The DESSH Foundation

A new trial in the UK?

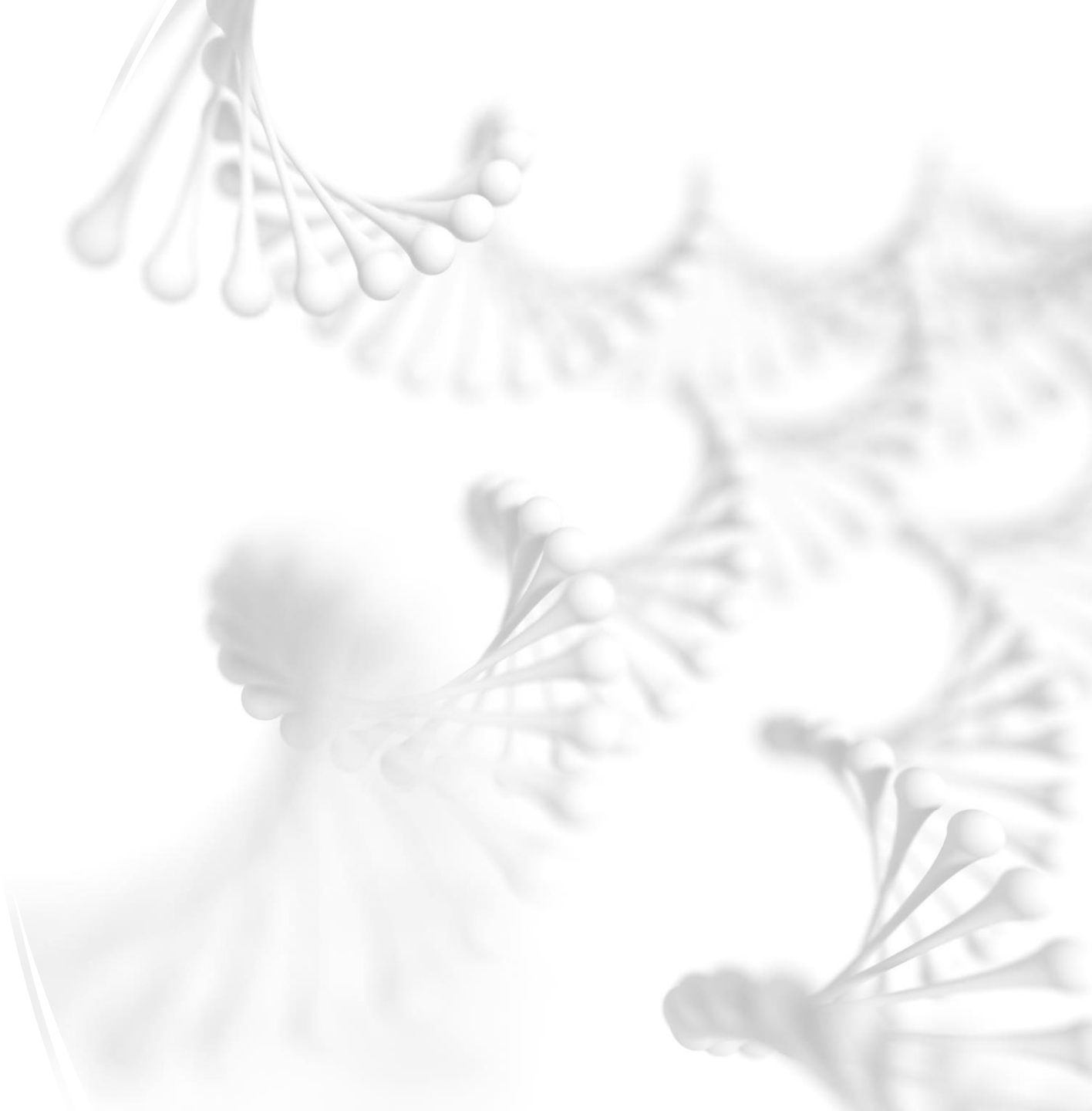
A presentation to UK families In partnership with the DESSH Foundation

Introductions

- Introductions
- Introduction to Caitlin’s role as President of DESSH
- Who am I and why I've set this meeting up
- Before we talk about research – explanation of Science. Apologies as some are experts but starting on assumption of limited knowledge
- I am not an expert and the science is my explanation and understanding **and has not be reviewed by the DESSH Medical advisory board**

What is DNA?

- DNA is the instruction manual for building and running your body.
- Nucleotides make up the DNA – they are made of sugars and types of nitrogen groups Made of four 'letters': A, T, C, G.
- Stored inside almost every cell, packed into chromosomes.
- Half from your mother, half from your father.



What are Genes?

- A gene is a specific section of DNA.
- Each gene carries instructions to make one protein.
- Proteins do most of the work in the body.

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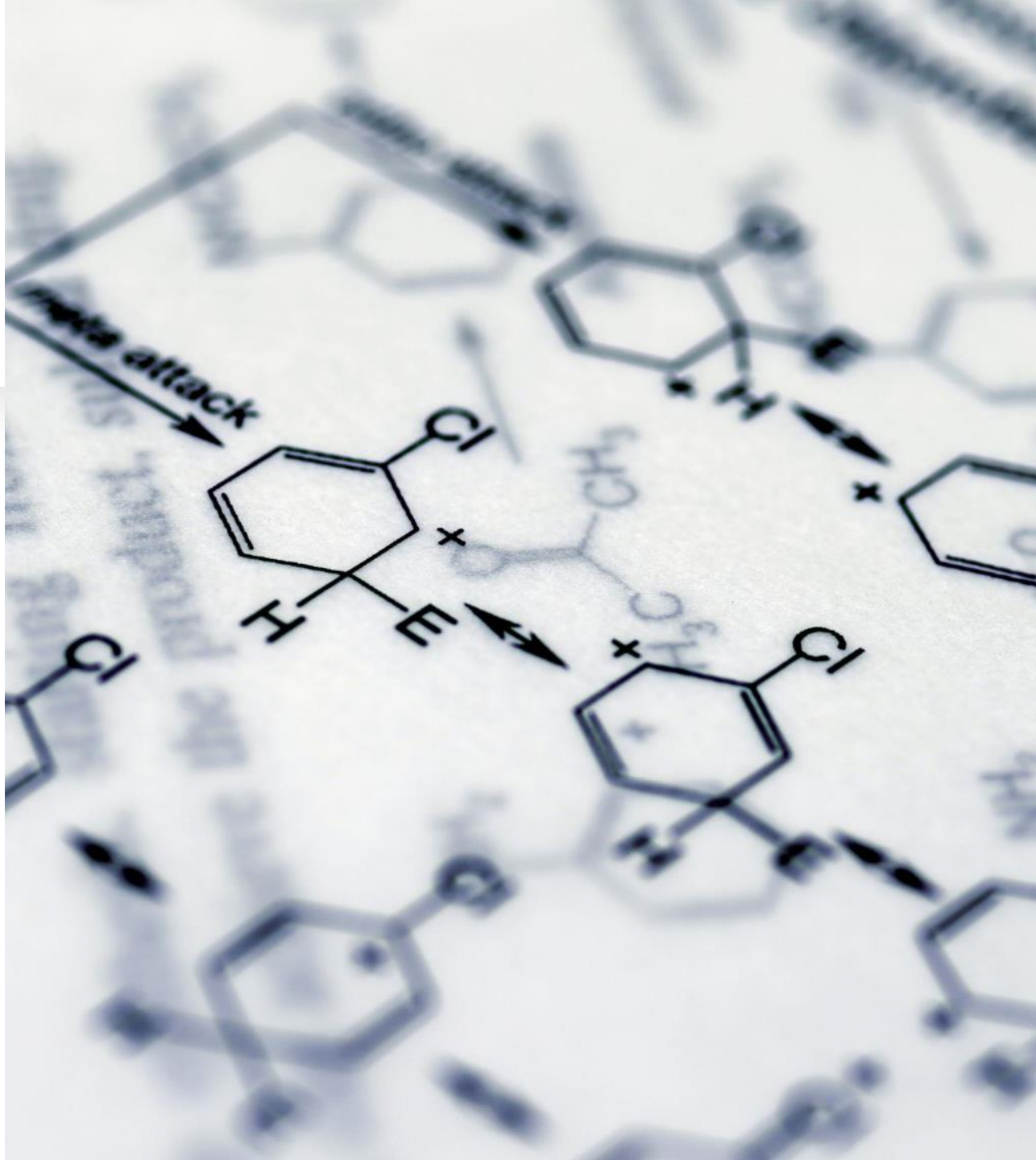
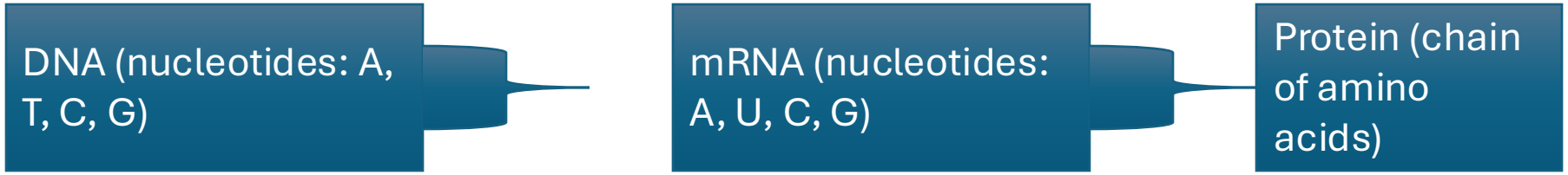


DNA to Protein - The Journey



1. DNA's nucleotides hold the instructions for making proteins.
2. Transcription copies DNA into mRNA.
3. Ribosomes read mRNA in codons (3 nucleotides) to add the correct amino acids.
4. Amino acids join to form a protein, which folds into its working shape.

