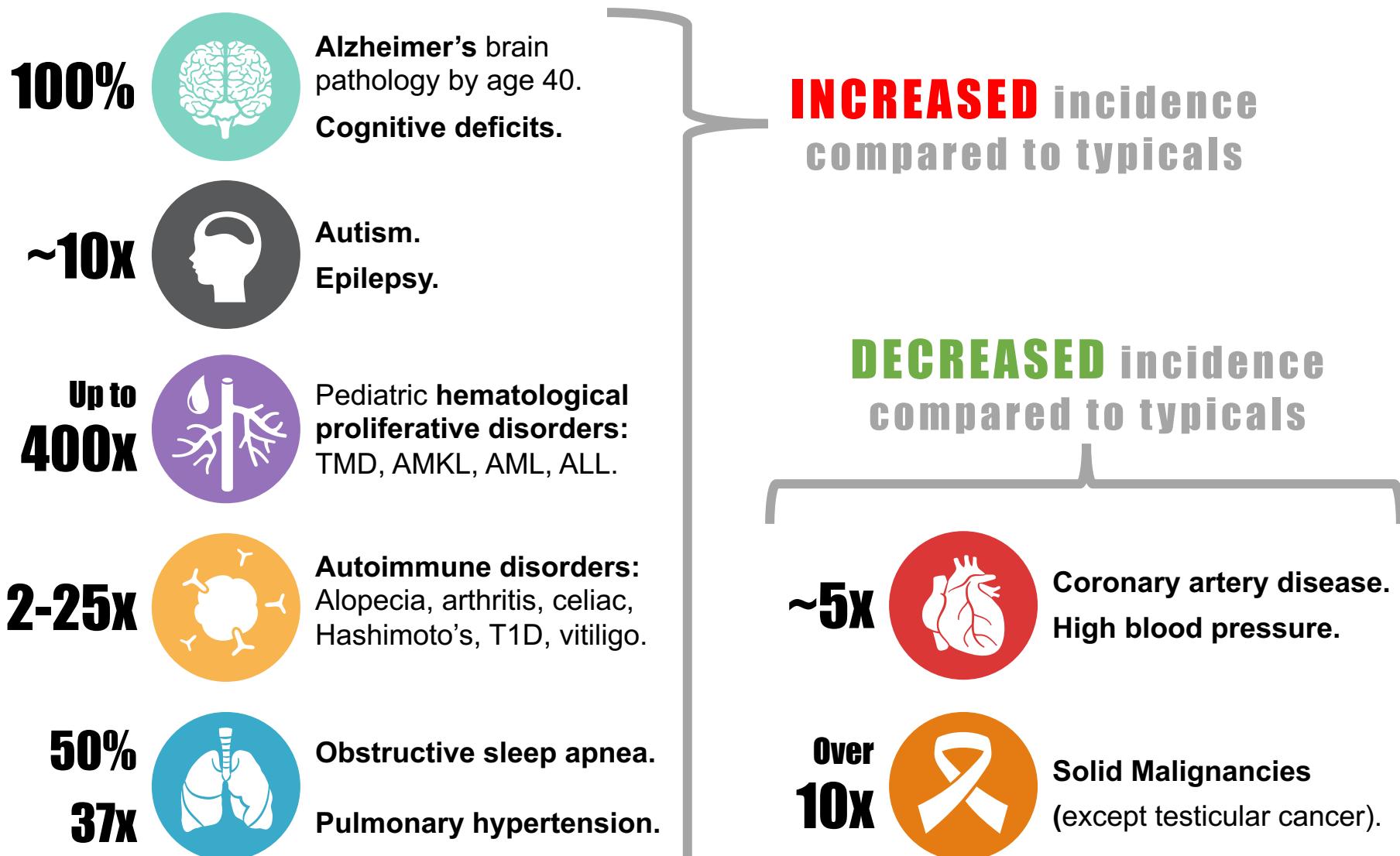


ANNA & JOHN J. SIE  
FOUNDATION

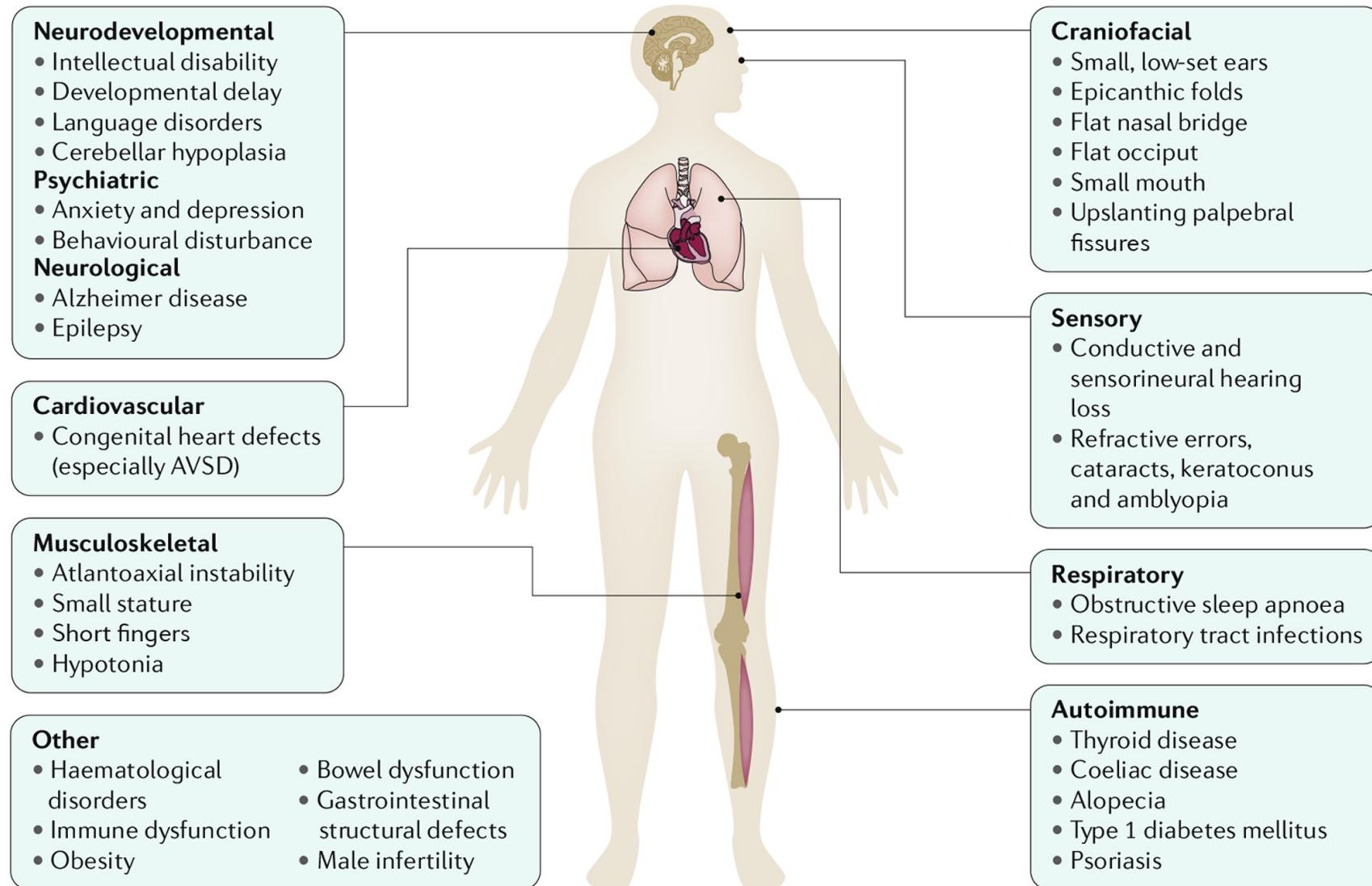
# Down Syndrome is caused by Trisomy 21 (T21)



# People with Down syndrome have a unique disease spectrum



# Trisomy 21 adversely affects virtually every tissue and organ system in the body



# How does Trisomy 21 cause Down syndrome?

Trisomy 21



Down syndrome



**100%**



**~10x**



**Up to  
400x**



**2-25x**



**50%  
37x**



**~5x**

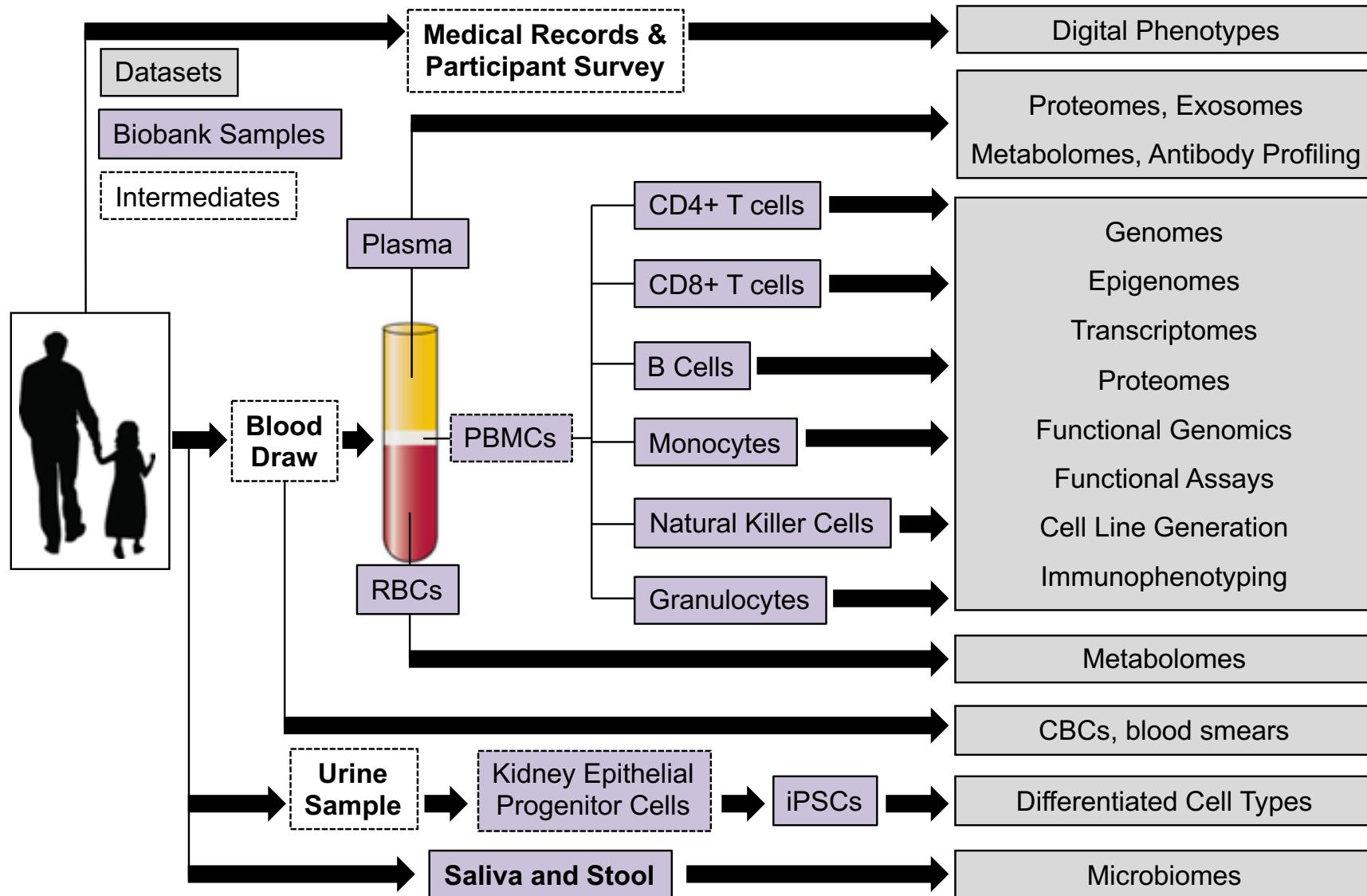


**Over  
10x**



# The Crnic Institute Human Trisome Project (HTP)

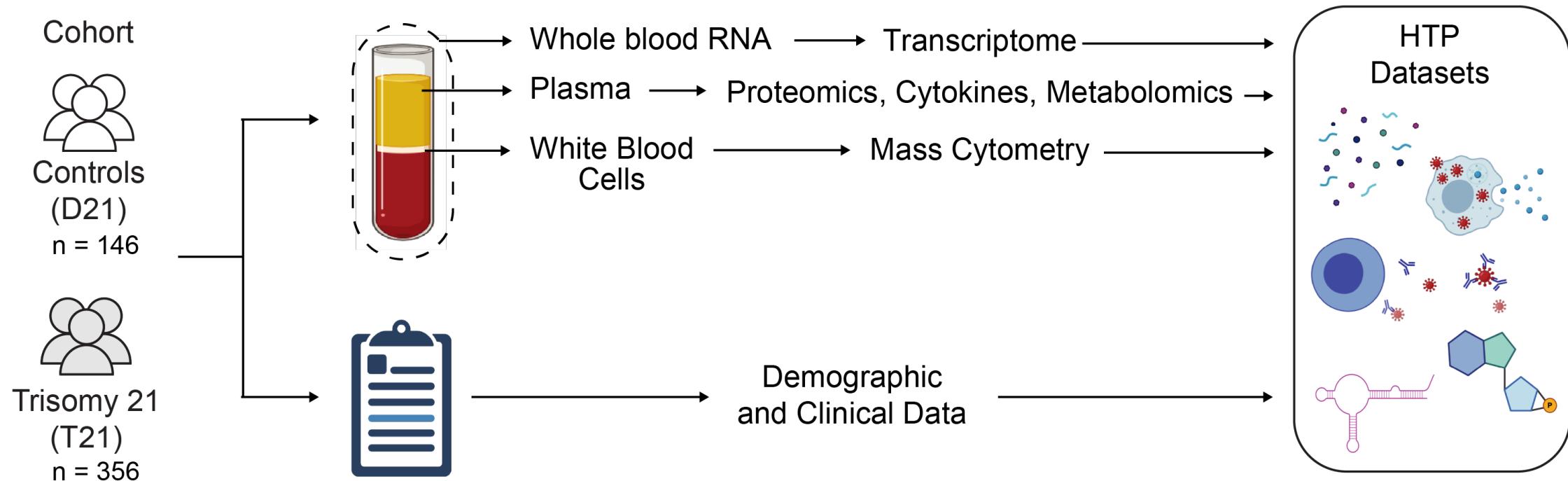
## A pan-omics cohort study with deep clinical metadata



NCT02864108

[www.trisome.org](http://www.trisome.org)

# Many HTP datasets are publicly available



Datasets available at:

INCLUDE Data Hub – <https://portal.includedcc.org>

Synapse – <https://www.synapse.org/Synapse:syn31472301>

# Many HTP samples are available: Virtual Biorepositories

HTP Plasma Biospecimens

Study Code = HTP X and Availability = Available X and Sample Type = Plasma X

868 Labels

Summary Participants (868) Biospecimens (12,749) Data Files (893)

20 items selected Select all results

Sample ID	Sample Type	Parent Sample ID	Parent Sample Type	Participant ID	Collection ID	Collection Sample Type	Age
bs-23e6nj93ee	Plasma	bs-h4hyb2k3n2	Peripheral Whole Blood	pt-y3j8pbe9	bs-gnq7eqi6ta	Peripheral Whole Blood	26 years 358 days
bs-23e6nj93ee	Plasma	bs-h4hyb2k3n2	Peripheral Whole Blood	pt-y3j8pbe9	bs-gnq7eqi6ta	Peripheral Whole Blood	26 years 358 days
bs-23e6nj93ee	Plasma	bs-h4hyb2k3n2	Peripheral Whole Blood	pt-y3j8pbe9	bs-gnq7eqi6ta	Peripheral Whole Blood	26 years 358 days
bs-23e6nj93ee	Plasma	bs-h4hyb2k3n2	Peripheral Whole Blood	pt-y3j8pbe9	bs-gnq7eqi6ta	Peripheral Whole Blood	26 years 358 days
bs-23e6nj93ee	Plasma	bs-h4hyb2k3n2	Peripheral Whole Blood	pt-y3j8pbe9	bs-gnq7eqi6ta	Peripheral Whole Blood	26 years 358 days

**Filters**

**Demographics**

**Karyotype**  
 Trisomy 21  Control

**Sex**  
 Female  Male

**Age at time of sample collection**  
0 100

[Reset Demographics Choices](#)

**Co-occurring Conditions**

**Biospecimens**

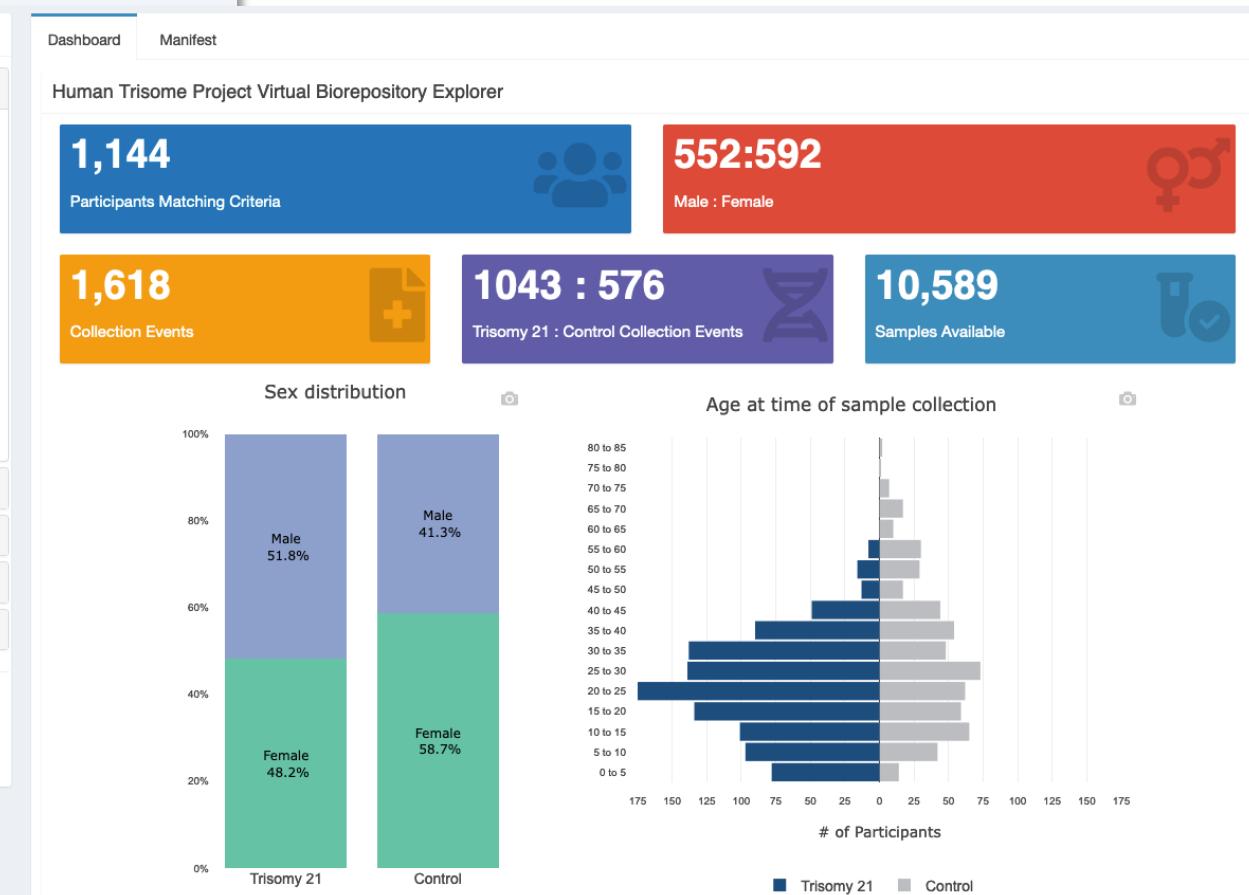
**Datasets Available**

**Further Refine Selections**

[Biospecimen Request](#)

[Reset All Filters](#)

TrisomExplorer  
<http://explorer.trisome.org/Virtual-Biorepository/>

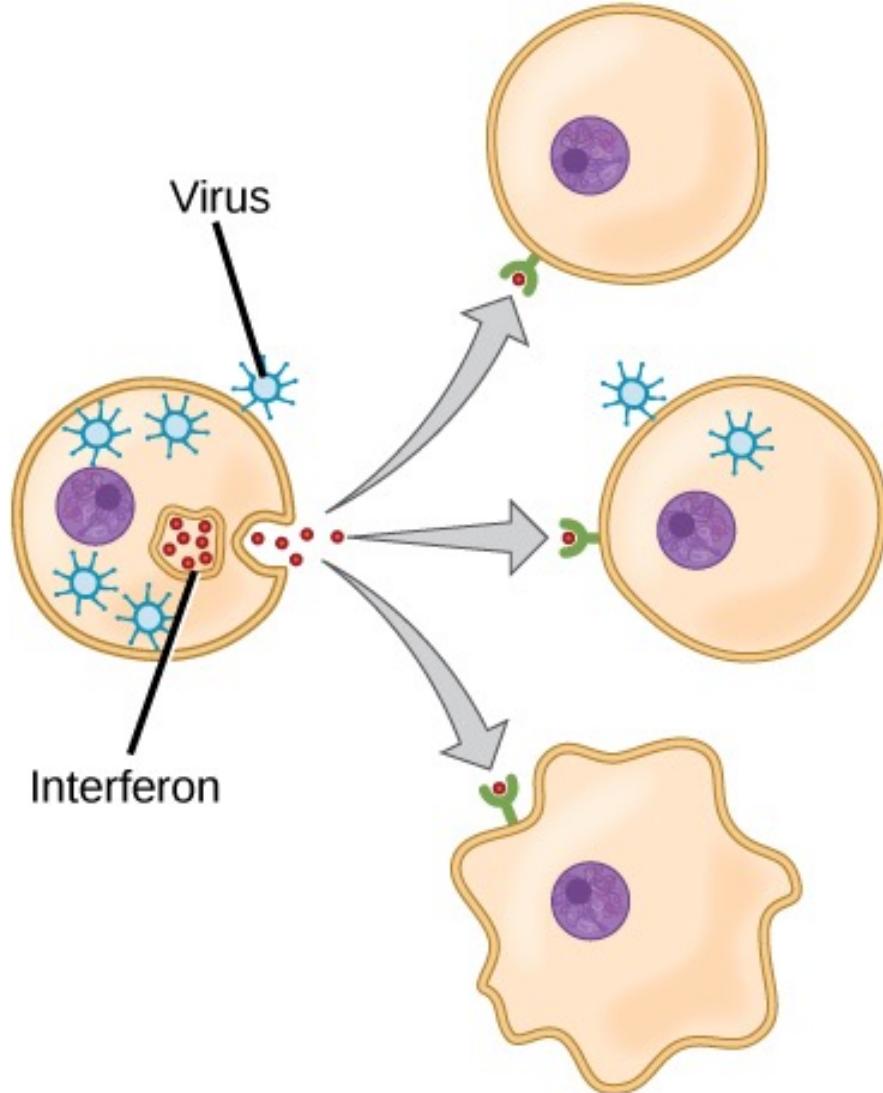


INCLUDE Data Hub

<https://portal.includedcc.org>

Facilitating requests for HTP biospecimens for qualified research

# Trisomy 21 activates the interferon response



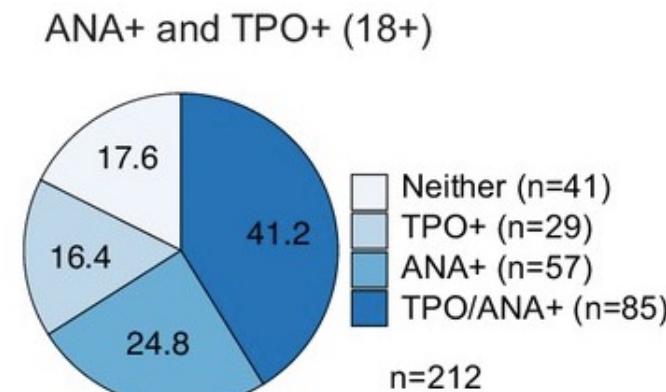
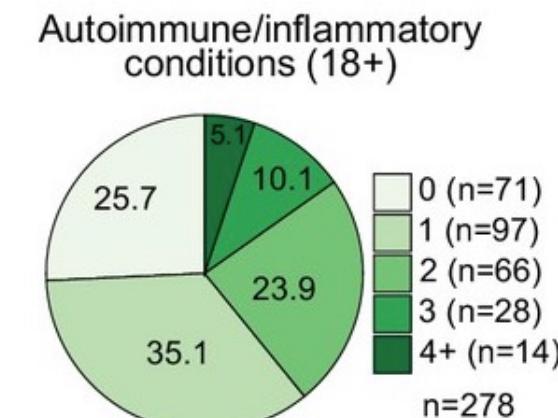
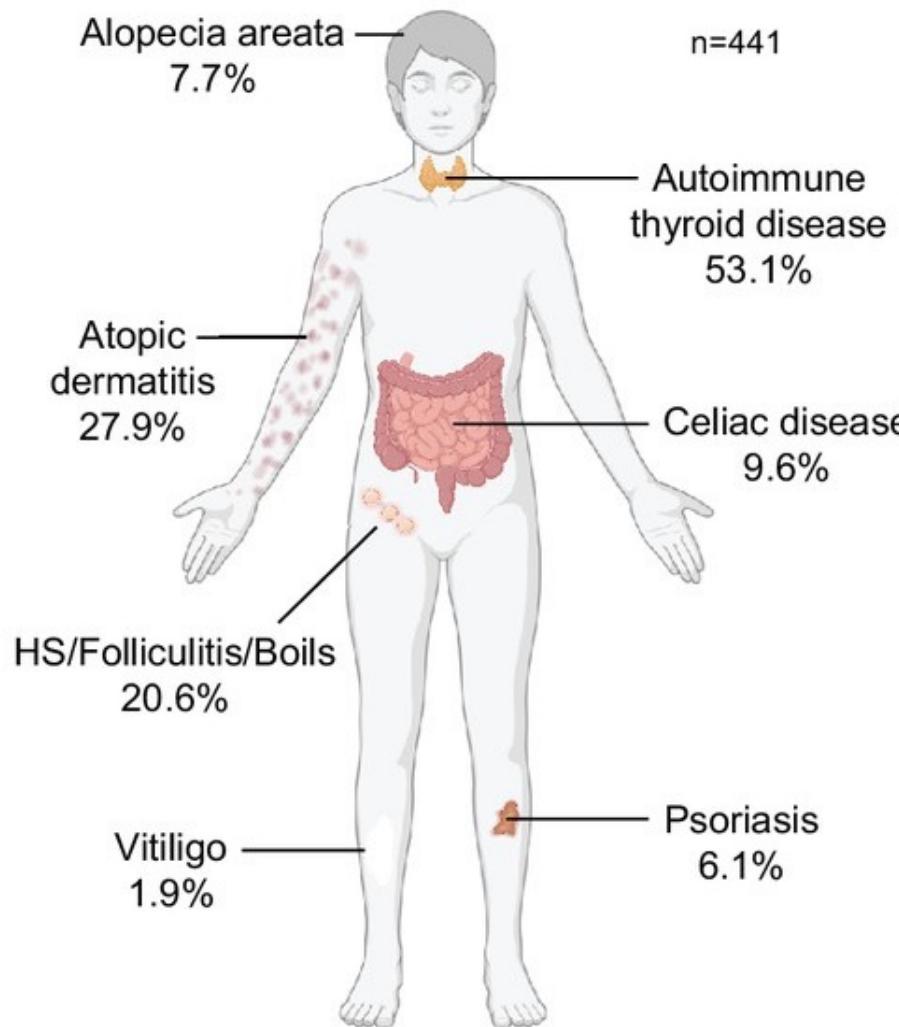
**People with Down syndrome show a hyperactive ‘interferon response’**

The interferon response is a key aspect of the innate immune system acting throughout the human body

Exacerbated interferon signaling is known to cause autoimmunity (e.g., during treatment of chronic HCV infections with IFN- $\alpha$ )

