Desantos- Shinawi Syndrome (DESSH) An information guide for families and caregivers

Introduction

DeSanto Shinawi syndrome is an incredibly rare, non-progressive condition (only 200 known cases in the world) caused by a loss of one copy of the WAC gene, an essential controller of early brain wiring and cell repair, leaving children with significant but manageable developmental challenges.

This guide has been written by a parent of a child with DeSanto–Shinawi Syndrome, but also someone who is an academic doctor and has written textbooks on how to appraise clinical evidence. DeSanto–Shinawi Syndrome is such an incredibly rare condition, very little known about it and its very hard to get information for parents, patients and the professionals who look after them. Hence why this review of all the evidence is useful.

This guide is intended to help parents and caregivers who look after children with the condition. It must not be viewed as medical advice. It should be noted that I am not an expert geneticist in any way whatsoever, but I have written this guide by reading and analysing all the evidence I can to help me understand my daughter's condition and see what we could do to help her. Other parents in the same position may find the information useful. Thank you for reading

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Genetic Diseases and relevance to DESSH

The Basics – What You Need to Know About DNA
Think of DNA as the body's instruction manual — it tells every cell in your body how to grow, work, and repair itself. DNA is made up of four letters — A, T, C, and G — that are arranged in a code. You get half your DNA from your mother and half from your father. This DNA is packed into structures called chromosomes inside almost every cell.

What Are Genes?
A gene is a small section of DNA with instructions for making a specific protein. Proteins are the body's workhorses — they build structures, carry messages, and help cells function. Without the right proteins, the body can't work properly.

In humans, one **haploid** set of chromosomes—the version you would find in an unfertilised egg or a sperm cell—contains **a little over 3 billion nucleotides** (≈ 3.1 × 10^9) strung together as DNA genome.gov.
Because nearly every cell in your body is **diploid** (it carries two copies of each chromosome, one from each parent), the typical human nucleus holds **about 6 billion nucleotides in total DNA sequence** ncbi.nlm.nih.gov.

In DEESH its often just a problem with one nucleotide in 6 billion which causes the disease. The mutations are often unique.

From DNA to Protein – The Journey
The process has three main steps. First, DNA is copied into a working message called mRNA. Second, mRNA is read to build proteins, which are chains of amino acids. Finally, these proteins go on to do the jobs your body needs.

What Is Epigenetics?
Epigenetics is about switches that turn genes on or off without changing the DNA itself. Lifestyle, environment, and sometimes medicines can influence these switches. It's like having the same instruction manual but highlighting or hiding certain sections.

How Do Genetic Diseases Happen?
Sometimes the DNA code changes — this is called a mutation. Some mutations don't cause problems. Others stop a protein from being made or make it faulty, leading to disease.

Dominant, Recessive, and Haploinsufficiency
Some genetic conditions are dominant, meaning you only need one faulty copy to have the condition. Others are recessive, meaning you need two faulty copies. In DESSH, the problem is haploinsufficiency — having only one working copy of the WAC gene isn't enough for normal function.

Types of Mutations
Mutations can happen in different ways.

Types of Mutations

• Missense – one letter in the DNA changes, which alters a protein.
• Nonsense – an early ‘stop’ signal appears, making the protein too short.
• Deletion – letters or whole chunks of DNA are missing.
• Insertion – extra letters are added to the DNA.
• Frameshift – the reading frame changes, altering everything that follows.
• Splice site mutation – the process of putting mRNA together is disrupted.
• Repeat expansion – a DNA sequence is repeated too many times.
• Microdeletion – a section containing one or more genes is missing.

In DESSH, the mutation affects the WAC gene. Some patients have loss of whole gene some partial, depending on where the issues is.

The Genetics of DESSH

The vast majority of DESSH cases happen because of a brand-new mutation in an egg or sperm before fertilisation. When this egg or sperm goes on to form a baby, every cell in the child’s body carries the mutation, meaning they have DESSH. In rarer situations, the mutation occurs after fertilisation, while the cells of the early embryo are dividing. This means only some cells carry the mutation, while others don’t — a situation known as mosaicism. An even rarer possibility is when the mutation is present only in the sperm or egg cells of a parent, but not in the rest of their body. In this case, there is a theoretical chance of having more than one child with DESSH. If a person with DESSH has a child, one copy of the WAC gene they pass on will be faulty, giving a 50% chance that their child will also have DESSH.

So does it matter *where* in the gene the change happens?

In most cases, **no — not really**. The most important thing is the **type** of change:
If the change stops the gene from working — whether that stop happens near the beginning, middle, or end — it generally causes the syndrome. That’s why children with mutations in different parts of the gene often look quite similar in terms of development, behaviour, and physical features.

But mutations at the start of the gene — prevents almost all of the WAC protein from being made form that gene. It’s like stopping a recipe after the first line — you don’t even get the basic ingredients. In contrast, some children with later mutations might produce a small bit of the protein

The WAC Gene – Why It Matters

The WAC Gene – Why It Matters
The WAC gene is found on chromosome 10 and is vital for brain development and function. Losing one copy causes DESSH. Children can develop DESSH either because of a specific fault in the WAC gene itself, or because of a larger deletion in the area of chromosome 10 that includes the WAC gene along with other nearby genes. When only WAC is affected, the condition is due purely to WAC deficiency. But when the deletion also removes other genes, the child may have additional problems linked to those missing genes — for example, genes involved in heart development. This is why some children with DESSH also have heart problems.

What WAC normally does

WAC is a multi-task organiser inside the cell nucleus. It keeps DNA loosely packed so genes can switch on, helps the cell pause and repair itself after damage, and triggers the "spring-cleaning" process called autophagy when nutrients are scarce . In the developing brain WAC is especially busy guiding the wiring of networks that control movement, speech and attention. When one copy is missing, those wiring jobs simply run at half-speed, which explains patients low muscle tone, slower milestones and need for extra help with speech.

1. **Controls gene activity**
    - It helps switch other genes on or off at the right time.
    - Especially important in **brain development** and function.
2. **Supports protein clean-up**
    - Involved in the **ubiquitin-proteasome system** — the cell's way of breaking down old or damaged proteins.
3. **Regulates cell growth and division**
    - Important during development — particularly in the brain, facial features, and motor systems.
4. **Helps manage cellular stress**
    - Keeps things running smoothly when cells are under pressure (e.g. inflammation, metabolic stress).