What is Epigenetics?

- Epigenetics is about switches that turn genes on or off.
- Chemical control gene activity without changing DNA sequence.
- Lifestyle and environment and potentially some drugs can influence these switches.

How Do You Get Genetic Diseases?

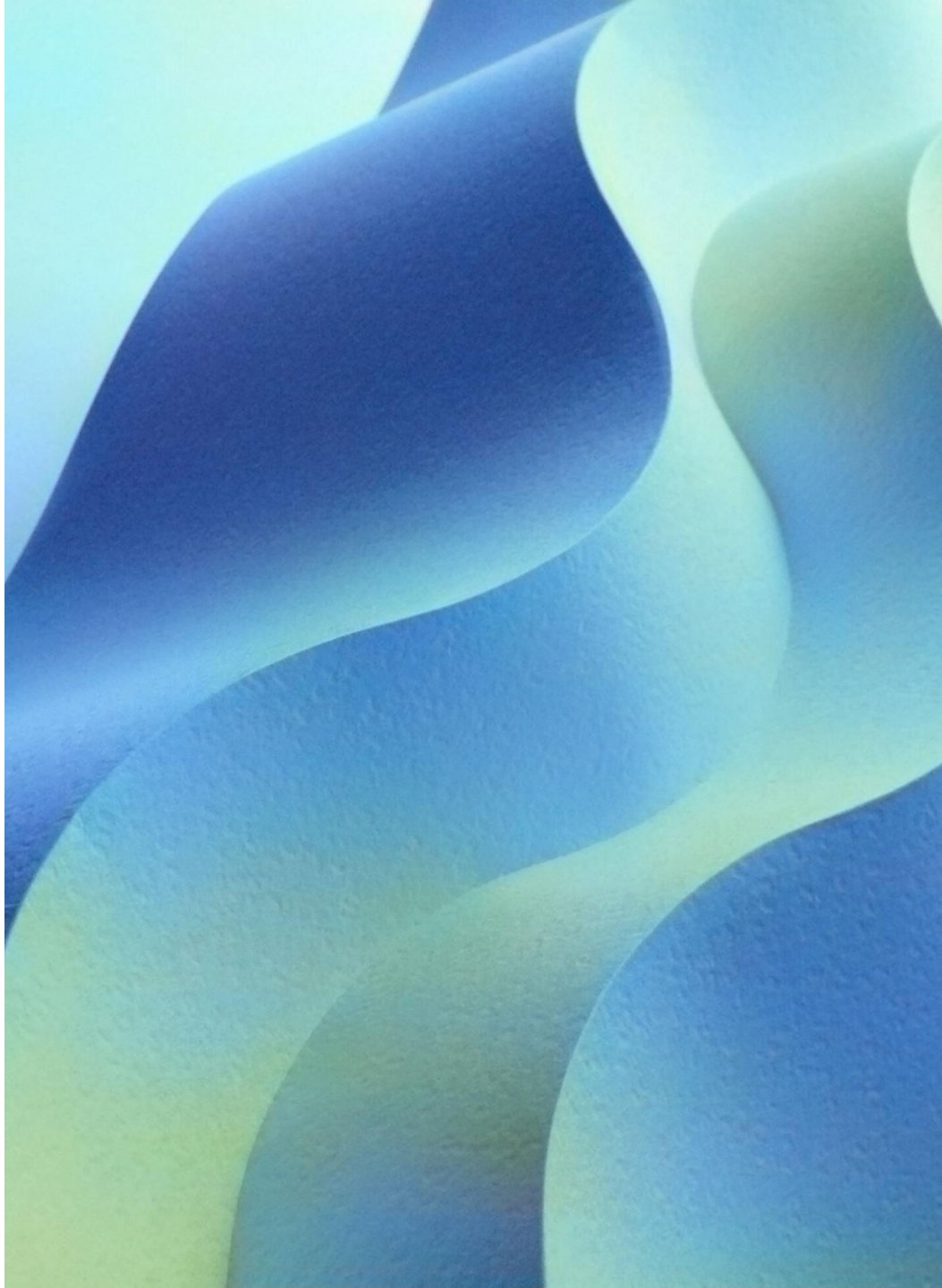
- Mutations are changes in DNA instructions.
- Some mutations cause faulty proteins or stop production.
- Some are harmless, others cause disease.

Dominant vs. Recessive Inheritance

Dominant: One faulty copy is enough for disease.

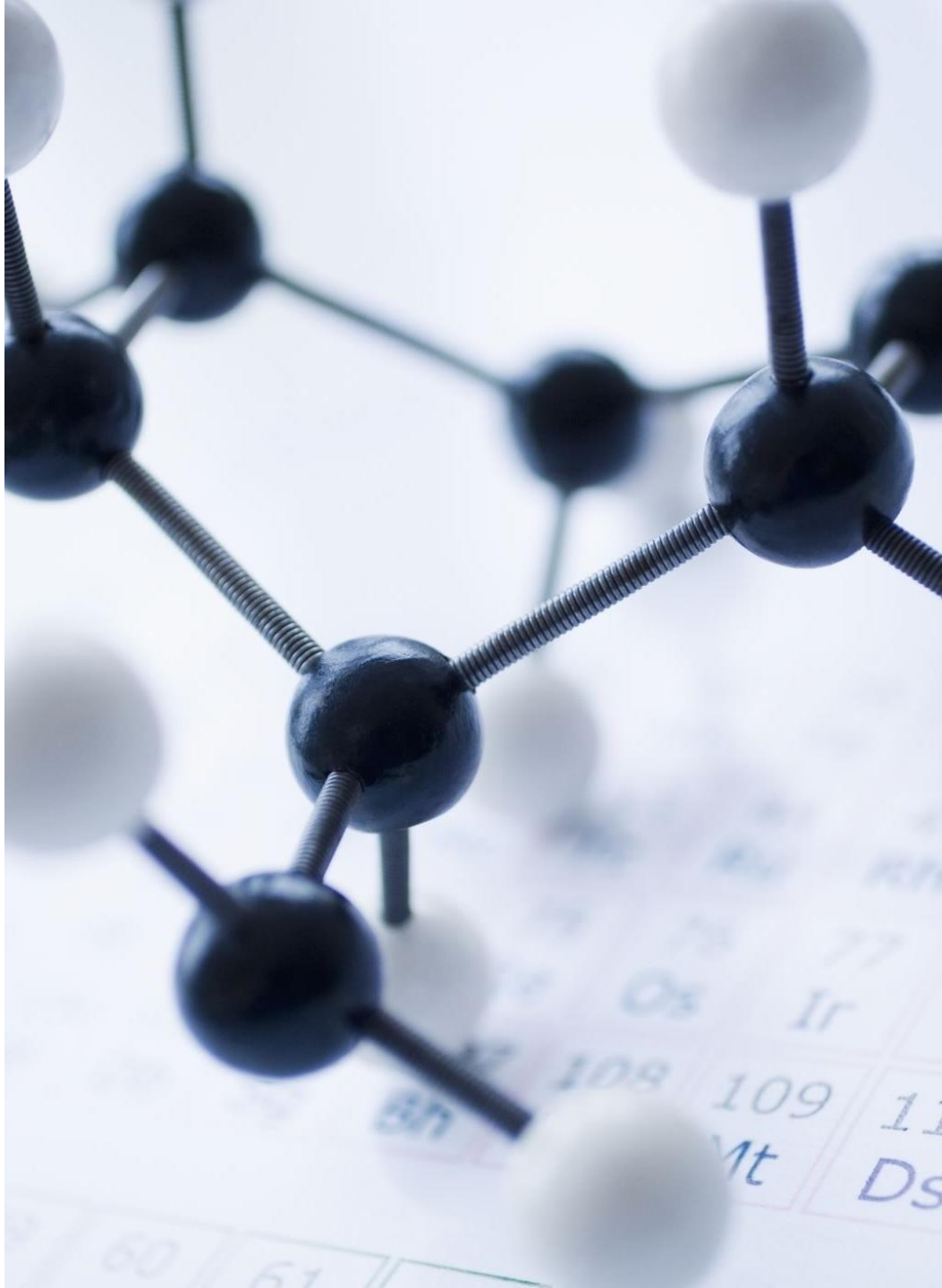
Recessive: Need two faulty copies to have the disease.

Carriers have one faulty copy but no symptoms.



What is Halpoinsufficiency?

