IGF1 deficiency in Down syndrome: it's about much more than just height

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GLOBAL DOWN SYNDROME FOUNDATION

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Disclosures

- Provided consulting services to: Elli Lilly and Co., Gilead Sciences Inc., Biohaven, and Perha Pharmaceuticals.
- None of this consulting activity was related to growth hormone or IGF1.
- I do intend to discuss unapproved/investigative uses of commercial products/devices in my presentation.

Quiz time!

On average, people with Down syndrome display greater rates of obesity relative to their peers in the general population:

- ❑ True
- ❑ False

Quiz time!

On average, people with Down syndrome display greater rates of obesity relative to their peers in the general population:

- ✓ True (99% correct answers)
- ❑ False

Quiz time!

On average, people with Down syndrome are heavier relative to their peers in the general population:

- ❑ True
- ❑ False

Quiz time!

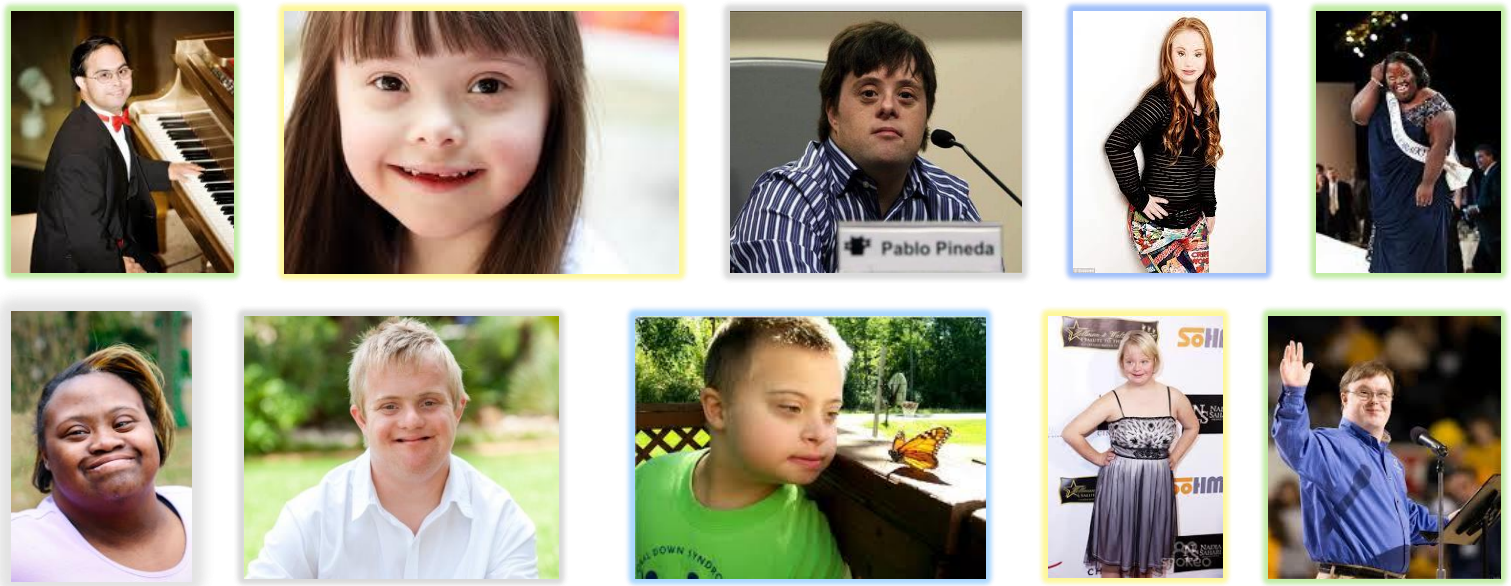
On average, people with Down syndrome are heavier relative to their peers in the general population:

- ✓ True (50%)
- ✓ False (50%)

Oh no, cognitive dissonance!!!

Soundbite #1:

People with Down syndrome display greater rates of obesity not because they are heavier, but because they are shorter.



The Human Trisome Project (HTP)

A large and diverse cohort study with deep clinical data,
a multidimensional biobank, and a public researcher portal

More than **1150** participants recruited since 2016

www.trisome.org

Thousands of datasets generated

1100+ Clinical histories

500+ Metabolomes

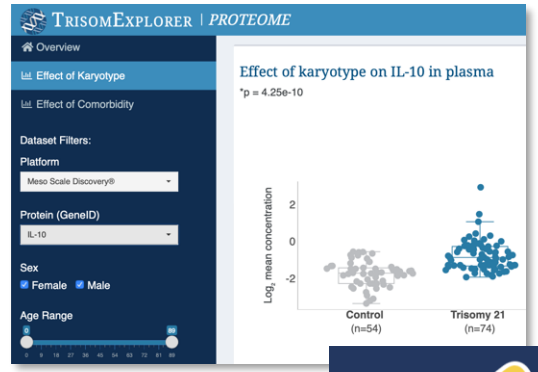
500+ Genomes

400+ Immune maps

650+ Transcriptomes

500+ Microbiomes

TRISOMEXPLORER



INCLUDE Data Hub

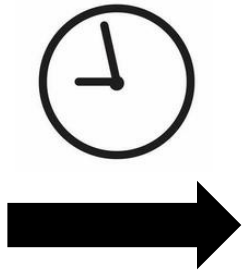
40+ Projects supported

25+ Papers published / under review

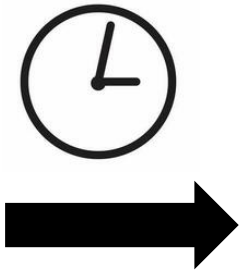
A multidimensional analysis of development and ageing in Down syndrome

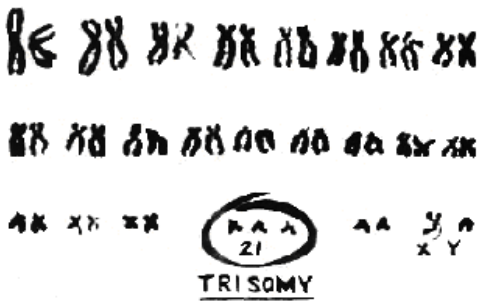
Down syndrome is a condition of delays and accelerations

slower



faster

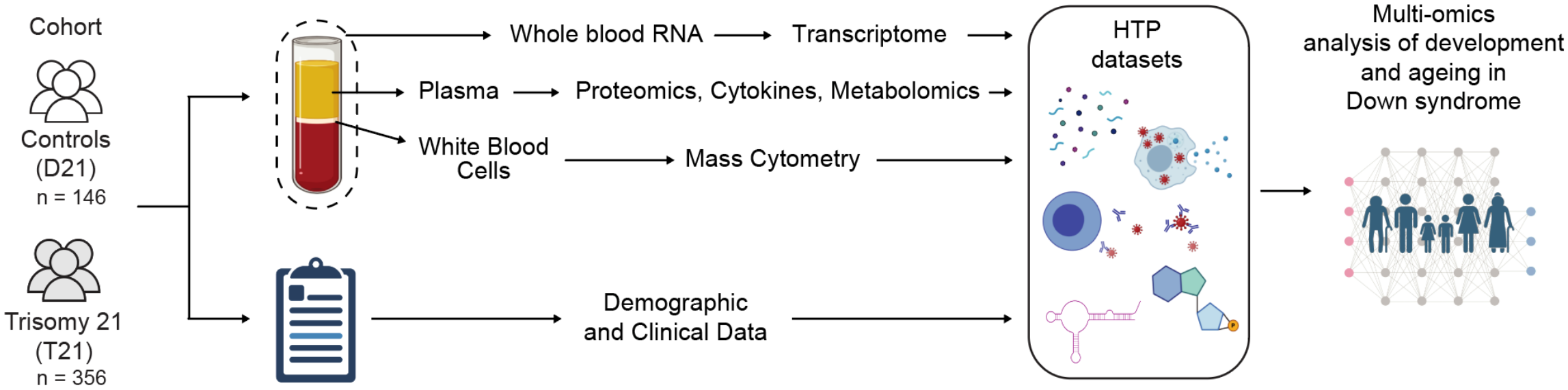




What is the interplay between the developmental and clinical hallmarks of Down syndrome?