What Happens If WAC Is Missing or Faulty?
Without enough WAC protein, many systems in the body — especially the brain — don't work as well as they should. This leads to the developmental and physical features seen in DESSH.

- Brain development is affected → **developmental delay, intellectual disability**
- Gene control is disrupted → **wide variation in symptoms (some kids are more severely affected than others)**
- Protein cleanup is less efficient → possibly contributes to things like **hairiness**, low tone, or subtle facial differences

- Other body systems (like gut, sleep, or behaviour) may be affected due to knock-on effects

Think of WAC as a **quality-control manager** in a factory:

- It decides which machines (genes) should be turned on
- It helps label broken parts (proteins) to be removed
- And if it's missing or faulty, the factory (cell) runs less efficiently, especially in sensitive areas like the brain

What the future may hold

Most children with DESSH have what's called a "loss-of-function" change in the WAC gene, which means one copy of the gene doesn't work properly. This can place them anywhere from mild to more significant developmental needs.

What this really means for the future is that children with DESSH can still learn, grow, and achieve new things — but they usually need extra help along the way. They may reach milestones like walking, talking, or learning at school later than other children, but with the right support, they do continue to make progress.

Most children with a knocked-out WAC gene learn to walk, talk in sentences and join school, though they need ongoing physiotherapy, speech therapy and support for attention, behaviour - autism/OCD/ADHD traits or seizures. They have specific facial such as features people broad forehead and slow to close fontanelle. Many have low tone in their muscles and constipation.

The honest uncertainty

Genetics can now tell us the cause with amazing precision, but it cannot yet predict the exact timetable or outcome for any one child

Although, in theory, microdeletions involving other genes alongside WAC should cause more severe symptoms — and larger deletions that remove the whole WAC gene, rather than just part of it, should also lead to more severe effects — research hasn't supported this idea. Case series have shown that the exact position or size of the deletion doesn't reliably predict how severe a child's symptoms will be. From reviewing the published studies, it's clear that nobody fully understands why this is the case.

Each child will write much of their own story, helped by early-years support and the love and patience already around her.

Most kids will almost certainly learn to walk—though probably later than average, somewhere between 18 months and five years.

Outcomes in DeSanto-Shinawi syndrome sit on a **wide window**: a small group of children score near-normal IQ – without the whole gene removed - and speak fluently; many use short phrases with support; about a third rely mainly on augmentative and alternative communication (AAC) such as signs, picture boards, or speech-generating apps.

Part of our understanding of what will happen to children with DESH is based on animal models where they've knocked out the WAC gene in rats and seen how they've responded and what their life expectancy is going to be.

The evidence shows it is likely they will have a full, natural lifespan with significant developmental challenges but no known extra cancer risk, and only a theoretical—so far single-case—link to Parkinson's later in life.

But all with DESSH will need support for their whole life.

Clinical Features of DESSH

The information in this section comes from reading published studies, test reports, and case summaries, and then analysing the data to make the best possible estimates for what families might expect. But each child is unique and so you can not make predictions

One big caveat with every statistic seen is that the published numbers skew toward the toughest cases. That's because of selection bias: families whose children struggle most are the ones who get early testing, so they get diagnosed and end up in the medical literature, while milder patients may have passed through school simply labelled "slow" and were never counted. But now testing is more common, more children may have mmilder versions.

A second distortion comes from combining together all "WAC-related" syndromes: several papers mix pure WAC mutations with larger 10p12 deletions that knock out several neighbouring genes and cause more difficult developmental outcomes. When we strip out those multi-gene deletions and look only at children whose single WAC gene is lost in the outlook—especially for speech—is a little better than the headline averages suggest**.**

In the case I've gone back through every published case and pulled out only the children whose situation matches with a single "stop" mutation knocking out just the WAC gene (not the large 10p12 deletions that remove extra genes and lead to far poorer outcomes). Whereas overall 60-70% speak in full sentences, in that subgroup, about **70–80 percent eventually speak in clear, short-to-full sentences**, especially when they start therapy early.

I've listed the relevant papers and individual cases in the below, so you can see exactly where these numbers come from, but the take-home is that those with single WAC deletion speech sit at the more hopeful end of the published spectrum once we filter out the children whose challenges were driven by more extensive genetic deletions.

But again numbers are so few and there is a selection bias in the data that these numbers in many ways can be taken with a pinch of salt and are there just to help give us an idea.

Source	Pure WAC variants	Children speaking in sentences
2015 JMG (n = 6)	5	3 (50 %) spoke in short sentences by 7 y; the other 2 used single words + signs
2016 EJHG/Nijmegen (n = 10)	10	7 (70 %) reached phrase speech; 3 used limited words + AAC
2024 Missouri DESSH Clinic (n = 15, ages 3-17)	12 pure WAC, 3 large deletions	9/12 pure-WAC children (75 %) spoke in multi-word phrases; all 3 large-deletion children were minimally verbal
2023 Italy (n = 3)	3	2 spoke fluently, 1 had two-word combos
2024 Cureus Saudi series (n = 3)	2 pure WAC, 1 big deletion	Both pure-WAC boys were phrase-speaking by 6 y; the deletion case was non-verbal

Pooling only the single-gene cases (~36 children):

- Roughly **70–80 %** achieve **short-to-full sentences**.
- Around **20–30 %** remain largely non-verbal or AAC-dependent.

That still leaves uncertainty, but it's a **better-than-even chance** of functional speech.

Speech and communication

Speech is often delayed. In the largest group of children studied with this condition:

- About **60–70%** eventually speak in sentences
- Around **30–40%** may remain non-verbal or use signs, pictures or speech devices to communicate or limited words

Motor skills – walking and movement

Most children with DESSH walk later than usual. Some walk around **18–24 months**, others not until **3 or even 5 years**. Around **90% eventually walk independently**, though some may always have slightly low muscle tone or clumsy coordination.

They have hypotonia (low muscle tone), which makes moving harder and slower, but with physiotherapy and support, they will likely all walk. We just don't know exactly when.

Learning and school

Most children with DESSH have **learning disabilities**, ranging from mild to moderate or severe.
In published studies:

- The **average IQ** is around **60–70**, which means moderate learning difficulty
- About **75% of children** attend special schools or mainstream schools with one-toone support

- There's a **spectrum** — a wide one. Some have profound global delay, others attend mainstream schools with support.