- Haploinsufficiency: One working copy of a gene is not enough.
- Can cause problems even if other copy is normal.
- This is what happens in DEESH with the WAC gene



Main Types of Mutations – this is why everyone's genetics are different but all loose WAC function

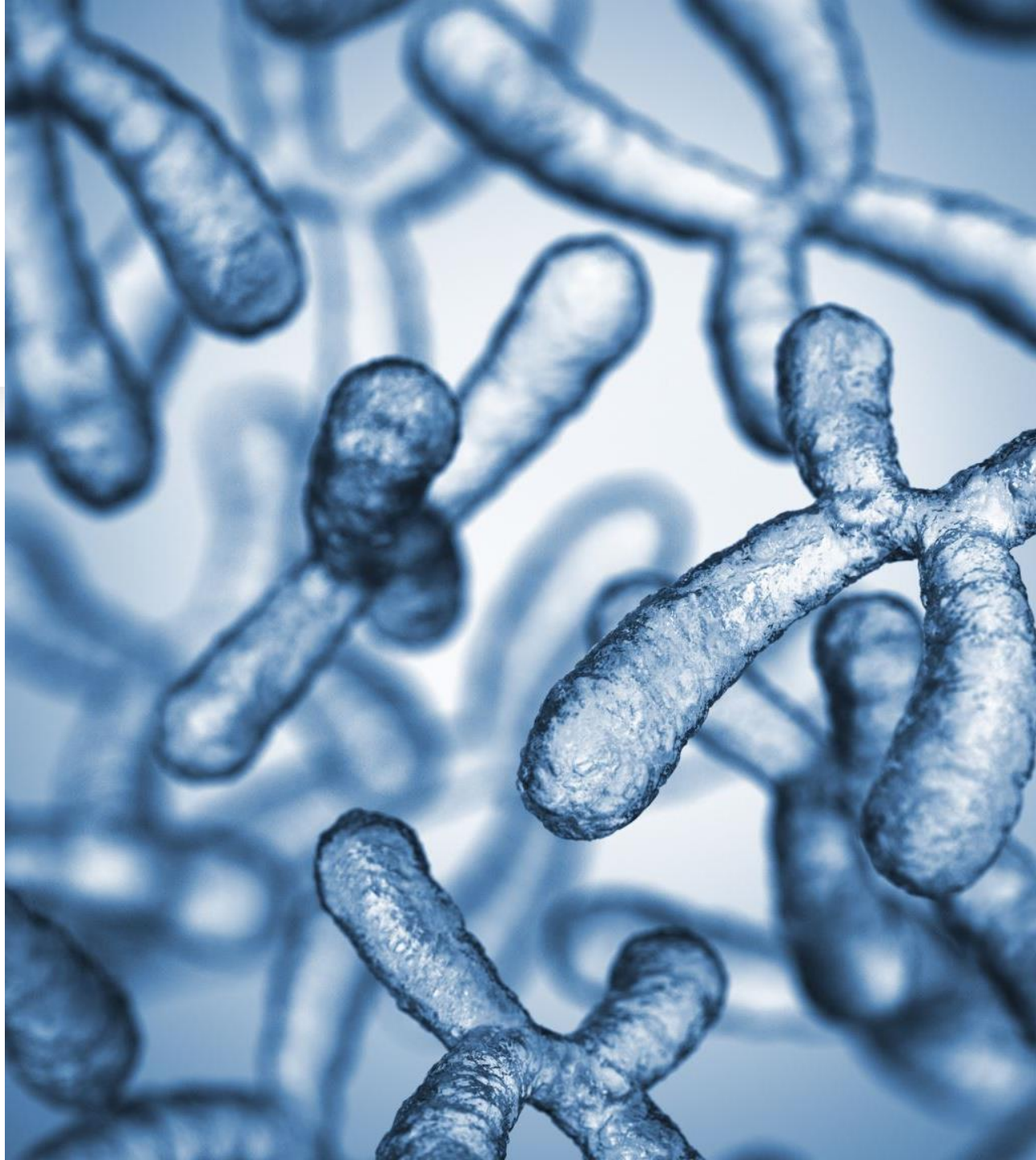
- Missense mutation: One letter swapped → different amino acid (e.g., sickle cell disease).
- Nonsense mutation: One letter change creates STOP → short, non-functional protein (e.g., Duchenne muscular dystrophy).
- Deletion: Letters removed → may cause frameshift or remove whole amino acids (e.g., cystic fibrosis).
- Insertion: Extra letters added → may cause frameshift (e.g., Tay–Sachs disease).
- Frameshift mutation: Reading frame shifts → completely different protein sequence.
- Splice site mutation: Disrupts cutting/joining of mRNA segments → abnormal protein.
- Repeat expansion: Sequence repeated too many times (e.g., Huntington's disease).
- Microdeletion: Missing chunk of DNA containing one or more genes (e.g., 10q microdeletion in DESSH affecting the WAC gene, causing haploinsufficiency and can occur with other issues form other gene loss).

The genetics of DEESH

- Usually new mutations completely random in egg or sperm
- So it is not an inherited disease and usually do not pass it on
- But can get mutations after fertilization – then only affects a proportion of cells. This is called mosacism and is why you may get some only partially affected
- You can theoretically have more than one child with DESSH if its only in your sperm or eggs which have mosacism
- If people with DESSH have children 50% chance of having a child with DESSH

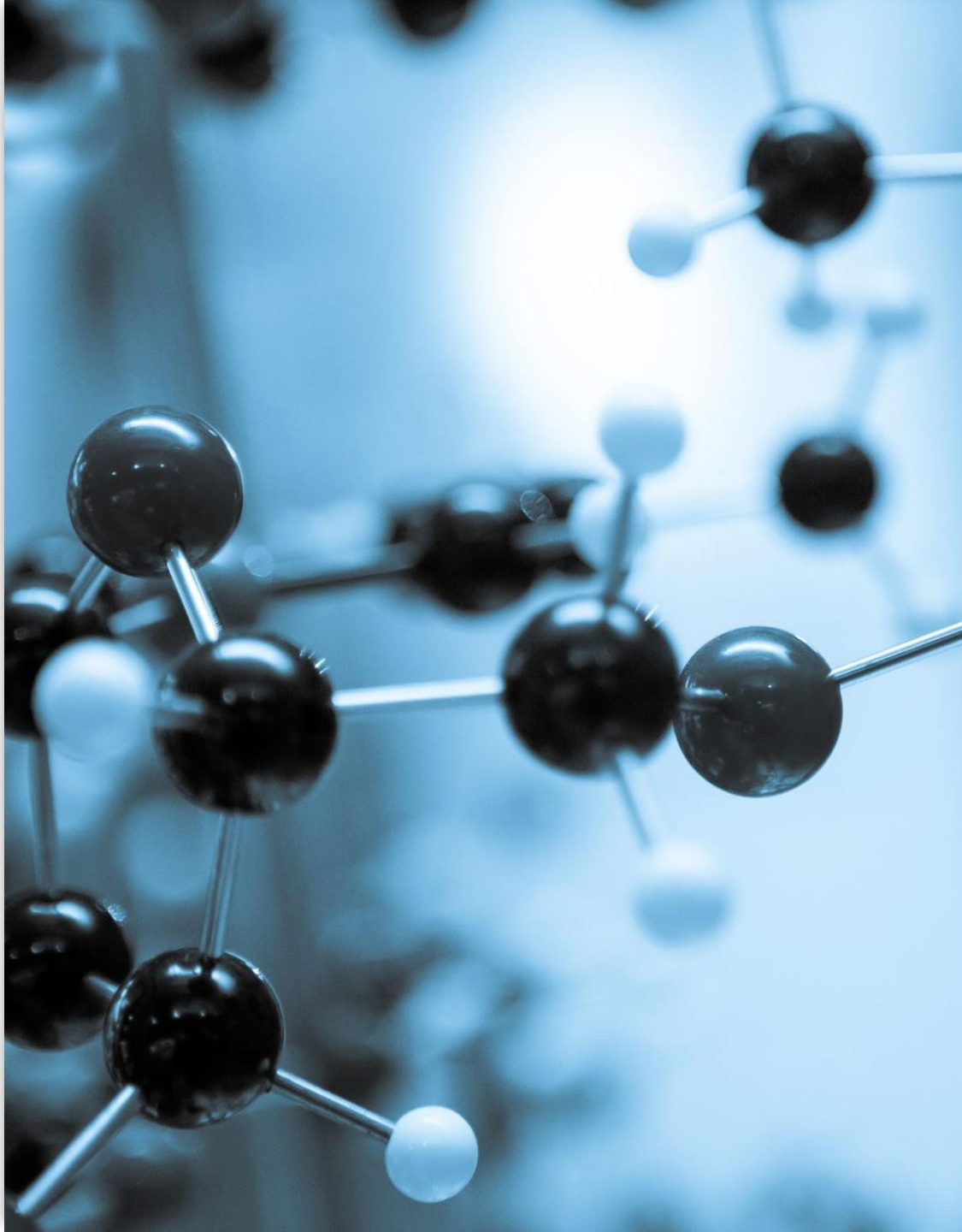
WAC Gene – General Overview

- Located on the long arm (q) of chromosome 10.
- Full name: WW domain–containing adaptor with coiled-coil region.
- Encodes a protein with multiple cellular roles in regulation and quality control.
- Expressed widely but with critical importance in brain development and function.
- Loss of one copy (haploinsufficiency) causes DeSanto–Shinawi syndrome (DESSH).



