Cure DHDDS Virtual Conference: Summary Report

Meeting Date | 21st September 2023

Introduction

DHDDS (short for dehydrodolichyl diphosphate synthase) is a **gene** that controls the production of a protein involved in helping other proteins maintain their structure, function and stability.[1] Changes to the **DNA** sequence in the *DHDDS* gene (referred to as '*DHDDS* variants') can result in a disorder that, for the purposes of this report, will be referred to as DHDDS.

DHDDS is a very rare disorder which changes the development of the brain and causes brain cell damage.[1,2] **Only 70 individuals with DHDDS have been identified worldwide.**

Most individuals with DHDDS experience, with different degrees of severity, learning difficulties, tremors and seizures. Other symptoms include lack of coordination (due to loss of muscle control, known as 'ataxia') and epilepsy.[1]

Interestingly, similar symptoms can be caused by variants of a gene called *NUS1* (short for nuclear undecaprenyl pyrophosphate synthase 1), which has a similar role to *DHDDS*.[1] In this report, the disorder resulting from *NUS1* variants will be referred to as NUS1. Currently, there is no cure for DHDDS or NUS1.

Gene
A section of deoxyribonucleic acid (DNA) located on a chromosome at a fixed position, that controls the inheritance of particular traits

DNA
A long molecule that carries instructions for making proteins that the body requires for reproduction, growth, development and general functioning

Variant on *DHDDS* gene

Variant on *NUS1* gene

On **Thursday 21st September**, Cure DHDDS hosted their first Virtual Conference with the aim of bringing key scientists within DHDDS and NUS1 research together.

A total of **33** people attended the Virtual Conference, including:

26	**5**	**2**
Scientists	**Cure DHDDS representatives**	**Medical writers from Costello Medical**

A list of scientists who attended the Virtual Conference can be found in the **Appendix**.

The Virtual Conference was a success!

"I was introduced to **new**, **unpublished research** in the field"

"These meetings are **invaluable** to keep momentum going in a research community"

"It is **easier to collaborate** with people you have **met** and **formed a trusting relationship** with"

Based on the discussions during this Virtual Conference, this report summarises why we are at a pivotal moment in DHDDS and NUS1 research, and the next steps that patient organisations, such as Cure DHDDS, can make to accelerate DHDDS and NUS1 research.

Cure DHDDS is a charity which provides information and support for families diagnosed with the ultra-rare *DHDDS* gene mutations. By driving research into *DHDDS* variants, Cure DHDDS aims to help find treatments so that everyone with a *DHDDS* variant can lead the best life possible

Exciting Developments in DHDDS and NUS1 Research

Biomarkers

Positive progress is being made in identifying the first **biomarkers** for DHDDS, with research ongoing.

Why is this important?

Without a validated biomarker, it could be difficult to effectively monitor how well a treatment can slow, stop or reverse the progression of DHDDS in clinical trials.

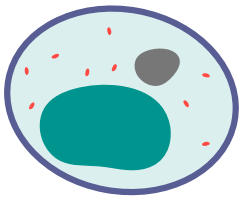
Biomarker
A characteristic that can indicate the presence or severity of a disease

DHDDS and NUS1 Models

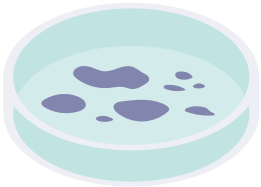
DHDDS and NUS1 **disease models** have been, or are currently being, developed.

The scientists noted that disease models have been developed in:

Disease Models
An animal or cell which displays all or some of the disease processes observed in people affected by the disease



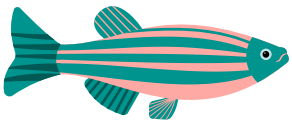
Yeast cells



Human cells

Mice

For DHDDS



Zebra fish

For NUS1

Why is this important?

Scientists can test treatments that have already been approved by health authorities to see if they are effective in treating DHDDS or NUS1. This is known as **drug repurposing**.

The drug discovery process is long and challenging. Exhaustive studies in the laboratory and in clinical trials of humans need to be conducted on new treatments to demonstrate that they are safe, and to understand their effect on the body. If treatments already used in other conditions were found to be effective for treating DHDDS or NUS1, it could reduce the length of time it would take for these treatments to be accessible to people with DHDDS or NUS1.

Drug Repurposing
Finding new uses for existing treatments

Scientists can examine the brains of the DHDDS or NUS1 animal models, which can improve understanding of **disease pathology** and help to identify **targets** for treatments.