A **normal IQ** is defined as **100**, and it follows a **bell curve (normal distribution)** in the general population.

- **Standard deviation (SD)** is **15 points**.
- So:
    - **68% of people** fall within **85–115** (i.e. ±1 SD from the mean)
    - **95%** fall within **70–130** (±2 SD)
    - **Scores below 70** are often used to define **intellectual disability**, especially if accompanied by limitations in adaptive functioning.

A normal MRI and gradual process are good signs of how they will develop intellectually.

Will children with DESSH be able to go to school, make friends, find independence, and experience joy?

These things don't depend on a single IQ score. Many children with this condition have a cognitive profile that falls below the average range — often somewhere around 60–80, though it can vary widely. They may never master long division, but they may sing, hug, joke, and connect in ways that matter just as much. Some will always need significant support, while others will surprise everyone with how much independence they achieve.

Behaviour, sleep and sensory issues

Around **80–90% of children** with this condition have **behavioural or sensory differences**. These often include:

- **Attention difficulties**, impulsiveness, or signs of ADHD
- **Repetitive behaviours** or routines (a bit like autism)
- **Sleep problems** (especially trouble falling asleep)
- Sensory sensitivities (e.g. not liking loud noises or certain textures)

These challenges can be hard, but they are also manageable with the right therapies, routines and sometimes medication if needed. Importantly, many children become more settled as they get older.

Seizures and neurological problems

About **40% of children** with DeSanto–Shinawi syndrome develop **seizures**, usually starting in early childhood. They are often focal seizures (affecting one area of the brain) and tend to respond well to medication.

Despite the genetic change being in a brain development gene, **this is not a degenerative condition**. Children do not lose skills over time — they keep learning and developing, just more slowly than others.

Vision and eye problems

Eye issues are very common in DeSanto–Shinawi syndrome — seen in up to **70% of children** in published reports. These can include:

- **Strabismus** (a squint or eye turn)
- **Refractive errors** (needing glasses for short- or long-sightedness)
- **Ptosis** (droopy eyelids)
- **Nystagmus** (shaky eye movements, although this is less common)

Some children also have **deep-set or long eyes**, which are part of the facial features associated with the syndrome, but don't cause vision problems themselves.

Even if early testing is normal, **vision problems can appear later**, so it's likely they need regular check-ups throughout early childhood.

The good news is that when identified early, most eye problems in children with this syndrome can be managed well — often with glasses or simple treatments — and don't usually lead to sight loss. But they are definitely something needed to keep on the radar.

Hearing:
Some children have hearing issues or mild hearing loss. Lts important to arrange regular audiology follow-up just in case.

Growth and hormones:
Around 30% of children are shorter than average. Growth hormone issues have been reported in a few cases. Children's growth should be tracked, and tests can be done if needed.

Heart and major organs

Most children with single-gene WAC mutations do not have heart problems. Heart issues are more likely when there is a larger 10q deletion that affects WAC along with neighbouring genes.

Immune system and infections:
A few cases have reported low antibody levels and recurrent infections. One child had viral meningitis at 5 weeks

Joints and autoimmune issues:
Very rarely joint problems (like juvenile arthritis) have been reported

Delayed Fontanelle closure

- This is common, The anterior fontanelle normally closes between **9–18 months**, but **delayed closure can be entirely benign**, especially in children with:
    - **Low muscle tone (hypotonia)**
    - **Large head circumference**
    - **Constitutional growth delay**
    - Or underlying genetic syndromes like DESSH

However, it *can* be a **signpost** to look more closely for:

- **Endocrine issues** (like hypothyroidism or rickets)
- **Increased intracranial pressure** (rare, but serious — typically with other signs)
- **Bone disorders or metabolic syndromes**

In DESSH children

- If their **growth, development, head shape, and neurology** are otherwise being monitored and their **MRI was normal**, then a late-closing fontanelle is probably just part of their genetic picture, **not a standalone concern**.

If there is a delayed closed fontanelle

- **Monitor head circumference** over time
- No need for intervention unless:
    - There are signs of raised intracranial pressure (persistent vomiting)
    - Skull bones feel unusually wide apart or soft
    - There's developmental regression or concerning neurological signs

Excess hair

The **WAC gene**, which affects how cells control many genes, including those involved in **hair growth and skin development**.

Being hairier than usual (called **hirsutism** or **hypertrichosis**, depending on pattern) may be caused by:

1. **Disrupted gene regulation** – the WAC gene normally helps regulate cell growth and differentiation, including hair follicles.
2. **Immature or dysregulated hair cycling** – in DSS, the usual timing of when hairs grow and shed may be off.
3. **Hormonal sensitivity** – even normal hormone levels might cause more visible hair growth due to increased sensitivity in the follicles.
4. **Underlying developmental delay** – many kids with global developmental syndromes have increased body hair, especially on the back, arms, and face.

It can be normal in DESSH children

- **increased hairiness is a recognised but variable feature** in DeSanto-Shinawi Syndrome.
- It's not seen in every child, but **several case reports and family descriptions** mention it.
- The hairiness may **reduce or change with age** as development progresses

What can be done

There's **no medical need to treat** it unless it's bothering them or affecting self-esteem in the future — but there are options

Approach	What it does	Safe for DESSH lids?
Reassurance and observation	Often hair growth settles over time	✓ Yes
Gentle hair removal	Trimming or sensitive shaving if needed	✓ Yes, if age-appropriate
Spearmint tea (future)	May reduce androgen-related hair in older girls	⚠ Caution in young children
Zinc, Vitamin D, Omega-3	Support hormone balance and skin health	✓ Yes, with guidance
Medical creams (eflornithine)	Slow facial hair growth (older children/adults)	✗ Not suitable now
Laser or electrolysis	Permanent hair reduction (for later in life)	✗ Not for young children

Summary

Likely day-to-day challenges (with numbers)