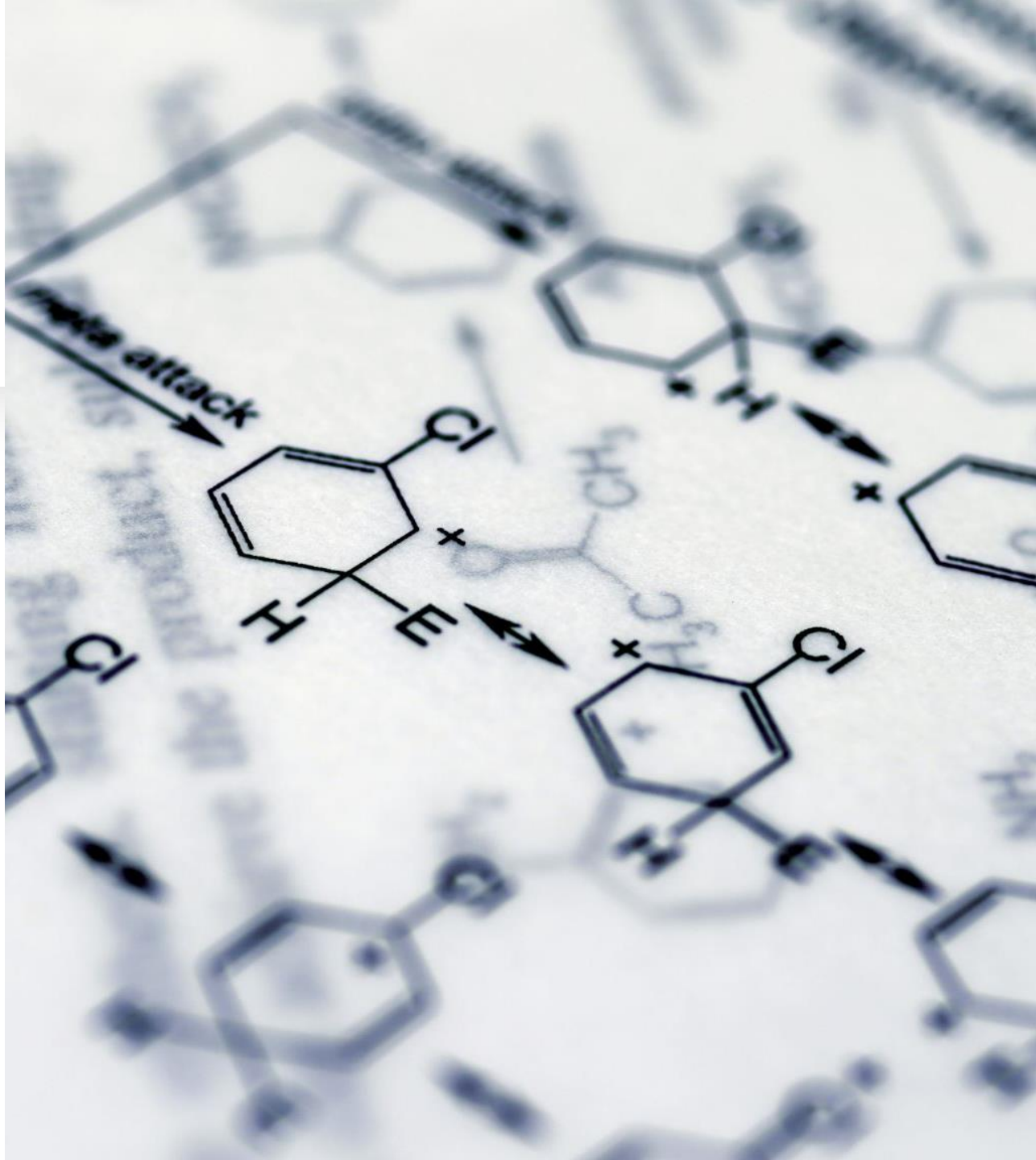
WAC Role in Gene Transcription

- Acts as a co-regulator of transcription – helps control when genes are turned on or off.
- Links transcription factors to chromatin-modifying machinery.
- Ensures the right genes are expressed at the right time, especially during development.
- Crucial for precise brain development and neuron function.



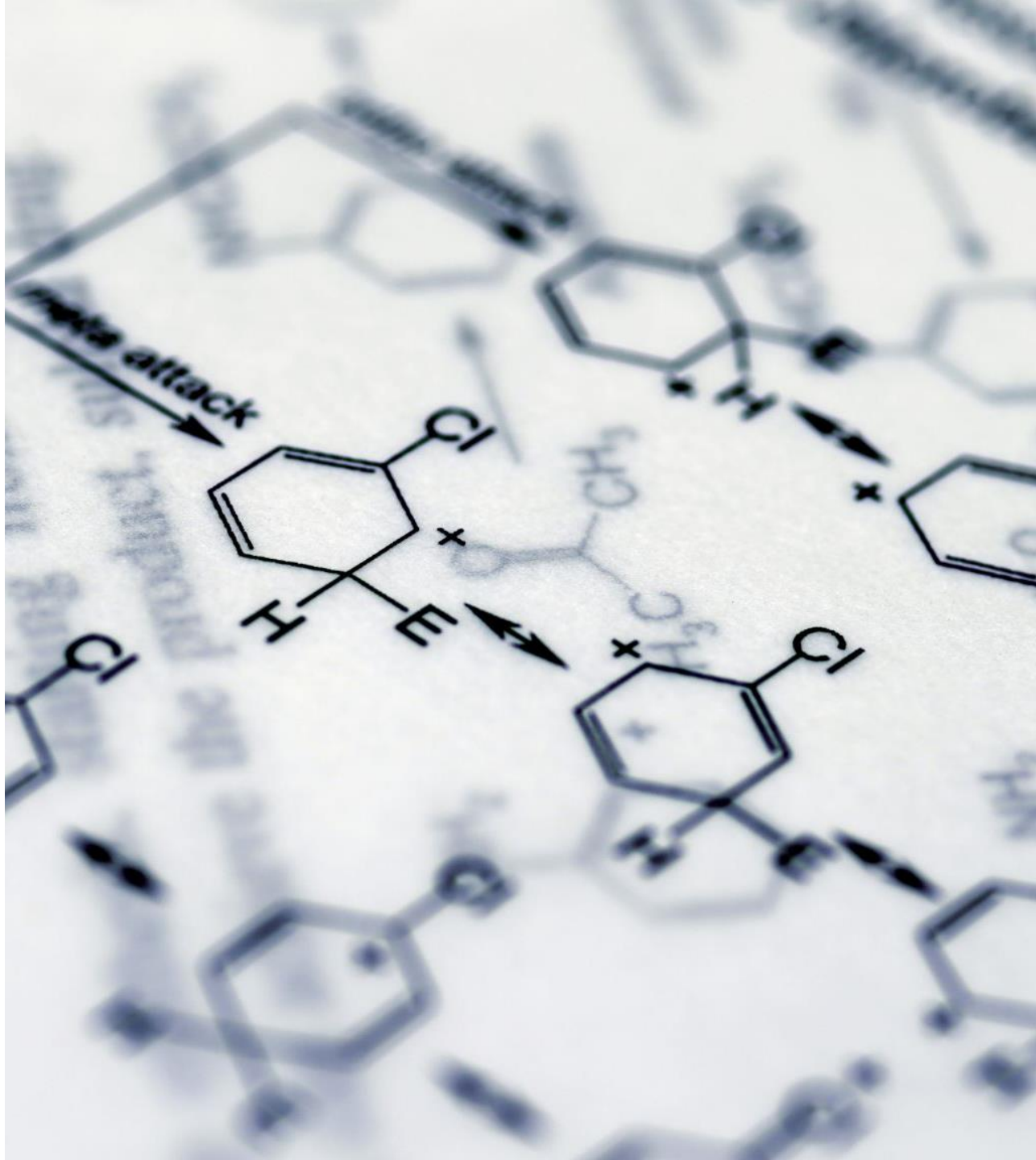
WAC Role in Protein Tagging

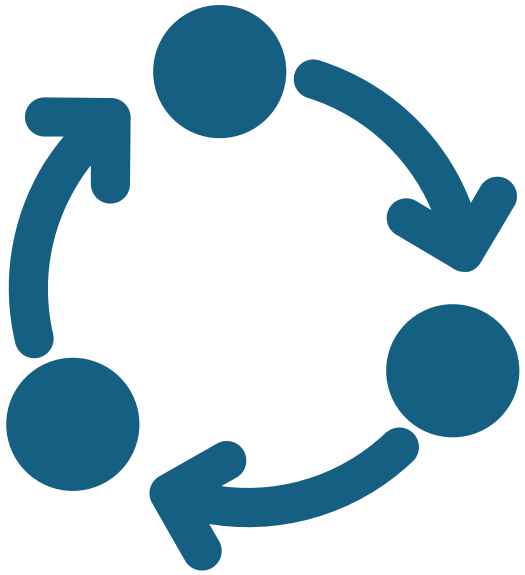
- Interacts with the ubiquitin ligase complex.
- Attaches 'ubiquitin' tags to proteins, marking them for destruction or altering their function.
- Removes damaged or misfolded proteins from the cell.
- Maintains protein quality and prevents toxic build-up.



WAC Role in Cell Self-Checkpoints

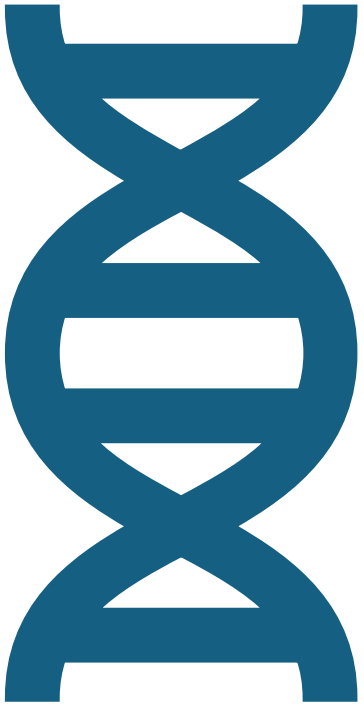
- Acts as a safety inspector for the cell cycle.
- Delays or halts cell division if DNA is damaged or conditions are not right.
- Prevents errors in cell division that could harm developing tissues.
- Particularly important in rapidly growing tissues like the brain.