A ‘multi-omics’ analysis of development and ageing in Down syndrome

500+ research participants, ages 0.6 to 65, with and without trisomy 21

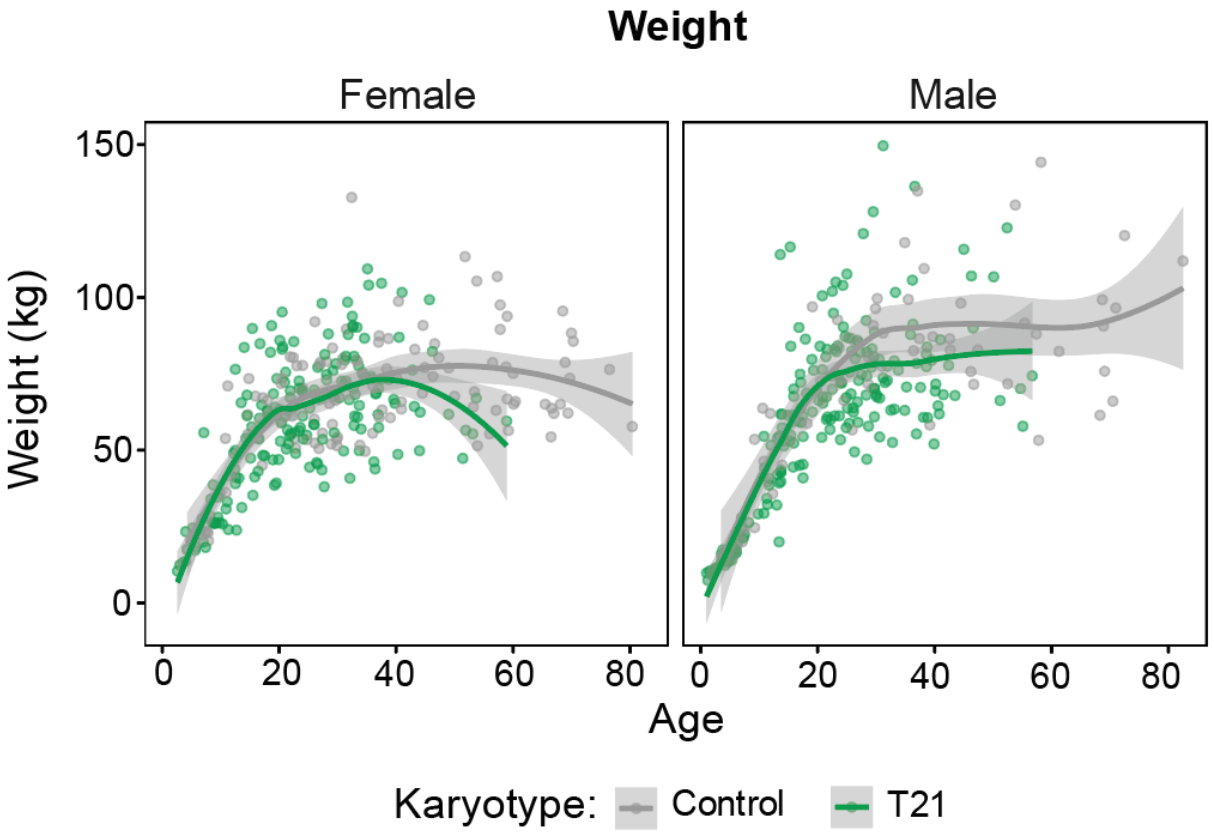


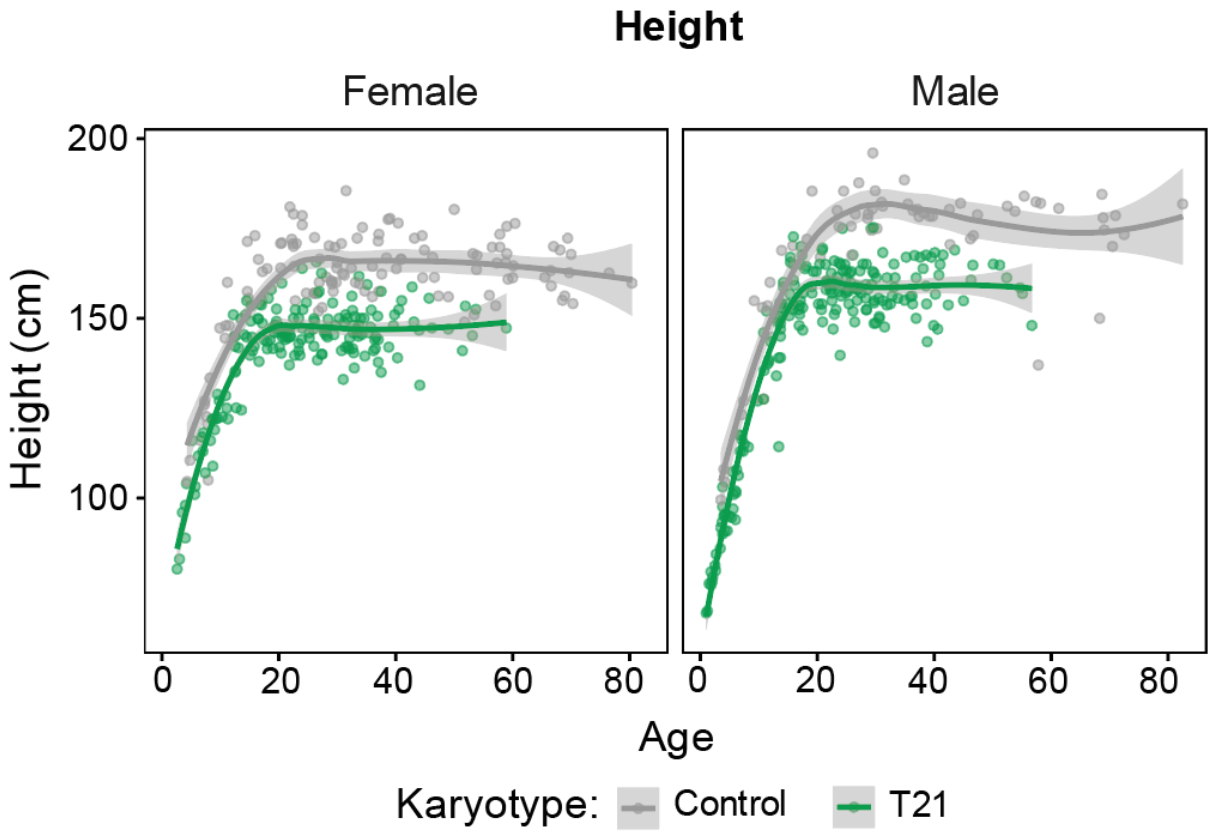
>22,000 data points:

16,000 mRNAs | 5,000 proteins | 170 metabolites | 54 immune markers | 100 immune cell populations, 400+ autoantibodies | 100s of clinical data fields