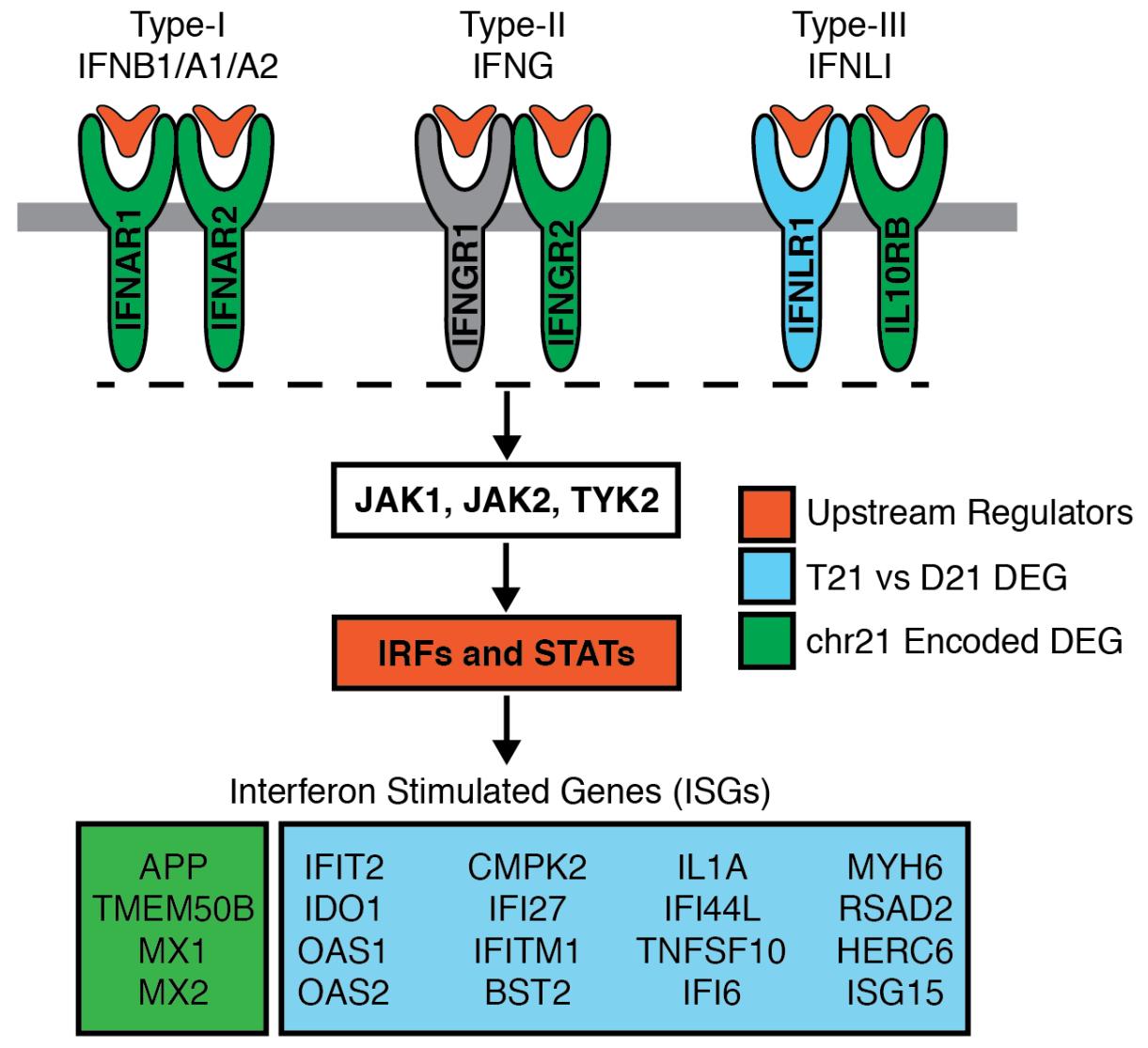
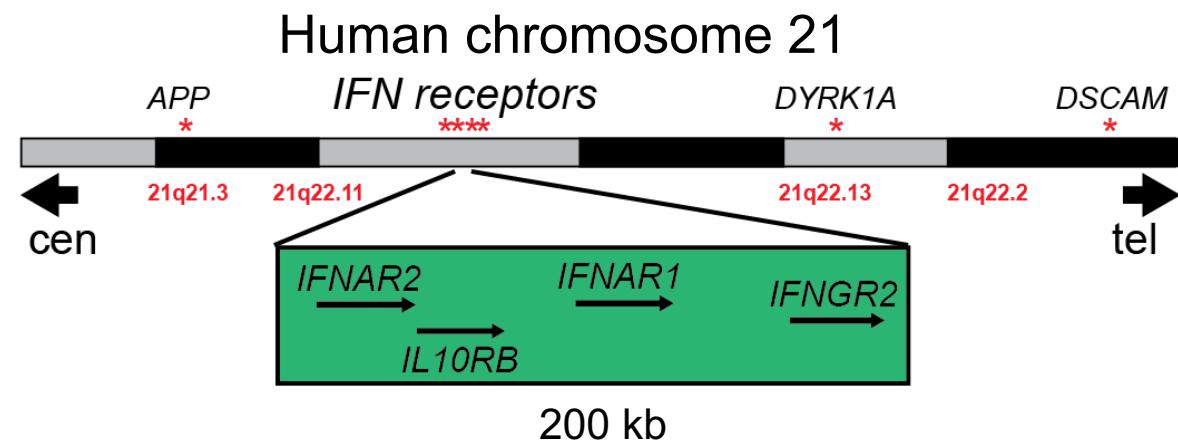
Polymorphisms in components of the IFN pathway are commonly associated with autoimmunity in euploid individuals

# Multi-organ autoimmunity and widespread autoantibody production in Down syndrome



# Why is IFN signaling hyperactive?

## 4 of the 6 IFN receptors are encoded on chr21!



# What are the (molecular) impacts of hyperactive IFN signaling in Down syndrome?

**Science Advances** | AAAS  
SIGNIFICANT RESEARCH, GLOBAL IMPACT  
<https://doi.org/10.1126/sciadv.adg6218>

> Sci Adv. 2023 Jun 28;9(26):eadg6218. doi: 10.1126/sciadv.adg6218. Epub 2023 Jun 28.

## Multidimensional definition of the interferonopathy of Down syndrome and its response to JAK inhibition

Matthew D Galbraith <sup>1 2</sup>, Angela L Rachubinski <sup>1 3</sup>, Keith P Smith <sup>1</sup>, Paula Araya <sup>1</sup>,  
Katherine A Waugh <sup>1 2</sup>, Belinda Enriquez-Estrada <sup>1</sup>, Kayleigh Worek <sup>1</sup>, Ross E Granrath <sup>1</sup>,  
Kohl T Kinning <sup>1</sup>, Neetha Paul Eduthan <sup>1</sup>, Michael P Ludwig <sup>1</sup>, Elena W Y Hsieh <sup>4 5</sup>,  
Kelly D Sullivan <sup>1 6</sup>, Joaquin M Espinosa <sup>1 2</sup>

## What is the role of IFN receptor dosage in Down syndrome?



<https://doi.org/10.1038/s41588-023-01399-7>

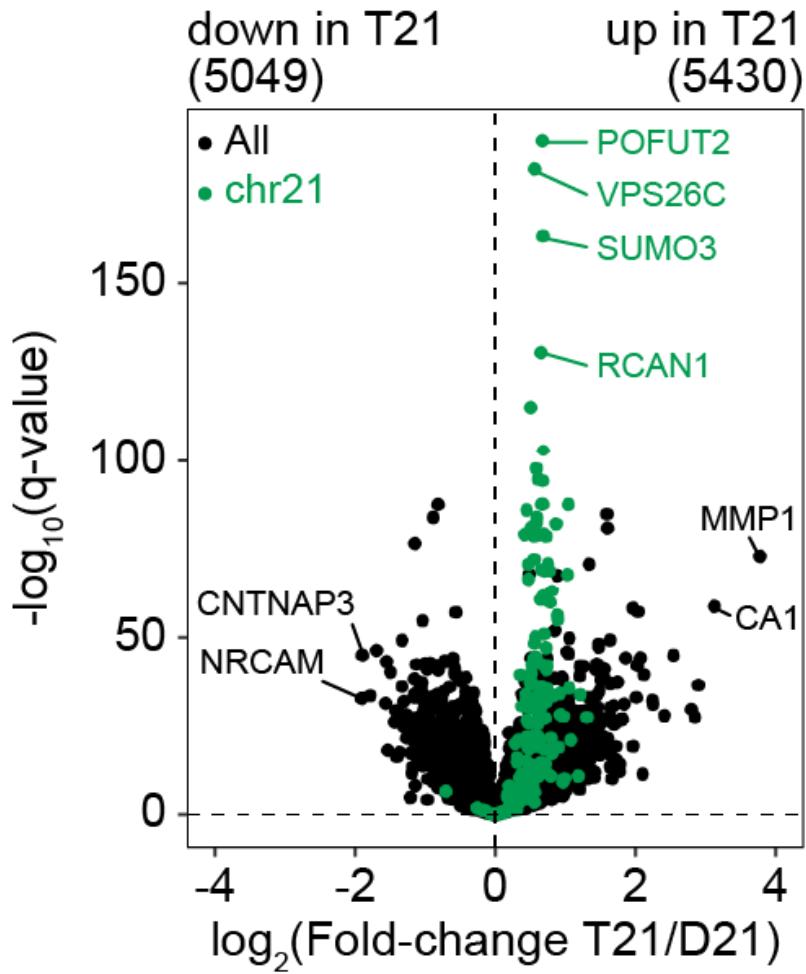
> Nat Genet. 2023 Jun;55(6):1034-1047. doi: 10.1038/s41588-023-01399-7. Epub 2023 Jun 5.

## Triplification of the interferon receptor locus contributes to hallmarks of Down syndrome in a mouse model

Katherine A Waugh <sup>1 2</sup>, Ross Minter <sup>1</sup>, Jessica Baxter <sup>1</sup>, Congwu Chi <sup>3 4 5</sup>,  
Matthew D Galbraith <sup>1 2</sup>, Kathryn D Tuttle <sup>1</sup>, Neetha P Eduthan <sup>1</sup>, Kohl T Kinning <sup>1</sup>,  
Zdenek Andrysik <sup># 1 2</sup>, Paula Araya <sup># 1</sup>, Hannah Dougherty <sup># 1</sup>, Lauren N Dunn <sup># 1 6</sup>,  
Michael Ludwig <sup># 1 2</sup>, Kyndal A Schade <sup># 1</sup>, Dayna Tracy <sup># 1</sup>, Keith P Smith <sup>1</sup>,  
Ross E Granrath <sup>1</sup>, Nicolas Busquet <sup>7 8</sup>, Santosh Khanal <sup>1 2</sup>, Ryan D Anderson <sup>9</sup>, Liza L Cox <sup>9</sup>,  
Belinda Enriquez Estrada <sup>1</sup>, Angela L Rachubinski <sup>1 10</sup>, Hannah R Lyford <sup>1</sup>, Eleanor C Britton <sup>1</sup>,  
Katherine A Fantauzzo <sup>11</sup>, David J Orlicky <sup>12</sup>, Jennifer L Matsuda <sup>13</sup>, Kunhua Song <sup>1 3 4 5</sup>,  
Timothy C Cox <sup>9 14</sup>, Kelly D Sullivan <sup>15 16</sup>, Joaquin M Espinosa <sup>17 18</sup>

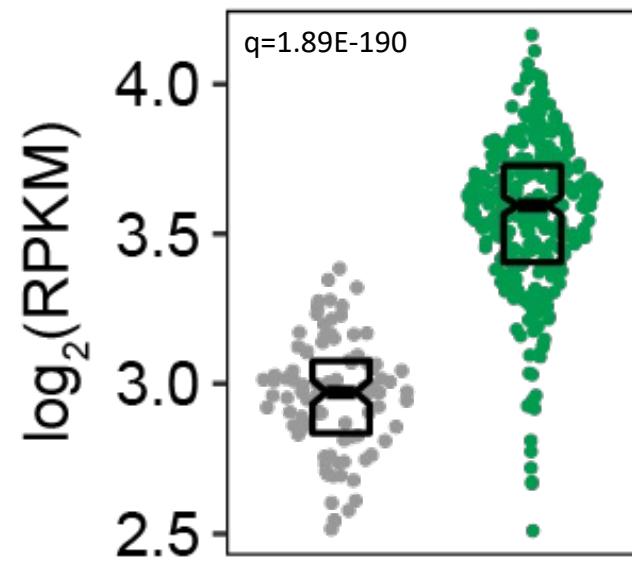
# Trisomy 21 causes widespread changes in the transcriptome, proteome, metabolome, and immune cells

Whole-blood polyA RNA-seq



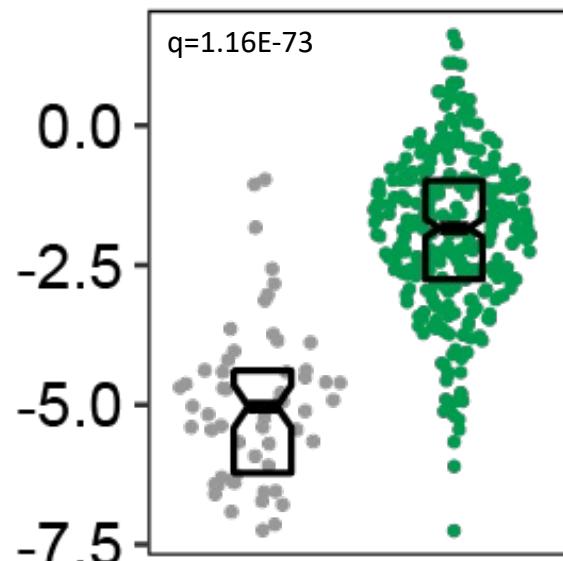
Chr21 encoded

POFUT2



Not chr21  
encoded

MMP1

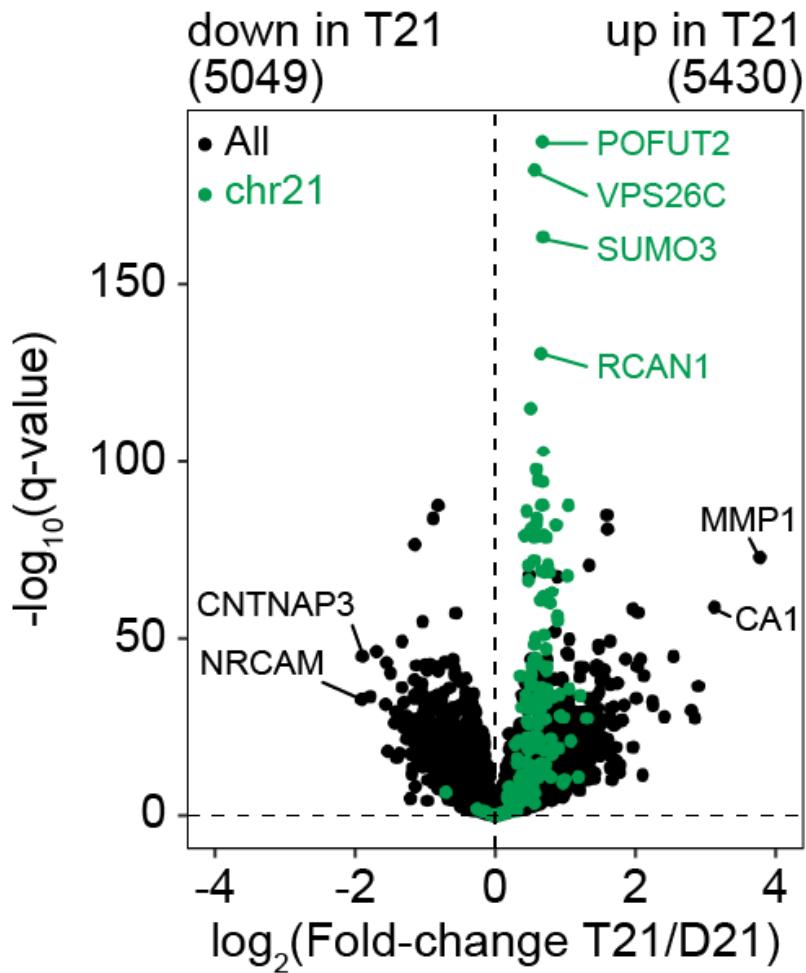


Karyotype: • Control • T21

Not just Chr21 genes

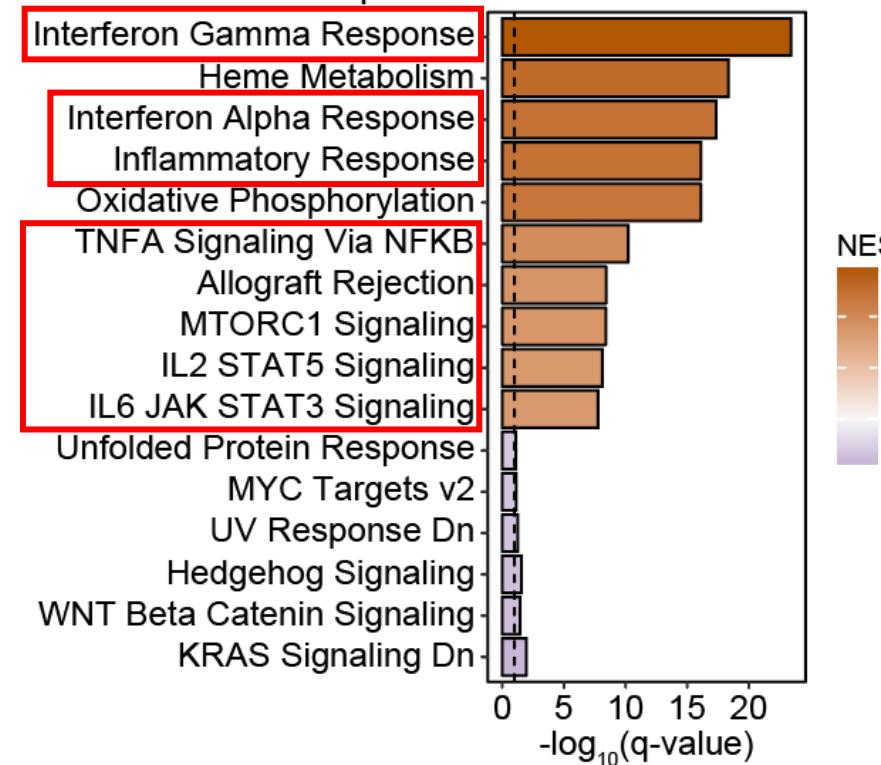
# Trisomy 21 causes widespread changes in the transcriptome, proteome, metabolome, and immune cells

Whole-blood polyA RNA-seq



The blood of people with Down syndrome looks like it is fighting a viral infection...

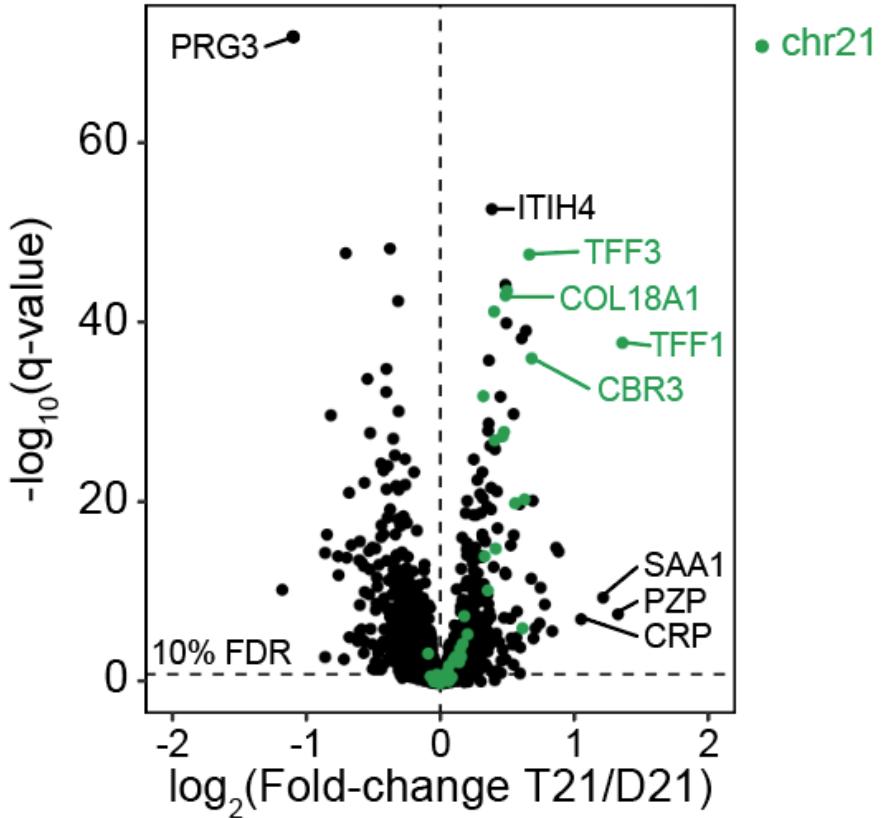
GSEA: Top Hallmark gene sets  
Transcriptome T21 vs. Control



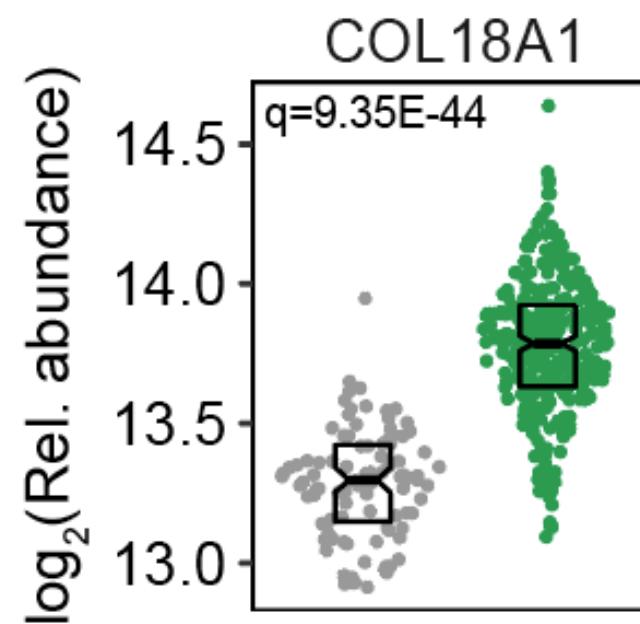
# Trisomy 21 causes widespread changes in the transcriptome, **proteome**, metabolome, and immune cells

## Plasma proteomics (SOMAscan platform)

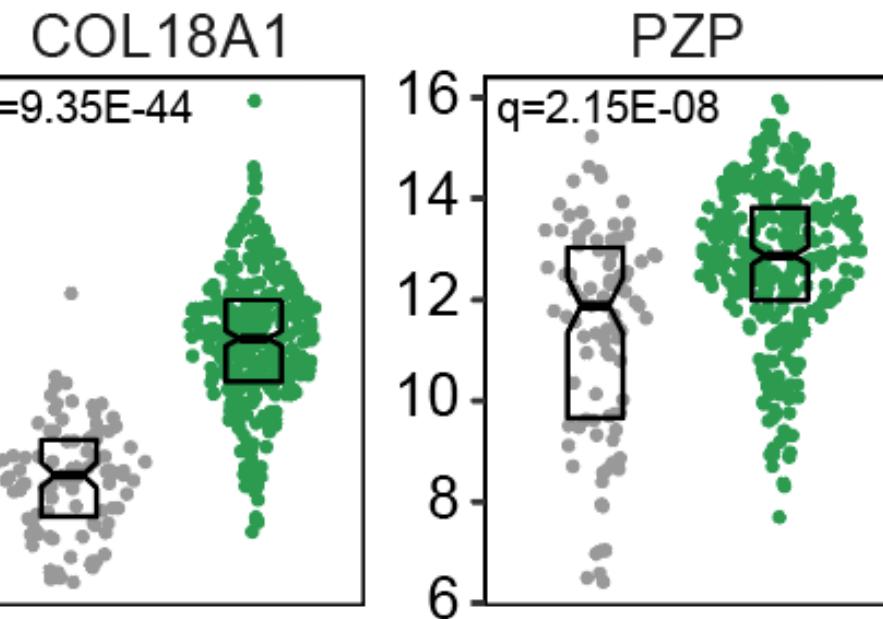
down in T21  
(867)      up in T21  
(1031)



## Chr21 encoded



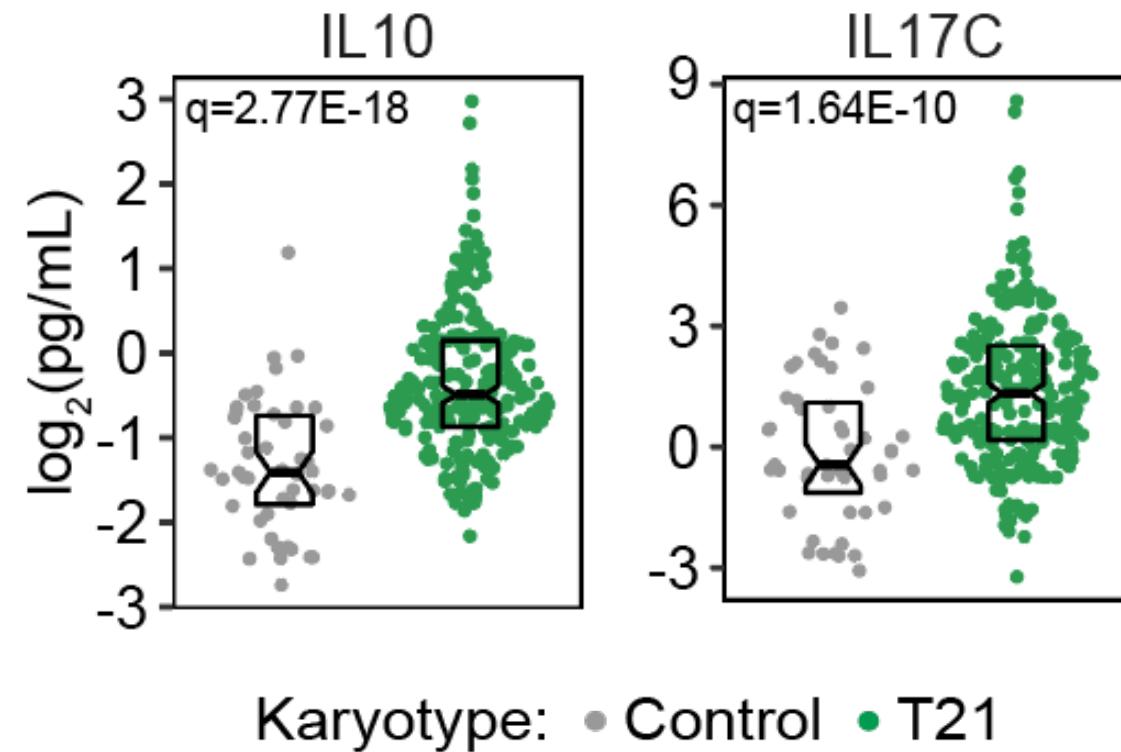
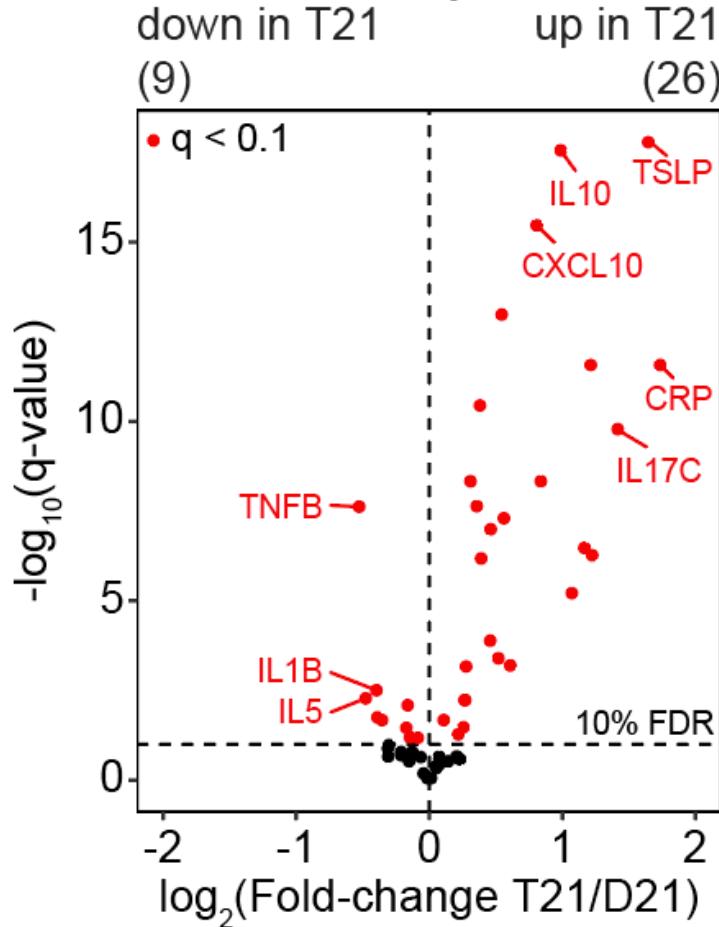
## Not chr21 encoded