WAC Role in Autophagy

- Helps initiate autophagy – the cell's recycling and clean-up process.
- Breaks down old or damaged cell parts to reuse components.
- Maintains cellular health and energy efficiency.
- Protects long-lived cells, such as neurons, from waste accumulation.



WAC Role in Oxidative Stress Protection

- Participates in pathways that detect and respond to oxidative stress.
- Activates protective genes to counter reactive oxygen species (ROS).
- Supports removal of oxidatively damaged proteins via proteasome and autophagy.
- Helps decide if a damaged cell should repair itself or self-destruct.

What Happens If You Lose WAC?

Haploinsufficiency – one copy of the gene is not enough for normal function.

Disruption of transcription timing during brain development → developmental delay.

Reduced protein quality control → possible build-up of damaged proteins.

Weakened oxidative stress response → more vulnerable cells, especially in brain and immune system.

Features seen in DESSH: intellectual disability, autism-like traits, motor and speech delays, distinctive facial features, sometimes immune differences, hypotonia and constipation

Possible Scientific Strategies

- Gene replacement therapy – adding a healthy copy of WAC via viral vector. Technology unlikely to be available for many years as need to get into every brain cell
- Gene editing (CRISPR, base editing) – fixing or replacing the faulty section of DNA. Technology unlikely to be available for many years as need to get into every brain cell
- **Boosting the remaining WAC copy's activity – drugs or epigenetic modifiers to increase protein production.**
- Targeted delivery to brain and other affected tissues remains the main challenge.

What Can Be Done Now

- Support WAC’s downstream systems:
- - Protein quality control: healthy diet, regular exercise, possible autophagy-promoting compounds (some supplements such as spermatidine theoretically could work).
- - Reduce oxidative stress: antioxidant-rich diet, minimise environmental toxins.
- **- Support brain development: early intervention, speech and occupational therapy, tailored education.**
- Medical monitoring for associated health issues.
- Lifestyle and therapy approaches aim to improve quality of life while research develops long-term treatments.

Boosting the remaining WAC copy's activity – drugs or epigenetic modifiers to increase protein production

Baby Force Trial

018

BabyFORce: A pioneering program translating variants identified via rapid genome sequencing to targeted therapeutics for neonatal intensive care unit patients

Whitney Thompson[1], Christopher Schmitz[1], Filippo Pinto e Vairo[1], Andrew Haak[1], Brandi Smith[1], Eric Klee[1], Christopher Colby[1], Lisa Schimmenti[1], Christopher Moxham[2], Natalie Downs[2], Nicole Perfito[2], Laura Lambert[1]

[1]*Mayo Clinic;* [2]*TranscriptaBio*

Introduction: Rapid genome sequencing (rGS) has accelerated the timeline for achieving precision diagnoses in critically ill neonates in the neonatal intensive care unit (NICU). Yet, variants of uncertain significance and pathogenic variants without therapeutic options continue to pose significant challenges. Mapping gene-function relationships offers a promising path for developing diagnostic tools and therapies tailored to individual genetics and environmental contexts. Herein, we introduce Baby Functional Omics Resource (BabyFORce), a pioneering program bridging discovery, translation, and clinical application to develop targeted therapies following rGS for NICU patients.

Methods: Following clinical rGS for NICU patients, positive cases are prioritized based on factors such as gene and variant significance, phenotype, sample availability, feasibility, family interest, and therapeutic potential. An artificial intelligence-powered drug repurposing infrastructure—NIH Translator—is used to identify potential drug opportunities, which are then reviewed for safety by a NICU pharmacist. When feasible, patient fibroblasts or whole blood samples are used for expression analysis or protein stability assays. Additionally, residual NICU tissue, such as umbilical stumps, is now being explored as a model for functional assays and drug testing. CRISPR-based gene editing is applied to modify cell lines and develop animal models for therapy validation.

Case examples: *MADD*: A newborn female born at 37 and 1/7 weeks gestation presented to the NICU with low birth weight, respiratory distress, club feet, feeding difficulties, and exocrine pancreatic insufficiency. rGS identified pathogenic/likely pathogenic loss of function variants (c.979C>T, p.(Arg327*); c.1603dup, p.(Gln535Profs*23)) in trans in *MADD*. Translational readthrough compounds were assessed in patient-derived fibroblasts to assess restoration of full-length protein by Western Blot. A high-throughput RNAseq-based screen in wild-type cells indicated upregulation by oxytetracycline.

WAC: A newborn female born at 33 weeks gestation presented with fetal growth restriction, anorectal malformation, tethered spinal cord, and hypoplastic aortic arch, aortic valve and mitral valve. rGS revealed a de novo heterozygous deletion of ~1651 KB at 10p12.1, associated with WAC-related intellectual disability. Therapeutic upregulation of the remaining WAC allele is being investigated, with FDA-approved compounds identified by NIH Translator undergoing validation in patient fibroblasts using qPCR, Western blot, and immunocytochemistry.

DPM1: A newborn female born at 33 and 2/7 weeks gestation presented with shortened long bones, atrial septal defect, rocker-bottom feet, clenched hands with overlapping fingers, and hypotonia. Prenatal exome sequencing confirmed by postnatal rGS identified biallelic pathogenic/likely pathogenic variants in *DPM1* (c.274C>G, p.(Arg92Gly); c.107A>T, p.(Glu36Val)), an enzyme involved in glycosylation. Patient-derived and CRISPR engineered cells will be analyzed via glycoproteomics and other mass spectrometry-based methods to assess response to treatment.

Results: *MADD*: Treatment with geneticin, ataluren, and gentamicin failed to restore full-length protein, but oxytetracycline resulted in a dose-dependent increase in MADD protein levels in control cells, indicating a potential treatment option for patients with hypomorphic alleles. Six additional patients with combinations of missense or missense/truncating alleles have been identified internationally and studies assessing therapeutic impact of oxytetracycline are underway.

WAC: Patient-derived and wild-type fibroblasts were established for drug screening by immunocytochemistry, with several repurposing candidates, including clonazepam, prioritized. Assays confirm reduced WAC expression in patient cells, establishing a reliable platform for further compound testing. Clonazepam demonstrated a dose-dependent increase in WAC protein expression in patient-derived fibroblasts.

Conclusion: BabyFORce represents a transformative approach that links rGS with functional and translational insights to advance care for critically ill neonates. Case studies in *MADD*, *WAC*, and *DPM1* highlight BabyFORce's potential to validate individualized therapies tailored to each patient's unique genetic profile.

https://doi.org/10.1016/j.gimo.2025.102094

BabyFORce – Helping Sick Newborns with Genetics

- A program that uses rapid genetic testing in intensive care newborns.
- Finds the exact genetic cause of illness within days.
- Looks for possible treatments, even if they are experimental or used for other conditions.
- Tests treatments in the baby's own cells in the lab before trying them.

How BabyFORce Works

- 1. Baby in NICU has rapid genome sequencing (rGS).
- 2. If a disease-causing change is found, the team searches for possible treatments.
- 3. AI tools suggest drugs that might help.
- 4. Baby's cells are grown in the lab to see how they behave and respond to drugs.

The WAC Gene Case

Baby born small with heart defects and spinal cord issues.

Genetic testing showed a deletion in chromosome 10 affecting the WAC gene.

Baby’s cells were tested with different drugs to see if WAC protein could be increased.

Clonazepam showed a dose-related improvement in WAC protein levels in lab tests.

One Baby Jori – improved after the drug. ? Placebo effect ? Real effect

Why BabyFORce is Important

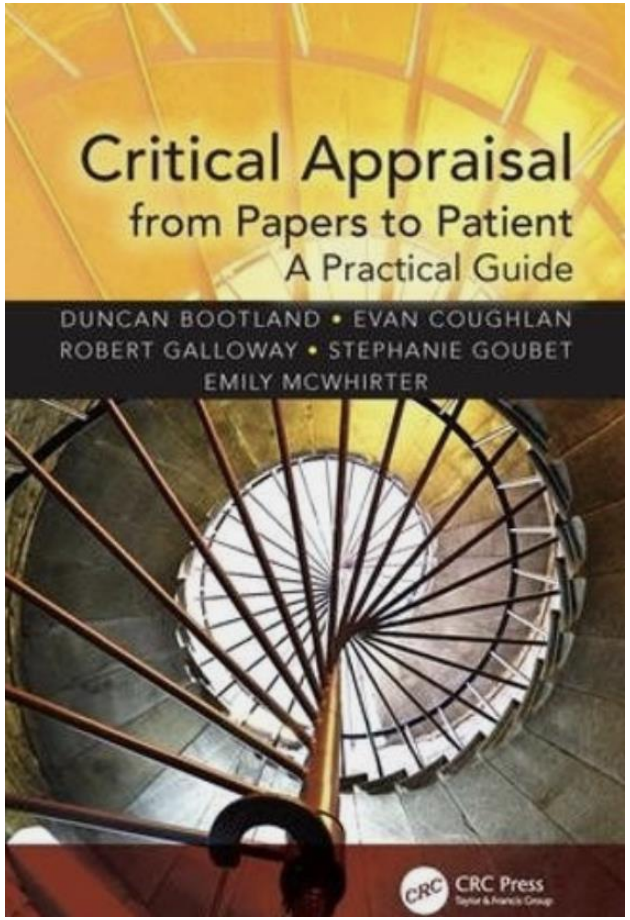
- Shows it’s possible to go from diagnosis to potential treatment testing in days.
- Could lead to personalised treatments for rare genetic disorders.
- Gives hope for babies with currently untreatable genetic conditions.
- Still early-stage research, but promising for the future.
- NEED TRIALS ON MORE THAN ONE PATIENT

Was the effect on Jori real or was it a placebo effect and she was developing anyway?