Not heavier, but shorter

In Down syndrome, growth is both delayed and stunted

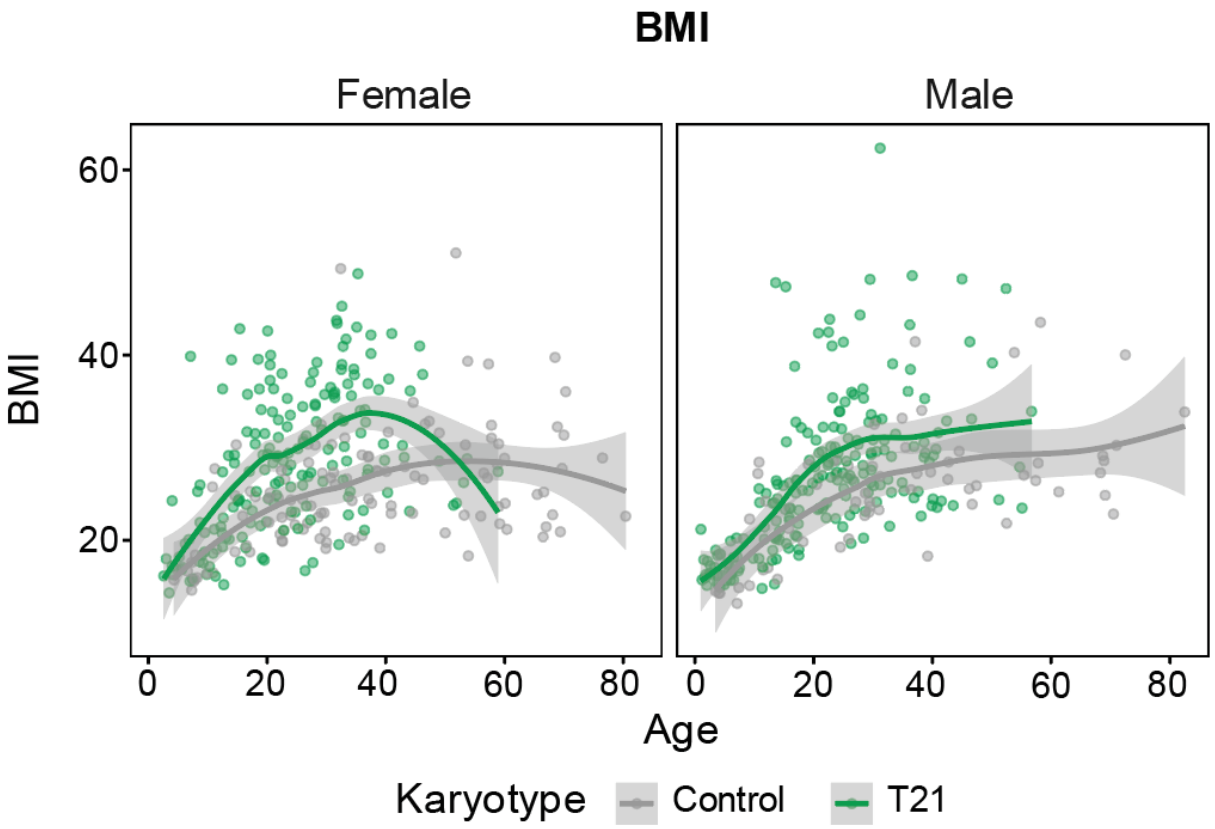


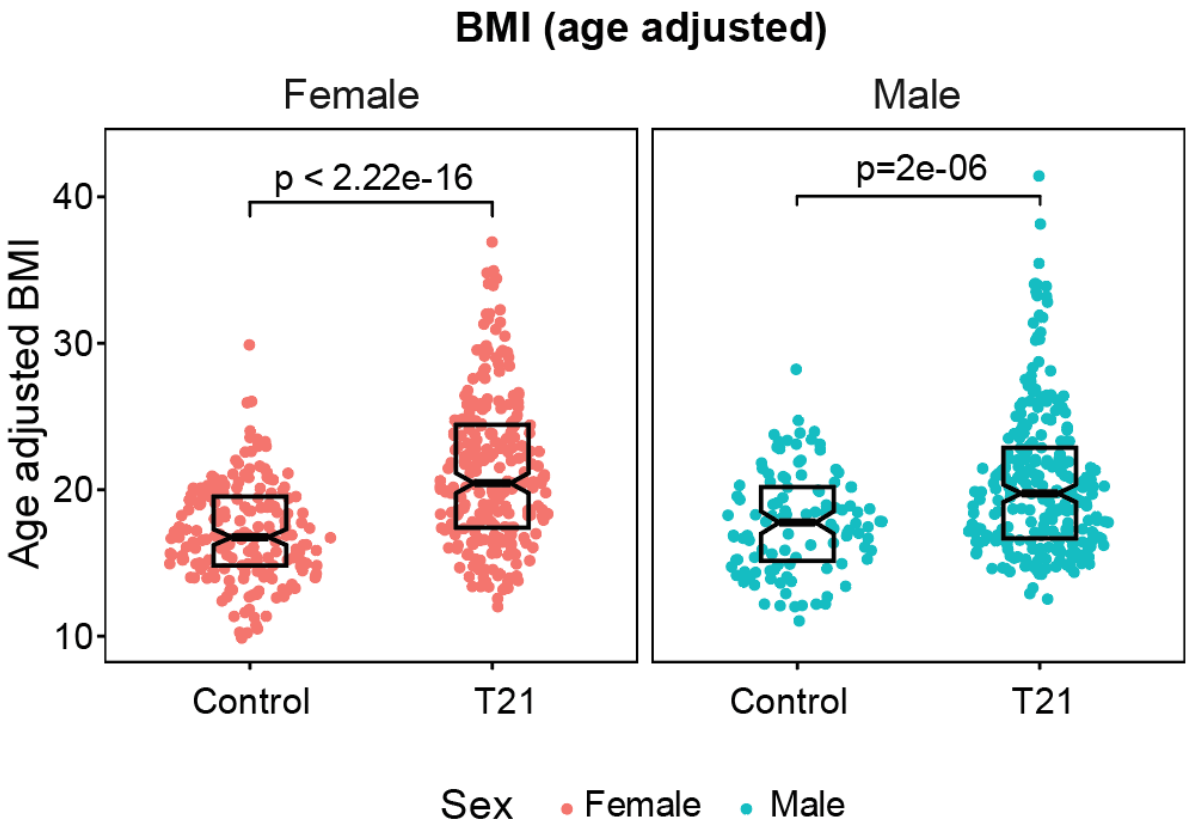


Adults with Down syndrome are missing 8-10 inches!