Karyotype: • Control • T21

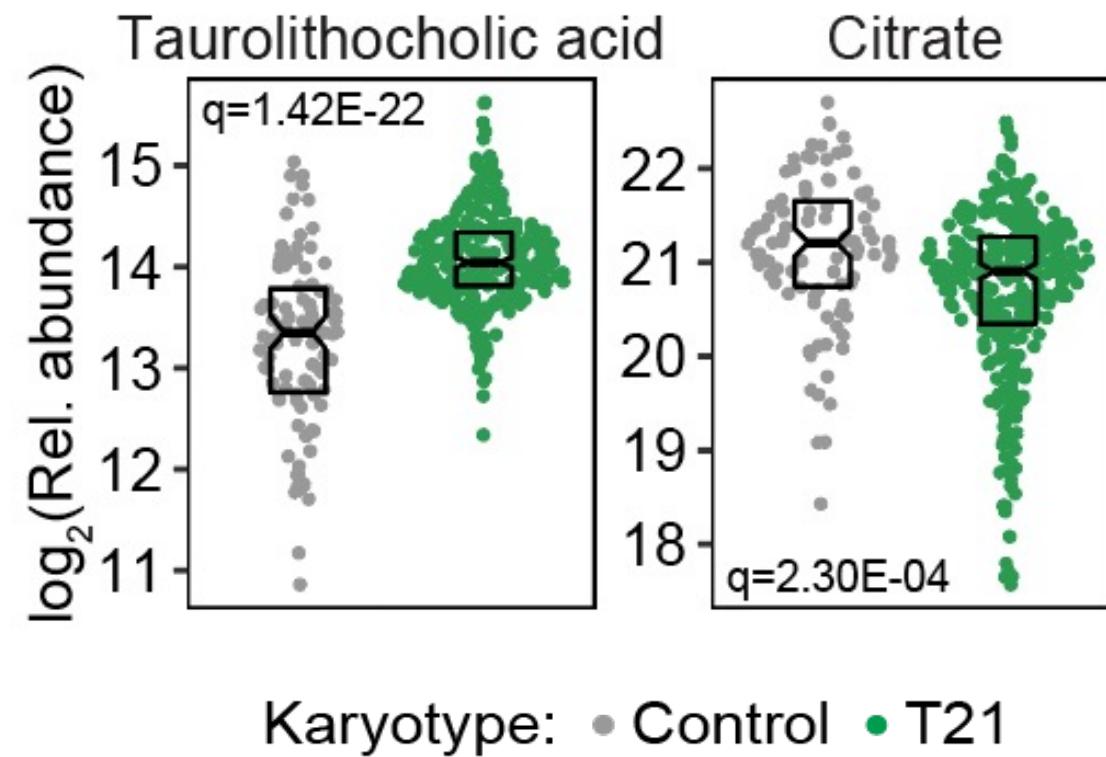
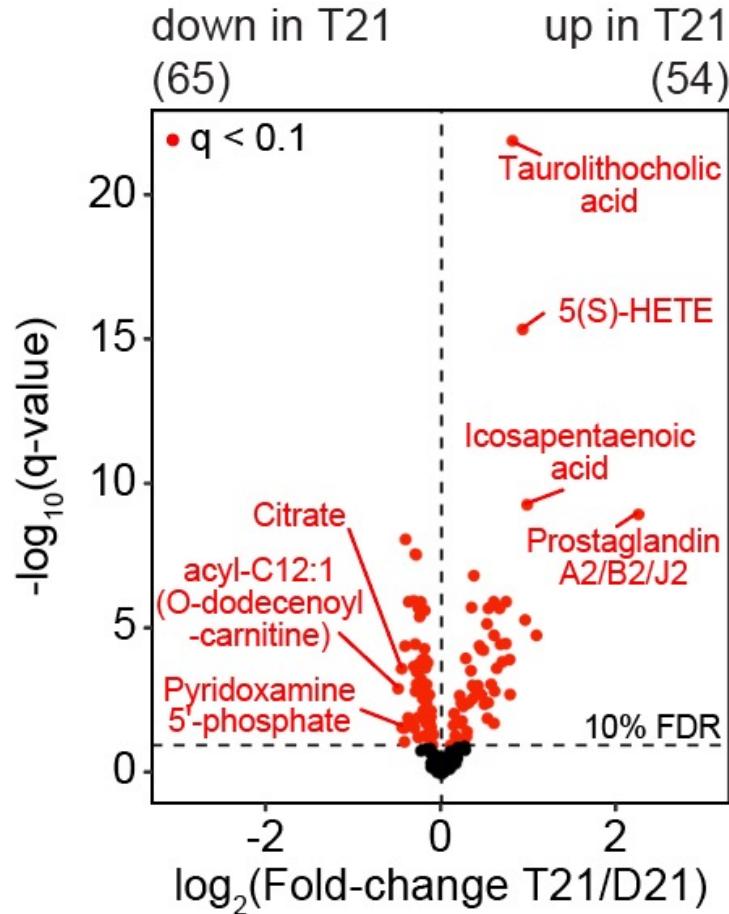
# Trisomy 21 causes widespread changes in the transcriptome, **proteome**, metabolome, and immune cells

Plasma cytokines and immune factors  
(MSD multiplexed ELISA)



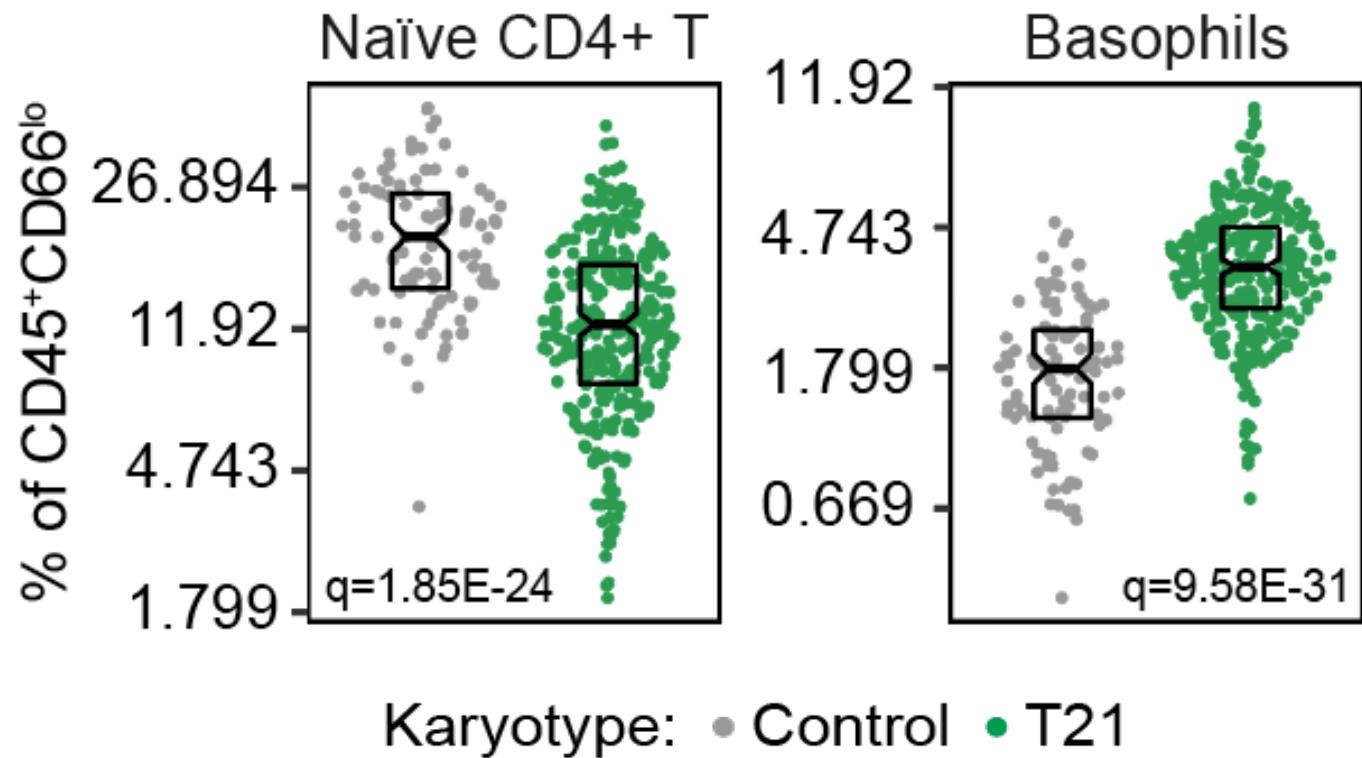
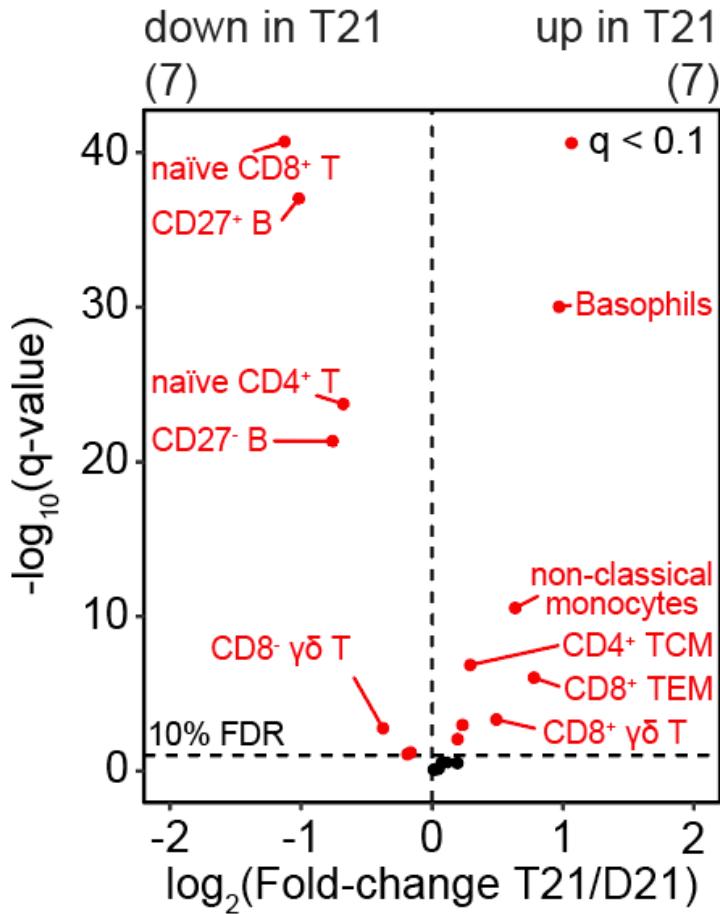
# Trisomy 21 causes widespread changes in the transcriptome, proteome, **metabolome**, and immune cells

## Plasma metabolomics (UHPLC-MS)



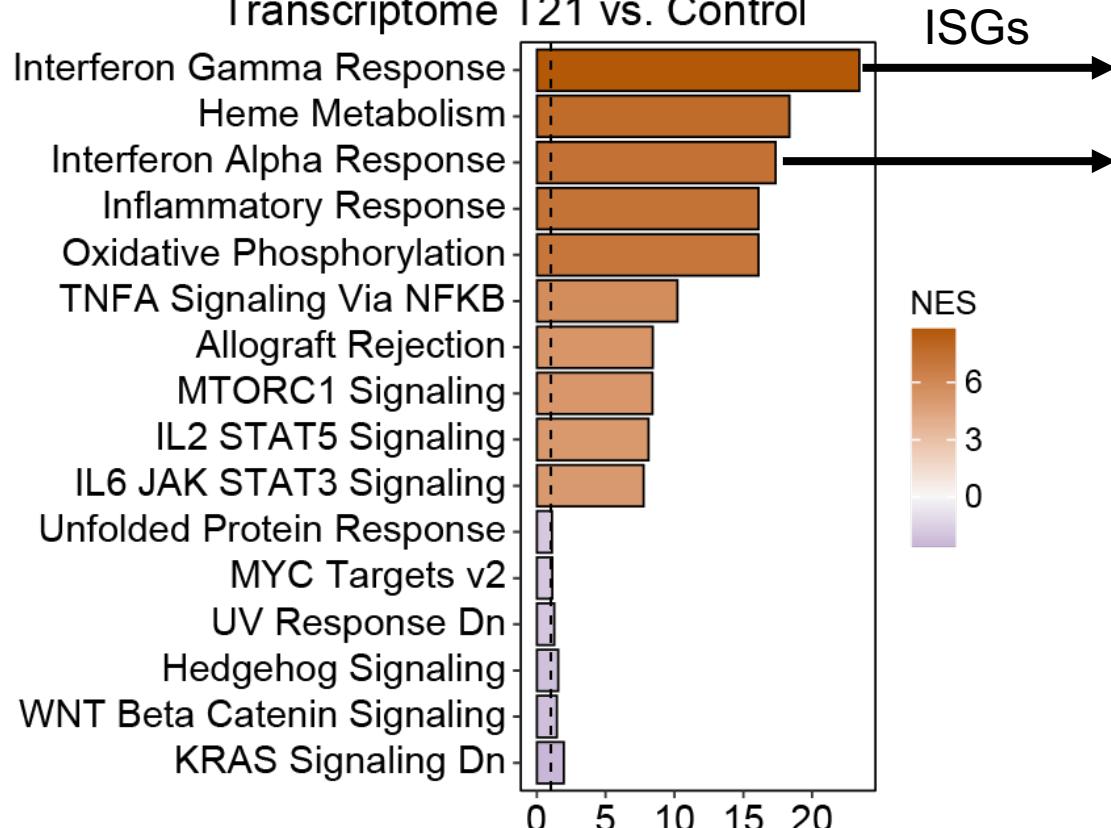
# Trisomy 21 causes widespread changes in the transcriptome, proteome, metabolome, and immune cells

# Mass cytometry (CyTOF)



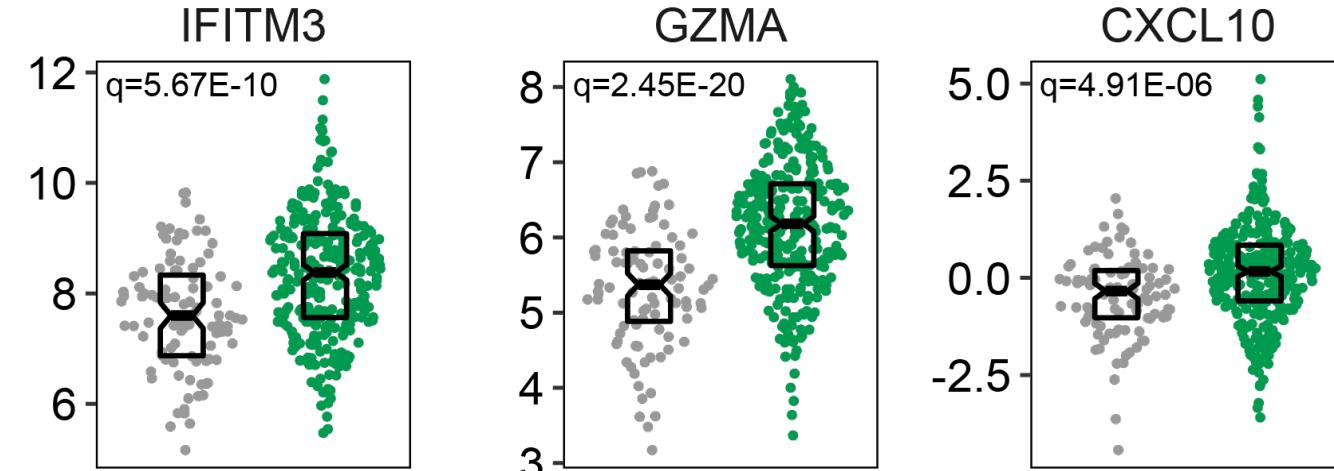
# Interferon activation is the top biosignature in the whole blood transcriptome

GSEA: Top Hallmark gene sets  
Transcriptome T21 vs. Control



Gene Set Enrichment Analysis

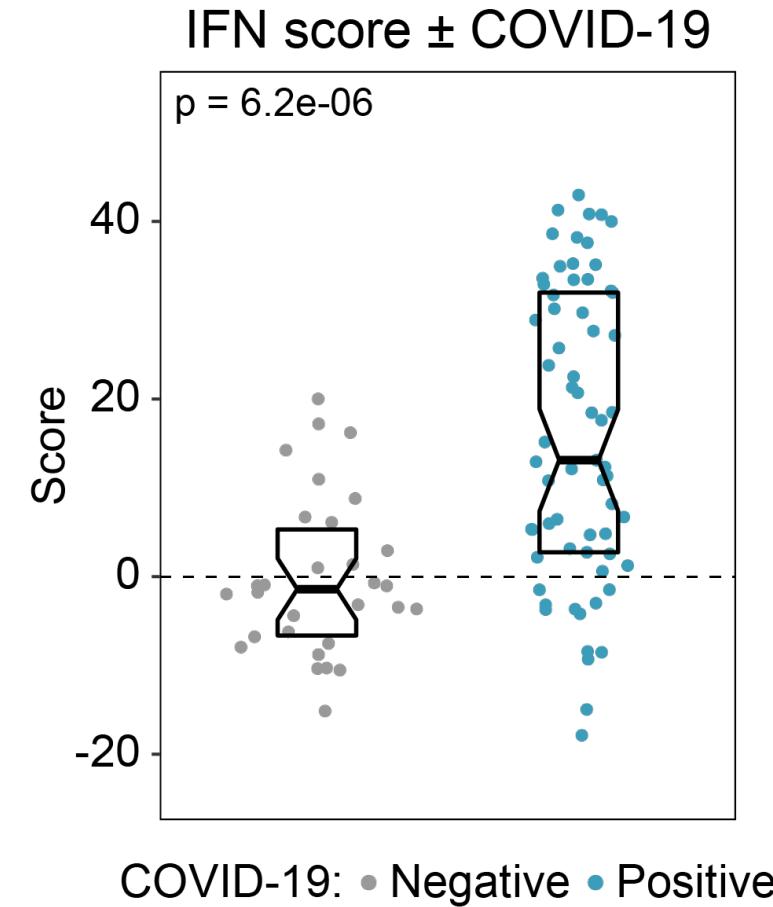
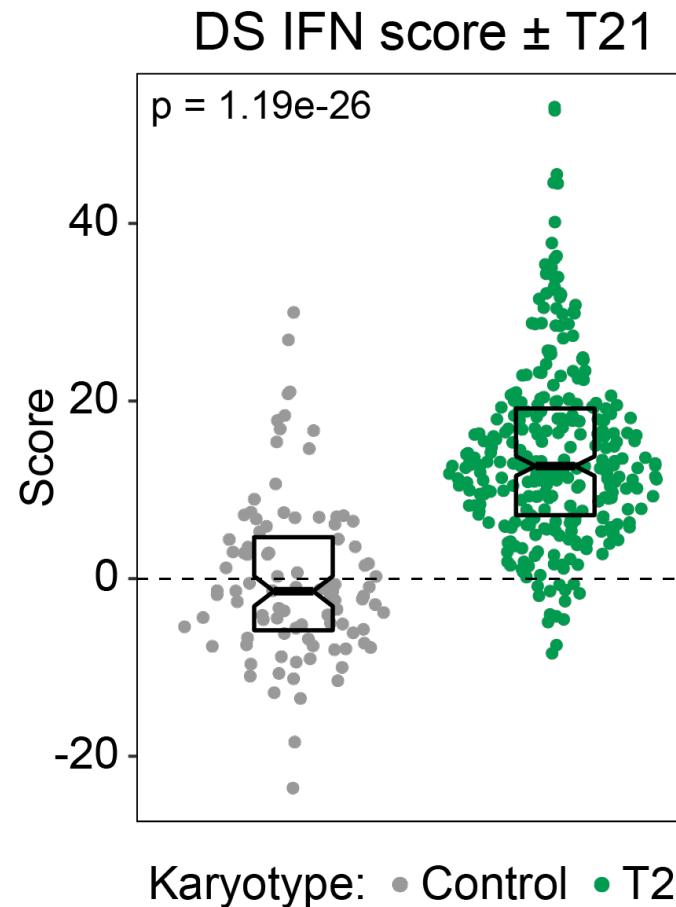
Strong inter-individual variation



18 ISGs with >1.5x fold-change

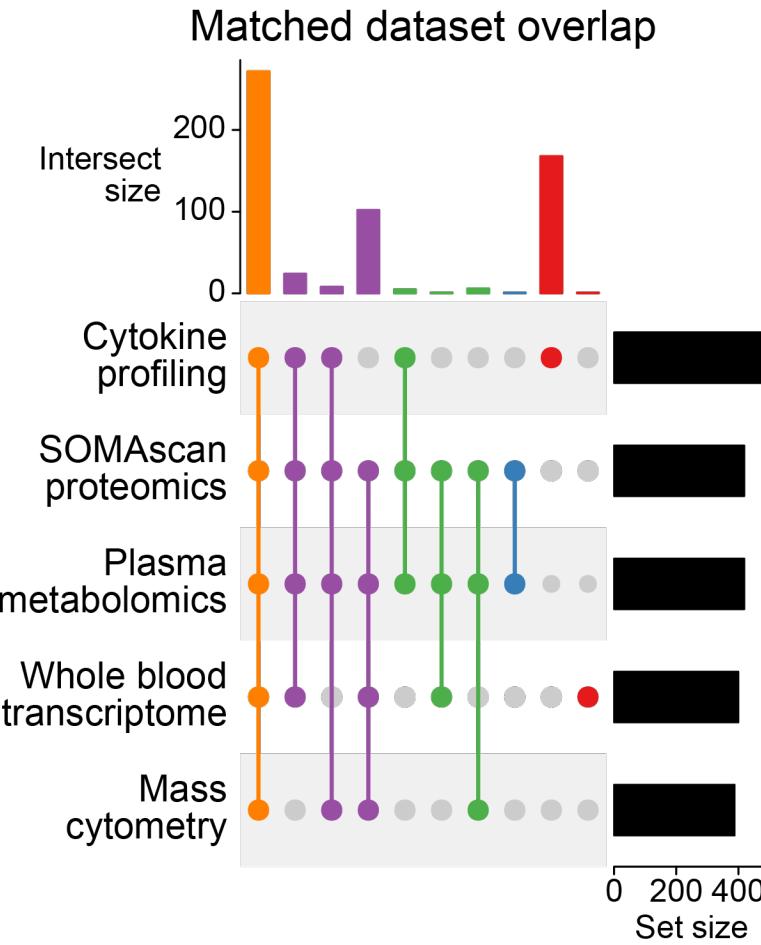
Sum Z-scores

# Individuals with Down syndrome display elevated yet variable DS IFN scores



As do people with COVID-19

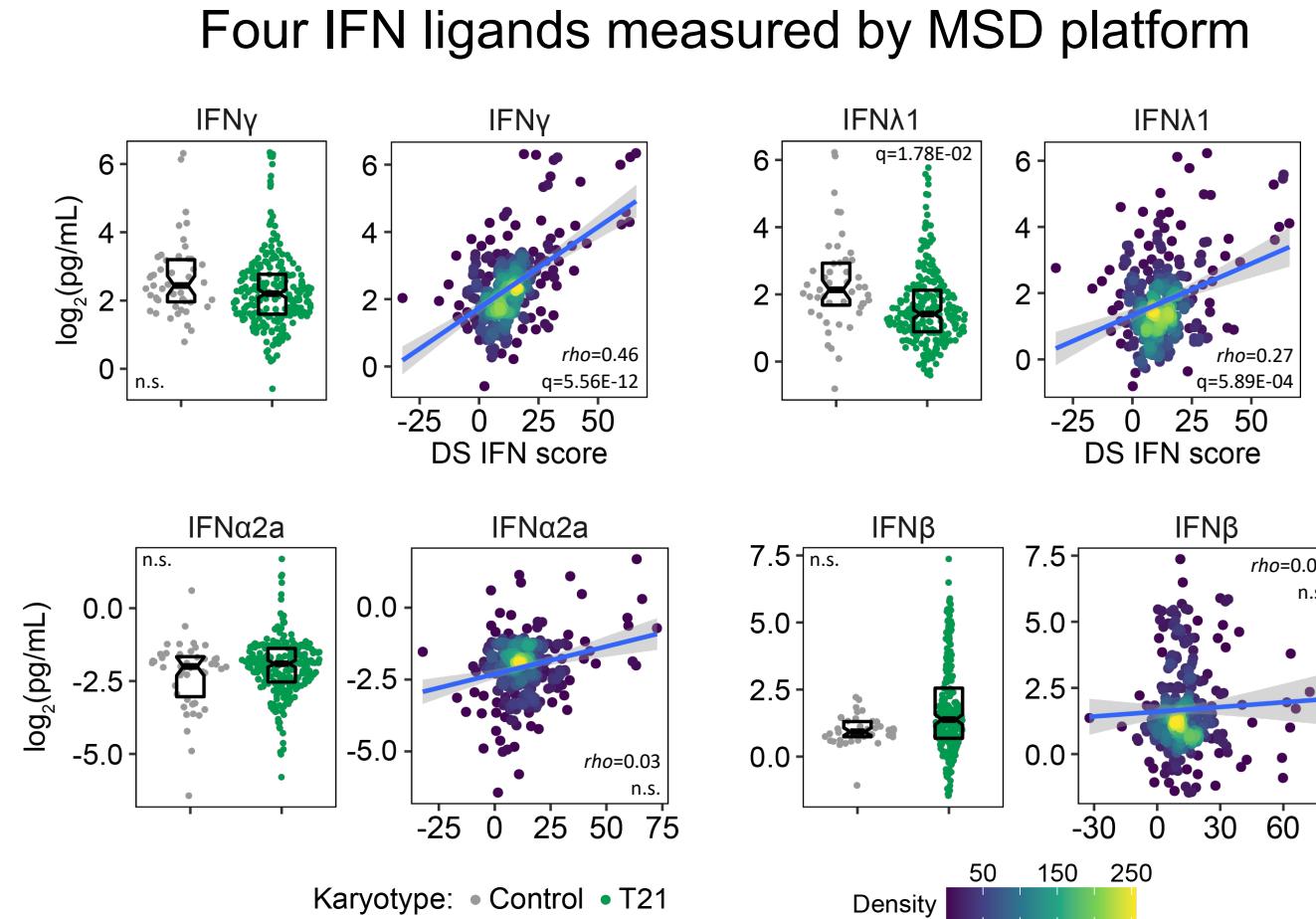
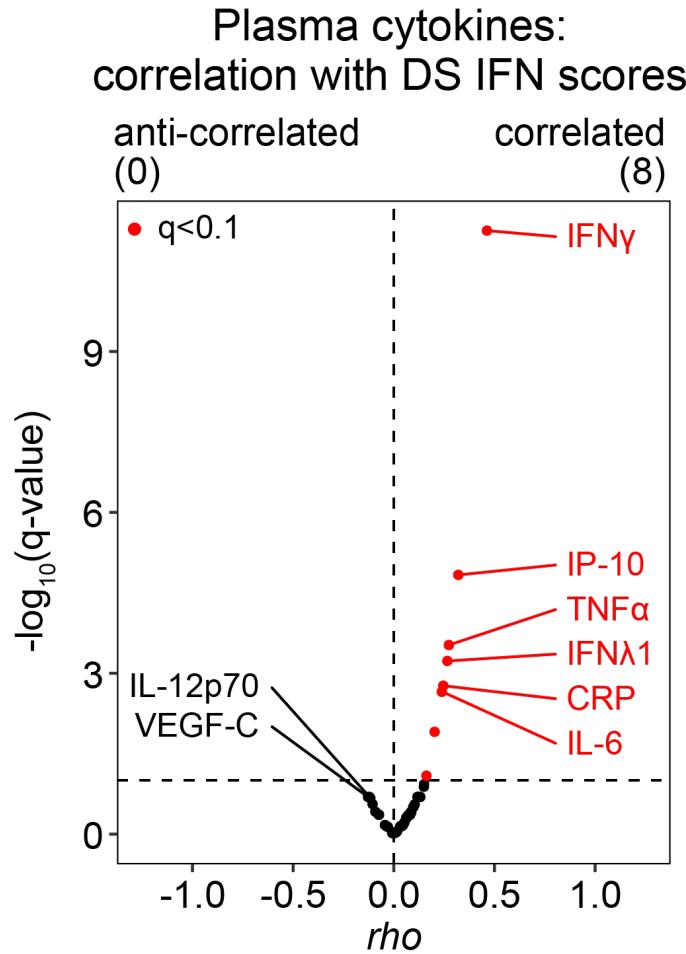
# Many HTP Omics datasets are matched from the same blood draw