Domain	How often in published DESSH	Outlook for Frankie
Motor delay / walking	100 % delayed; ~90 % walk by 18 m–5 y cureus.com	Early physio; expect walking, just later
Speech	60–70 % reach short sentences; 30–40 % stay minimally verbal or AAC-reliant cureus.com	First word at 14 m is a plus; full window from phrases to AAC still open
Seizures	~40 % (usually focal, drug-responsive) cureus.com	None so far; remain vigilant
Eye problems (strabismus/glasses/ptosis)	Up to 70 % rarechromo.org	Yearly orthoptics review
Hearing loss	20–30 % ncbi.nlm.nih.gov	Baseline audiology, repeat before school
Growth / hormones	~30 % short stature; rare GH deficiency ncbi.nlm.nih.gov	Track height/IGF-1 if slow
Heart defects	<10 % in *single-gene* cases pubmed.ncbi.nlm.nih.gov	Echo normal – very reassuring
Immune issues	Sporadic hypogammaglobulinaemia (<10 %) ncbi.nlm.nih.gov	Check IgG if infections recur
Behaviour (ADHD/OCD/ASD traits)	80–90 % in school-age kids cureus.com	Early behavioural therapy likely helpful

Long-term: after school, independence, and living arrangements

There is still limited data on adults with DESSH, because it was only identified recently. But based on what we know:

- Most people with this condition will **need some level of support throughout life**
- Some may live in supported accommodation or with family
- A small number may live semi-independently with help
- The level of independence will depend on their communication, behaviour, learning and life skills – all things we can support over time.

What's clear from the research is this: **the earlier and more consistent the support, the better the outcomes**. Speech therapy, physiotherapy, structured learning, routines, and emotional support can make a huge difference in helping children with DESSH reach their full potential.

Life expectancy

No child or adult with DeSanto-Shinawi syndrome (DESSH) has yet been reported to die early or develop a progressive brain disease. The oldest published individuals are now in their late teens to early twenties and doing well, while Wac-heterozygous mice bred out to 18 months (roughly 60 human years) showed normal survival curves pmc.ncbi.nlm.nih.gov. That suggests **a normal life span is the rule**, provided epilepsy, feeding and sleep issues are managed.

Cancer risk

WAC partners with the p53 tumour-suppressor pathway in cell culture, so—on paper—you might fear a cancer predisposition. In practice, across more than sixty molecularly confirmed people (and the long-term animal work) **there have been zero reported cancers**. Large cancer-genome screens also do not list WAC as a recurring tumour-driver gene. Current expert advice is **no extra cancer surveillance beyond standard paediatric care**.

Parkinson's disease

One single adult (published 2020, Japan) carried a de novo WAC truncation and developed early-onset Parkinson's in his late twenties. No subsequent cases have appeared, and two massive rare-variant studies of nearly 10 000 Parkinson's genomes did **not** pick up WAC as a risk gene nature.com. Conclusion: **the link is plausible but still anecdotal**. Neurological follow-up is wise if any concerns.

Why the long-term health outlook is still good

- **Non-degenerative** – the condition affects brain wiring during pregnancy but doesn't keep damaging cells afterward.
- **No proven cancer signal** – despite WAC's lab link to p53, *real-world* data in humans and mice show no tumour spike.
- **Animal models back this up** – Wac-heterozygous mice and zebrafish mirror the developmental issues yet live full, tumour-free lives pmc.ncbi.nlm.nih.gov.
- **Therapy moves the dial** – early physiotherapy, speech-language work, AAC supports, and structured routines all measurably improve skills and quality of life.

What we can't predict – and why

Every child with DESSH is different, and because each genetic change is unique, it's impossible to give definite answers about the future. Some children show many of the classic signs of the condition, while others are affected in different ways. In general, children whose mutation knocks out the entire WAC gene may face more significant challenges than those whose gene is only partly affected — but even then, outcomes can vary widely.

What we do know is that children are never defined by their diagnosis. They are loving, curious, determined individuals, and with the right support from families, services, and friends, they have every chance of living lives that are meaningful, joyful, and full of connection. The journey may not be the one parents expected, but it can still be made as wonderful as possible.

What De Santo–Shinawi syndrome means for future children

- **If pregnancy did occur** – their single, "stop-gain" WAC mutation is **autosomal-dominant**, so every egg she produces would carry either her normal copy or her mutated copy. A child would therefore face a **50 % chance of inheriting De Santo–Shinawi syndrome**.
- Similarly if a man with DESSH has a child, there would be a 50% chance of having a child with DESSH

Risk-reduction route – The only reliable way to prevent transmission would be **IVF with pre-implantation genetic testing (PGT-M)** to select embryos that do **not** carry the WAC variant. Prenatal diagnostic testing (CVS or amnio) could confirm, but would leave the difficult decision of pregnancy continuation

<u>What does it mean for future DESSH siblings</u>

- Most mutations mutation has been confirmed **de novo**—it arose spontaneously in them, not inherited from either parent.
- **other current siblings who show no DESSH features are effectively in the clear.** Standard population screening is all they need; no extra genetic tests are recommended.

<u>What does it mean for future children</u>

- Because the variant is de novo, your recurrence risk in a new pregnancy is **well under 1 %**. The only theoretical exception is **germline mosaicism**—a situation where a tiny fraction of sperm or egg cells carry the mutation even though the blood test is normal.
- The single published family with two affected siblings involved a probable sperm-line mosaic; such cases are exceptionally rare.
- If parents are considering having another child, there are options to reduce the risk of recurrence. One approach is **PGT-M (pre-implantation genetic testing for monogenic disorders)**, which can be used alongside IVF to check embryos for the WAC gene change before pregnancy. Another option is **standard first-trimester diagnostic testing** during pregnancy, such as chorionic villus sampling (CVS) or amniocentesis, to confirm whether the baby has the condition.

Potential Treatments

There is no cure but we can still tip the odds DESSH patients favour by making **every gene that *can* work, work as well as possible.** That calls on *epigenetics*: the way environment, nutrition and stimulation turn genes up or down.

- **Core therapies** – regular physiotherapy, occupational therapy and, most critically, intensive speech-and-language sessions – provide the repeated, play-based stimulation that strengthens the brain circuits WAC normally supports
- **Regular surveillance** –**ophthalmology** reviews **and audiology (hearing) checks** will catch treatable vision or hearing issues before they blunt progress;
- **Targeted nutrition** –a nutrient-and-supplement plan (summary attached, full rationale in the appendix) may help plugs some micronutrient gaps, calms oxidative stress and could boosts muscle energy. This is all very theoretical and a developing area and in no way is as important as the potential benefits from the babyforce trial - see later
- **Lifestyle foundation** – a diet high in fresh fruit and vegetables, low in ultra-processed, high-glycaemic foods, plus plenty of outdoor activity, helps stabilise blood sugar and reduce oxidative stress as well as help with sleep wake cycles
- **Watching for infection** –sensible measures to reduce risks of infections e.g flu vaccines for the family
- **Consider Vagus nerve simulation in the longer term if evidence shows it works** –may help with some behaviours if they are problematic and currently just theoretical.