Not heavier, but shorter

Body-mass index is significantly elevated in Down syndrome

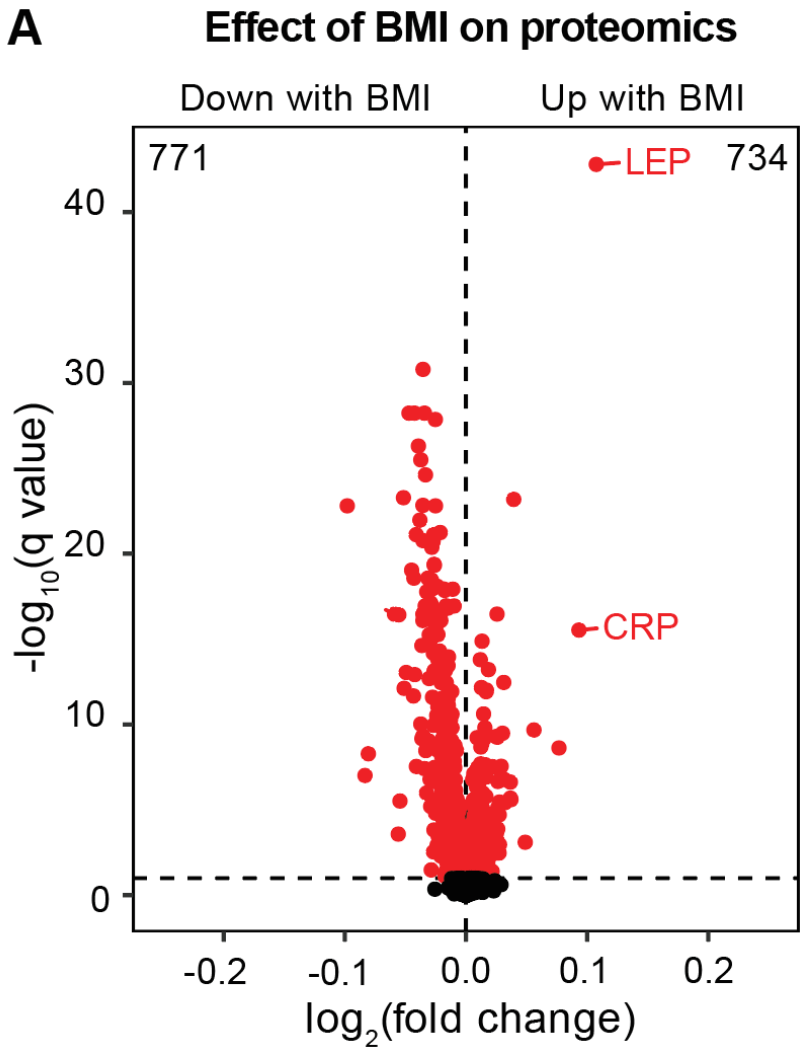


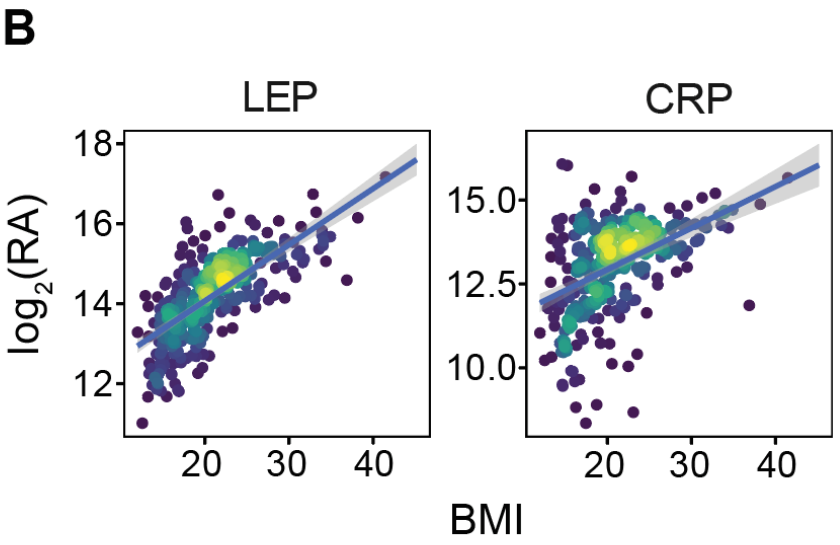


BMI: weight (lb) / [height (in)]^2 x 703. CDC says: BMI>25 is overweight, >30 is obese

What are the impacts of higher BMI?

A ‘multi-omics’ analysis of BMI in Down syndrome





For example, both leptin and CRP increase in plasma with BMI

LEP: leptin, a hormone produce by adipocytes (fat cells)

CRP: C-reactive protein, a general marker of inflammation

What are the effects of BMI on the biology of Down syndrome?

What are the impacts of higher BMI?

A ‘multi-omics’ analysis of BMI in Down syndrome

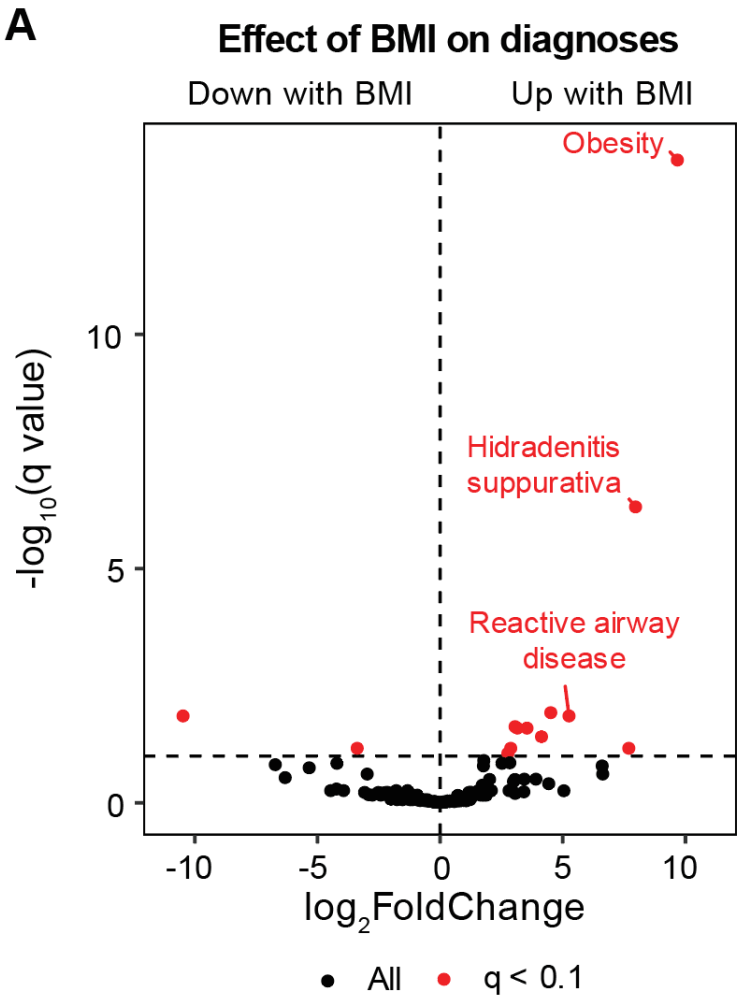
Higher BMI associates with:

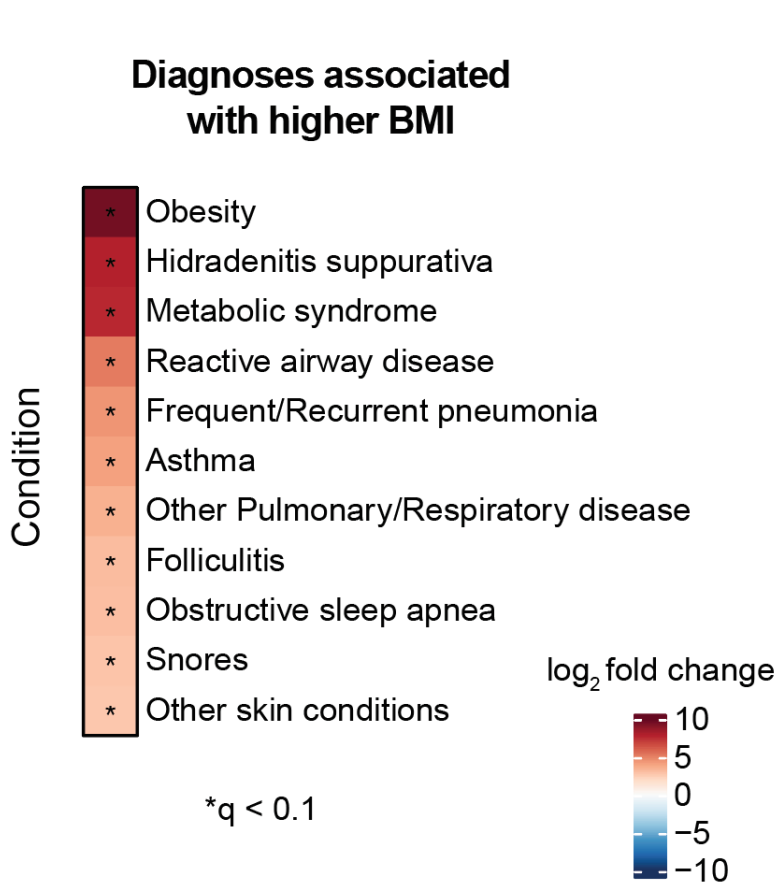
- Dysregulation of the leptin / ghrelin hormonal circuit (metabolism, appetite)
- Systemic inflammation
- Immune hyperactivity (e.g., elevated cytotoxic T cells)
- Markers of hypoxia and dysregulated red blood cell formation
- High circulating levels of glutamate, a neurotoxic metabolite

And much more!