# **What are the impacts of hyperactive IFN signaling in Down syndrome on cytokines?**

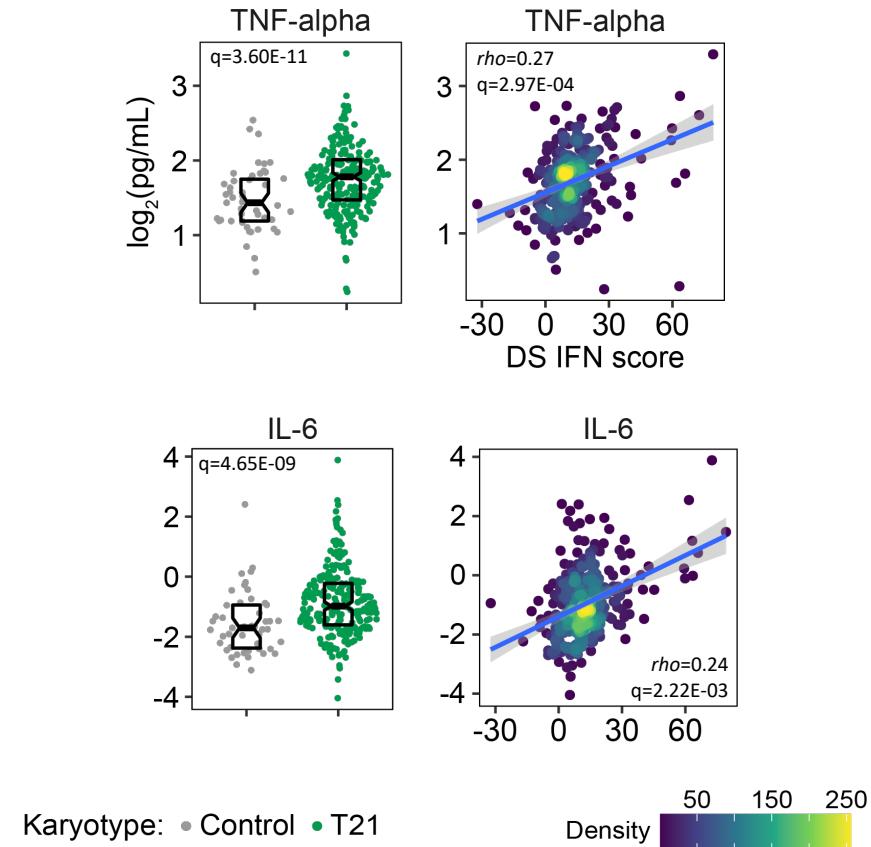
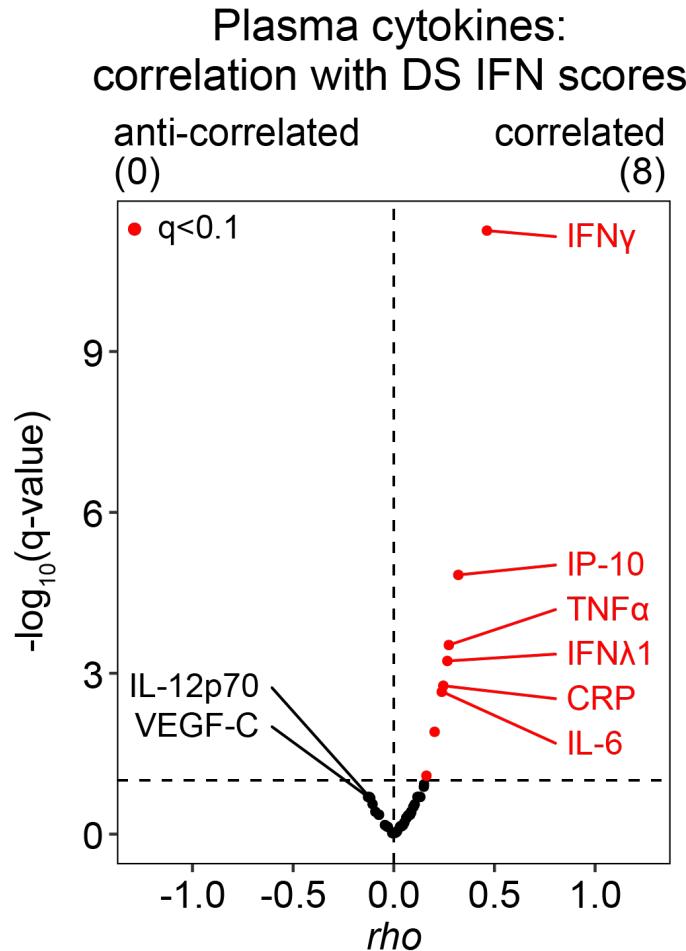
RNA-based DS IFN score → Spearman correlation with MSD cytokine profiling

# IFN hyperactivity in Down syndrome is strongly associated with Type II (IFNG) and Type III (IFNL) interferons



- None are significantly elevated in T21
- IFN $\gamma$  (Type II) and IFN $\lambda$ 1 (Type III) are *significantly* correlated
- IFN $\alpha$ 2a and IFN $\beta$  (both Type I) are not correlated

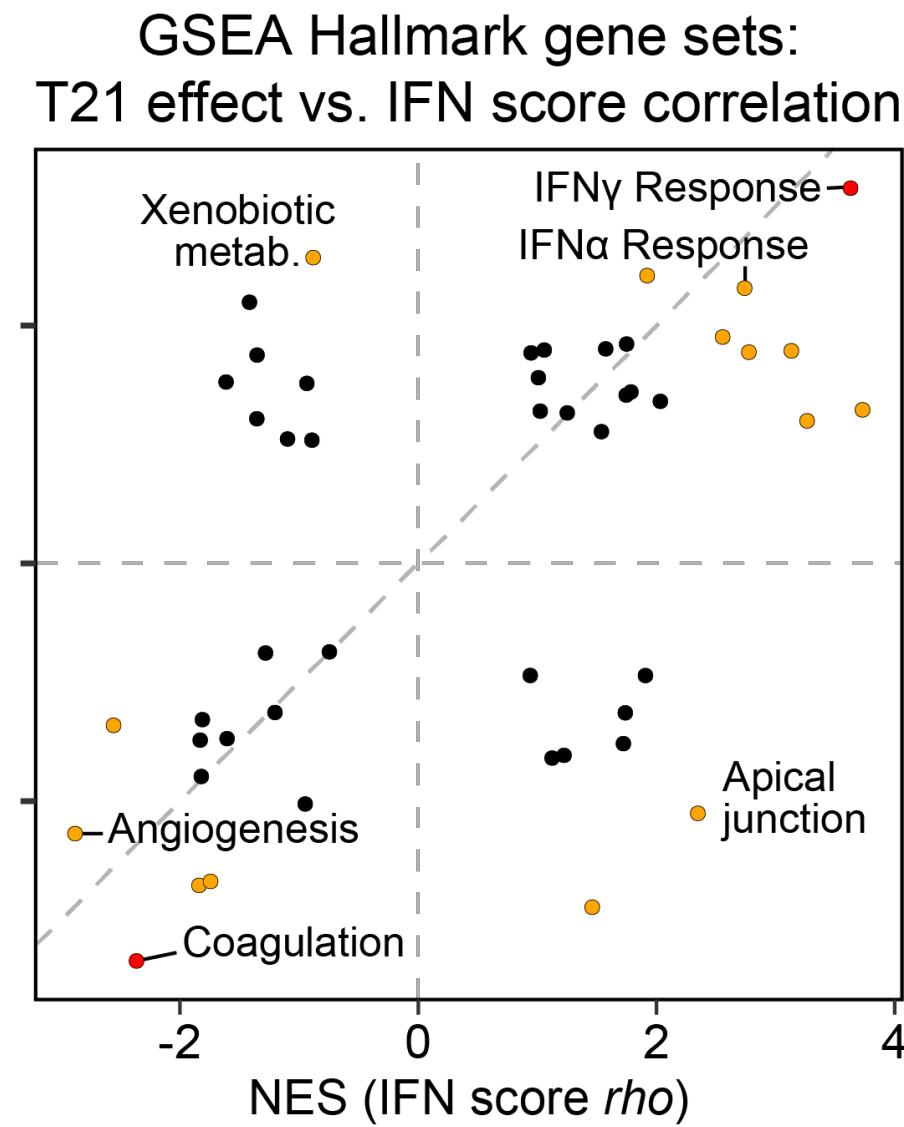
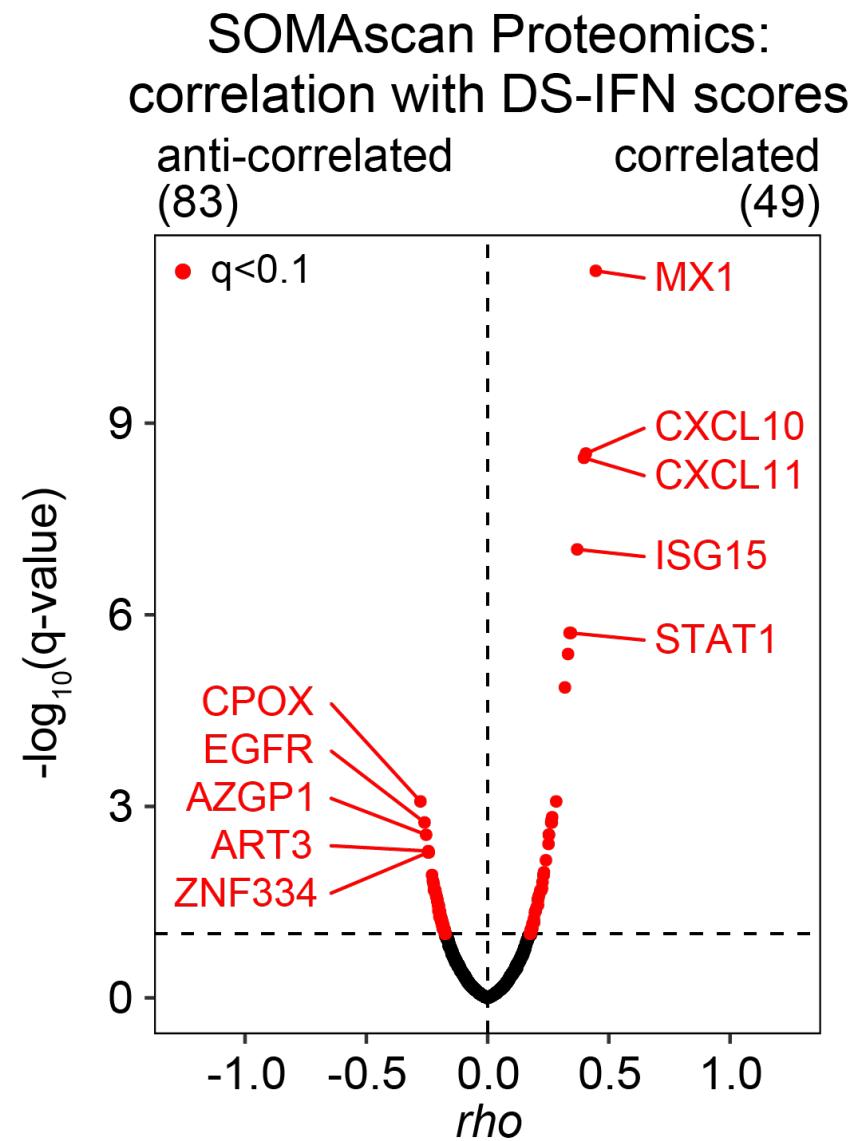
# IFN hyperactivity associates with elevated TNF $\alpha$ and IL6 signaling



# **What are the impacts of hyperactive IFN signaling on the proteome?**

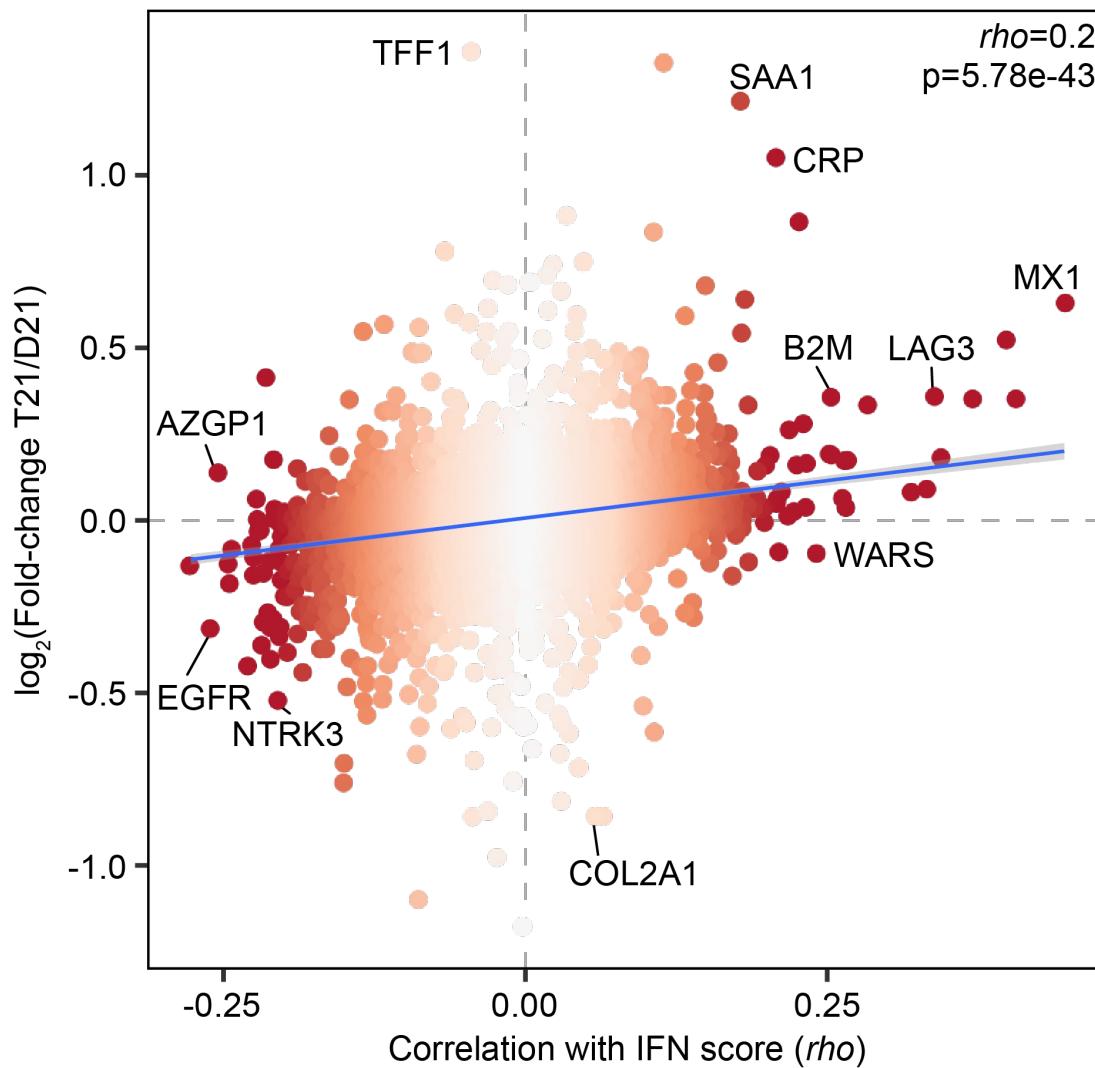
RNA-based DS IFN score → Spearman correlation with SOMAscan proteomics

# IFN hyperactivity shapes the proteome in Down syndrome



# IFN hyperactivity shapes the proteome in Down syndrome

Fold-change T21/D21 vs.  
correlation with DS-IFN score



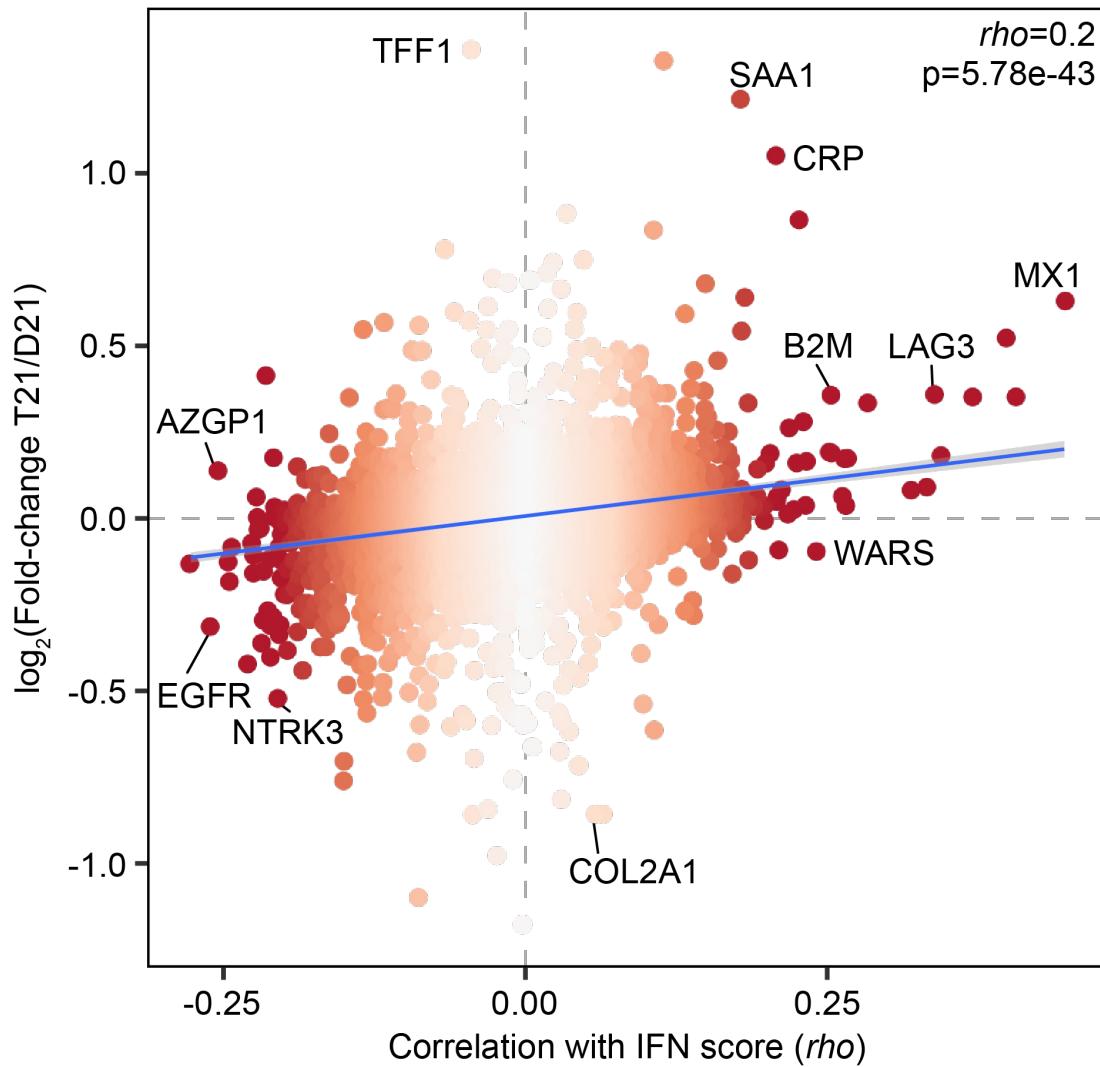
Overall positive relationship between  
fold-change (T21/Controls)  
and correlation (within T21):  
**The higher the IFN score,  
the stronger the proteomic changes**

i.e. blood-based IFN signaling helps  
shape the plasma proteome

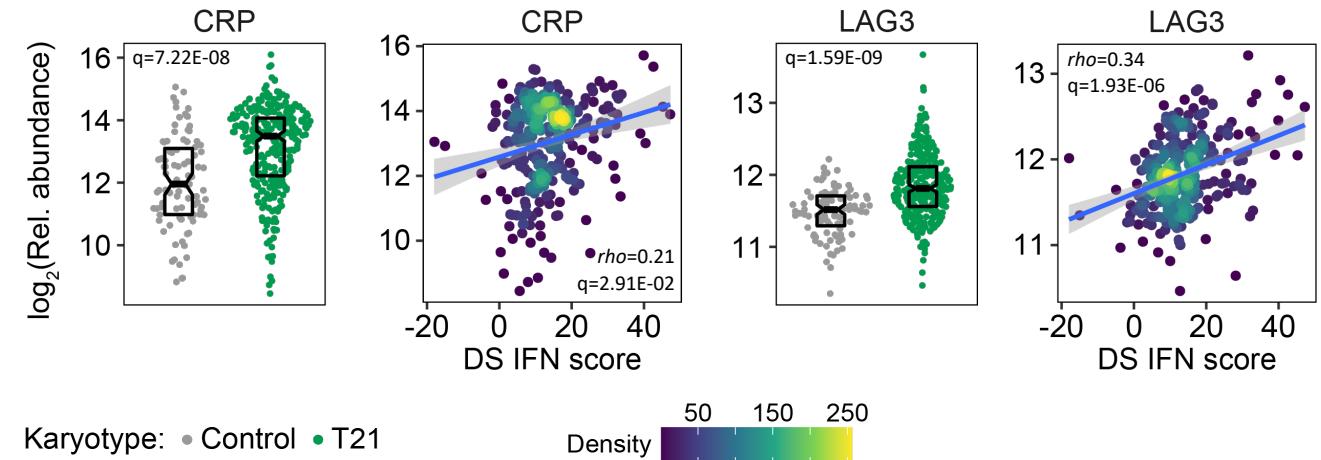
Some changes are not associated with  
DS IFN score = independent of IFN signaling?