I asked for a meeting with the clinicians and scientists.....

As a skeptical academic, as a journalist and crucially as a dad desperate to help their child only diagnosed 5 weeks ago

I needed convincing……after the meeting, I believe it could help…hence why I would like Frankie to be on it in a trial setting



MAYO CLINIC

BabyFORce:

A Pioneering Program Bridging Discovery, Translation and Application to Develop Targeted Therapies Following rGS for NICU Patients

Whitney S. Thompson, M.D. M.Phil
Assistant Professor, Pediatrics & Medical Genetics
Fellow, Division of Neonatal Medicine & Department of Clinical Genomics

Laura J. Lambert, Ph.D
Assistant Professor, Physiology
Director, Functional Omics Resource

DESSH Foundation Medical Advisory Board
July 22, 2025

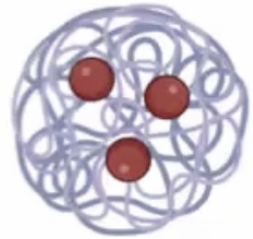
00:09 25:07

WAC: DRUGGABILITY

Assess Druggability

ASO

Gene Therapy



AI Repurposing

AI: mediKanren

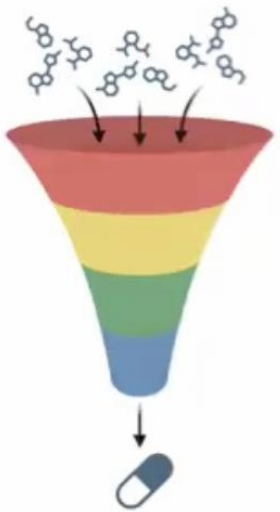
logical reasoning

+

biomedical knowledge

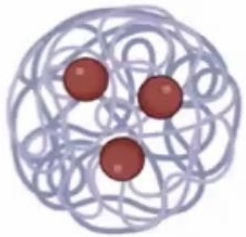
WAC: DRUGGABILITY

Assess Druggability



ASO

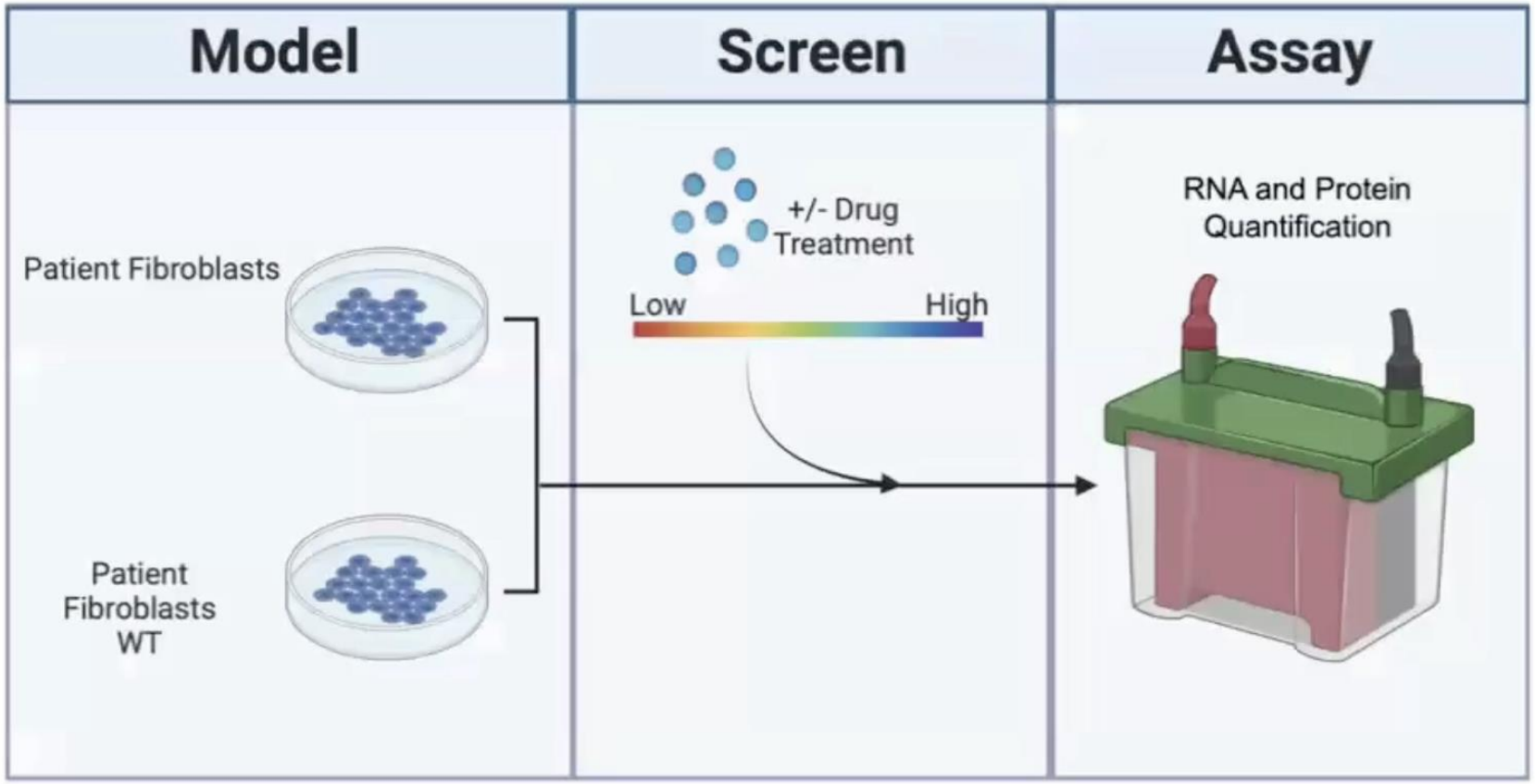
Gene Therapy

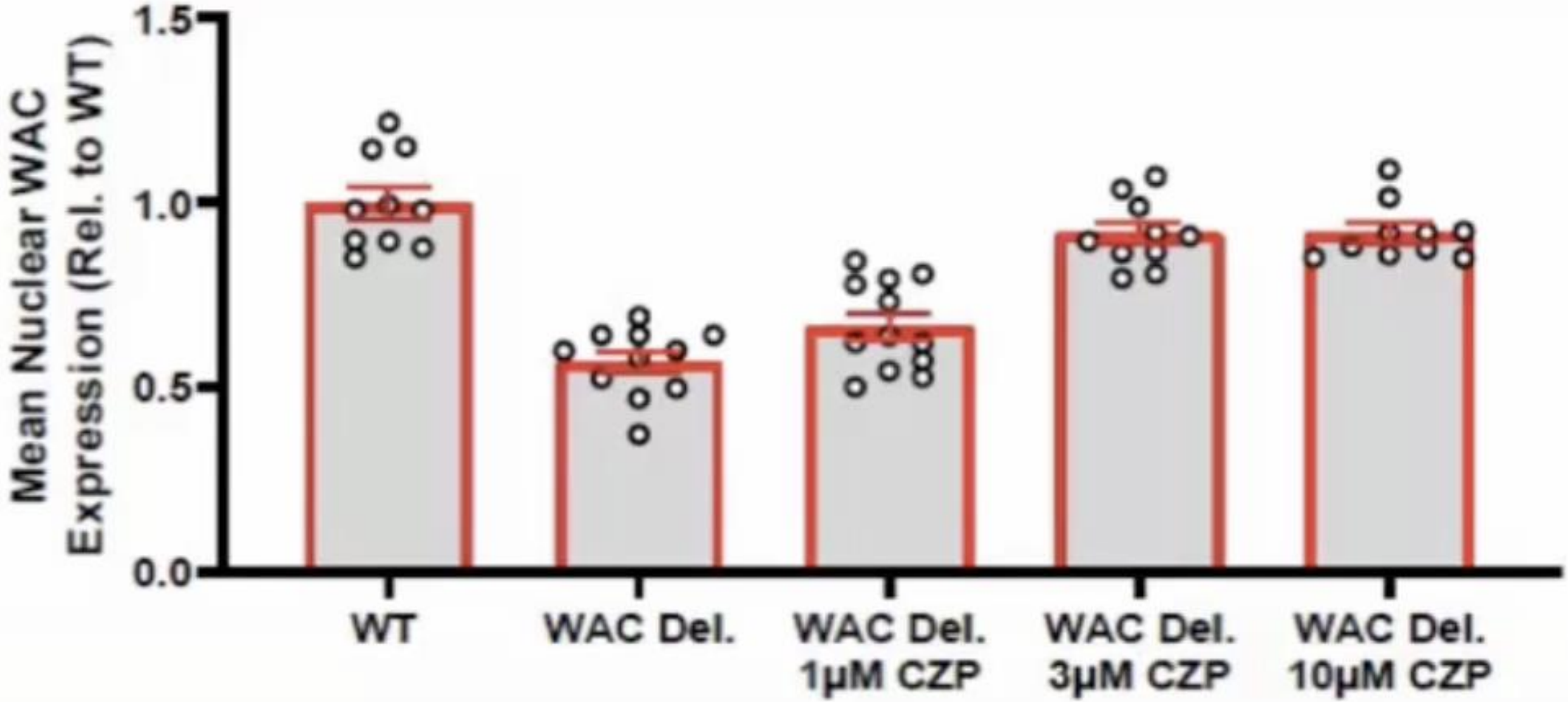


AI Repurposing

Intervention	Description
Tolcapone	A benzophenone derivative and a catechol-O-methyltransferase (COMT) inhibitor.