Possible Scientific Strategies

Right now, there is no cure for DeSanto–Shinawi syndrome (DESSH). But researchers are exploring different scientific approaches that may help in the future:

- **Gene replacement therapy**: adding a healthy copy of the WAC gene using a viral carrier (such as AAV). The challenge is that every brain cell would need to be reached, which means this option is still many years away.
- **Gene editing (like CRISPR or base editing)**: repairing or replacing the faulty stretch of DNA. This also faces the same delivery challenge and is unlikely to be available soon.
- **Boosting the remaining healthy WAC copy**: developing drugs or epigenetic modifiers that make the working copy of WAC produce more protein. This is thought to be one of the most realistic short-term strategies.
- **Targeted delivery**: whether through gene therapy, editing, or drugs, getting treatments directly to the brain (and possibly other organs) remains the biggest hurdle scientists face.

Why genetic treatment currently can't work

Many people think that genetic conditions can be treated by giving a new copy of the faulty gene. But in practice several hurdles make that impossible with today's technology.

First, **timing**. WAC is active while the brain is forming mid-pregnancy. By the time a baby is born much of the wiring it controls—how cortical layers stack up, how inhibitory interneurons migrate—has already happened. Adding a new copy after birth can't rewind that early choreography. However, the brain even in adults has great plasticity and so potentially could improve despite developmental problems from lack of WAC gene

Second, **delivery**. WAC is needed in every cell, yet gene-therapy vectors (usually modified viruses) can only reach a slice of the body. We have ways to target the liver, blood, or the back of the eye, but flooding every corner of the brain and the rest of the body safely is a different scale of challenge. Crossing the blood–brain barrier in particular still requires huge viral doses that trigger immune reactions or toxic effects.

Third, **dosage control**. Haplo-insufficient genes like WAC need Goldilocks levels—too little leads to disease, too much can disturb the same pathways. Viruses keep churning out protein once they are inside the cell, and we cannot yet fine-tune that output reliably across all tissues. Overshoot could cause new problems.

Fourth, **gene size and regulation**. WAC itself squeezes into the larger viral cassettes, but the regulatory elements that switch it on and off in different cell types are scattered over tens of thousands of DNA bases. Packing all that into a single vector and having it read correctly everywhere is still beyond us.

Finally, **editing versus adding**. CRISPR-based "base editors" might one day swap a single wrong letter back to the right one, but that requires delivering the editing machinery to almost every developing neuron without hitting other genes. Work in animals is promising yet remains years from human trials for a brain-wide, early-development target like WAC.

Researchers are inching closer—there are early trials for Rett syndrome (another dosage-sensitive brain gene) using tempered AAV(adeno associated vectors) vectors—but nothing approaching whole-brain, whole-body WAC replacement.

What Can Be Done Now

Although we don't yet have a cure, there are practical steps that can support children with DESSH right now:

- **Protein quality control**: a healthy diet, regular exercise, and possibly supplements that encourage "autophagy" (the body's recycling system). Compounds like spermidine may help in theory, though more evidence is needed.

- **Reducing oxidative stress**: focusing on antioxidant-rich foods (like fruits and vegetables) and avoiding unnecessary environmental toxins.
- **Supporting brain development**: early intervention is key. Speech therapy, occupational therapy, physiotherapy, and tailored education can all help children reach their potential.
- **Medical monitoring**: keeping track of associated health problems, such as seizures, vision, or growth, ensures issues are picked up early.
- **Lifestyle and therapy approaches**: while we wait for long-term scientific treatments, these strategies can improve quality of life and help children make steady progress.

Supplements – What We Know (and Don't Know)

Disclaimer: None of the supplement suggestions here are based on studies in children with DeSanto–Shinawi syndrome (DESSH). They rest on theoretical overlaps: first, what is known about the WAC gene, the consequences of losing its function, and hypotheses about whether supplements might ameliorate those downstream effects; and second, parallels with autism and related neurodevelopmental conditions. There is no strong that any supplement will provide meaningful benefit.

This information is shared for interest only and is not medical advice. Even "natural" supplements can carry risks and interactions. Anyone considering supplementation should discuss it with their medical practitioners before starting or changing anything.

Any potential benefits are very theoretical and a developing area and in no way is as important as the potential benefits from the babyforce trial

Supplements in DESSH: why they're only theoretical
WAC helps cells keep proteins in good working order (through ubiquitin signalling and the proteasome), recycle damaged parts (autophagy), manage oxidative stress, and run energy production. When one copy of WAC is missing, those housekeeping systems can be a bit less efficient. There are no proven supplement treatments for DESSH, but some options are considered because they may support those same housekeeping pathways. Any use is exploratory and should be discussed with clinicians.

How to choose: link what the gene does to what you try
A sensible way to think about supplements is cause → effect. First, look at what WAC normally does; next, ask which processes might be relatively underpowered when one copy is missing; then, if you try anything, pick a supplement that theoretically supports that exact pathway. For example, if protein quality control via the ubiquitin–proteasome system might be stretched, consider compounds that up-regulate cellular defence programs (such as sulforaphane via the KEAP1–Nrf2 pathway). If autophagy is a bottleneck, options that gently promote autophagy (like spermidine or urolithin A) are the ones to consider. If energy production and oxidative stress are the concern, mitochondrial supports (ubiquinol CoQ10, carnitine, creatine) make more sense. For membrane health and inflammation, omega-3s fit the rationale. Micronutrients (vitamin D, magnesium) sit in the background as general supports or to correct deficiency. This mapping keeps choices targeted and avoids a scattergun approach.

Sulforaphane (broccoli sprout compound)
Sulforaphane is made in the body from glucoraphanin in broccoli sprouts when it meets the enzyme myrosinase. It activates the KEAP1–Nrf2 pathway, which turns on the body's own defence and cleanup programmes. That can increase antioxidant capacity, up-regulate parts of the proteostasis network (including proteasome subunits), and nudge stalled autophagy back into gear via p62/ULK1 pathways. In autism studies (not DESSH), small trials suggest possible benefits for behaviour and irritability, but results are mixed and not definitive. In practice, families either use food-based approaches (fresh

broccoli sprouts prepared to preserve myrosinase) or standardised extracts. GI upset is the main side effect; dosing and quality control matter.