# IFN signaling is associated with proteome changes – but not all

Fold-change T21/D21 vs.  
correlation with DS-IFN score

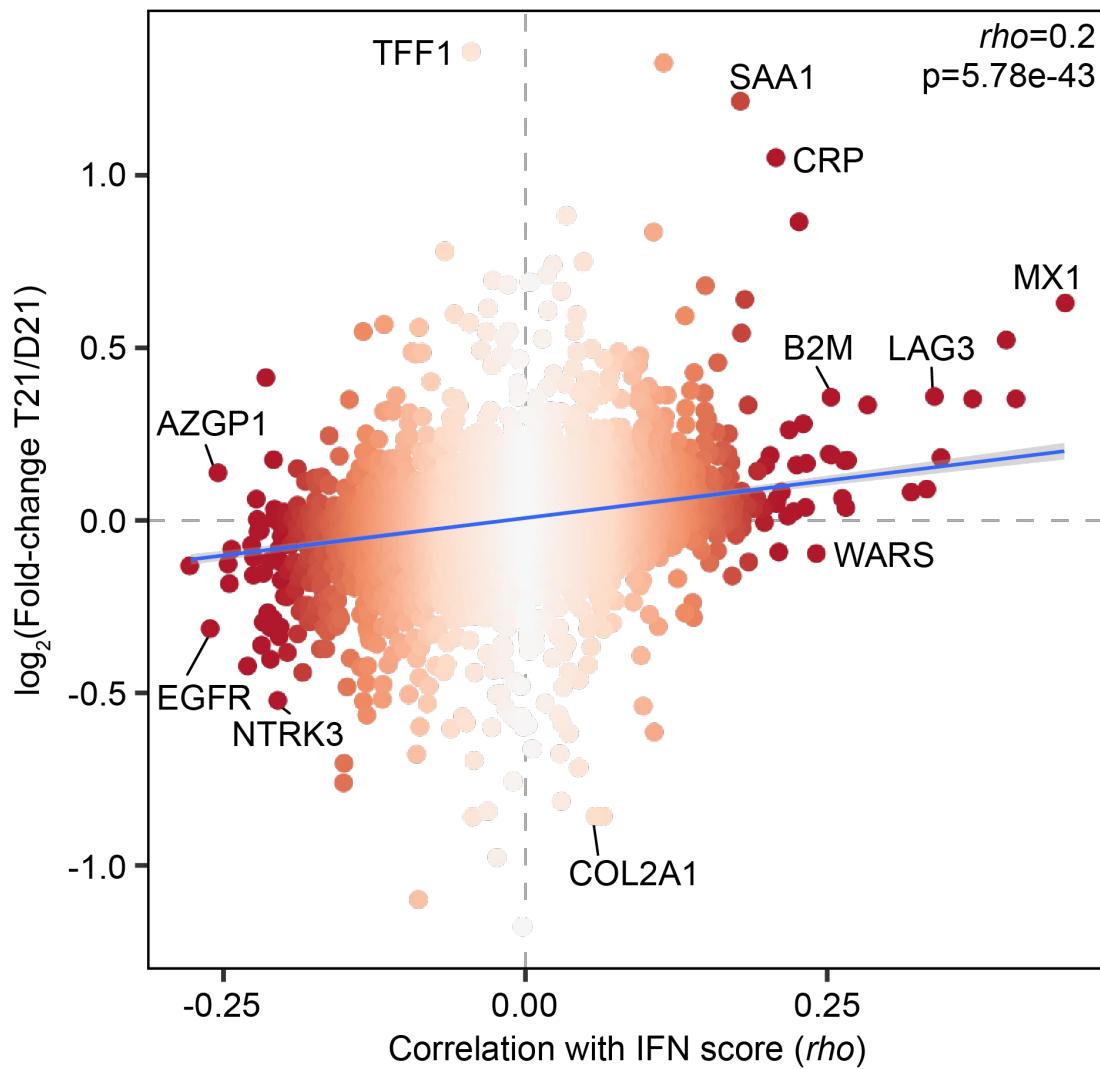


Up in T21; significant positive correlation

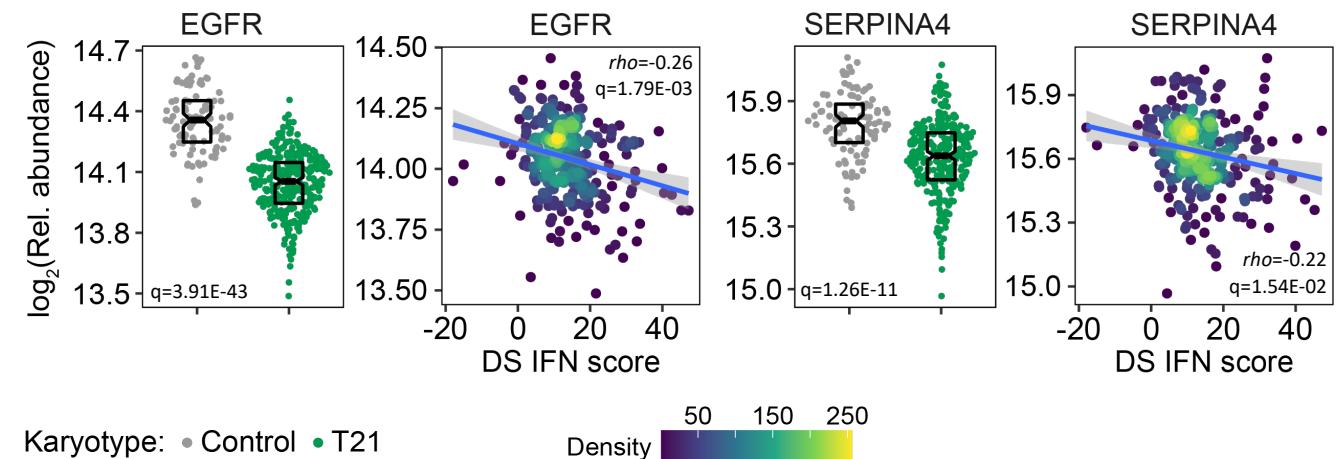


# IFN signaling is associated with proteome changes – but not all

Fold-change T21/D21 vs.  
correlation with DS-IFN score

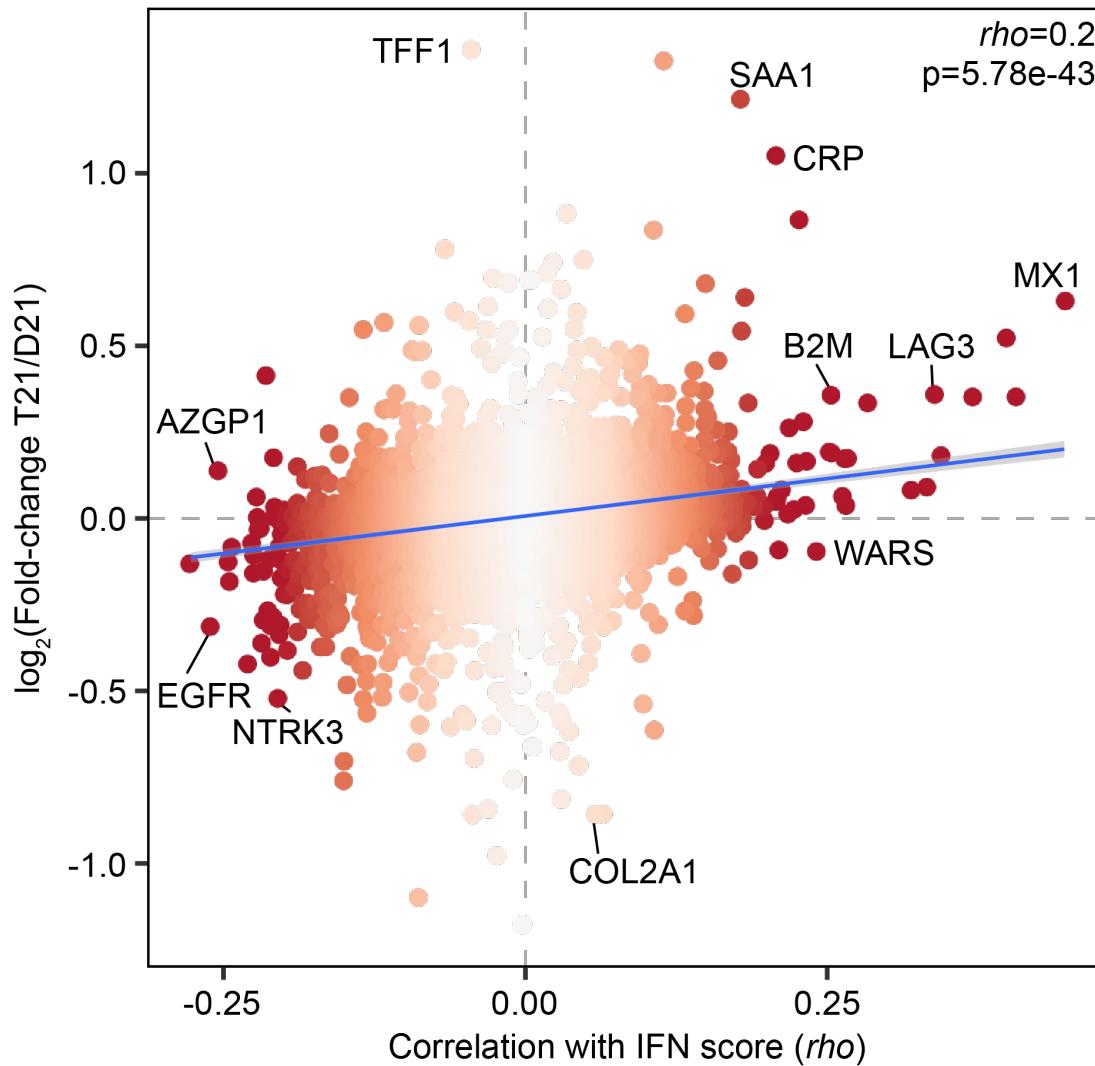


Down in T21; significant negative correlation

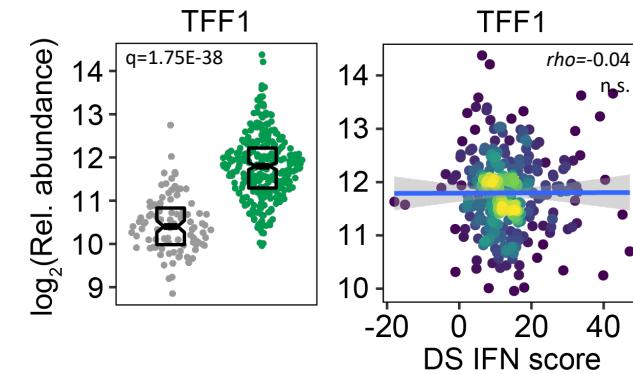


# IFN signaling is associated with proteome changes – but not all

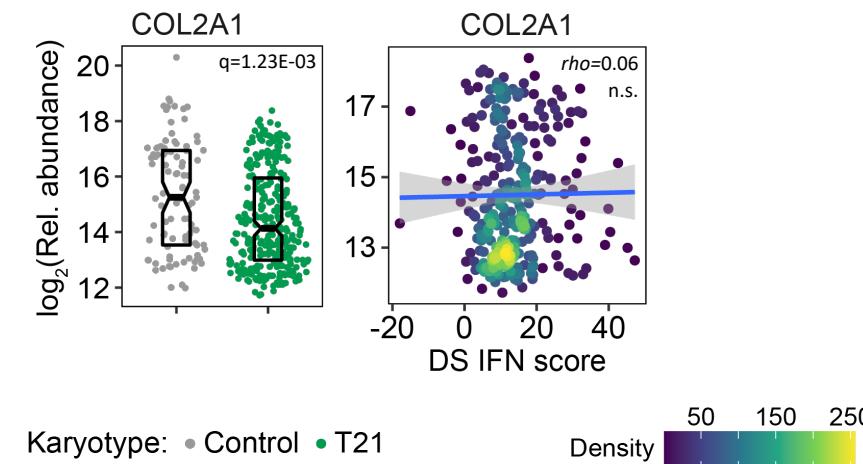
Fold-change T21/D21 vs.  
correlation with DS-IFN score



Up in T21; no significant correlation with DS IFN score



Down in T21; no significant correlation



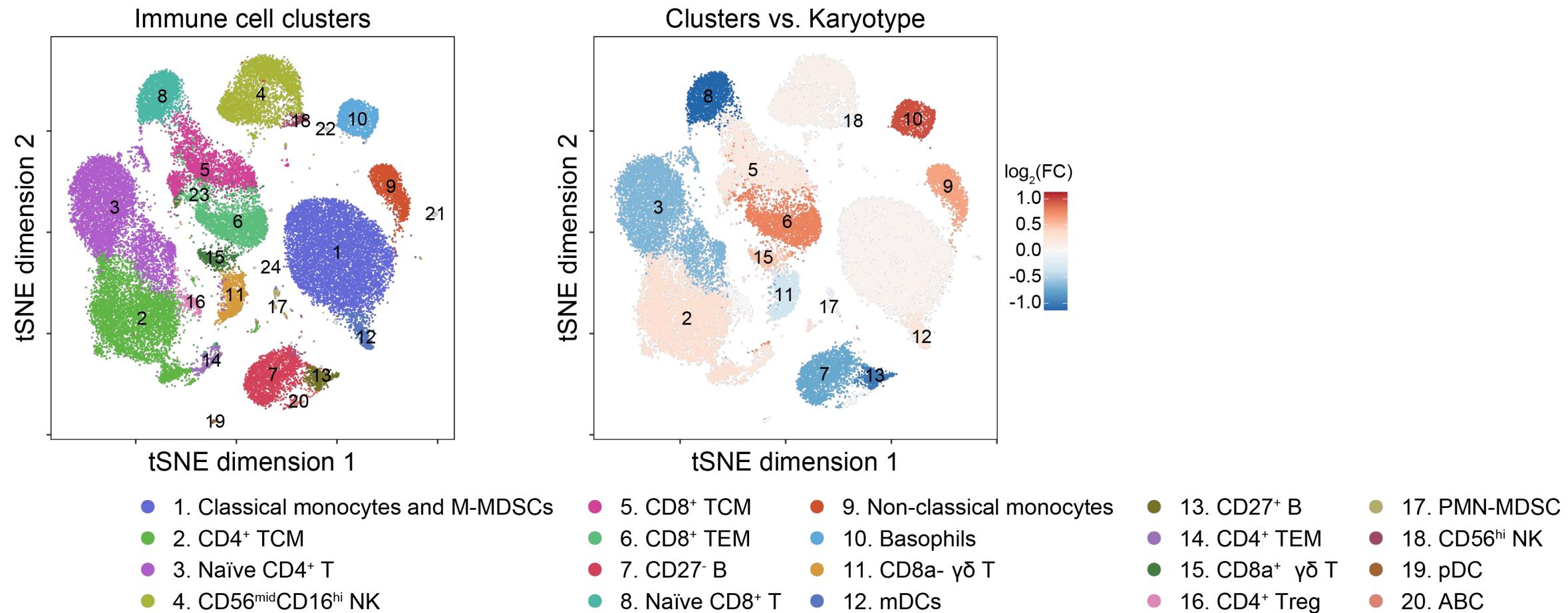
Karyotype: • Control • T21

Density 50 150 250

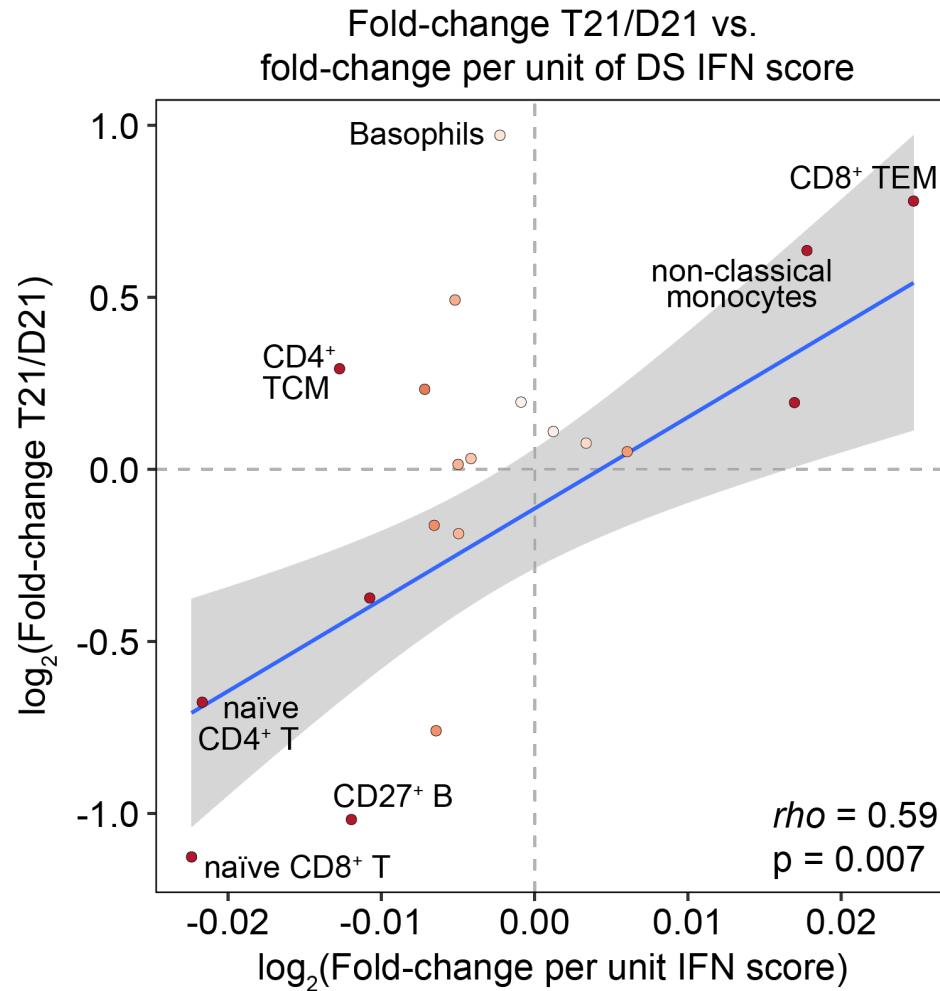
# **What are the impacts of hyperactive IFN signaling on immune cell lineages?**

RNA-based DS IFN score → beta regression vs. immune cell subpopulations

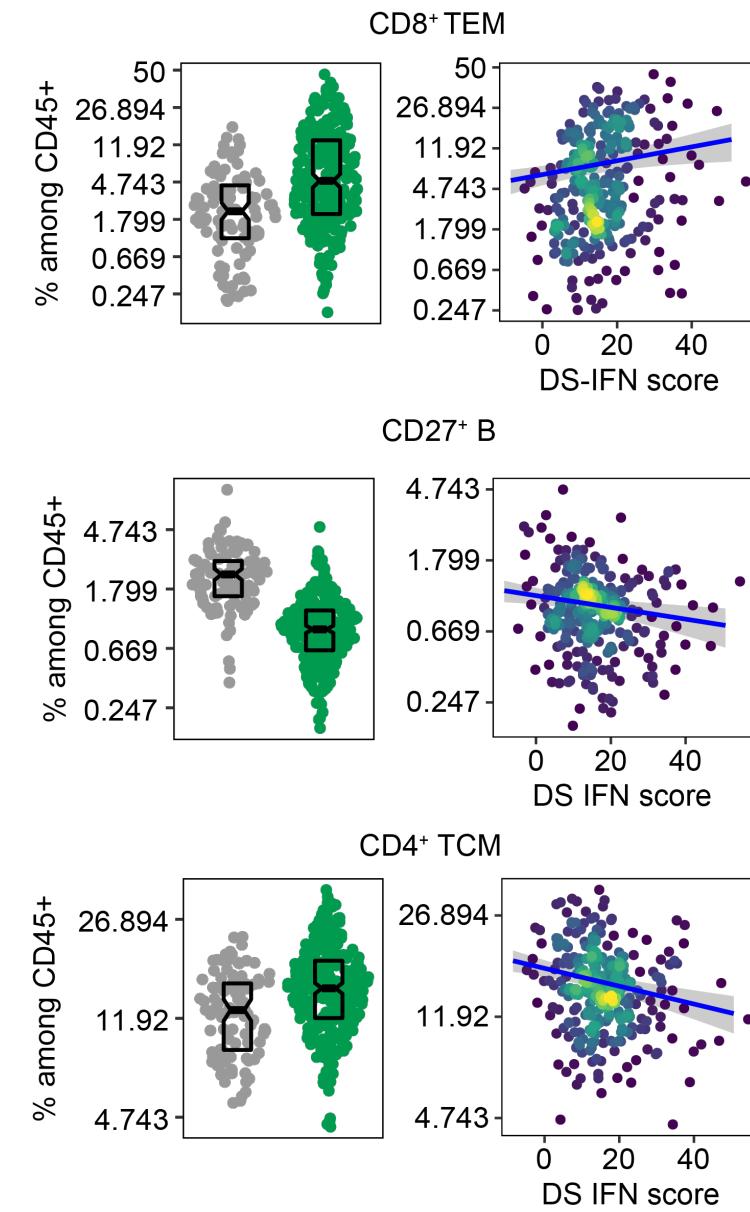
# IFN hyperactivity shapes the peripheral immune system



# IFN hyperactivity shapes the peripheral immune system



The higher the IFN score,  
the stronger the immune dysregulation

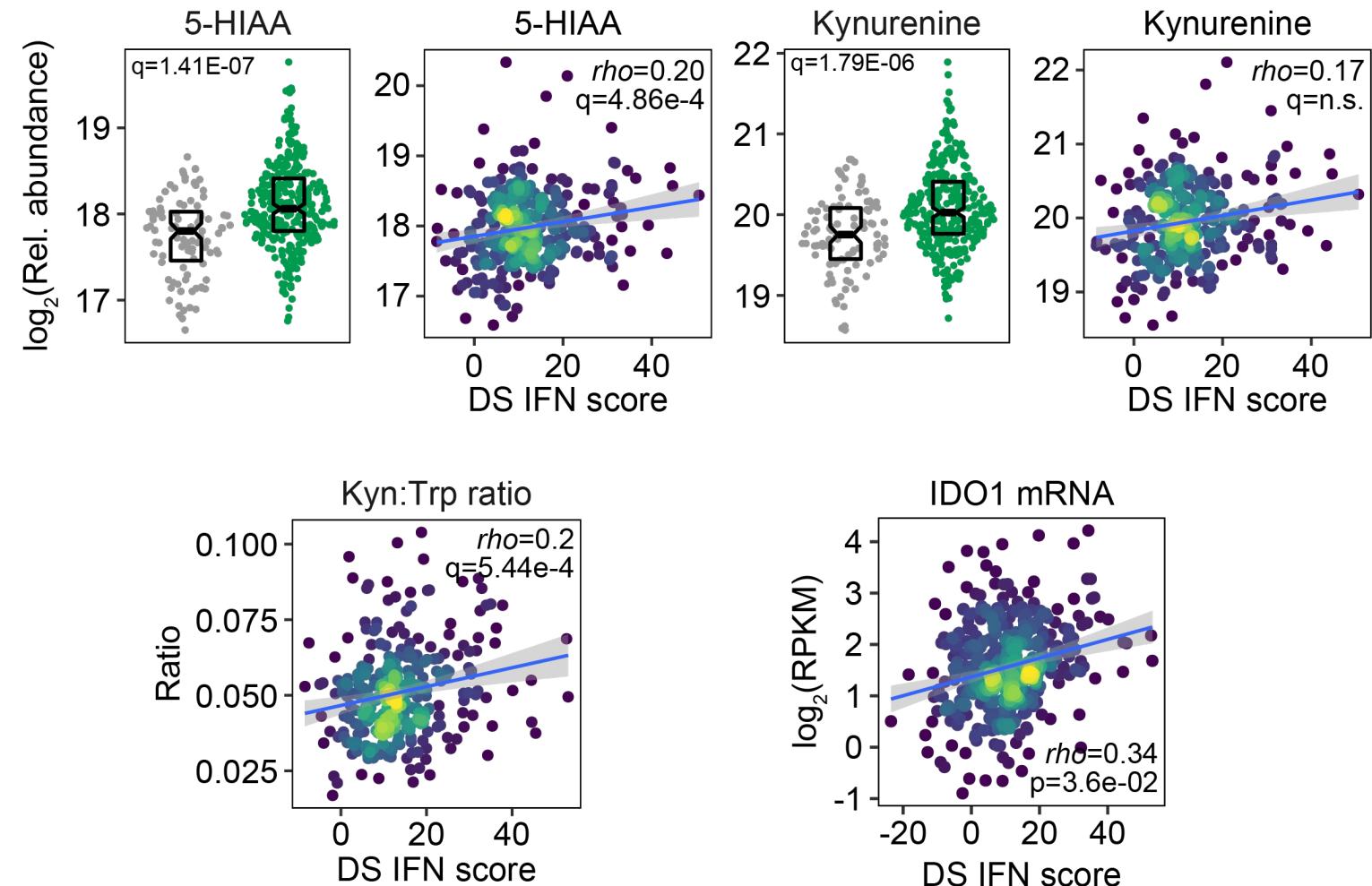
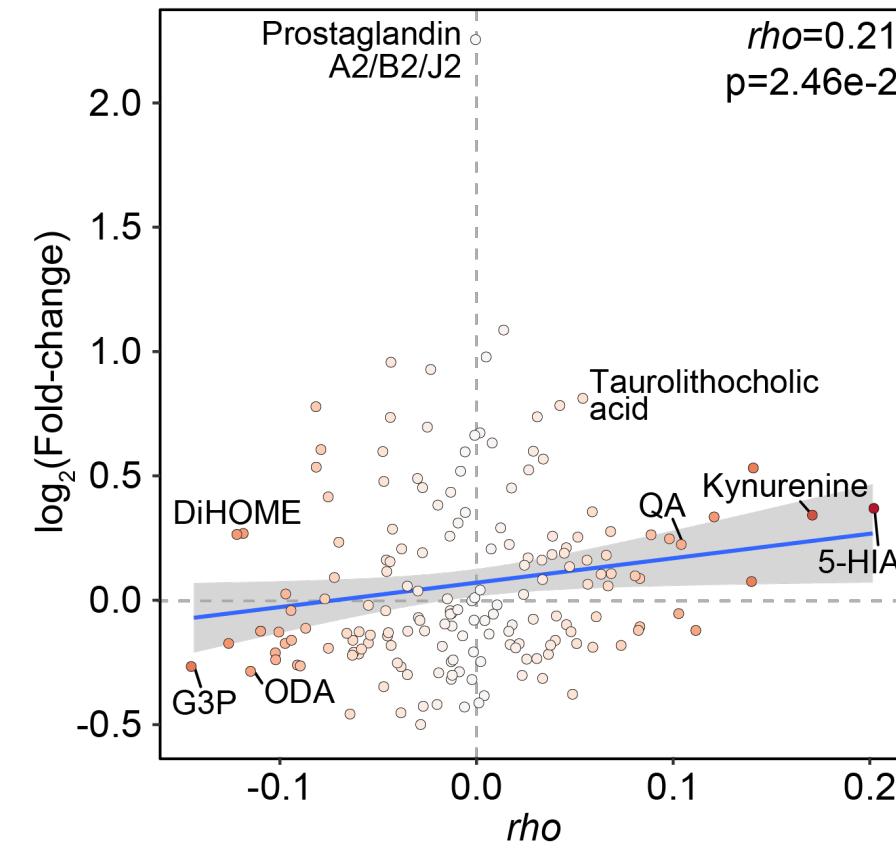


# **What are the impacts of hyperactive IFN signaling on metabolism?**

RNA-based DS IFN score → Spearman correlation with LC-MS metabolomics

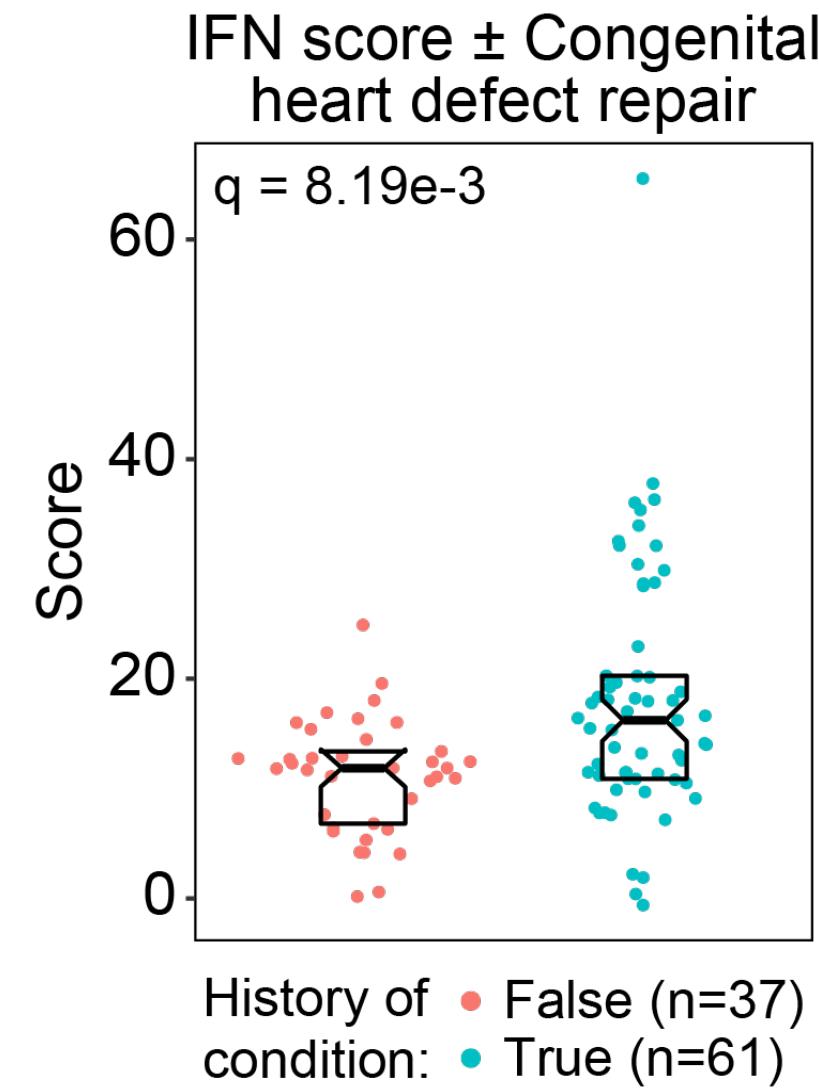
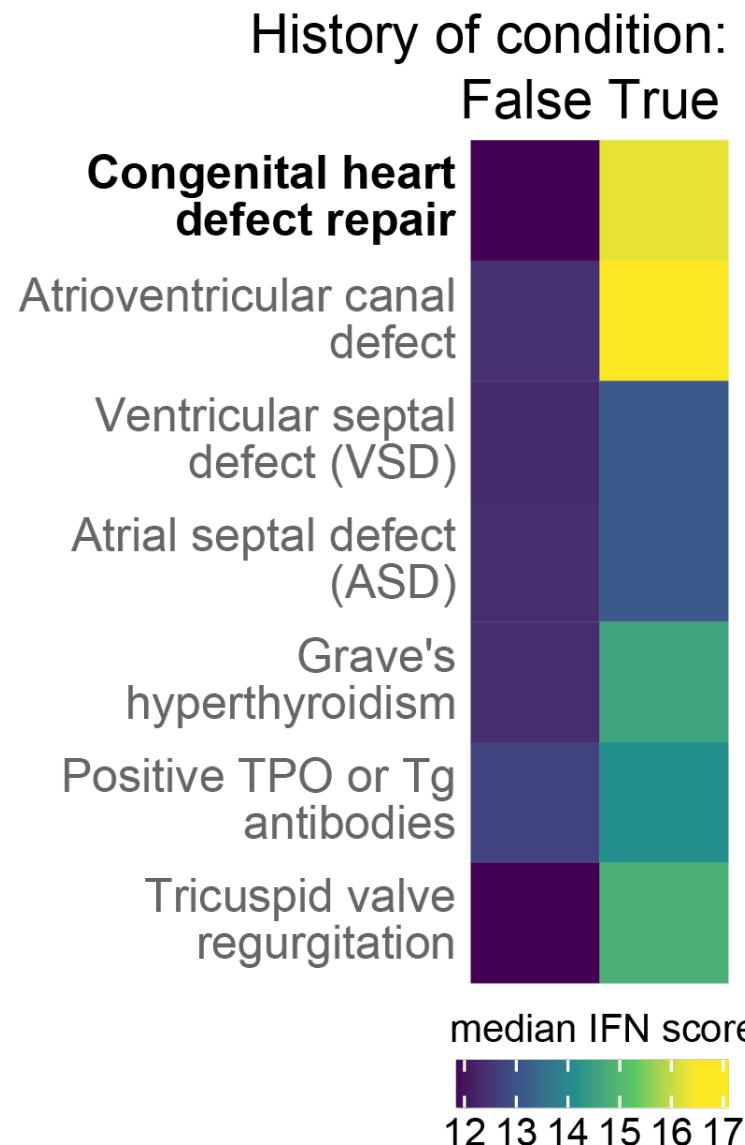
# IFN hyperactivity correlates with altered tryptophan metabolism

Fold-change T21/Control vs.  
Correlation with DS IFN score



**What is the relationship between hyperactive IFN signaling  
and co-occurring conditions  
in Down syndrome?**

# Individuals with congenital heart defect repairs tend to have higher DS IFN scores



**Can the interferonopathy be treated to  
improve health outcomes in Down syndrome?**

# The first clinical trial of a JAK inhibitor in Down syndrome (NCT04246372)

Research Article

Immunology and Inflammation, Medicine



## JAK inhibition decreases the autoimmune burden in Down syndrome

Angela L Rachubinski ✉, Elizabeth Wallace, Emily Gurnee, Belinda A Enriquez-Estrada, Kayleigh R Worek, Keith P Smith, Paula Araya, Katherine A Waugh, Ross E Granrath ... Joaquín M Espinosa [see all »](#)

