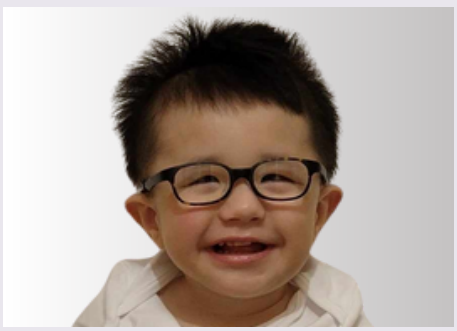
HUWE1

WELCOME GUIDE for NEWLY DIAGNOSED FAMILIES

NEW HERE? WELCOME, WE WERE THERE NOT LONG AGO. THIS GUIDE IS A COMPILATION OF INFORMATION WE HAVE LEARNED FROM OTHER INDIVIDUALS WITH HUWE1 AND THEIR PARENTS / CAREGIVERS.

At this time, to our knowledge very few individuals have been officially diagnosed with HUWE1-related neurodevelopmental disorder around the world. We believe approximately **100 individuals** have a confirmed diagnosis. Understanding of the impact of changes in the HUWE1 gene is still developing and people can vary in the range and extent of symptoms they experience such as developmental delays, intellectual disability and growth issues. Each individual with HUWE1 will have their own unique profile, challenges and strengths.

Note: research is currently emerging and information is growing every day.



We believe approximately 100 individuals have a confirmed diagnosis of HUWE1. Of these individuals, 47 of them / their parent(s) took part in a data-collection study in partnership with RARE-X. This data was compiled, creating the table below. It is believed that many other individuals have this condition and have either not been tested or do not currently have profound enough symptoms to prompt testing. Although unknown, and currently being studied, it is believed that symptoms are generally present in the individual at birth and most individuals do not experience additional deterioration with age. There are some exceptions to this, such as if a child were to develop seizures. One of the best ways to contribute to what is known about this condition is to **participate in research**. See more information at the end of this document.

APPROXIMATELY

100

INDIVIDUALS DIAGNOSED TO DATE

Most frequently reported conditions in order of relative frequency are shown below, along with clinical guidance. Keep in mind that each person with HUWE1 may not necessarily experience these conditions, but will have their own unique profile.

COGNITIVE IMPAIRMENT

Early consideration of **Speech Therapy** and **School Assistance**.
Consideration of **Neuropsychologist** testing -for IQ testing and school assistance / optimization.

SHORT STATURE

Consideration of **Endocrinology** evaluation: some parents have explored growth hormones.
Some parents report growth hormone deficiency.

HYPOTONIA

Consideration of **Physical Therapy** interventions.

COORDINATION ISSUES

Consideration of **Physical Therapy** interventions for gross motor (big muscles) and **Occupational Therapy** interventions for fine motor (eating, writing, etc.).

CONSTIPATION

Often managed by a **Primary Care Provider**, but if severe, consider **Gastroenterology** evaluation.

AUTISM

Consider early testing and intervention. Early detection and interventions greatly improve outcomes. Many parents report benefits from **behavioural therapies**. Most children aren't diagnosed until 3, but generally some symptoms are present up to 2 years prior. A nonverbal / minimally verbal child generally prompts evaluation.

VISUAL IMPAIRMENT

Consider early (<2 years of age) evaluation with an **optometrist / ophthalmologist**.

FEEDING DIFFICULTIES

Consider **occupational therapies** to assist with coordination / arm movements and **speech therapy** to assist with chewing / swallowing / identifying food consistencies. Some children require feeding tubes to assist with feeding or procedures to help facilitate nutrition. Parents reported difficulties swallowing, also known as dysphagia. Some children were evaluated by pediatric **ENTs** for consideration of interventions.

SEIZURES

If you notice any abnormal movements like blank stares / staring off, jerking /shaking motions or signs of seizures primary care providers will often send a referral for evaluation by a **neurologist**. EEG testing is generally performed. Seizures in some HUWE1 children seem refractory to current treatment. Some have noticed improvement with the ketogenic diet.

HEARING DEFICIT

Consider being evaluated by an **audiologist** to rule out any hearing concerns. If hearing loss is present - hearing aids / cochlear implant.

Additional members of care teams for children with HUWE1 often include **primary care providers** who help facilitate referrals to specialists and monitoring of overall growth / development, a **developmental pediatrician** who tends to dive a little deeper into care for children with special needs, and a **geneticist**. Geneticists help explain what is known about the condition and help provide counseling on the condition and its ability to be passed down to future children. **Additional considerations:** MRI to r/o craniosynostosis and Chiari's Malformation, r/o scoliosis and hip issues, echocardiogram to r/o structural heart defects, dental evaluation.