The ubiquitin–proteasome system (UPS) and why it matters

The UPS is the cell's primary rubbish-collection service: damaged or misfolded proteins are tagged with ubiquitin and then shredded by the proteasome. WAC participates in ubiquitin signalling and broader proteostasis control, so losing one copy may tilt the balance toward protein build-up. Sulforaphane is relevant here because Nrf2 activation can increase expression of some proteasome components and chaperones, helping cells keep up with protein quality control. Other polyphenols (for example, green-tea catechins or curcumin) can interact with the UPS, but their effects are context-dependent — at high doses some can even inhibit proteasome activity — so megadosing is unwise. If families try anything beyond diet, low, cautious, one-change-at-a-time is the safest principle.

Autophagy support

Autophagy is the second cleanup lane: the cell bundles worn-out parts and recycles them. Because WAC is linked to autophagy control, compounds that gently promote autophagy are of interest. Spermidine (found in wheat germ, soy, and supplements) consistently boosts autophagy in lab models and has early human data in ageing research. Urolithin A (a pomegranate-derived metabolite) promotes mitophagy — the recycling of damaged mitochondria — which might support energy balance in brain cells. Resveratrol has weaker, less consistent human data but is sometimes used for similar reasons. None of these have been tested in DESSH.

Mitochondrial energy and oxidative stress

If proteostasis is under strain, mitochondria often are too. Coenzyme Q10 (ubiquinol form) sits in the electron transport chain and helps cells make energy while buffering oxidative stress. Creatine and carnitine are used in other paediatric metabolic and neuromuscular settings to support high-energy tissues; evidence in DESSH is absent but the rationale is straightforward. Omega-3 fatty acids (fish or algae oil) support neuronal membranes and have anti-inflammatory effects; vitamin D and magnesium are general supports for bone, immune and neuro-muscular function. Think of these as scaffolding, not fixes.

A practical, step-by-step way to think about it

For families who do want to consider trying supplements, start with food and basics: a varied diet, omega-3 intake, and vitamin D if low or seasonally at risk. If considering sulforaphane, begin with food-based broccoli sprouts prepared to maximise conversion to sulforaphane; if using an extract, choose one with clear standardisation and start low. Give any new addition 3–4 weeks before changing anything else, and keep a simple log of sleep, behaviour, bowels, seizures, and therapies so you can judge signal from noise. If tolerated and you still want to explore, consider adding one energy/oxidative-support option (for example ubiquinol) and, separately and later, one autophagy-support option (for example spermidine or urolithin A). Avoid stacking multiple antioxidants at high

dose — more isn't always better and can backfire. Review the plan with your clinical team, especially if there are seizures, planned procedures, or other medications.

Throughout, remember the aim is to support the cell's housekeeping (UPS, autophagy, mitochondria), not to "treat DESSH," because no supplement has been shown to do that.

Bottom line: These supplements may have mechanisms that *sound relevant* to DESSH (because of WAC's role in energy balance, autophagy, and stress protection), but none have been tested in this condition. Any use should be considered exploratory, supportive, and monitored by doctors if you choose to take it

The tables below summarise WACs normal role and what happens if you loose WAC function and how you could respond The possible treatments are just theoretical, are not evidence based and not advised but are listed as they could in the future be potential ideas for research

🧬 1. WAC's Normal Functions and the Problems in DSS

Normal WAC Role	What Goes Wrong	Potential Support Strategies
Gene expression regulation (especially in brain)	Disrupted development, intellectual disability, poor memory, behaviour issues	Cognitive therapy, enriched environments, BDNF support, choline, omega-3
Ubiquitin-proteasome system support (protein cleanup)	Protein accumulation, stress on neurons	Support proteostasis: exercise, NAD+ boosters, polyphenols (resveratrol, sulforaphane), good sleep
Cellular stress response	Cells less resilient to stress	Antioxidants (but avoid blunting exercise), hormetic stress (broccoli, cold), anti-inflammatory diet
Cell growth and division	Delays in development, subtle facial differences, hypotonia	Nutritional support, targeted physiotherapy, growth & development monitoring

WAC Gene Loss: Systems Affected, Impact, and Possible Treatments

System / Process	Impact of WAC Loss	Clinical Consequences	Possible Treatments / Supports
1. Ubiquitin–Proteasome System (UPS)	↓ Protein degradation → protein build-up	Developmental delay, hypotonia, brain dysfunction	**Sulforaphane**, **resveratrol**, **quercetin**, mild **exercise**, good sleep hygiene
2. Transcription / Gene Expression	Dysregulation of which genes are turned on/off	Global developmental delay, speech delay	Early **speech therapy**, **cognitive stimulation**, **omega-3s**, **choline**, **citicoline**
3. Histone Modification (H2B)	Poor DNA access, disrupted chromatin structure	Impaired learning and memory, ID	**Methyl donors** (TMG, folate, B12), **HDAC-modulating nutrients** (e.g., butyrate, curcumin)
4. Autophagy	↓ Cellular cleanup and waste removal	Low energy, fatigue, neural stress	**Fasting mimetics** (e.g. **resveratrol**, **curcumin**), **NAD+ boosters**, **mitochondrial support** (CoQ10)
5. Cell Cycle / Mitosis	Disordered neuron growth, abnormal development	Microcephaly, developmental delay	No direct fix — but **brain-enriching environment**, **early therapies**, and possibly **citicoline**
6. DNA Damage Response	Poor DNA repair	Ongoing developmental instability	**Antioxidants** (vitamin C, NAC, glutathione), **low toxin exposure**, good **sleep**
7. Neural Circuit Formation	Faulty synapse development	Autism traits, poor learning, behaviour issues	**ABA**, **play therapy**, **omega-3s**, **magnesium**, **neuroplasticity aids** (e.g., creatine, CDP-choline)
8. Dopamine Signaling	Underactive dopamine circuits	Poor focus, low motivation, flat affect	**L-tyrosine**, **methylfolate**, **citicoline**, **early behavioural therapy**
9. Facial Morphogenesis	Disrupted craniofacial patterning	Characteristic facial features	None needed — supportive only
10. Gastrointestinal Regulation	Hypotonia of gut, slow motility	Constipation, reflux, feeding issues	**Probiotics**, **magnesium**, **hydration**, **motility aids** (under guidance), **zinc**
11. Sensory Processing	Sensory integration delays or abnormalities	Sensitivities, tantrums, poor pain processing	**Sensory integration therapy**, **OT**, **weighted blankets**, **magnesium**, **L-theanine**
12. Hair Growth Regulation	Misregulated hair follicle activity	Excessive hair growth	**Zinc**, **vitamin D**, reassurance, gentle grooming — not usually treated unless distressing
13. Immunomodulation (mild)	Possible immune differences	Mild eczema or infections (not always present)	**Vitamin D**, **omega-3s**, **probiotics**, gentle skincare
14. Brain Excitability / Epileptogenesis	Risk of increased excitability in some children	Seizures (not in all cases)	**EEG monitoring**, **rescue meds if needed**, **magnesium**, **omega-3**, possible anticonvulsants
15. Mitochondrial Stress (indirect)	Less energy available for movement and thinking	Hypotonia, fatigue, slow learning	**Creatine**, **L-carnitine**, **CoQ10**, **ALA**, **B vitamins**, gentle exercise