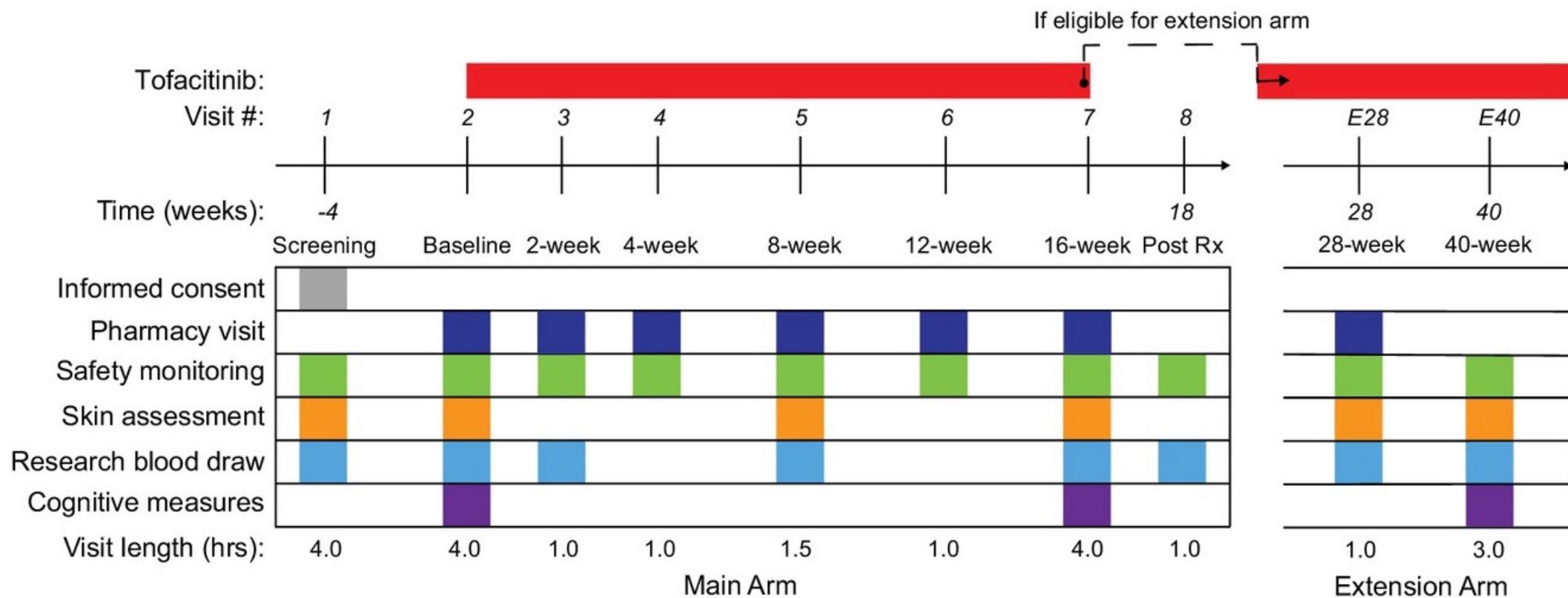
Linda Crnic Institute for Down Syndrome, University of Colorado Anschutz Medical Campus, United States; Department of Pediatrics, Section of Developmental Pediatrics, University of Colorado Anschutz Medical Campus, United States; Department of Dermatology, University of Colorado Anschutz Medical Campus, United States; Department of Pharmacology, University of Colorado Anschutz Medical Campus, United States; Department of Internal Medicine, University of Colorado Anschutz Medical Campus, United States; Department of Pediatrics, Section of Developmental Biology, University of Colorado Anschutz Medical Campus, United States; Department of Psychiatry, Child and Adolescent Division, University of Colorado Anschutz Medical Campus, United States; Department of Human Development and Family Studies, Colorado State University, United States

Dec 31, 2024 • <https://doi.org/10.7554/eLife.99323.3>

Preliminary results for first 10 participants  
Stay tuned for publication of full results from this clinical trial

# The first clinical trial of a JAK inhibitor in Down syndrome (NCT04246372)

Eligibility: select autoimmune skin conditions  
Primary Endpoints: Safety, Change in IFN scores

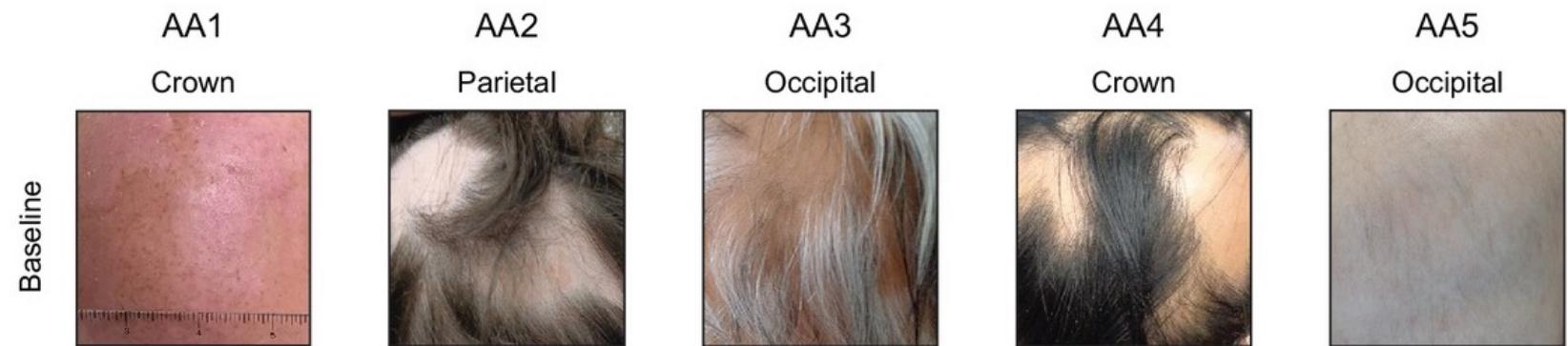
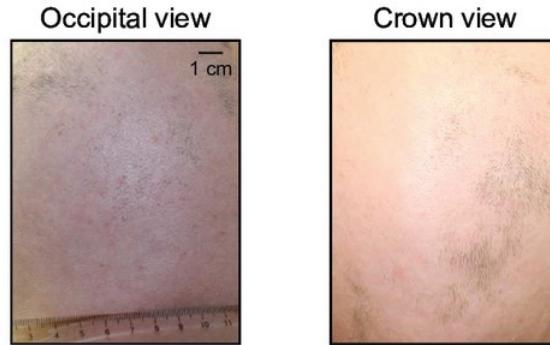


# Tofacitinib improves immune skin pathologies in Down syndrome

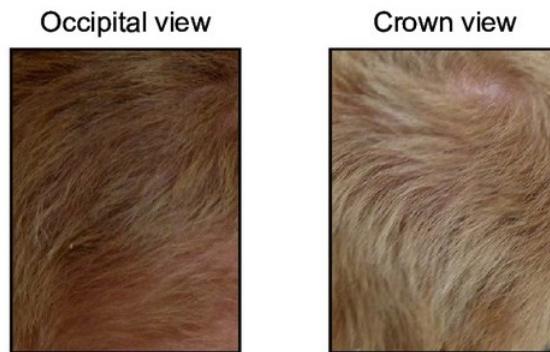
d

Alopecia areata - AA6

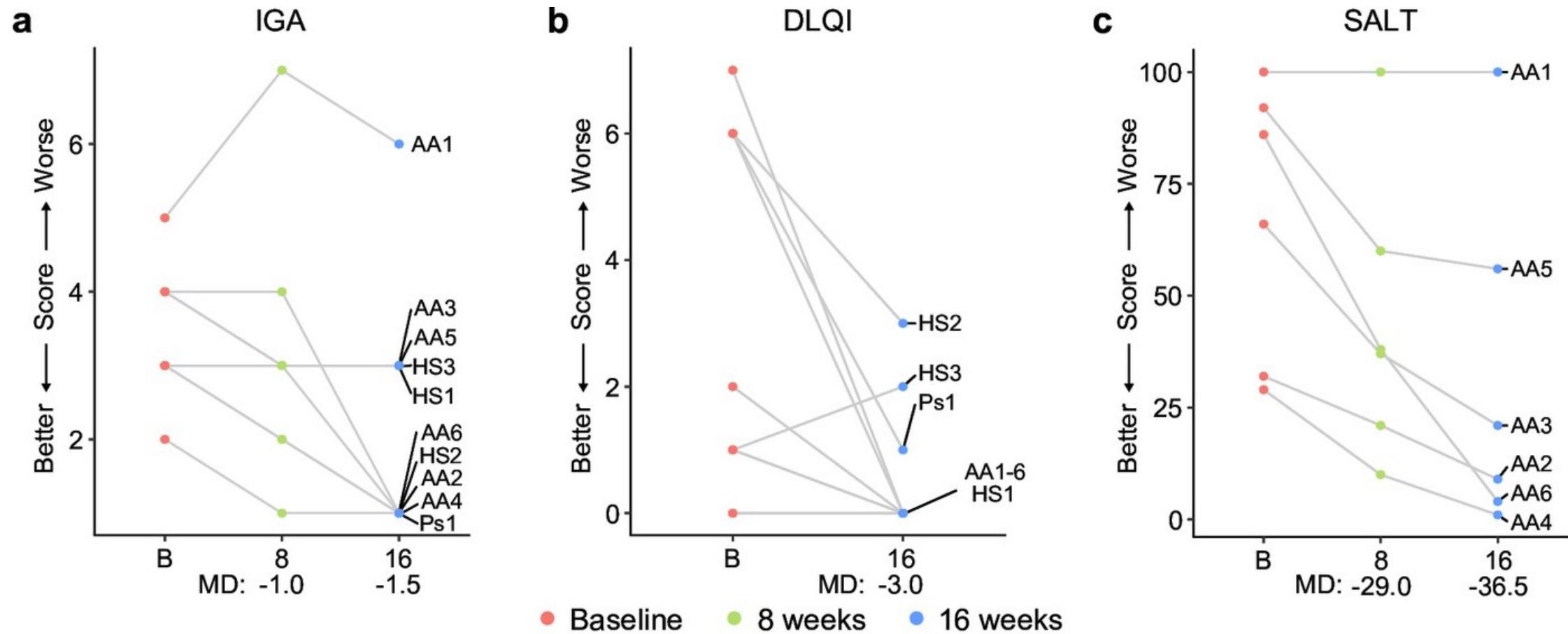
Baseline - SALT=86



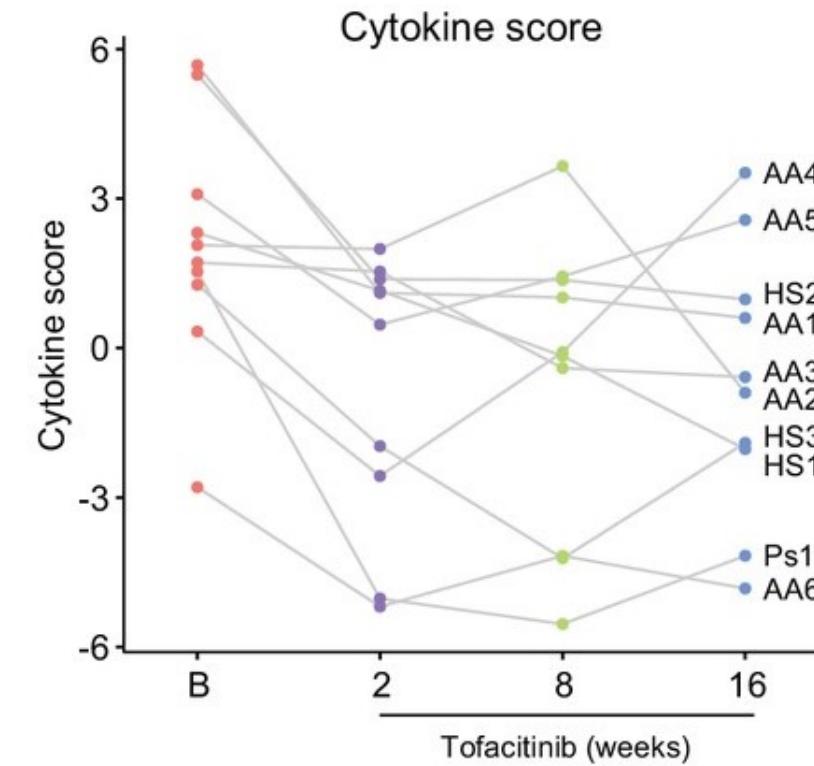
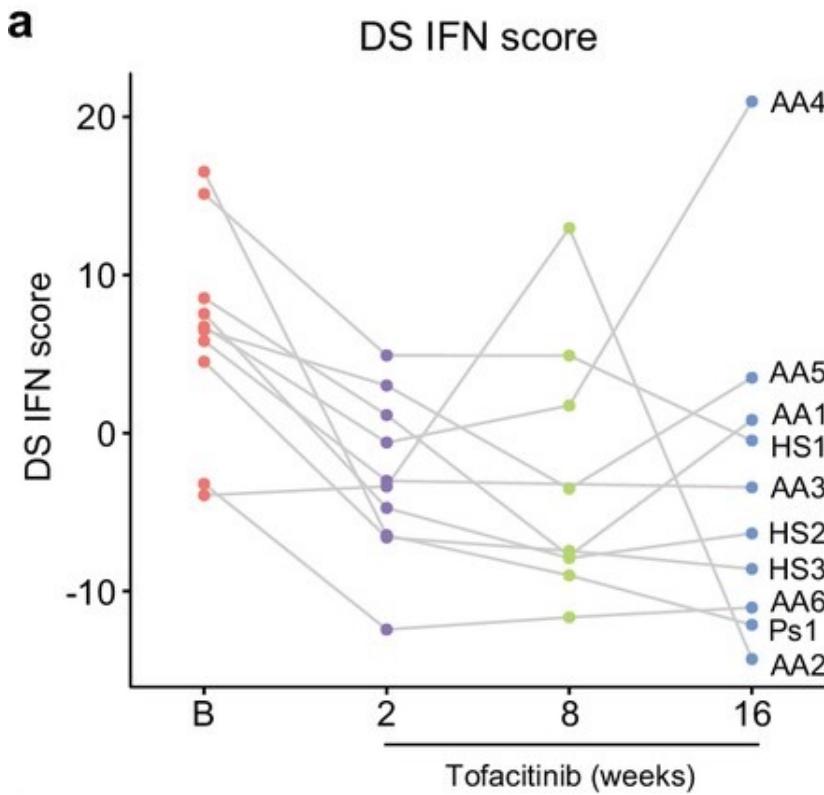
Week 16 - SALT=4



# Tofacitinib improves immune skin pathologies in Down syndrome



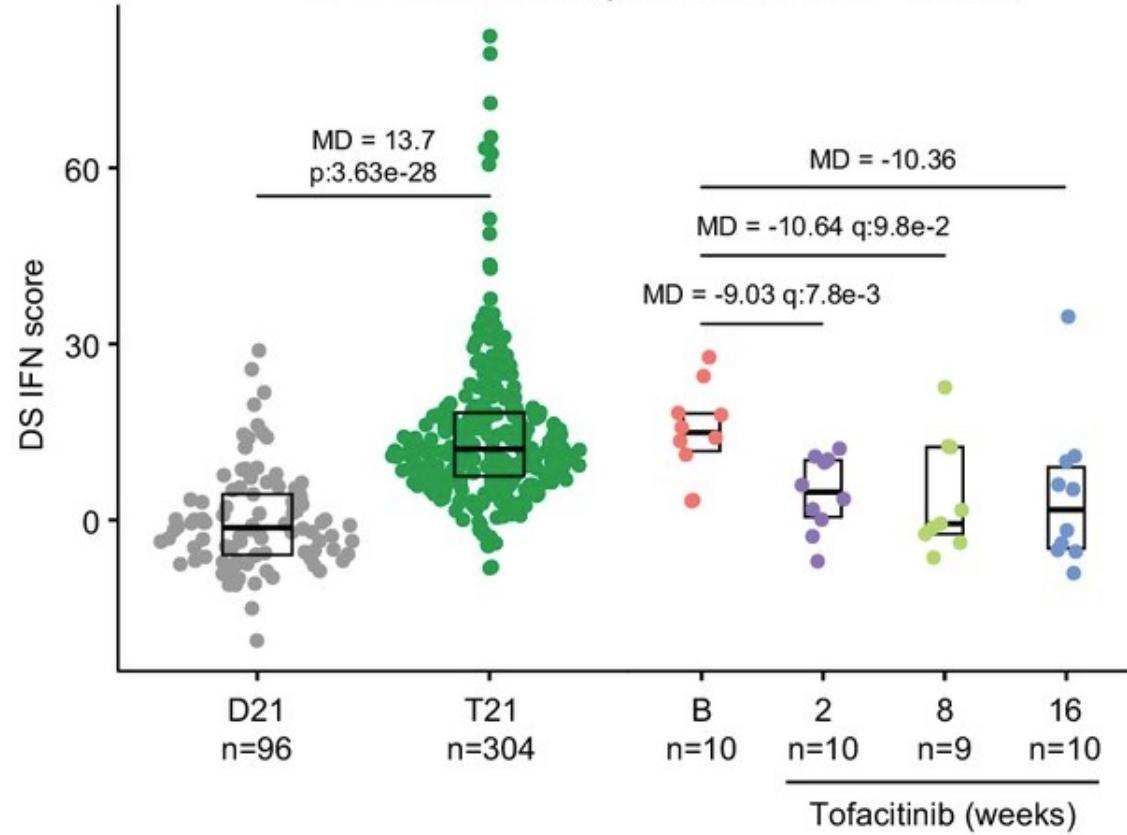
# Tofacitinib reduces IFN scores and hypercytokinemia in Down syndrome



# Tofacitinib reduces IFN scores and hypercytokinemia in Down syndrome

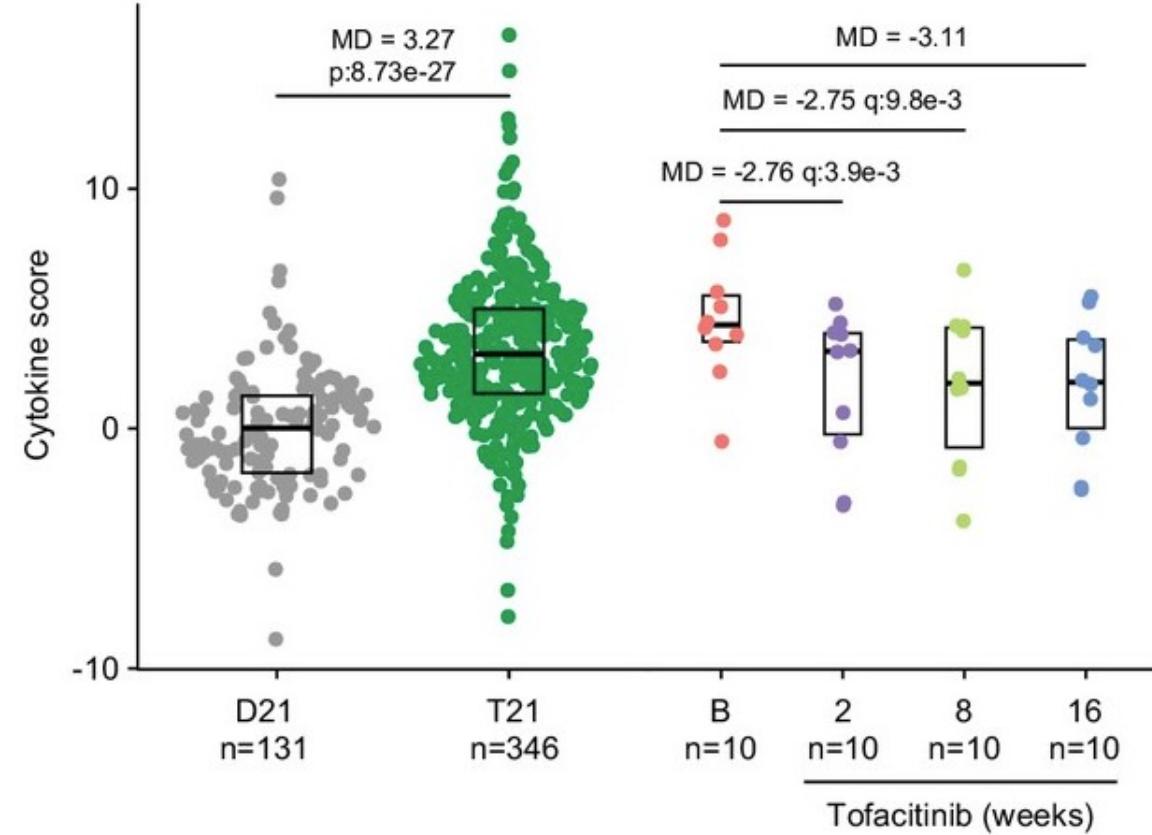
a

IFN score: comparison to HTP cohort



d

Cytokine score: comparison to HTP cohort



# What else can HTP datasets reveal about the pathophysiology of Down syndrome?

> *Cell Rep.* 2022 Dec 27;41(13):111883. doi: 10.1016/j.celrep.2022.111883.

## IGF1 deficiency integrates stunted growth and neurodegeneration in Down syndrome

Paula Araya <sup>1</sup>, Kohl T Kinning <sup>2</sup>, Christina Coughlan <sup>3</sup>, Keith P Smith <sup>1</sup>, Ross E Granrath <sup>1</sup>, Belinda A Enriquez-Estrada <sup>1</sup>, Kayleigh Worek <sup>1</sup>, Kelly D Sullivan <sup>4</sup>, Angela L Rachubinski <sup>5</sup>, Kristine Wolter-Warmerdam <sup>6</sup>, Francis Hickey <sup>6</sup>, Matthew D Galbraith <sup>2</sup>, Huntington Potter <sup>3</sup>, Joaquin M Espinosa <sup>7</sup>

Affiliations + expand

PMID: 36577365 PMCID: [PMC9876612](#) DOI: [10.1016/j.celrep.2022.111883](https://doi.org/10.1016/j.celrep.2022.111883)

> *Cell Rep.* 2024 Aug 27;43(8):114599. doi: 10.1016/j.celrep.2024.114599. Epub 2024 Aug 8.

## Multimodal analysis of dysregulated heme metabolism, hypoxic signaling, and stress erythropoiesis in Down syndrome

Micah G Donovan <sup>1</sup>, Angela L Rachubinski <sup>2</sup>, Keith P Smith <sup>3</sup>, Paula Araya <sup>3</sup>, Katherine A Waugh <sup>4</sup>, Belinda Enriquez-Estrada <sup>3</sup>, Eleanor C Britton <sup>3</sup>, Hannah R Lyford <sup>3</sup>, Ross E Granrath <sup>3</sup>, Kyndal A Schade <sup>3</sup>, Kohl T Kinning <sup>3</sup>, Neetha Paul Eduthan <sup>3</sup>, Kelly D Sullivan <sup>5</sup>, Matthew D Galbraith <sup>6</sup>, Joaquin M Espinosa <sup>7</sup>

Affiliations + expand

PMID: 39120971 PMCID: [PMC11479675](#) DOI: [10.1016/j.celrep.2024.114599](https://doi.org/10.1016/j.celrep.2024.114599)

> *Nat Commun.* 2024 Jun 28;15(1):5473. doi: 10.1038/s41467-024-49781-1.

## Variegated overexpression of chromosome 21 genes reveals molecular and immune subtypes of Down syndrome

Micah G Donovan <sup># 1</sup>, Neetha P Eduthan <sup># 1</sup>, Keith P Smith <sup>1</sup>, Eleanor C Britton <sup>1</sup>, Hannah R Lyford <sup>1</sup>, Paula Araya <sup>1</sup>, Ross E Granrath <sup>1</sup>, Katherine A Waugh <sup>1 2</sup>, Belinda Enriquez Estrada <sup>1</sup>, Angela L Rachubinski <sup>1 3</sup>, Kelly D Sullivan <sup>1 4</sup>, Matthew D Galbraith <sup>5 6</sup>, Joaquin M Espinosa <sup>7 8</sup>

Affiliations + expand

PMID: 38942750 PMCID: [PMC11213896](#) DOI: [10.1038/s41467-024-49781-1](https://doi.org/10.1038/s41467-024-49781-1)

> *Sci Adv.* 2024 Dec 13;10(50):eadq3073. doi: 10.1126/sciadv.adq3073. Epub 2024 Dec 13.

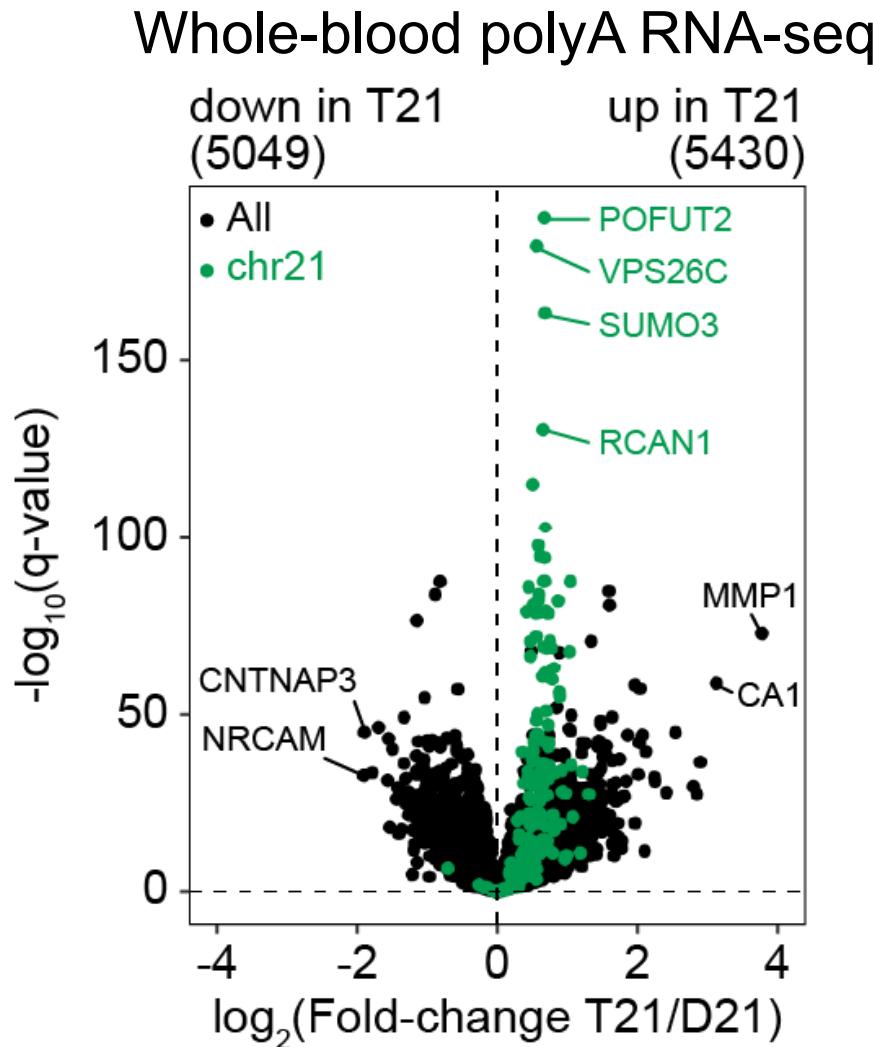
## Integrated analysis of immunometabolic interactions in Down syndrome

Lucas A Gillenwater <sup>1 2 3</sup>, Matthew D Galbraith <sup>1 2</sup>, Angela L Rachubinski <sup>1 4</sup>, Neetha Paul Eduthan <sup>1</sup>, Kelly D Sullivan <sup>1 5</sup>, Joaquin M Espinosa <sup>1 2</sup>, James C Costello <sup>1 2 3</sup>

Affiliations + expand

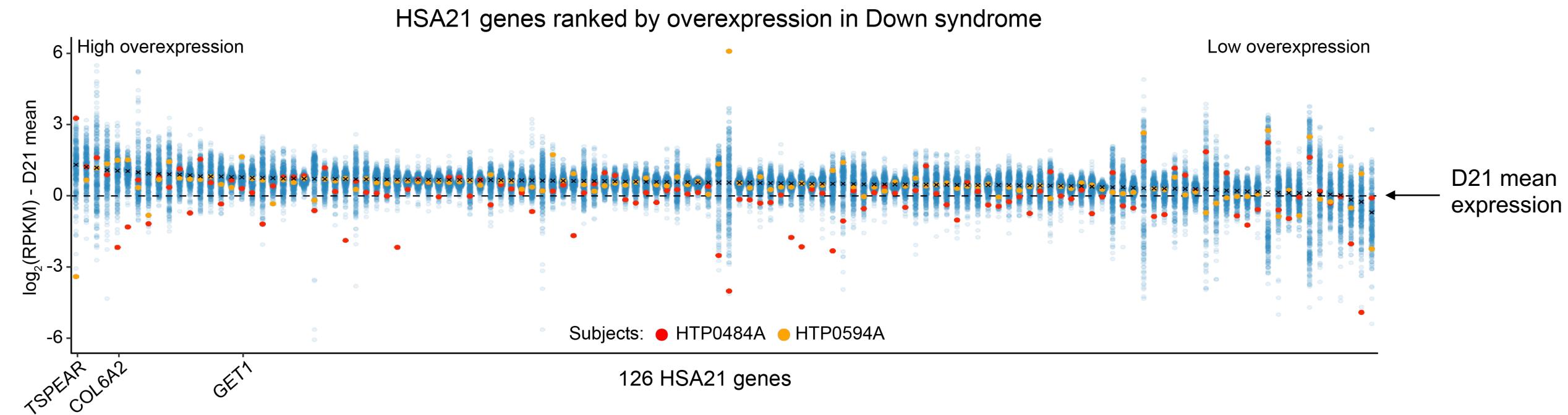
PMID: 39671500 PMCID: [PMC11641111](#) DOI: [10.1126/sciadv.adq3073](https://doi.org/10.1126/sciadv.adq3073)