Disease models can be used to test whether new treatments are effective at modifying their target, whether they are likely to have an impact on disease progression in humans, and to ensure they are safe for the treatment of humans.

Disease Pathology
Understanding why and how people become unwell

Targets
Proteins, genes or biological systems in the body that can be modulated by a treatment, to change the course of a disease

Gene Therapy

A strategy for a DHDDS **gene therapy** approach in mice is being developed.

Why is this important?

By testing this approach in animal models, we can understand more about the safety and effectiveness of gene therapy before starting trials in humans.

Gene Therapy
A medical approach that involves altering or replacing disease-causing genetic variants within an individual's cells to treat or prevent genetic diseases

Unmet Needs in DHDDS and NUS1 Research

During the Virtual Conference, the scientists provided some guidance about how to drive research forward as a patient organisation. They noted the following areas which are lacking from DHDDS and NUS1 research:

- Funding of research
- Understanding of **clinical endpoints**
- Understanding how the variants in *DHDDS* and *NUS1* cause disease (disease pathology)

Clinical Endpoint
A measurable outcome that can describe how severely someone is experiencing their disease. In clinical trials, they are used to determine whether a treatment works. For example, a clinical endpoint could be how often a person with DHDDS experiences tremors. Without good clinical endpoints, it is not possible to tell whether a treatment works or not

Natural History Study
A study which observes how a disease develops in people without trying to change or treat it. It helps to understand the course of the disease

To gain understanding of clinical endpoints and disease pathology, it is very important to carry out a **natural history study**. The scientists suggested that a natural history study is one of the most useful things a patient organisation can support, provided that it is well funded.

Cure DHDDS' Pledge

Cure DHDDS have made a series of commitments based on these suggestions. Cure DHDDS will:

- Organise fundraising events and apply for grants
- Explore co-funding research projects with other charities
- Set up a research consortium who meet regularly to share findings, ideas and track progress on research priorities
- Encourage collaborative projects by organising meetings between people with DHDDS, healthcare professionals and researchers
- Share opportunities for people with DHDDS and NUS1 to get involved in research throughout the Cure DHDDS community
- Host webinars where key DHDDS and NUS1 researchers can share their latest findings with the wider research community
- Support a natural history study in conjunction with Dr Serena Galosi and Dr Giulietta Riboldi
- Recruit people with DHDDS and NUS1 to join the study using their Facebook group
- Set up a patient registry to better understand the full DHDDS and NUS1 disease spectrum and the unmet needs of patients and families

My loved one has DHDDS/NUS1. What can I do to help?

If you haven't already, visit **Cure DHDDS' private Facebook group** for support or advice, and learn about future opportunities to get involved in research, which include:

- Joining Cure DHDDS' patient registry
- Taking part in the upcoming natural history study

The families of people with DHDDS or NUS1 are also in a unique position to comment on the impact of their loved one's disease. Therefore, your insight will be crucial to help scientists understand realistic clinical endpoints in DHDDS or NUS1.

Keep an eye on the Cure DHDDS Facebook group for opportunities to share your insight!

The more we work together, the quicker we can find a treatment for all those suffering with *DHDDS* and *NUS1* mutations. Together, we are stronger.

Appendix

List of Scientists who Attended the Virtual Conference

Dr Serena Galosi	Dr Richard Steet
Dr Kariona Grabinska	Professor Christian Thiel
Justin Donnelly	Dr Rajvinder Karda
Dr Alexey Pshezhetsky	Professor Sara Mole
Dr Afitz Da Silva	Dr David Fischer
Dr Felix Chan	Dr Charles Steward
Dr Amy Williford	Catriona Crombie
Dr Frances Elmslie	Dr Mederic Jeanne
Professor Nick Lench	Dr Simone Martinelli
Ketsia Côté-Mashala	Professor Dirk Lefeber
Dr Emyr Lloyd-Evans	Professor Vincenzo Leuzzi
Dr Heather Flanagan-Steet	Dr Elisabetta Flex

References

1. Galosi S, Edani B, Martnelli S, Hansikova H, Eklund E, Caputi C et al. *De novo DHDDS* variants cause a neurodevelopmental and neurodegenerative disorder with myoclonus. Brain. 2022;145(1):208–23.
2. Piccolo G, Amadori E, Vari MS, Marchese F, Riva A, Ghirotto V et al. Complex neurological phenotype associated with a *de novo DHDDS* mutation in a boy with intellectual disability, refractory epilepsy, and movement disorder. J Pediatr Genet. 2021;10(3):236–238.