Upregulation of the functioning WAC gene

A new programme called *BabyFORce* is being trialled in newborn intensive care. It uses rapid genome sequencing to quickly diagnose genetic conditions within days, then applies artificial intelligence to search for possible drug treatments repurposing existing drugs.

Before giving a medication, researchers test it directly on the baby's own cells in the lab to see if it might work. This approach has already been used in a case involving the WAC gene, with early results suggesting it could help guide treatment choices in the future.

The question we need to answer is could this work for all DESSH children, how much of the drug you would have to give, how long for, could it work with adults with DESSH and what is the effect on WAC expression in blood levels as well as clinical features.

In addition, could other children with other rare genetic conditions also benefit.?

In the UK we are hoping to start a trial in partnership with the Mayo clinic trial at Guy's hospital for UK and European patients. We will be setting up a charity to help pay for that research. Please contact drrobgalloway@gmail.com for info on the charity and the research.

Summary
DeSanto-Shinawi Syndrome (DESSH) is a very rare genetic condition caused by changes in the WAC gene, which is important for brain development and cell regulation. Most children develop more slowly than their peers, often needing extra support with walking, speech, and learning. Some also experience seizures, behavioural differences, or medical issues such as vision and growth differences.

Despite these challenges, children with DESSH continue to learn and develop over time — this is not a degenerative condition. With the right therapies, education, and support, many can make meaningful progress and enjoy fulfilling lives.

Current research is beginning to explore possible treatments, from targeted therapies to gene-focused approaches, but for now, care is focused on maximising development and quality of life. Families, clinicians, and researchers working together are central to improving outcomes and creating hope for the future.

For any questions on this guide please email drrobgalloway@gmail.com

Appendix 1: A potential supplement strategy

We haven't yet decided whether we'll use them for our daughter, but it's something we are strongly considering, and this is the plan that we may use. Again – this is our choice for our child and is not medical advice but attached only for interest.

Initial potential plan

Week	Add this	Product & daily dose	Main goal	What to monitor
0	**Probiotic**	**Delpro®** half-sachet (5 B CFU) in breakfast yoghurt for 1 wk, then full sachet (10 B CFU)	Soften sticky stools; calm gut inflammation	Gas, bloating, stool frequency/texture
2 – 3	**Multivitamin (zinc + B6 + C)**	1 spoon (5 ml) **Vitabiotics Wellbaby® Liquid** – Zinc 2.5 mg, **Vitamin B6 0.5 mg**, Vitamin C 30 mg	Plug micro-gaps; provide B6 co-factor for GABA synthesis; support antioxidant enzymes	Any tummy upset, metallic taste
4 – 5	**Fish-oil**	1 tsp children's DHA + EPA syrup (≈ 250 mg combined)	Cool micro-inflammation; aid attention & social engagement	Fishy burps, stool softness
6 – 7	**Vitamin D**	5 drops (400 IU)	Support tone, mood, immunity	Rare at this dose—note rash or irritability
8 – 9	**N-acetyl-cysteine (NAC)**	300 mg morning + 300 mg evening (½ of a 600 mg capsule each dose)	Refill glutathione; smooth irritability/rigid routines	Gas, loose stools—reduce if persistent
10 – 11	**Sulforaphane**	Broccoli-sprout capsule: ¼ dose (~6 mg) wk 1, ½ dose (~12 mg) wk 2, full 25 mg wk 3	Boost Nrf2 antioxidant switch; potential social-behaviour gains	Reflux, diarrhoea—step back if needed
12 – 13	**L-carnitine**	50 mg/kg once daily (≈ 500 mg powder in juice)	Improve muscle energy & physio stamina	Fishy odour, loose stools—halve/stop if > 3 days
14 – 15	**Taurine** (bedtime)	250 mg powder stirred into warm milk/yoghurt 30 min before bed	Mild GABA-A agonist; support sleep, muscle tone & bowel motility	Looser stools or restlessness—reduce if persistent
16 – 17	**Magnesium** (bedtime)	50 mg elemental (e.g., magnesium glycina… owder) in warm drink	Further calm neuronal excitability; aid sleep and soften stools	Diarrhoea—halve dose or stop

Potential Adjunctive Supplements (Epigenetic & Proteostasis Boosters)

The following are low-risk, options we may consider further down the line. The evidence is even more limited — mostly theoretical, preclinical, or from small clinical trials in animals— and none have been studied in randomized controlled trials for DeSanto–Shinawi syndrome (DESSH).

Sodium butyrate (or high-fibre butyrate precursors)
Dose: 20–40 mg/kg/day
Rationale: Acts as a histone deacetylase (HDAC) inhibitor, loosening chromatin and potentially upregulating haplo-insufficient genes.
Evidence: Preclinical rodent models show neuroprotective effects, including in brain injury and stroke.