# On average, HSA21 genes are overexpressed ~1.5-fold in Down syndrome



# Is there variability in chromosome 21 gene overexpression among individuals with Down syndrome?

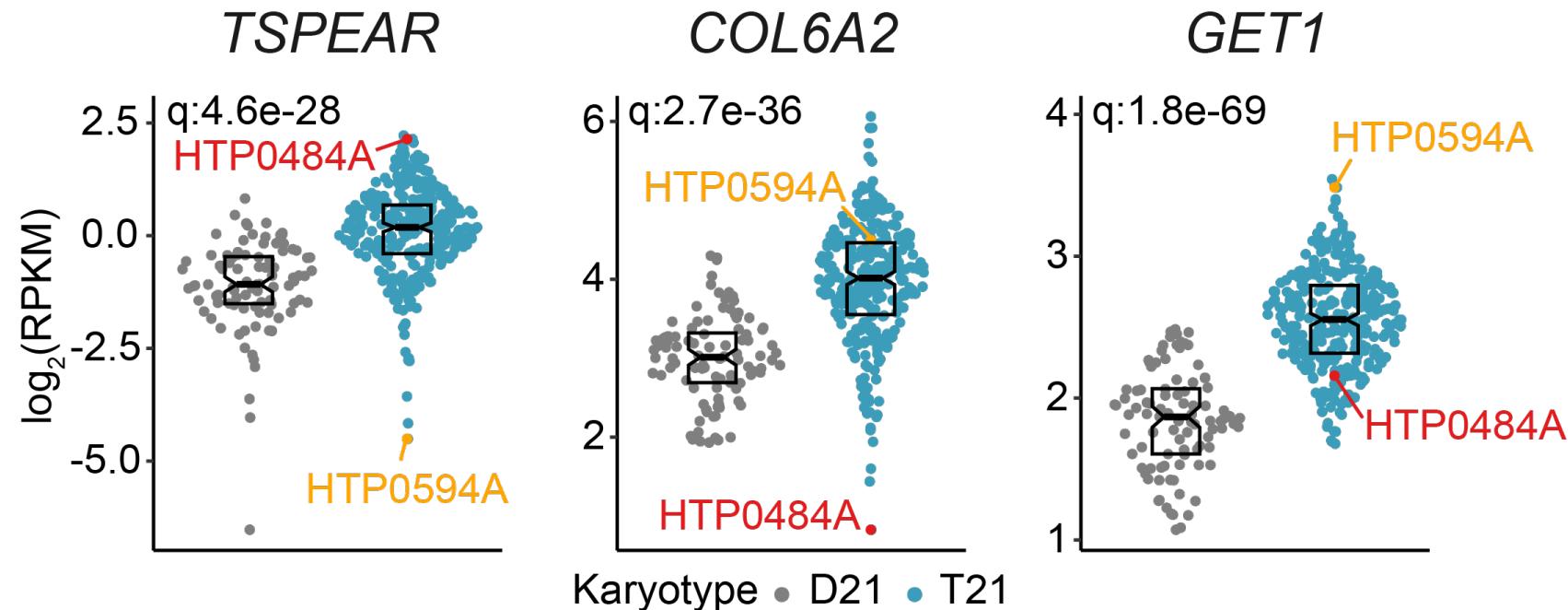
HSA21 genes show a wide range of overexpression relative to euploid controls



Not all individuals with Down syndrome overexpress all HSA21 genes

# Is there variability in chromosome 21 gene overexpression among individuals with Down syndrome?

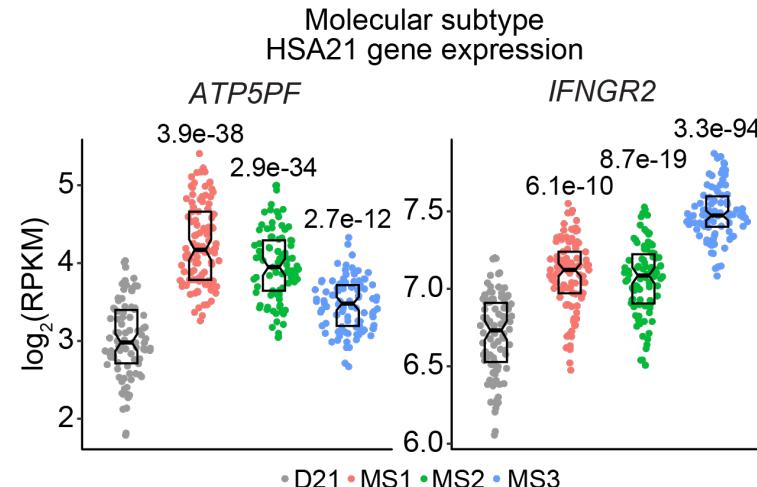
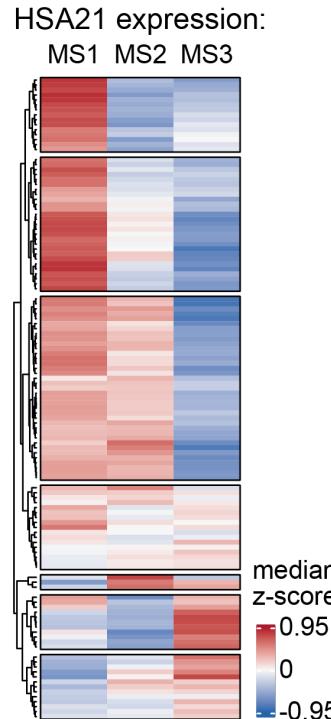
A **5-year-old boy** is the top overexpressor of *TSPEAR*, but the lowest expressor of *COL6A2*



A **30-year-old man** is among the top overexpressors of *GET1*, but the lowest expressor of *TSPEAR*

# Are there subtypes of individuals with trisomy 21 based on chromosome 21 gene expression?

Consensus clustering of HSA21 expression defines three subtypes among individuals with T21



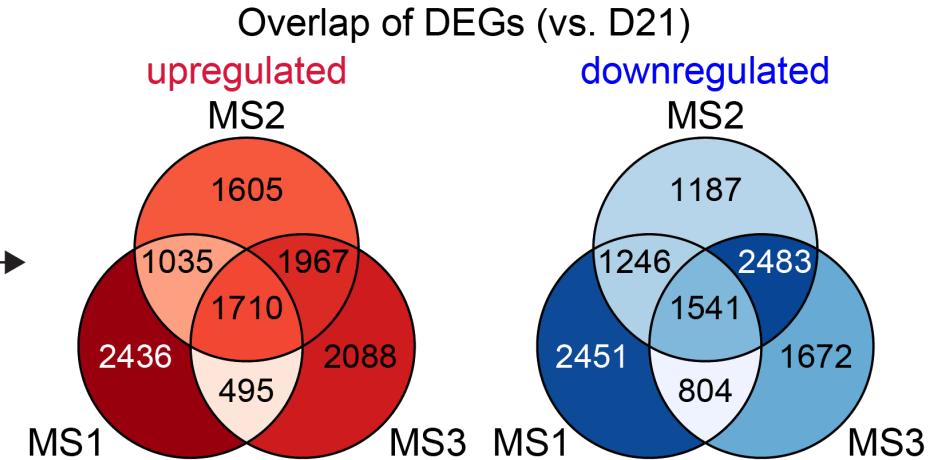
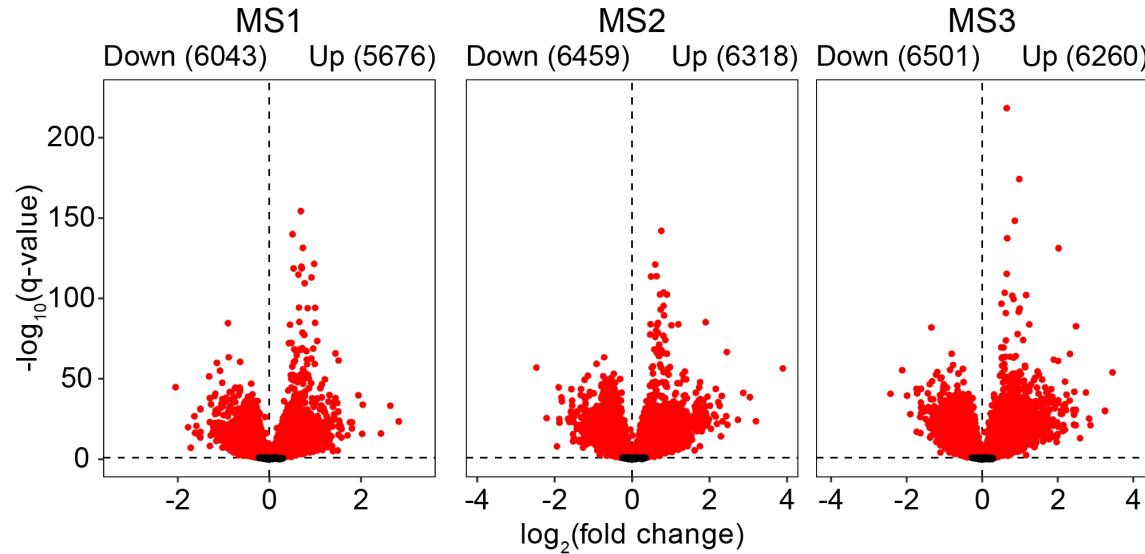
	Molecular subtype demographics		
	MS1	MS2	MS3
<b>Sex (n, %)</b>			
Male	57 (53.3)	52 (54.7)	54 (52.9)
<b>Age (years)</b>			
Median	22.9	24.4	22.4
Range	1.6-56.7	2.7-57.6	3.5-55.1
Std. dev.	13.2	11.4	11.3
<b>BMI (<math>\text{kg}/\text{m}^2</math>)</b>			
Median	25.9	28.5	27.6
Range	14.8-48.1	16.2-62.3	14.3-50.0
Std. dev.	8.81	7.63	7.43

All subtypes overexpress most HSA21 genes on average, but are distinguished by heightened expression of distinct genes

# Do these subtypes of trisomy 21 display unique global **transcriptomic** changes?

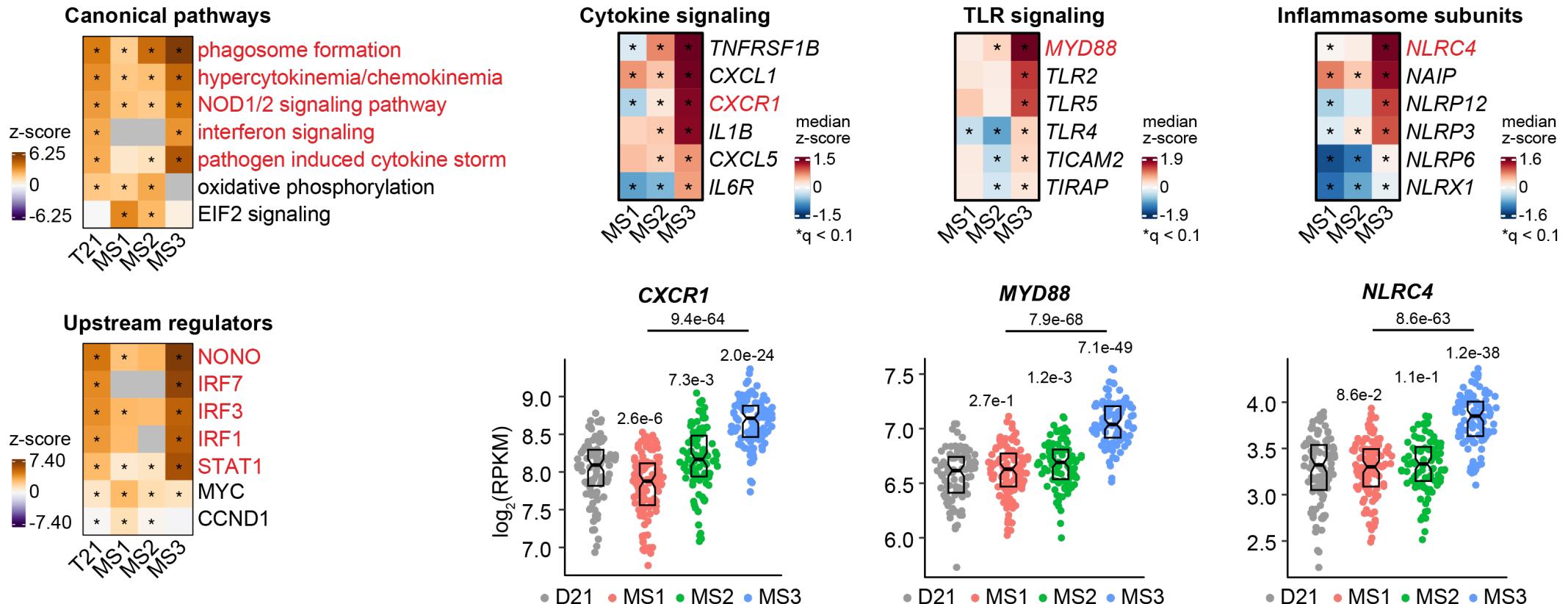
Most transcriptomic alterations in each subtype are specific to that subtype

T21 subtypes differential expression vs. D21:



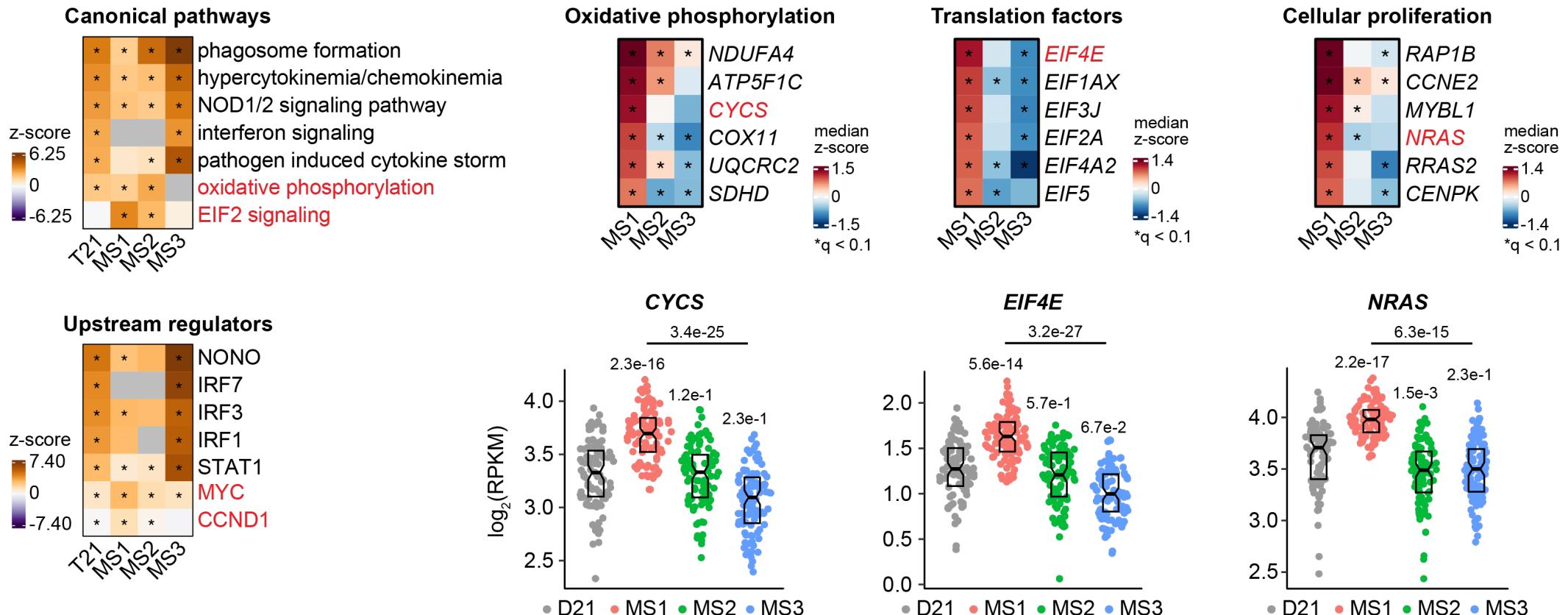
# Do these subtypes of trisomy 21 display unique global **transcriptomic** changes?

**Molecular subtype 3 displays the most prominent activation of immune and inflammatory signatures**



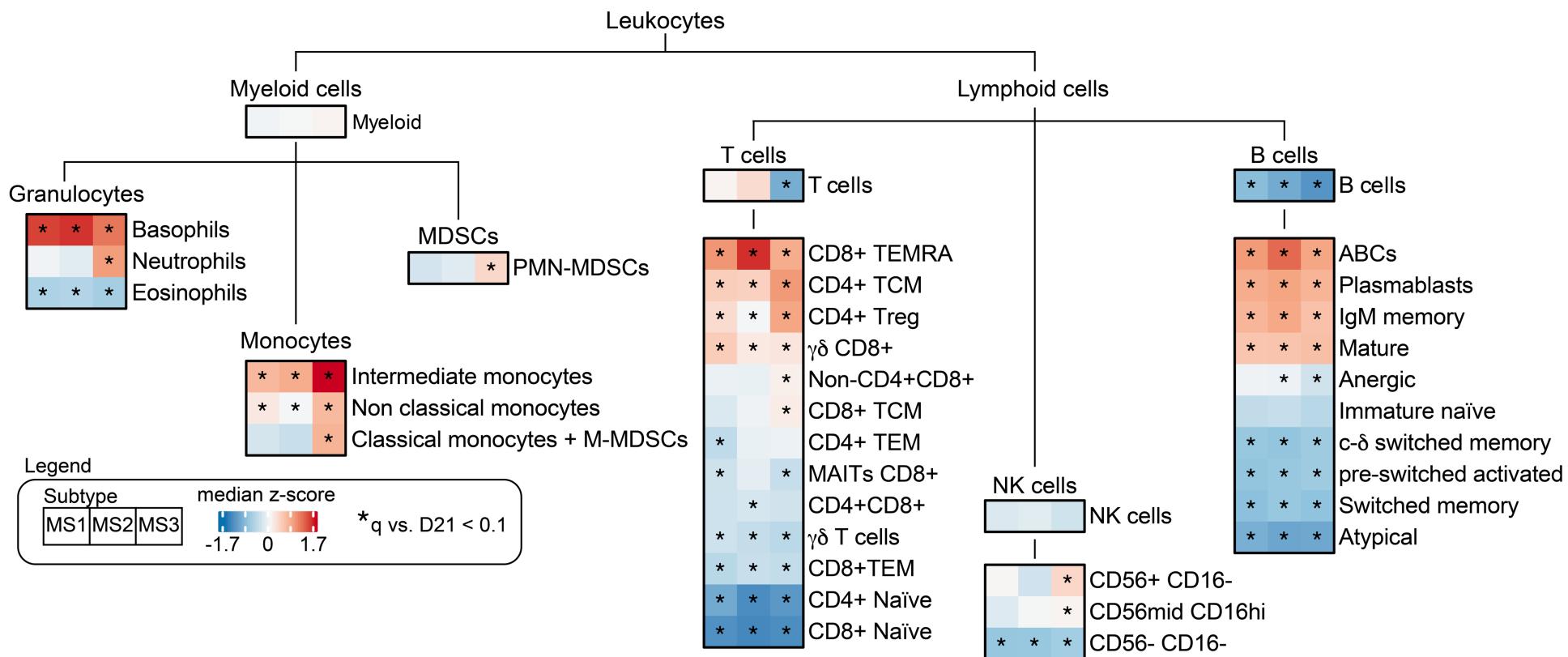
# Do these subtypes of trisomy 21 display unique global **transcriptomic** changes?

Molecular subtype 1 displays signatures of metabolism, translation and cellular proliferation



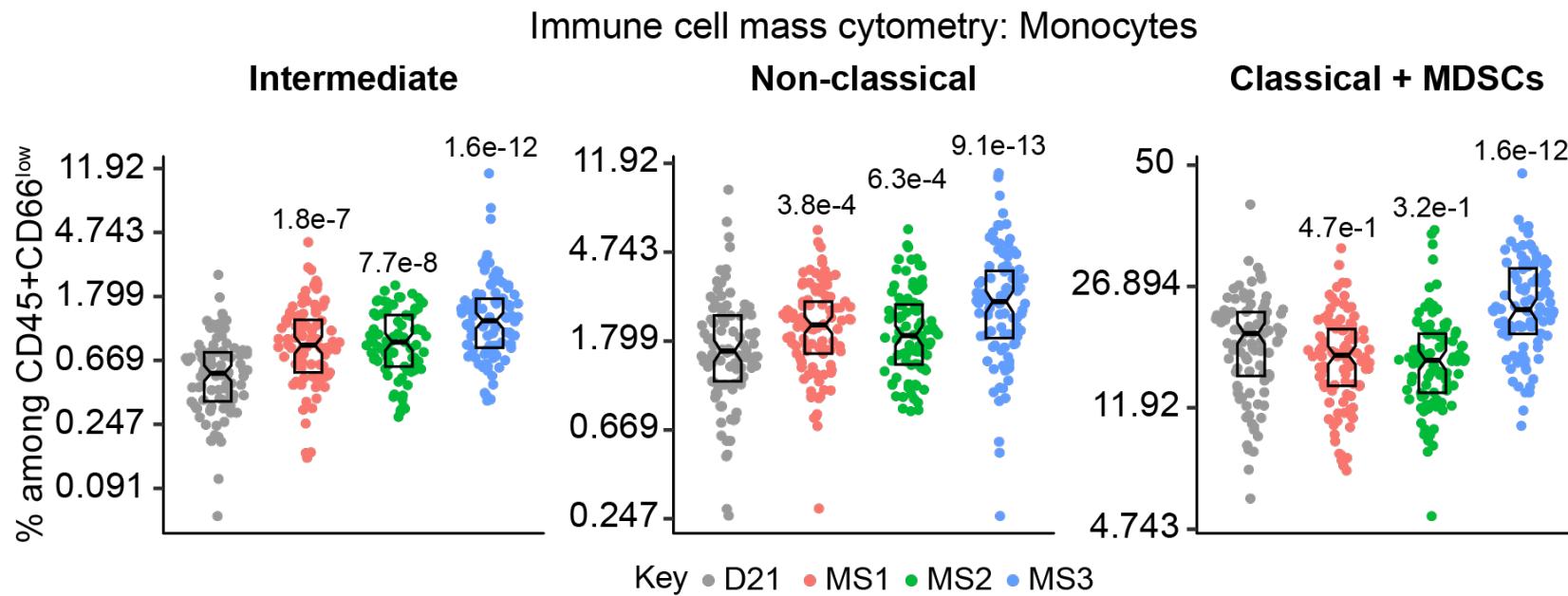
# Do these subtypes of trisomy 21 display unique immune cell profiles?

Immune cell profiles show common patterns punctuated by important distinctions



# Do these subtypes of trisomy 21 display unique immune cell profiles?

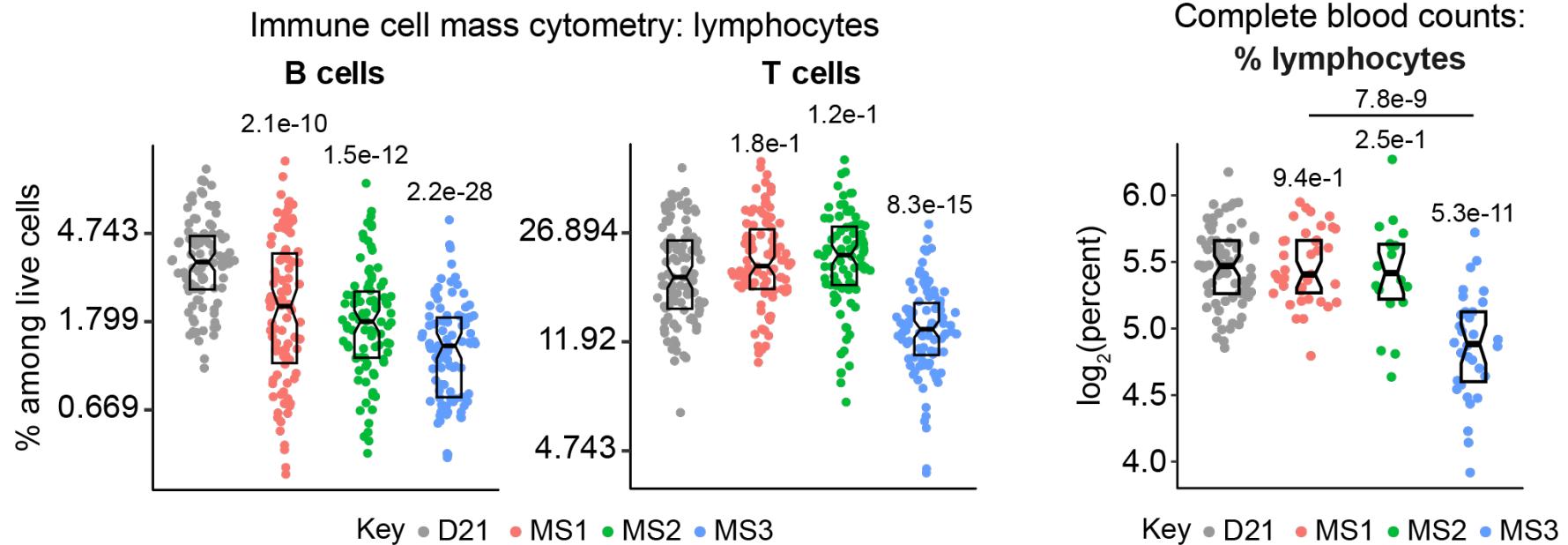
**Molecular subtype 3 has the most prominent elevation of pro-inflammatory monocytes (intermediate, non-classical)**



**Molecular subtype 3 alone shows elevation of classical monocytes**

# Do these subtypes of trisomy 21 display unique immune cell profiles?

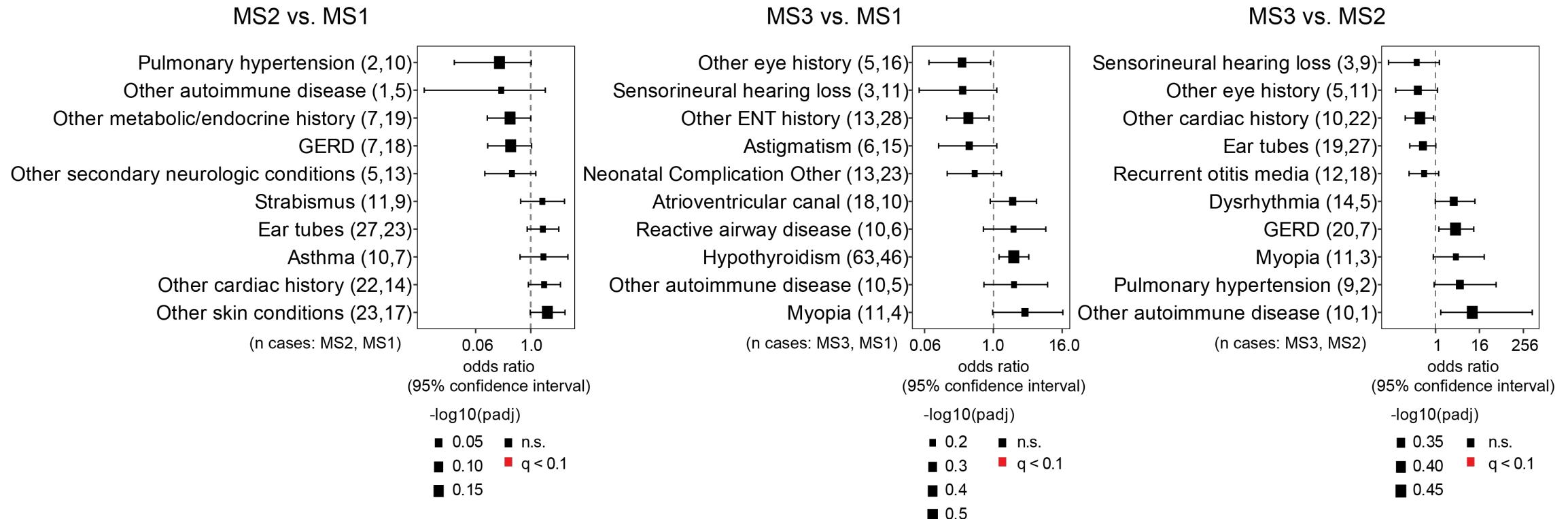
Molecular subtype 3 exhibits pronounced B cell lymphopenia and distinct T cell lymphopenia



This subtype-specific lymphopenia is also detected by clinical complete blood count