What are the impacts of higher BMI?

A ‘clinical’ analysis of BMI in Down syndrome





Take home message:

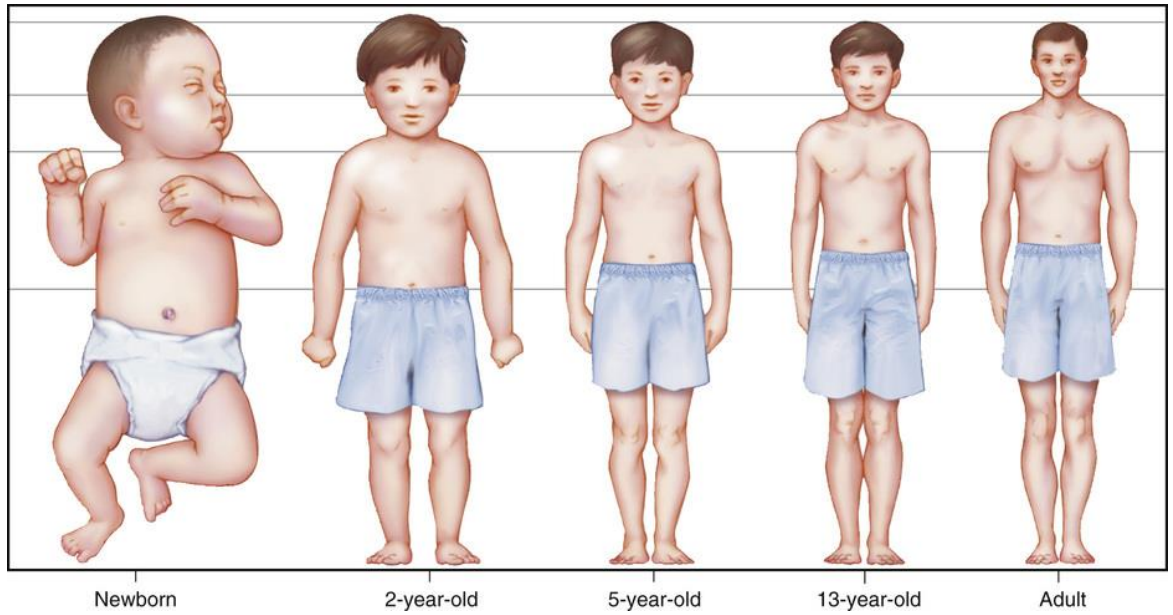
Beyond obesity, multiple co-occurring conditions associate with high BMI in Down syndrome, including diverse immune skin conditions and diverse forms of lung disease.

High BMI is no fun

Soundbite #2

There is nothing wrong with being short, the issue is when you are smaller than you should be…

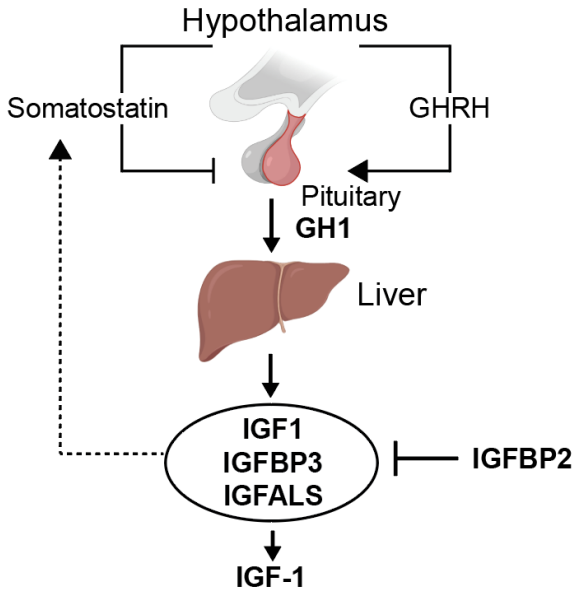
Human development: a shift in proportions

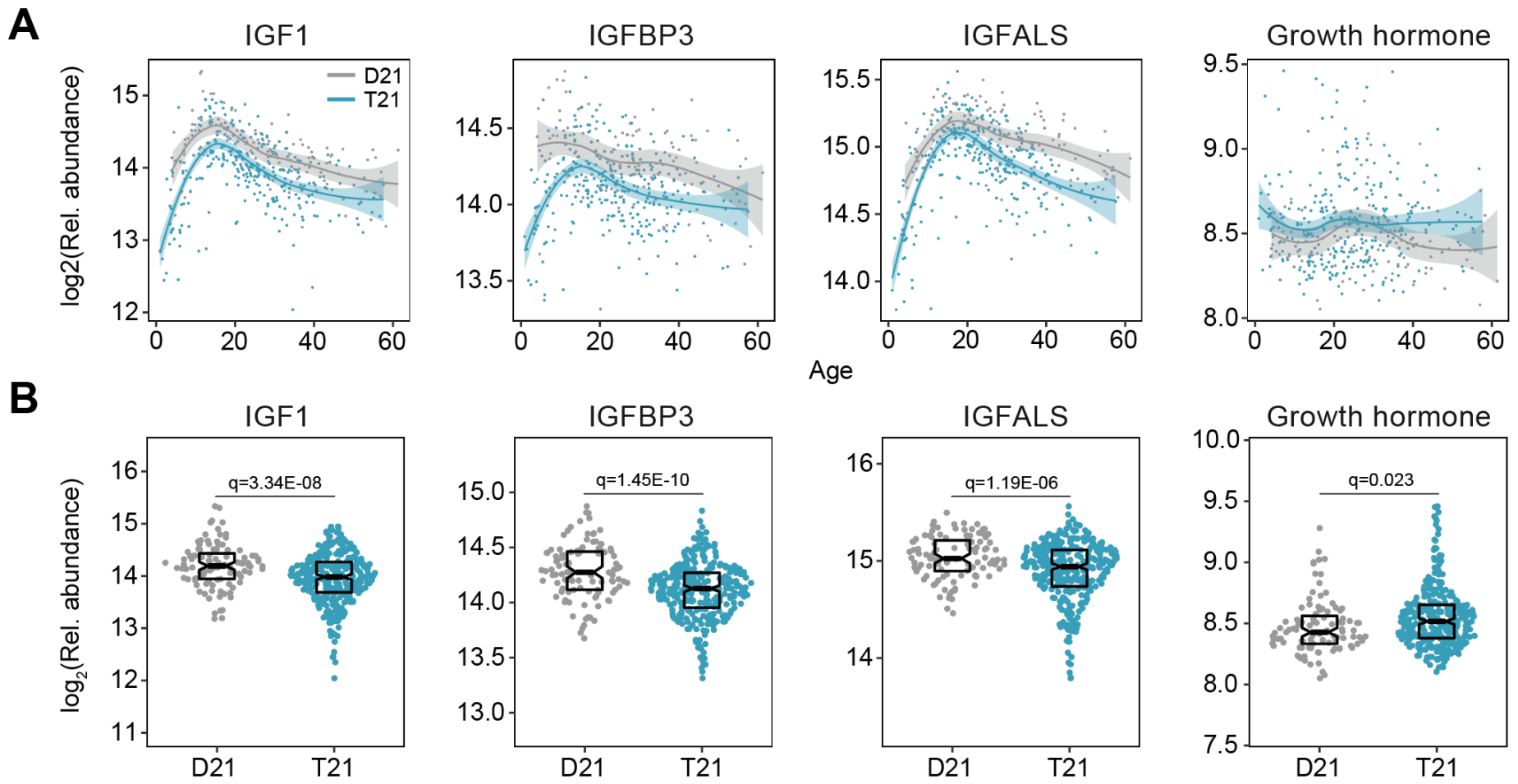


What happens when the proportions are off?