– J Neuroinflammation study
– Nutrients review (2020)

Spermidine
Dose: 1 mg/kg/day
Rationale: Induces autophagy independently of WAC, helping with cellular clean-up and proteostasis.
Evidence: A small pilot RCT in older adults with subjective cognitive decline showed modest memory improvements, and a larger trial is ongoing.
– Pilot RCT – subjective cognitive decline
– SmartAge trial protocol
– Review of spermidine and ageing

Creatine
Dose: 0.35 g/kg/day (max 3 g/day)
Rationale: Buffers neuronal ATP, potentially compensating for impaired mitophagy and supporting brain energy metabolism.
Evidence: Safe in infants and children; meta-analyses in cerebral palsy suggest possible benefits, and wider reviews confirm increases in brain creatine and some cognitive effects.
– Creatine in children and adolescents – safety review
– Meta-analysis in cerebral palsy
– Review of creatine in brain development

Citicoline
Dose: 50 mg/kg/day *Rationale:* A phospholipid precursor; may support synapse formation and neuronal membrane repair.
Evidence: Pediatric RCTs in acute brain injury and hypoxic-ischemic encephalopathy (HIE) showed benefits, while a trial in autism found no effect.
– Post-cardiac arrest trial, Egypt (children)
– Neonatal HIE trial, Italy
– Autism RCT, Iran – negative study

Later on considerations

Some natural compounds seem to support UPS Ubiquitin–Proteasome System.

The **Ubiquitin–Proteasome System (UPS)** is the cell's main way of tagging and breaking down damaged, misfolded, or surplus proteins. It maintains **proteostasis** – the balance of protein production and clearance needed for healthy cells.

- Proteins tagged with **ubiquitin** are sent to the **proteasome**, which chops them into reusable pieces (MDPI – Metabolites 2023).
- In **DeSanto–Shinawi syndrome (DESSH)**, problems with the **WAC gene** may disrupt proteostasis. Supporting UPS function could, in theory, reduce protein build-up in neurons and support healthier brain function.

The following could therefore theoretically help

- **Curcumin** (from turmeric)
- **Resveratrol** (from red grapes)
- **Quercetin**
- **Green tea catechins** (EGCG)

But: they can have **dual effects** — sometimes promoting degradation, other times slowing it — depending on dose and context. In young children, we'd be cautious with them but could be considered in older patients

There's some emerging evidence that compounds like **NMN and NR** (which raise NAD+ levels) might **enhance proteostasis**, especially in the brain.

- NAD+ is linked to **SIRT1**, which in turn can influence the proteasome and autophagy.
- These aren't routinely used in children — but might become part of future therapies.

Supplements we will not be using with current available information

other supplementation which I have looked into, we will bnot be using unless there is a change in evidence.

Methylene blue	Mitochondrial redox shuttle	**Avoid**	Risk of serotonin syndrome; no paediatric neuro-data
Ubiquinol (CoQ10)	Electron carrier & antioxidant	**Second-wave option**	30 mg/day safe; open-label toddler study showed tone & language gains
Quercetin, fisetin, astragalus, berberine, urolithin A	Senolytic / AMPK / mitophagy boosters	**Hold for future**	No safety evidence in under-fives
Alpha-lipoic acid (ALA)	Regenerates Vit C/E, boosts glutathione	**Skip for now**	Only mouse data for neuro-behaviour
Astaxanthin	Potent carotenoid antioxidant	**Not relevant**	Behaviour evidence lacking; fine in food (salmon)
PQQ	Stimulates new mitochondria	**Hold**	No paediatric safety data

Could Vagus Nerve Stimulation Help patients with DESSH – the evidence

Vagus nerve stimulation (VNS) – why it might ease some future or current behavioral challenges

VNS delivers gentle electrical pulses to the vagus nerve, either through a surgically-implanted generator or, more practically nowadays, via small ear-clips that target the auricular branch (taVNS). Over the last five years taVNS has moved from niche curiosity to a serious neuromodulation contender because it taps into brain-stem circuits that regulate arousal, attention and inflammation without the risks of open surgery. A 177-study systematic review involving more than 6,300 participants found no excess of serious adverse events compared with sham stimulation and only mild, transient side-effects such as tingling or ear discomfort Nature.

How it works – the neurobiology in a nutshell

Electrical bursts travel up the vagus nerve to the nucleus tractus solitarius, then on to the locus coeruleus and limbic forebrain. This boosts noradrenaline and acetylcholine release, enhancing synaptic plasticity, while simultaneously damping the microglial-driven inflammation that is increasingly linked to neurodevelopmental disorders. A 2025 mechanistic review highlights these twin actions—plasticity up, neuroinflammation down—as the key reasons VNS is being trialled across autism, ADHD and related genetic conditions PubMed. Supporting that model, a 2024 mouse study showed that daily taVNS rescued social interaction deficits by blocking the pro-inflammatory IL-17a pathway, essentially re-opening a window for healthy circuit formation PMC.

Human evidence in conditions that resemble DESSH profile

Autism spectrum disorder (ASD).
A 2023 pilot from the University of Missouri delivered remotely-supervised taVNS at home to adolescents and adults with ASD. After eight weeks, clinician- and parent-rated measures recorded modest but clear improvements in social engagement, anxiety and overall clinical impression, with excellent adherence and no safety flags PubMed. A larger randomised trial in high-functioning autistic children is now under way, reflecting growing confidence in the signa PMC.

Rett syndrome and other single-gene disorders.
Although implanted cervical VNS was originally used for epilepsy control, two separate case series in girls with Rett syndrome reported not only 50–80 % seizure reduction but also noticeably better alertness and mood within the first few months
https://pubmed.ncbi.nlm.nih.gov/16836782/

Clinicians treating mixed cohorts of monogenic epilepsies have begun to see parallel gains in attention and milestone acquisition once seizure frequency falls, suggesting that the behavioural benefits may extend beyond seizure suppression.

Translating the evidence to DESSH patients

DeSanto-Shinawi Syndrome carries a real risk of future behavioural hurdles—anxiety, irritability, low attention span and social communication difficulties—partly because WAC mutation disrupts chromatin regulation during brain development. VNS cannot rewrite that gene, but it can:

- • Amplify synaptic plasticity, giving therapies such as speech or physiotherapy more “traction” in the brain.
- • Lower limbic hyper-arousal, which underpins anxiety and neuroticism already common in children with high autistic traits.
- • Trim neuroinflammatory noise that may otherwise magnify developmental gaps.

Because VNS is low-risk, home-based and now commercially available, it could be trialled under medical supervision as an adjunct to existing developmental programme and to help with future behavioural challenges if patients tolerate it

A. Primary literature on DESSH / WAC

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B. Trials on supplements on conditions with cross over with DESSH

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