HUWE1 IS AN X-LINKED DISORDER, SO BOYS TEND TO BE MORE AFFECTED.
Females have two X chromosomes and often express fewer symptoms as they have another X chromosome.

HUWE1 is passed down from either the mother or father or it arrives 'de novo' (Latin: meaning from the beginning) and is expressed for the first time in an individual. In these cases, it was not passed down from a parent.

X-Linked dominant inheritance:

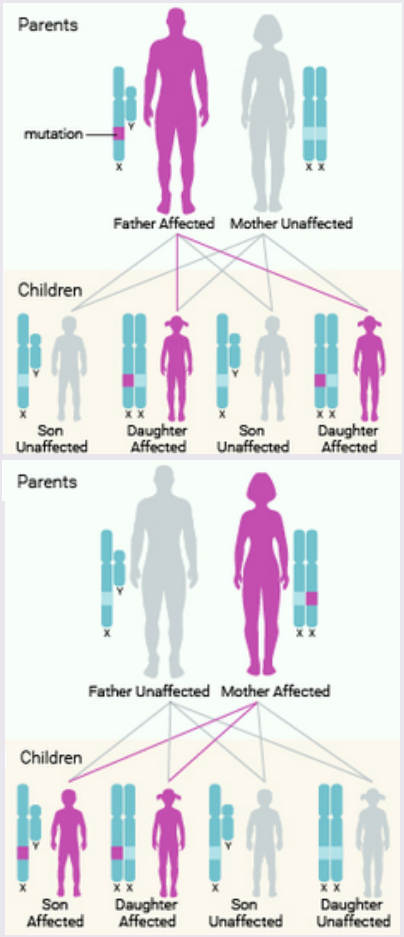


Image credit: U.S. National Library of Medicine

Tips on reading genetics report:
HUWE1 is a large gene, with over 4000 amino acids comprising the protein. Each amino acid is coded by four DNA letters, A, C, T, or G.

In your child's genetic testing report, you will see something that looks like:
HUWE1 c.999 T>A, p.A333Z

This is explaining exactly where in the HUWE1 gene your child's spelling change is. We are still trying to understand how each specific DNA change influences the severity of symptoms.

This change may be brand new (de novo), or inherited from the individual's parent, most typically the mother. This can only be determined by also testing biological parents.

On genetic testing reports, changes may be described as pathogenic, likely pathogenic, or variants of uncertain significance (VUS). If your child has a VUS in HUWE1, more investigations may need to be done to confirm that your child is affected.

RESEARCH

More research on HUWE1 is desperately needed. Unfortunately, research studies are very costly and because so few cases have been identified to date it is a very small pool of supporters to pull from. The primary focus of Louie's HUWE's nonprofit is to raise money to promote research and is currently funding a study through Seattle's Children's Hospital under direction of one of the Louie's HUWE scientific advisors, Dr. Brock Grill.

Some key research articles include the following:
Links to research articles can be found on HUWE1.org

2017, Moortgat et al. article, the largest research study to date of 21 individuals noted the following features:
• All individuals presented with intellectual disability (ID), 16/19 had severe to profound ID, three females were mildly affected. **84%**
• Almost all individuals had global developmental delay (20/21) **95%**, Hypotonia 14/20 **70%**, mean age of walking was 2 ½ years (three patients never achieved autonomous walking).
• Almost all individuals had speech delays (17/19) **89%** with absence of speech (or <5 words) in 13/19 **68%** patients.
• Microcephaly (-2.5 to -7 SD) occurred in 11/21 **52%** and was often postnatal in onset.
• Seizures were reported in 7/18 **39%** patients with onset between 9 months and 13 years.
• Brain MRI was normal in nine patients. Thin corpus callosum was noted in two and enlarged cerebral ventricles in four.
• Autistic features were reported in seven patients as well as hand stereotypies (8/17) **47%**.
• Low birth weight was noted in four patients and postnatal short stature (-2.5 to -6 SD) reported in 15/21 **71%**.
• Skeletal anomalies included small hands and feet (12/21) **57%**, overlapping toes (9/21) **43%**, craniosynostosis (2/21) **9%**, scoliosis (3/21) and contractures of knees (5/17).

***** Coming Soon: HUWE1 study by Dr. Kristin Barañano and Dr. Mindy Li.**

Helpful Websites:

WWW.HUWE1.ORG – parent-led / physician reviewed website and hub for HUWE1-related information. Includes links to key research.