Why are people with Down syndrome shorter?

The IGF1 ternary complex is depleted at all ages in Down syndrome



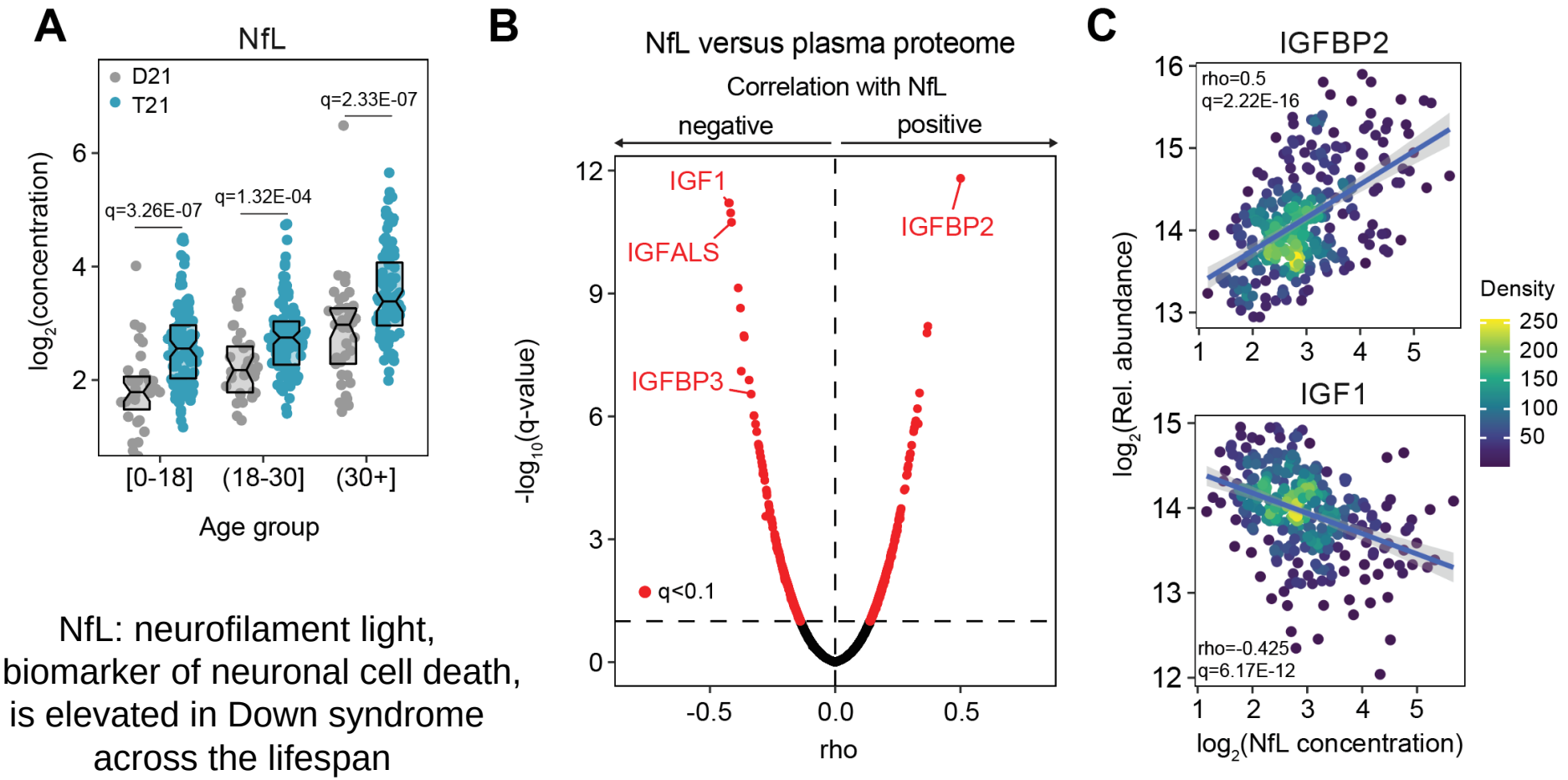


D21: euploid controls (n=103), T21: trisomy 21, Down syndrome (n=316)

Araya et al, Cell Reports 2022

A serendipitous (re)discovery

An unbiased analysis of neurodegeneration pathways in Down syndrome

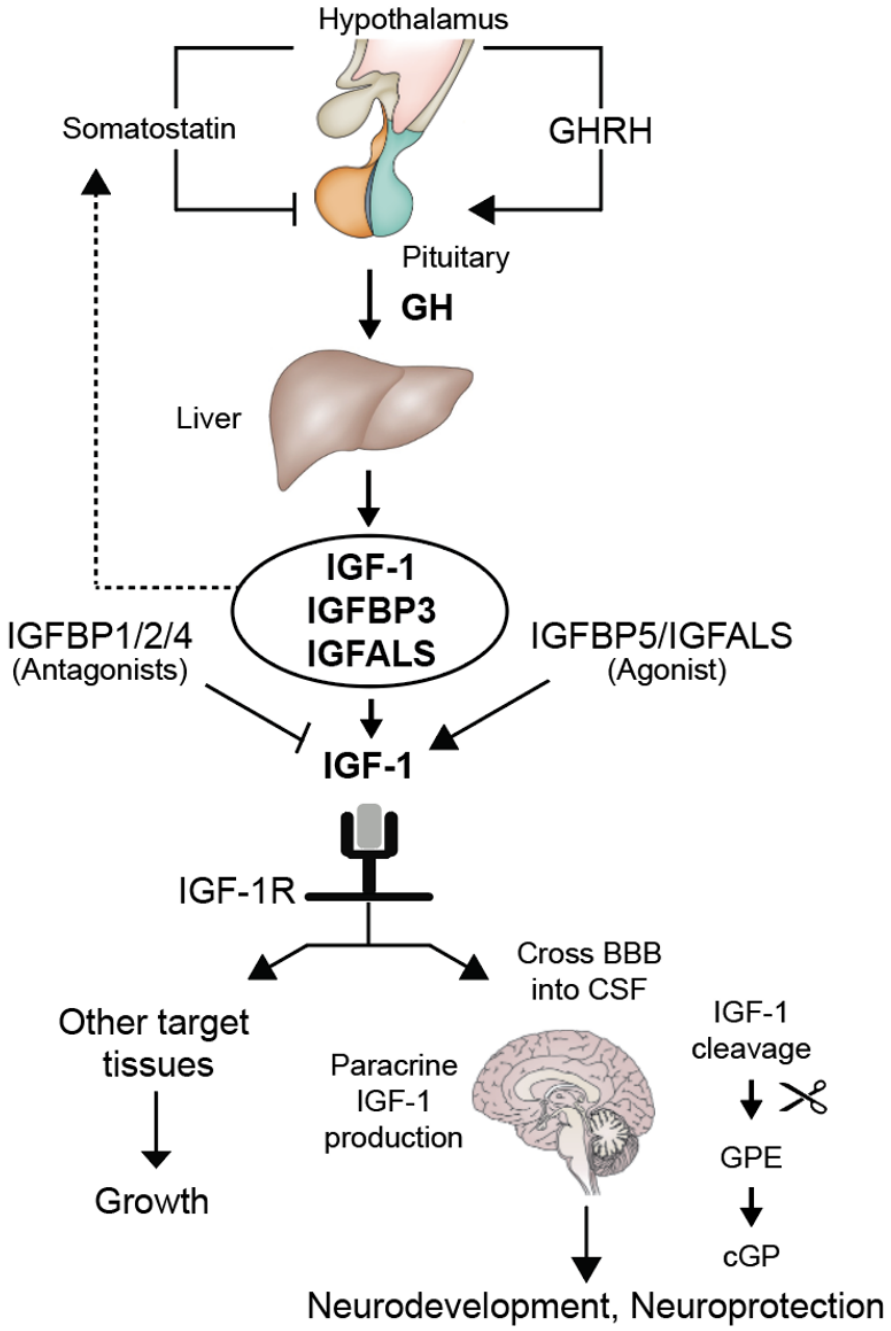


NfL: neurofilament light,
a biomarker of neuronal cell death,
is elevated in Down syndrome
across the lifespan

Low IGF1 signaling is the top ‘proteomic signature’ associated with high levels of NfL

Araya et al, Cell Reports 2022

IGF1: a master regulator of human development



Insulin-like growth factor 1 (IGF1) signaling is essential for early brain development and neurogenesis in the adult brain.