Clonazepam	A synthetic benzodiazepine derivative used for myotonic or atonic seizures, absence seizures, and photosensitive epilepsy, anticonvulsant Clonazepam appears to enhance gamma-aminobutyric acid receptor responses,
Diflunisal	Diflunisal competitively inhibits both cyclooxygenase (COX) -1 and -2, with higher affinity for COX-1, and subsequently blocks the conversion of arachidonic acid to prostaglandin precursors.
Meclofenamic acid	A nonsteroidal agent which has demonstrated anti-inflammatory, analgesic, and antipyretic activity
Triclosan	A polychloro phenoxy phenol with antibacterial and antifungal activity.
Salicylic acid	A beta hydroxy acid that occurs as a natural compound in plants.

WAC: EXPERIMENTAL PLAN



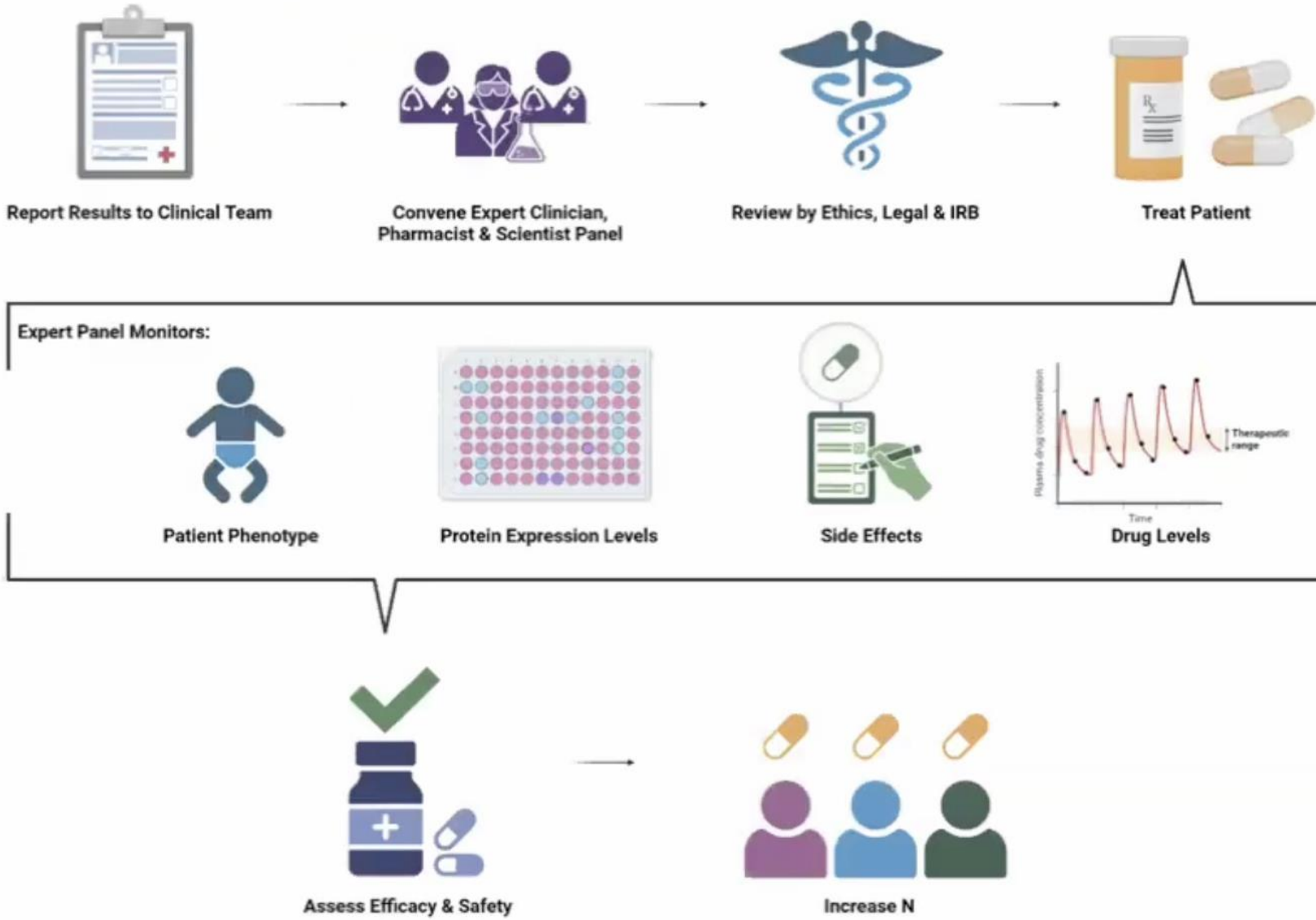

Mean Nuclear WAC Expression (Rel. to WT)
1.5
1.0
0.5
0.0
WT
WAC Del.
WAC Del. 1μM CZP
WAC Del. 3μM CZP
WAC Del. 10μM CZP

WAC: CONCLUSIONS

Developing therapeutic strategies for multigene deletions presents unique challenges due to the involvement of multiple genetic contributors. However, prioritizing known pathogenic genes with strong clinical correlations provides a rational starting point.

Clonazepam i) upregulates WAC expression in vitro in patient-derived fibroblasts relative to wild type controls, ii) is considered safe for use in children, and iii) is known to have significant CNS penetration

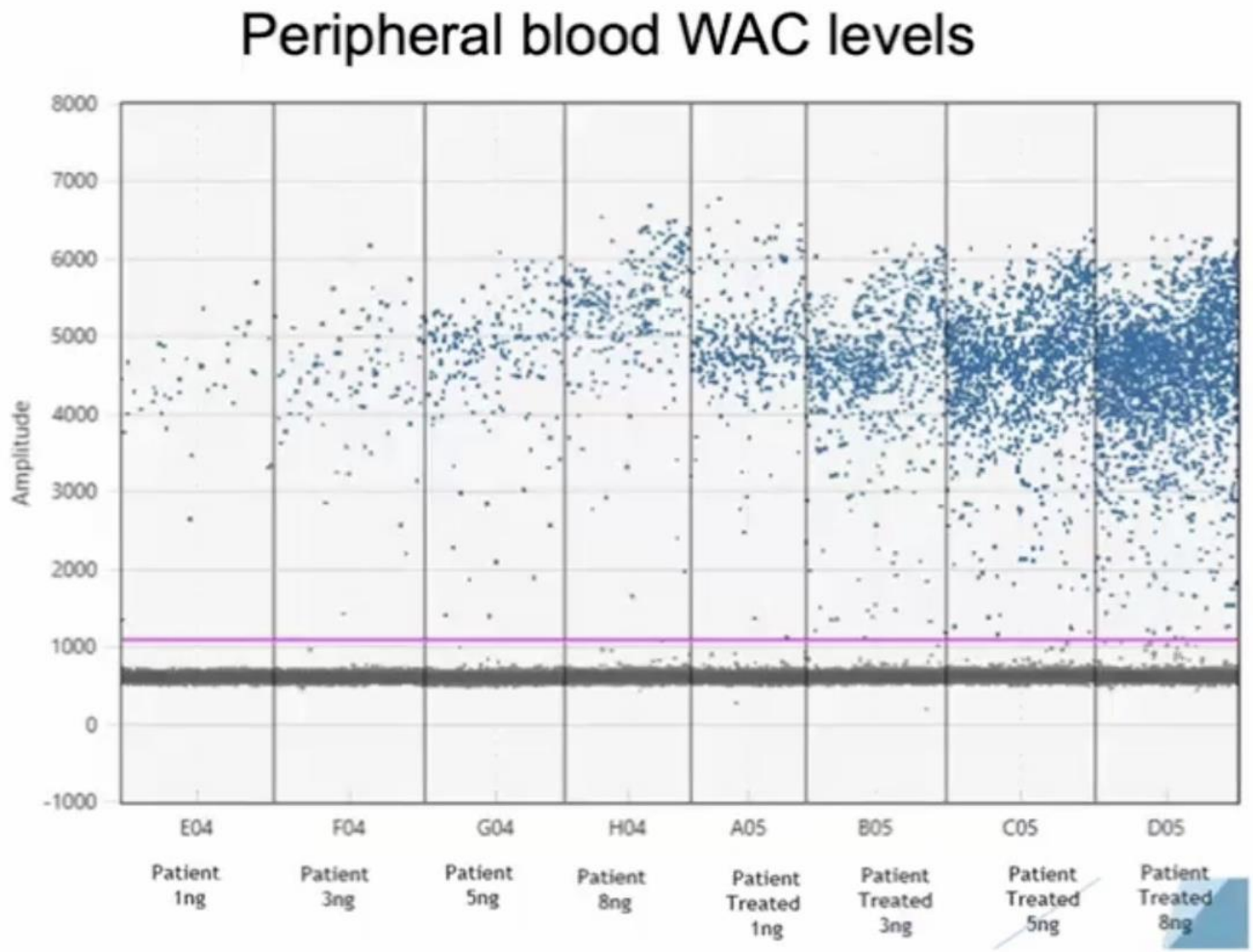
WAC: CLINICAL IMPLEMENTATION



JORIE – TREATMENT DAY 1!