# Are these subtypes of trisomy 21 associated with distinct co-occurring condition profiles?

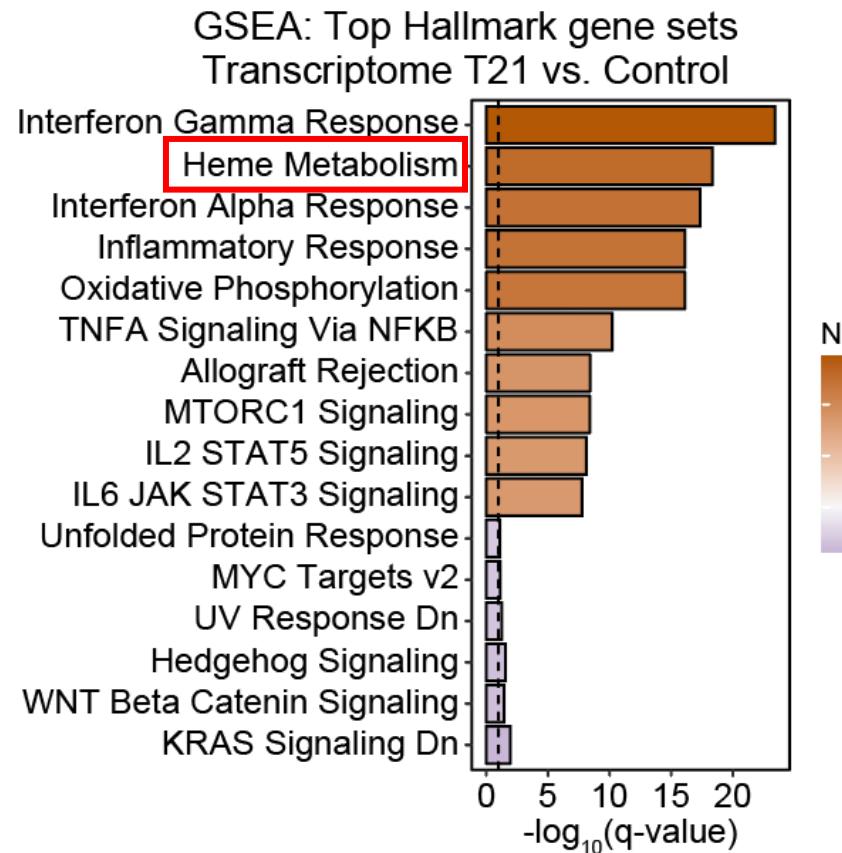
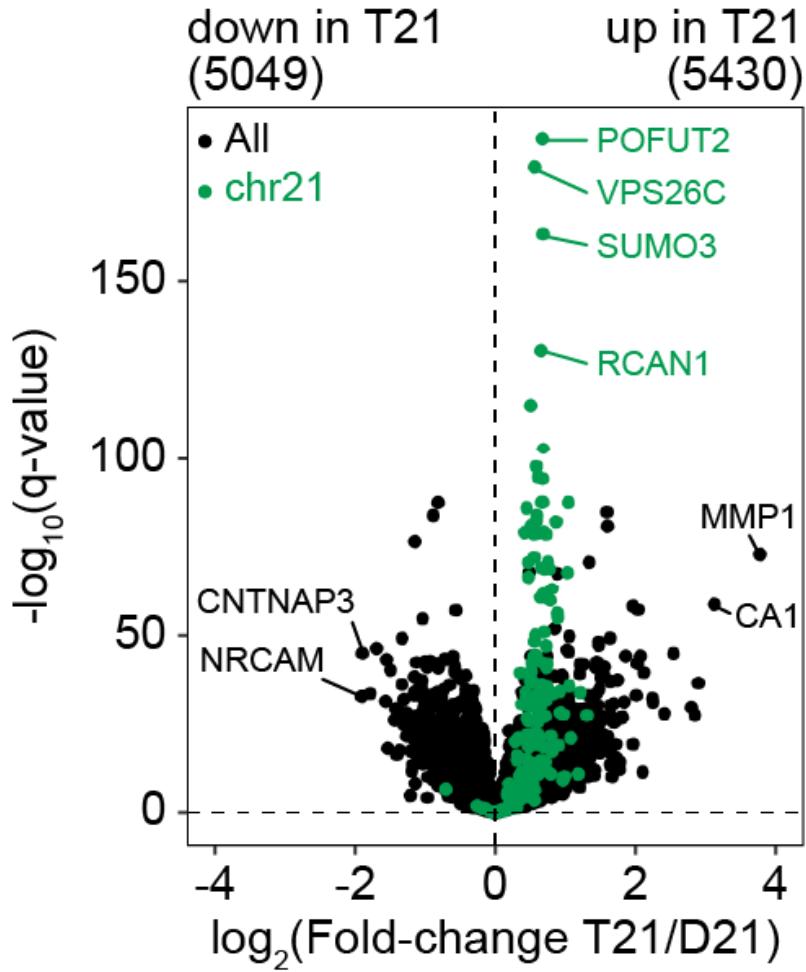
Prevalence of co-occurring conditions by molecular subtype



**Some trends but nothing significant with current case numbers and annotations**

# Trisomy 21 causes widespread changes in the transcriptome, proteome, metabolome, and immune cells

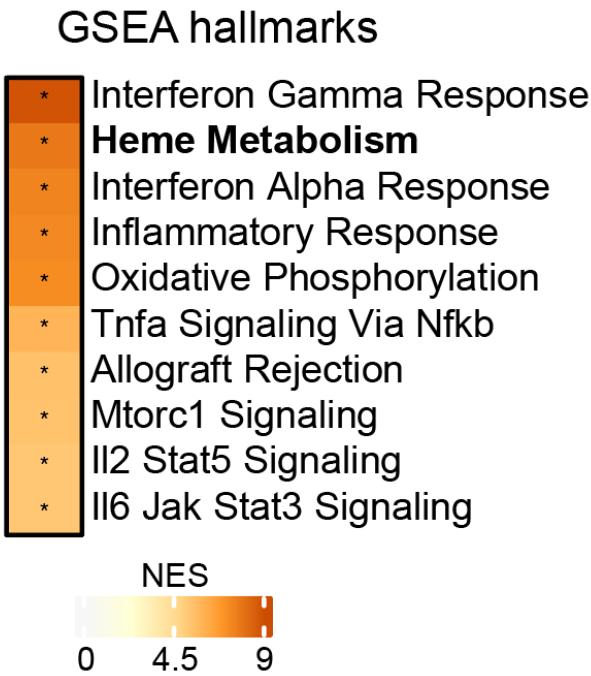
Whole-blood polyA RNA-seq



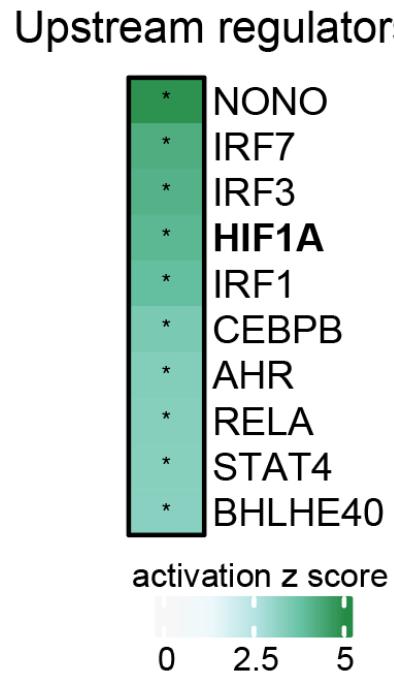
# Signatures of chronic hypoxia in Down syndrome?

Whole blood transcriptome analysis  
304 participants with Down syndrome versus 96 euploid controls

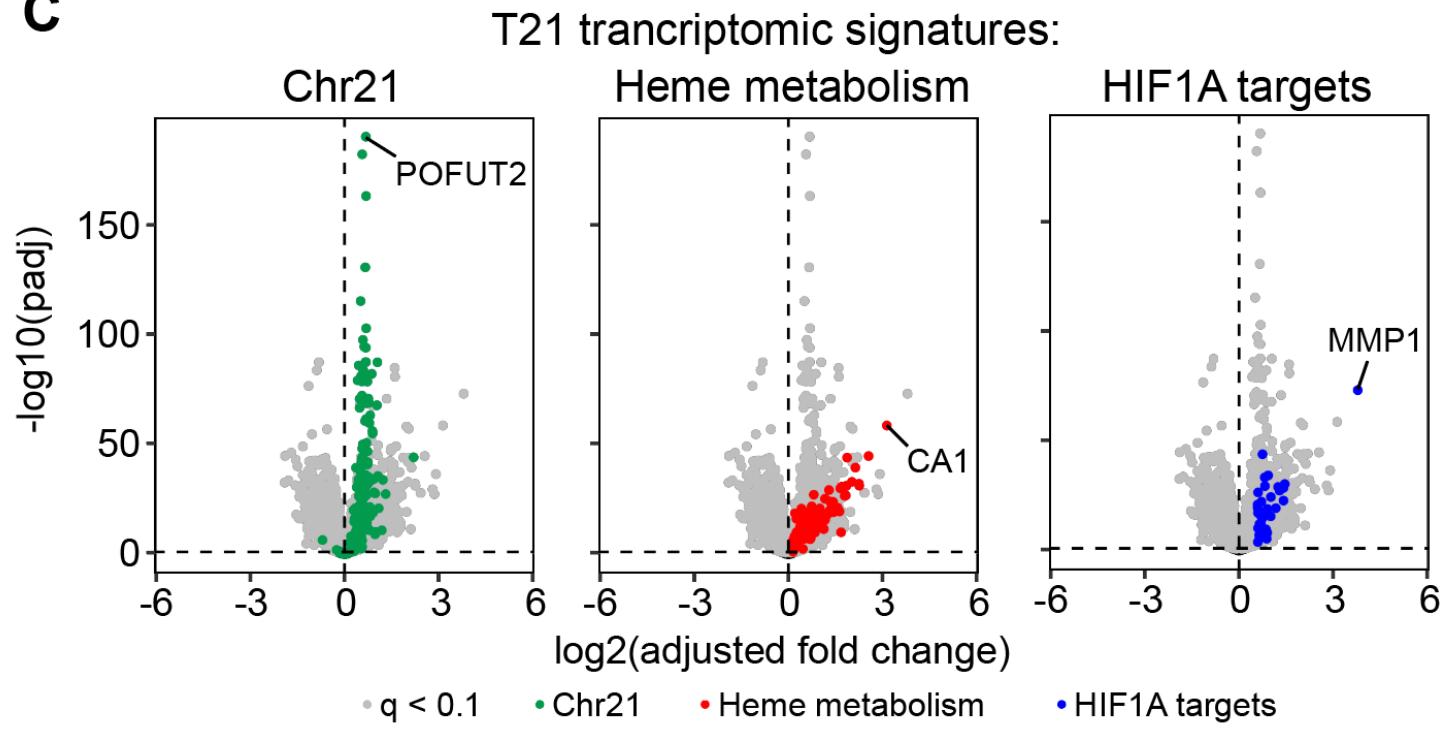
A



B

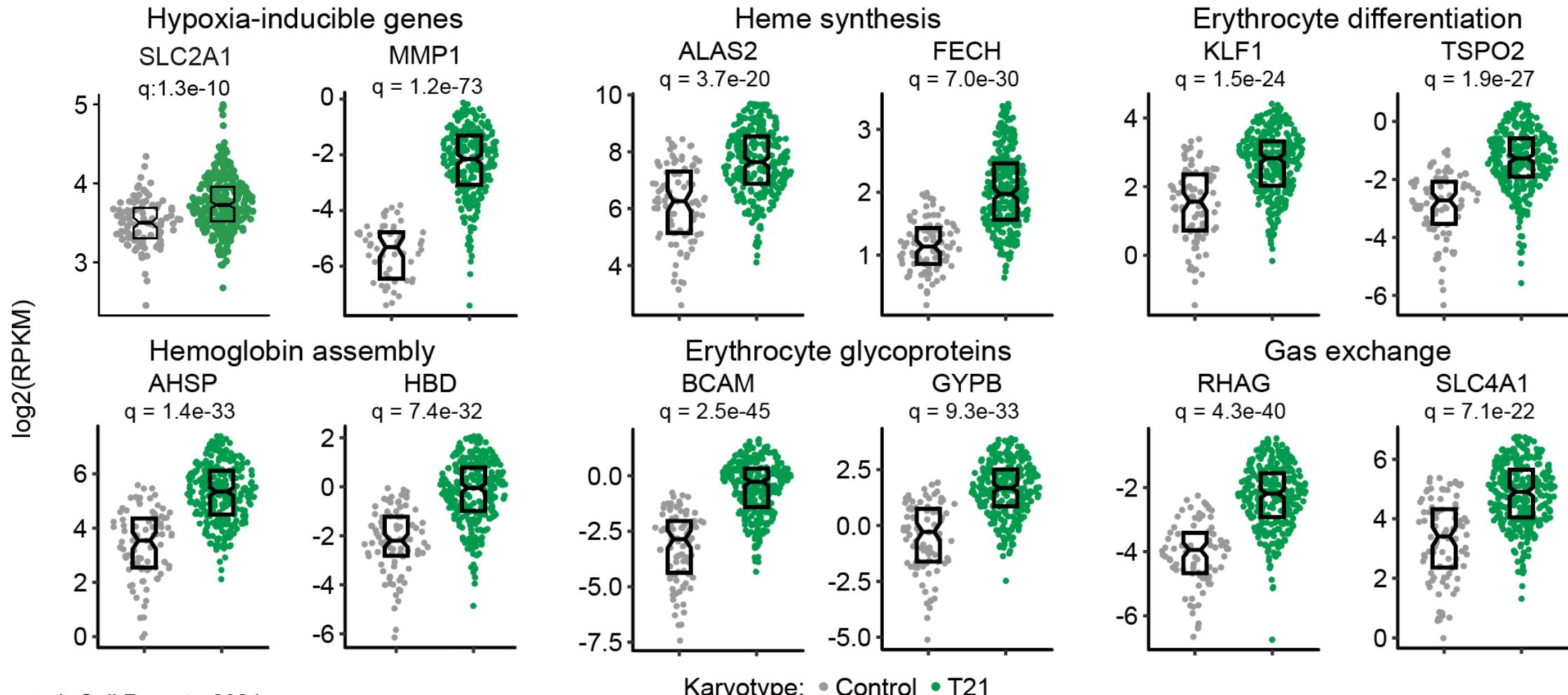


C



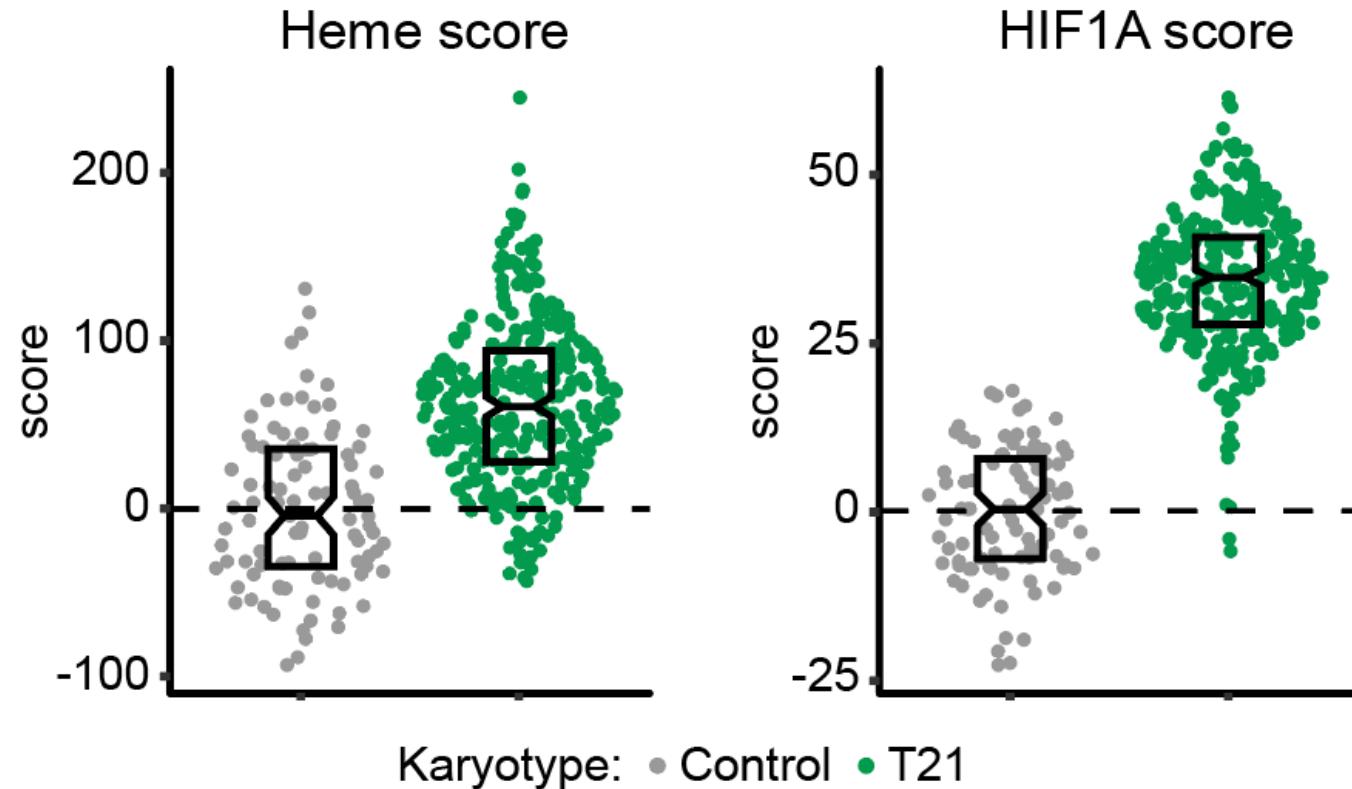
# Signatures of chronic hypoxia in Down syndrome?

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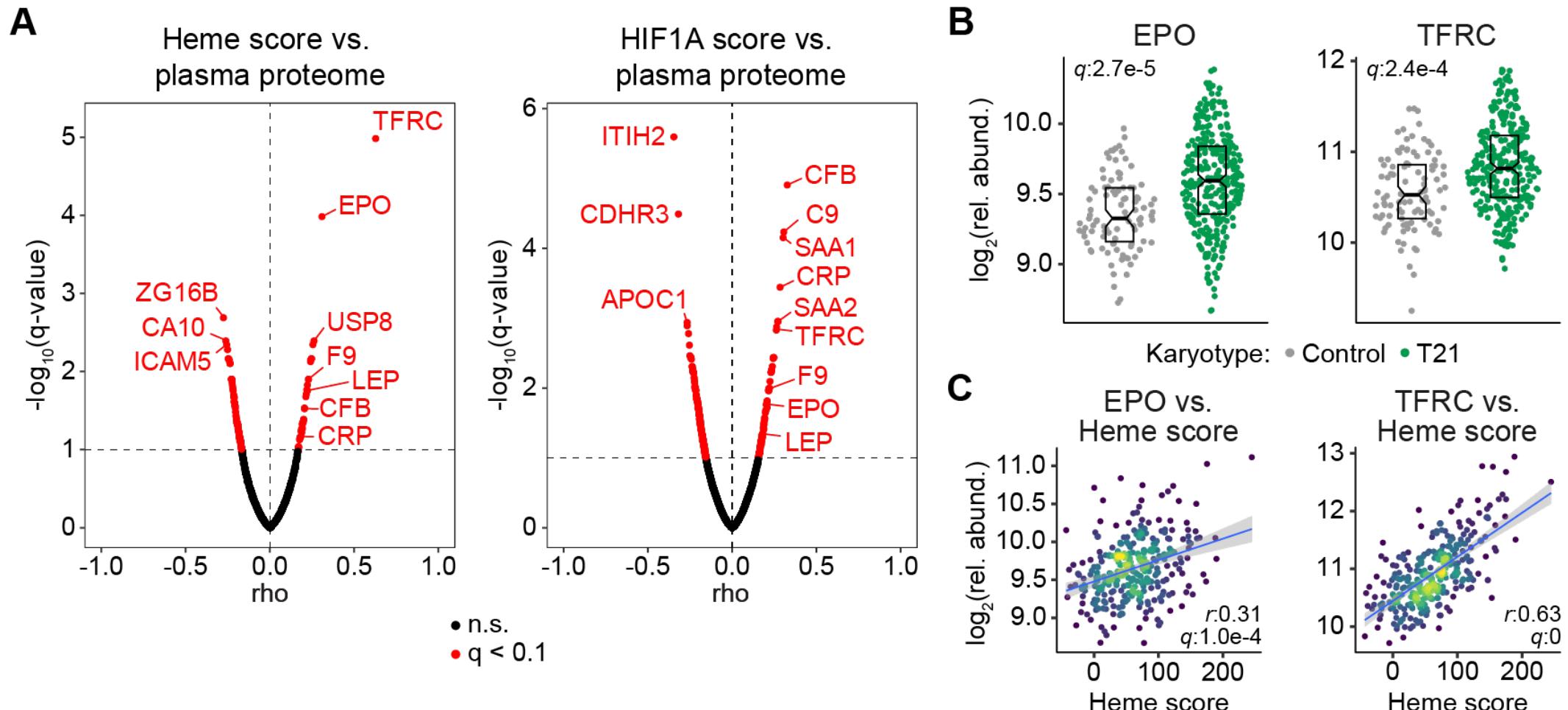


# Polygenic expression scores to study hypoxic signaling

Using gene signatures in the blood to gauge  
the degree of hypoxic signaling among research participants

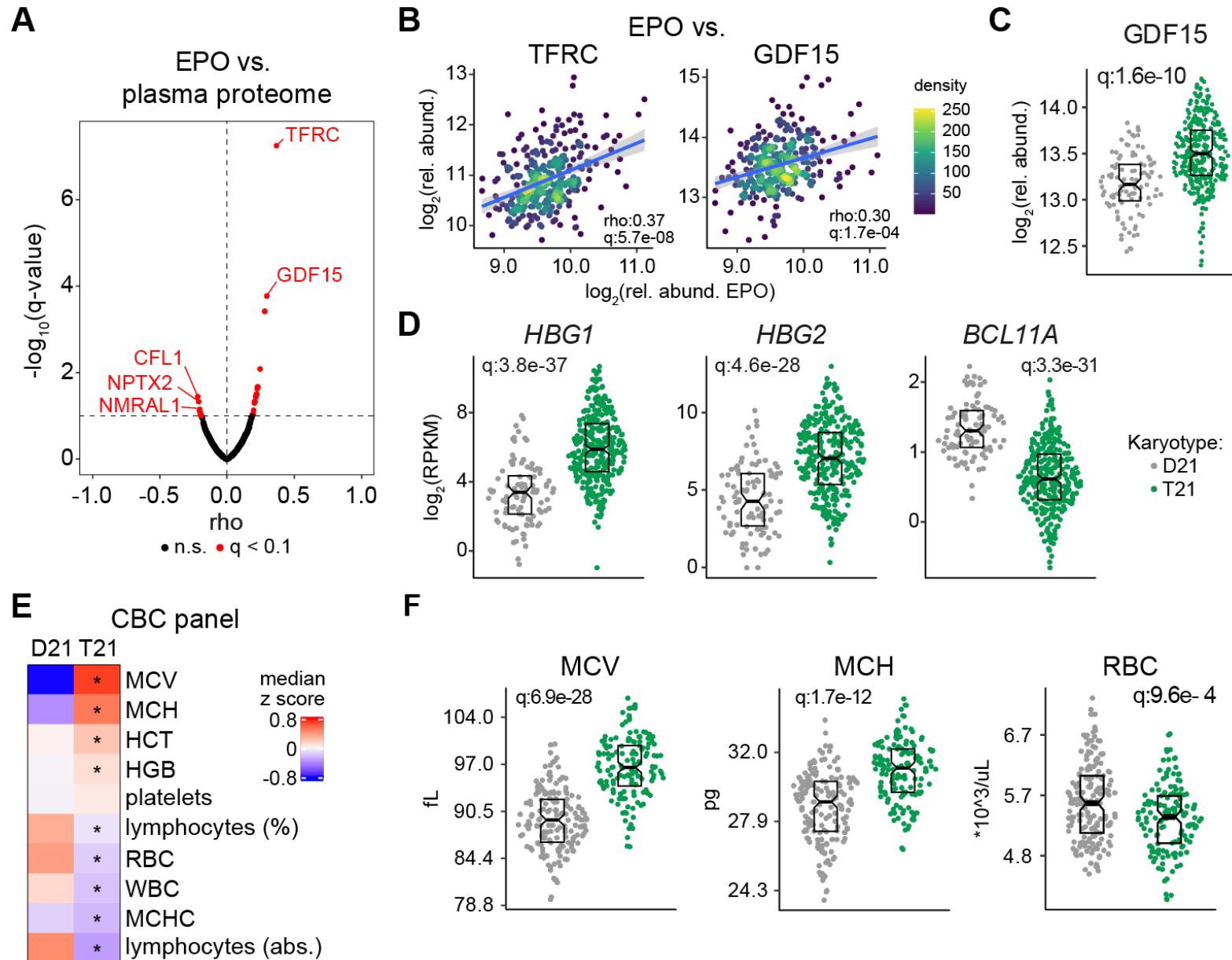


# The power of cross-omics: Which plasma proteins correlate with the Heme metabolism and HIF1A RNA scores?

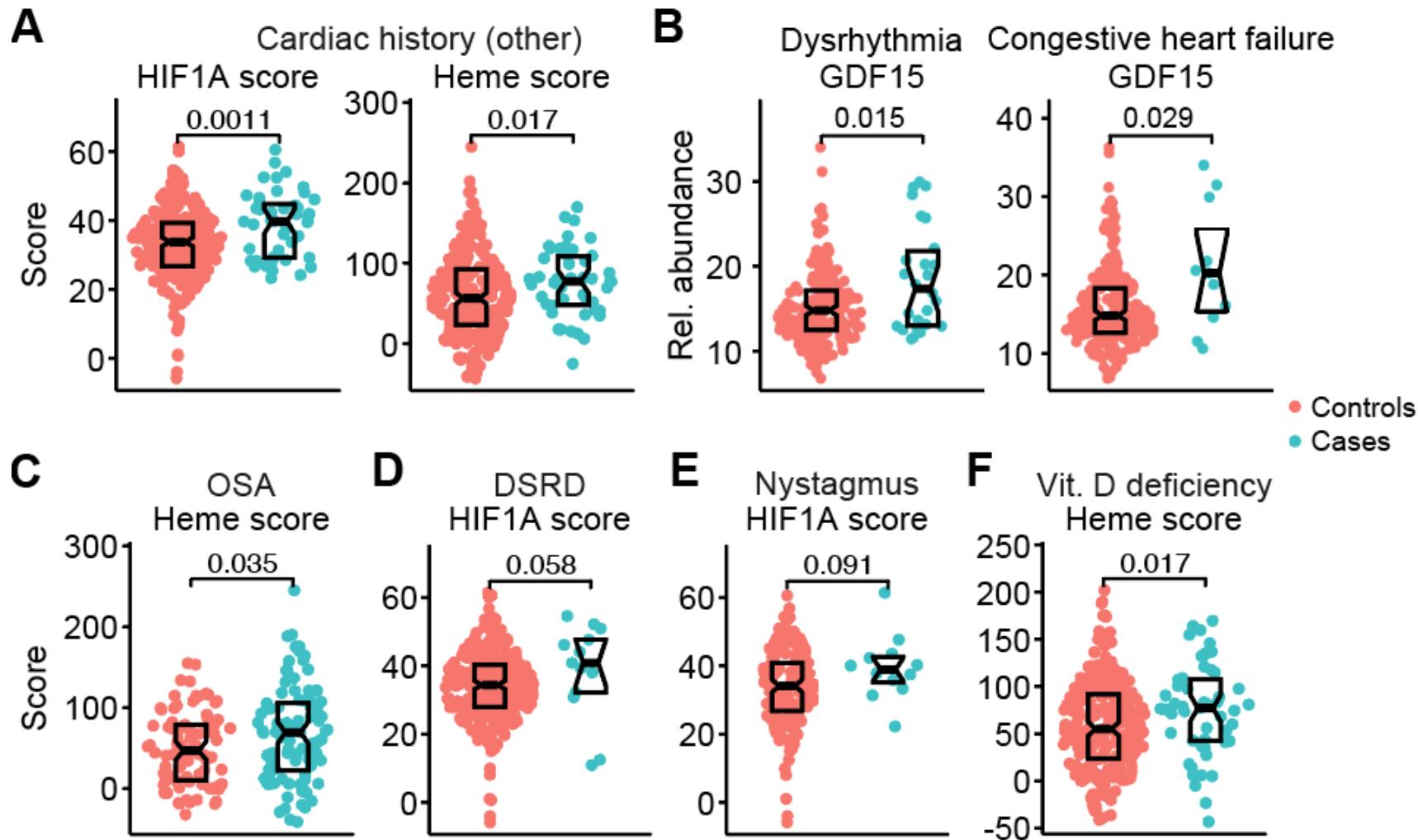


People with Down syndrome tend to have elevated levels of erythropoietin and the transferrin receptor

# People with Down syndrome exhibit signs of stress erythropoiesis



# Elevated HIF1A and Heme scores may be associated with some co-occurring conditions



Definitive analysis will require more detail and greater numbers