IGF1 is necessary for the growth-promoting effects of the growth hormone.

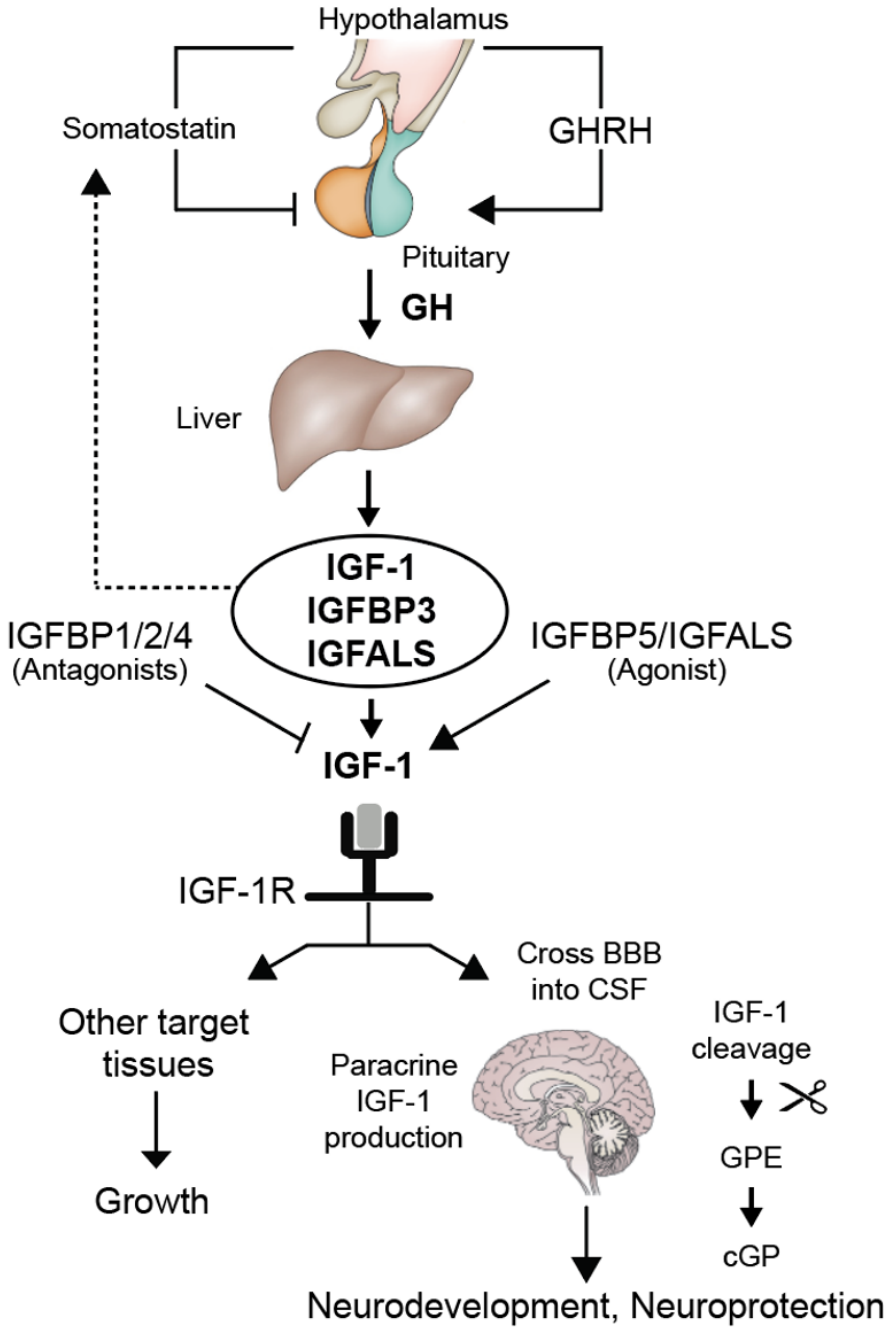
Mutations in IGF1, IGFBP3, IGFALS or the IGF1R cause neurodevelopmental disorders that share many phenotypes with Down syndrome.

Article

IGF1 deficiency integrates stunted growth and neurodegeneration in Down syndrome

Paula Araya,[1] Kohl T. Kinning,[1,2] Christina Coughlan,[1,3,4] Keith P. Smith,[1] Ross E. Granrath,[1] Belinda A. Enriquez-Estrada,[1] Kayleigh Worek,[1] Kelly D. Sullivan,[1,5] Angela L. Rachubinski,[1,6] Kristine Wolter-Warmerdam,[7] Francis Hickey,[7] Matthew D. Galbraith,[1,2] Huntington Potter,[1,3,4] and Joaquin M. Espinosa[1,2,8,*]

December 2022 Cell Reports



IGF1 deficiency in Down syndrome:

All three subunits of the IGF1/IGFBP3/IGFALS complex are depleted in Down syndrome

IGF1 deficiency associates with elevated markers of neurodegeneration and neuroinflammation in Down syndrome

Relatively shorter children with Down syndrome have lower IGF1, elevated markers of neurodegeneration and neuroinflammation, and elevated risk of:

- Autism spectrum disorders
- Lung disease
- Autoimmune conditions

Article

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IGF1 deficiency and Down syndrome

What could be the impacts of IGF1 deficiency?

Lifelong physiological properties of IGF-I	Growth	Bone metabolism	Lipid and glucose metabolisms	Neuroprotection
	Neurogenesis and synaptogenesis	Anabolizing	Antioxidant and antiinflammatory	Antiapoptotic
	Genital development	Proliferative	Hepato- and cardioprotection	Mitochondrial protection

IGF1 deficiency could contribute to:

- Stunted growth
- Poor bone health
- Accelerated ageing
- Decreased brain health
- Alzheimer's disease

Conclusion: a lot more research is needed to decipher the effects of IGF1 deficiency in Down syndrome.