Photos provided by Jorie's family and shared with permission

JORIE – 1 MONTH TREATED



JORIE – 1 MONTH TREATED

"IT'S LIKE THE LIGHTS HAVE TURNED ON."

-JORIE'S MOTHER

My thoughts…….

- Wow…..
- I want to get my daughter in it
- But I was thinking with my head not my heart…..
  - May or not work…depends on where the mutation is
  - Don’t know how long to give it for
  - May need to increase dose
  - Need to monitor effect with blood tests
  - Side effects

July 25, 2025

Dear DESSH Families,

We write to you together—as physicians, researchers, and advocates—because we know how deeply this community hopes for progress and how much care and thought each of you brings to navigating life with DeSanto-Shinawi Syndrome (DESSH) syndrome.

Recently, one child with DESSH experienced encouraging improvements while receiving an FDA-approved medication through a Mayo Clinic study. Understandably, this news has generated both excitement and questions about what this could mean for other individuals with DESSH syndrome.

After the press release of these preliminary findings, the DESSH Foundation's Medical Advisory Board and Board of Directors met with the Mayo Clinic team who led that study to share information and discuss next steps. We all share the same goal of finding a treatment that can alleviate the symptoms experienced by individuals with DESSH syndrome. At the same time, we agreed that this pursuit must be carried out responsibly using rigorous scientific methods and a systematic approach.

We also want families to be aware that, should a clinical trial move forward in the future, individuals who are already receiving this medication may be excluded from participation due to standard clinical trial design protocols.

WashU Medicine

MAYO CLINIC

The DESSH Foundation

In most clinical trials—especially those testing the safety and effectiveness of a drug—participants must begin the study without already being on the treatment being evaluated. This helps ensure the results are valid, consistent, and measurable across all participants. Allowing someone who is already on the medication could affect the integrity of the data, since their response to the drug wouldn't be measured from the same starting point as others.

We understand how difficult this is to hear, especially for families who are eager to try something that might help. We share this information now so that families can make fully informed choices and aren't unintentionally excluded from future opportunities by pursuing treatment independently before a formal study is launched.

We know this [illegible] uncertainty. We are committed to transparency, collaboration, and keeping this community updated as new information emerges.

Thank you for your continued trust, your courage, and your partnership in this journey.

Together for DESSH,

Dr. Marwan Shinawi, *Washington University*

Dr. Whitney Thompson and Dr. Laura Lambert, *Mayo Clinic*

Caitlin Piccirillo, Medical Advisory Board, and Board of Directors, *The DESSH Foundation*

So what….

- I want my daughter on a trial with no placebo…..and compare to expected development without treatment or historical behaviors
- USA is only country running a trial……therefore we may either have to have frequent trips or be excluded.
- Also to get good numbers need multiple centers for a trial

- Managed to get a clinical genetics review at Guys 6 days ago
- With Dragan Josifivoa
- Clinical Lead
- And expertise in genetics of hypotonia and neurodevelopmental delay
- And the loveliest person ever

From: JOSIFOVA, Dragana (GUY'S AND ST THOMAS' NHS FOUNDATION TRUST) <dragana.josifova@nhs.net>
Sent: 14 August 2025 12:01
To: Caitlin Piccirillo <caitlin@dessh.org>; GALLOWAY, Robert (UNIVERSITY HOSPITALS SUSSEX NHS FOUNDATION TRUST) <robert.galloway@nhs.net>
Cc: thompson.whitney@mayo.edu <thompson.whitney@mayo.edu>; lambert.laura@mayo.edu <lambert.laura@mayo.edu>; mshinawi@wustl.edu <mshinawi@wustl.edu>
Subject: Re: Introduction – Collaboration on European DESSH Research

Dear all

It is pleasure to meet you all very unexpectedly, but with a great ambition to help children and families who we see and look after. Without a doubt, Guy's Hospital and my department can host a clinical trial, and I am making steps to ensure that we can set this up in a timely fashion.

Catlin, thank you for offering to share the protocol you have developed for the DESSH patients. I would be grateful if you would send it across so that we can look into costing the project and any further aspects required by research governance to grant approval

I very much look forward to working together

With best wishes
Dragana

So what next

- Meeting with Guys hospital, and USA experts and protocol needs to be shared
- Start a trial on NHS
- If successful then can apply for NHS funding to make Guys a European center of excellence for DESSH and run clinics funded by NHS
- But we need to fund a trial in the UK….not silly money as drug is relatively cheap but need to pay for clinic time, lab test etc
- So setting up a charity to help fund the trial

An idea for a new charity

Why?

- Fund research into DESSH
- Fund research into other similar conditions which could benefit from same technique (also need this as the Guys team are more likely to do the research knowing its applicable beyond just 20 patients in the UK)

How

- Raise money and give out in grants to researchers
- Initially be as a Charitable Trust and then may move to be a Charitable Incorporated Organisation (CIO) if grows
- Initial aims- no employees, no costs and any costs I will absorb so 100% of raised money awarded in grants
- Board of trustees
- Medical advisory board
- Ambassadors/Patrons
- Why I think this will work
- We need connections and everyone's networks…. In UK and Europe….

Professor Rob Galloway

Professor Rob Galloway is an A&E consultant

TUESDAY 17 JUNE, 2025

The form you MUST ask your doctor about if you want to die at home surrounded by your loved ones

WORKING in A&E, I see the best of care but also the worst – and that's not

Good Health

FRIDAY 2 MAY, 2025

Fat jabs are great... if they're not abused

AS AN A&E consultant in a large NHS hospital, I see the effects of obesity on every shift; patients struggling to breathe; others needing emergency

News comment

TUESDAY 28 JANUARY, 2025

It's not lack of willpower that makes you put weight back on – it's cells that want to be fat again!

HAVE you ever lost weight on a diet only to see those pounds pile back on?

Good Health

TUESDAY 14 JANUARY, 2025

REAL reason men should be worried about erection problems

(and it's not to do with their sex life)

Good Health

TUESDAY 17 DECEMBER, 2024

I feel sorry for TikTok doctors who boast about the 'silly' money they get as locums

MEDFLUENCERS' – that's TikTok influencers who are doctors – are popping up on social media extolling

Good Health

TUESDAY 3 DECEMBER, 2024

Here's the proof anti-vaxxers have got it wrong – it's NOT the Covid jab making people ill

BEING known as the sick man of Europe is not the accolade anyone would want

Good Health

TUESDAY 19 NOVEMBER, 2024

The surprising reasons I believe so many young people are getting bowel cancer

TUESDAY 5 NOVEMBER, 2024

My back pain has vanished thanks to a £200 device... and it burns calories too!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What charity is and isn't

- Purely a research grant giving charity primarily set up for DESSH bit could move into other rare genetic childhood diseases
- It isn’t a support group for parents
- It isn’t to fund treatment – although treatment will be part of trials
- It isn’t for education
- But there is a need for a UK DESSH support group
- There is a superb worldwide one

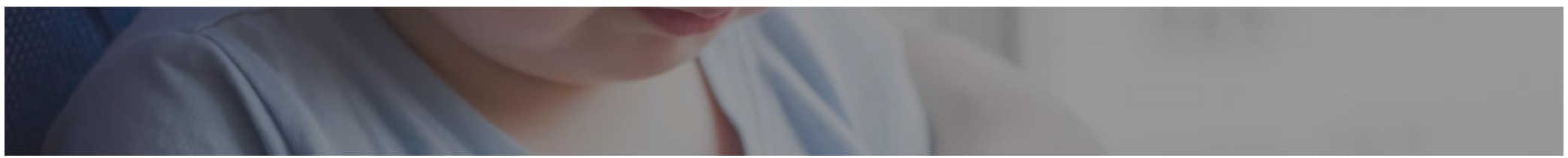
https://www.dessh.org/

RARE PEOPLE

THE RESEARCH CHARITY

DESSH is short for DeSanto-Shinawi Syndrome.

DeSanto-Shinawi Syndrome is a rare neurodevelopmental genetic syndrome caused by a mutation or deletion in the WAC gene. DESSH is characterized by global development delay, intellectual disability, hypotonia, dysmorphic facial features, epilepsy, and ocular, gastrointestinal, and behavioral abnormalities. WAC is identified as an autism gene.



Plans for the UK/Europe

- Hopefully Guys will be able to become a center of excellence and run clinics funded by the NHS
- We can start to run UK DESSH meet ups for support and education and expertise sharing within the DESSH organisation but separate to the charity

Summary

- UK center happy to lead on DESSH research
- Hopefully will then set up NHS funded DESSH clinics
- Adopt USA protocols
- Use as a proof of concept for other diseases
- Research funded through our charity
- Set up support groups
- But…….need help……with everything!!!!
- Crucially raising money when we have set up charity and also being part of the research when ready to go