Relationship between cognitive function and growth

*'The results showed that full-scale, verbal, and nonverbal **IQ correlated with height percentile…**'.*

*'The results of our study suggest an **association between growth and IQ in children with DS.** The presented findings may be valuable for improving access to Growth Hormone therapy for populations with genetic syndromes characterized by short stature.'*

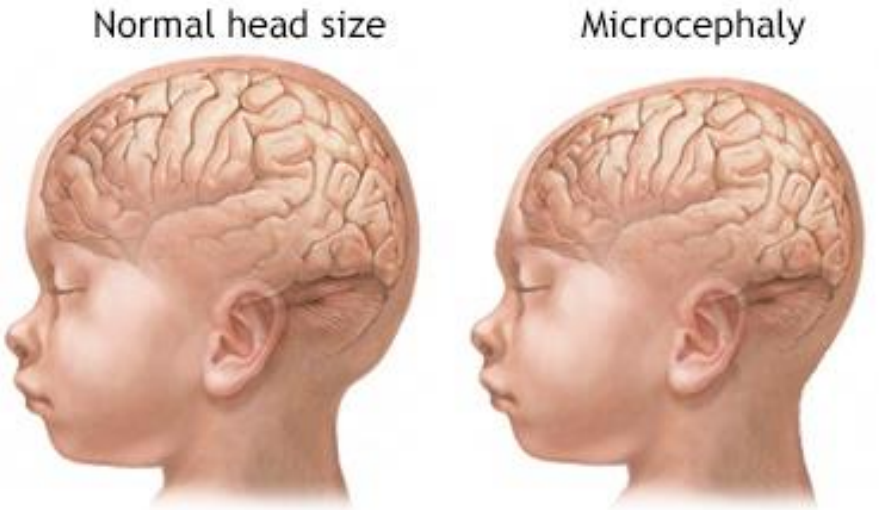
Relationship between growth and intelligence quotient in children with Down syndrome

Anna Kłosowska[1^], Agnieszka Kuchta[2^], Agnieszka Ćwiklińska[2^], Kornelia Sałaga-Zaleska[2^], Maciej Jankowski[2^], Przemysław Kłosowski[3^], Arkadiusz Mański[4^], Michał Zwiefka[4^], Paulina Anikiej-Wiczenbach[4^], Jolanta Wierzba[5^]

Published April 2022 TP TRANSLATIONAL PEDIATRICS

Microcephaly:

A condition where the head size is significantly smaller than that of other children of the same age and sex



Microcephaly is a hallmark of Down syndrome

Down syndrome is a leading cause of microcephaly

What causes microcephaly in Down syndrome?

How about IGF1 deficiency?

IGF1 knockout mice have brains that are 60% smaller than wild type littermates

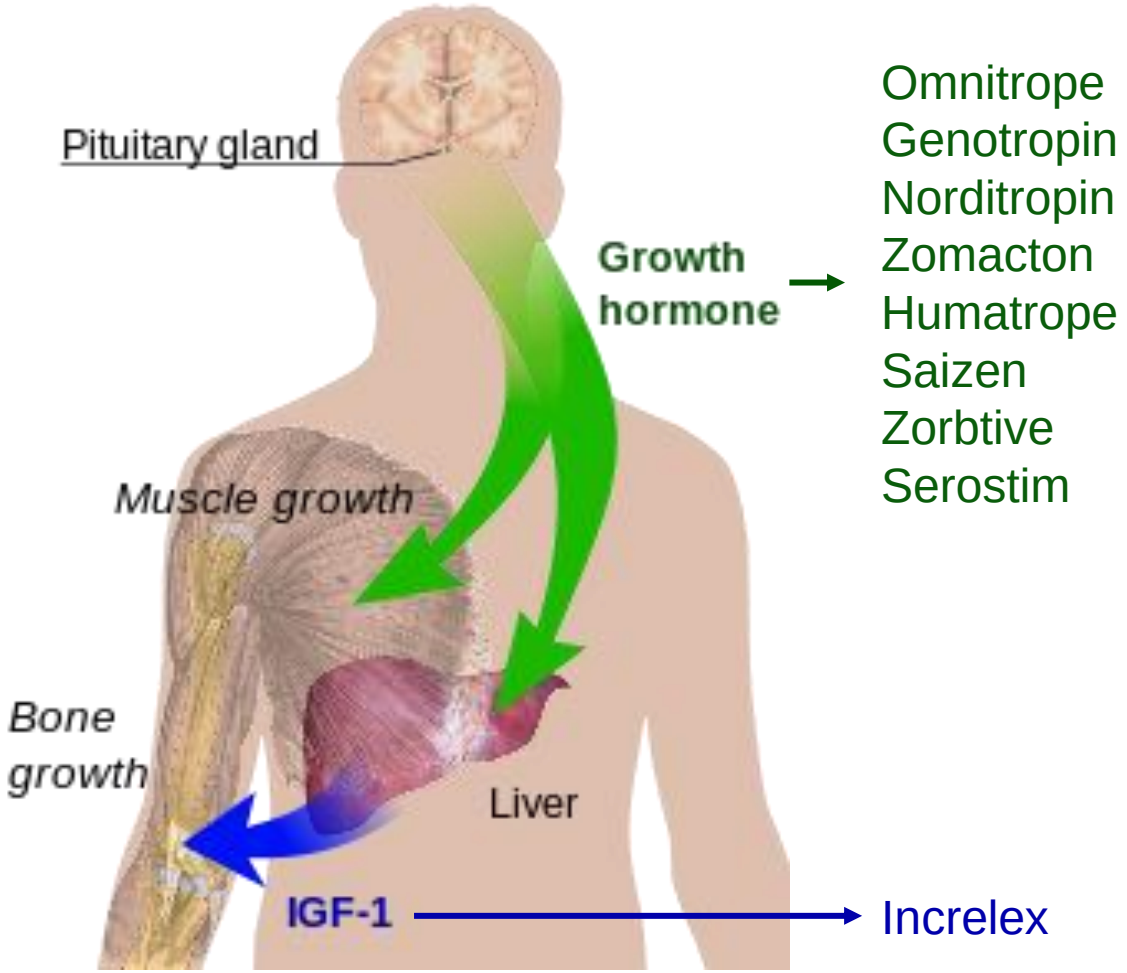
Brain size matters!

Adequate neurodevelopment can not occur
without proper brain growth

- The brain volume a child achieves by the age of 1 year helps determine later intelligence.
- Head growth during infancy is a significant predictor of intelligence, with full-scale IQ increasing an average of 1.56 points for each 1-standard deviation increase in growth.
- **IGF1 levels in the first decade of life are associated positively with intelligence. For every 100 ng/mL increase in IGF1, IQ increased by 3.18 points. This effect is due mostly to the verbal component of IQ.**

The AVON longitudinal study: Gunnell et al, Pediatrics, 2005; Gale et al, Pediatrics 2006

What could be the benefits of growth hormone therapy or IGF1 therapy in Down syndrome?



Omnitrope
Genotropin
Norditropin
Zomacton
Humatrope
Saizen
Zorbtive
Serostim

Increlex

Both growth hormone and IGF1 exist as FDA-approved therapies for some forms of growth disorders.

Growth hormone is approved for:

- Growth Hormone Deficiency
- Short Bowel Syndrome
- HIV-associated wasting
- More…

IGF1 is approved for:

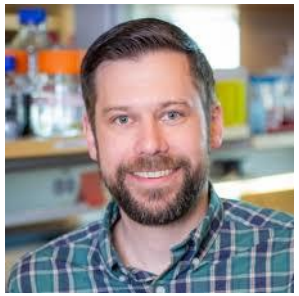
- Severe Primary IGF1 Deficiency (SPIGFD)

Conclusions

- Dysregulated growth trajectories are likely to have multidimensional impacts on the health of people with Down syndrome.
- More research on the effects of abnormal growth hormone / IGF1 signaling in Down syndrome is needed.
- The time is right to design and launch rigorous clinical trials for growth hormone and IGF1 supplementation in Down syndrome.

Credits

Program Directors at the Crnic Institute



Kelly Sullivan
Experimental Models Program

Angela Rachubinski
Clinical and Translational Sciences Program

Matthew Galbraith
Data Sciences Program

Lyndy Bush
Administrative and Outreach Program

THE INCLUDE PROJECT

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

NIH National Heart, Lung, and Blood Institute

NIH National Institute of Allergy and Infectious Diseases

NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases

NIH National Center for Advancing Translational Sciences

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School of Medicine
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

Many many wonderful collaborators

Michelle Sie Whitten and the amazing team at the Global Down Syndrome Foundation