Facebook: HUWE1 gene, private Facebook group for individuals and their family affected by this condition.

Facebook / Instagram: Louie's Huwe, non-profit's pages; Instagram @huwe1_gene

Tips from other parents:
Some countries have government funding for individuals with disabilities. This is helpful to explore early as the waitlists can be long. This will help protect / support your HUWE1 individual in the event you are unable to. (US)

Some countries have an early childhood developmental network that can provide therapies free of charge for individuals with developmental delays. (US)

WAYS TO GET INVOLVED:

1.

Participate in research!
Dr. Kristin Barañano is enrolling individuals in an ongoing study involving a structured clinical interview, to better understand HUWE1-related symptoms and to guide clinical management. She can be reached at kwb@jhmi.edu. This is the most robust way of compiling symptoms and recommendations.

You can also participate in the HUWE1 RARE-X Data Collection Program!
We cannot overstate how helpful this is in learning more about this condition. Parents who are carriers, please also consider logging data on yourself.
https://huwe1.rare-x.org/

2.

Engagement in the HUWE1 Facebook group. This group has been a great resource and way for parents / individuals affected by HUWE1 to connect. We frequently run polls to help learn more, ask questions, provide support and connect with one another. We have hosted several open forums to provide community education and use this site as our worldwide platform for posting updates on the work Louie's HUWE is doing to advance research. For the latest updates follow Louie's HUWE - the a 501c3 nonprofit dedicated to HUWE1 - on Facebook, Instagram, Twitter and LinkedIn.

3.

Consider a donation / fundraiser in support of Louie's HUWE to help fund HUWE1 research. We have currently partnered with Seattle Children's Hospital in hopes of better understanding the function of HUWE1 and to help identify treatments for individuals with HUWE1, with a focus on treatment of seizures. Presently individuals with HUWE1 often have seizures that do not always respond well or at all to traditional seizure medications. Any research on HUWE1 greatly benefits us all. Members have had great success raising money by hosting Facebook birthday fundraisers, through community events, and by grant application. We hope you will consider helping fund further scientific research.

FURTHER INFORMATION

MEDICAL PROFESSIONALS LIST

It is important to note, several medical professionals or providers have never heard of HUWE1 / have a poor understanding of the condition. Here is a list of medical professionals that parents of children with HUWE1 have recommended.

United States of America:

- Kristin Barañano, M.D., Ph.D.- Neurologist and Neurogeneticist, Johns Hopkins and the Kennedy Krieger Institute, Baltimore MD. Scientific advisor for Louie's HUWE.
- Mindy Li, M.D. - Clinical Geneticist, Lurie Children's Hospital, Chicago, IL.

United Kingdom:

- Karen Low, M.D- Clinical Geneticist and NIHR Clinical Research Fellow, University of Bristol. Karen coordinated UK participants in the Moortgat et al. study. She is also chief investigator on the GENROC Study - UK patients with HUWE1 can participate at http://tinyurl.com/GENROCStudy.

Please **email info@louieshuwe.org** if you have a **provider who has experience with HUWE1** and you would recommend, or if you are a **researcher currently studying the HUWE1 gene**, we would love to hear / learn from you. We have a scientific advisory board that is always eager to learn more about current studies and help advance the scientific knowledge of HUWE1.

OTHER INFORMATION SOURCES

Read HUWE1 family stories and meet HUWE1 kids:

https://www.huwe1.org/family-stories
Follow @huwe1_gene on Instagram

View a list of key research studies:

https://www.huwe1.org/research

Download the Unique information guide on HUWE1

English: https://tinyurl.com/UniqueHUWE1leaflet , **Spanish:** http://tinyurl.com/UniqueHUWE1Spanish , **Georgian:** http://tinyurl.com/UniqueHUWE1Georgian , **Russian:** http://tinyurl.com/UniqueHUWE1Russian

View the information page on HUWE1 from Health Centre for Genetics Education (part of NSW Gov, Australia):

https://www.genetics.edu.au/SitePages/HUWE1.aspx

Watch videos about HUWE1:

Youtube: https://www.youtube.com/@louieshuwe
Louie's HUWE Event Recording - Scientific Research & Funding with Dr. Brock Grill:
https://vimeo.com/huwe1/huwe1researchqa (Password: HUWE1)

Visit HUWE1 Italia website:

https://huwe1italia.wordpress.com

Visit HUWE1.org:

ABOUT THIS GUIDE

This information was put together by **Louie's HUWE**, a 501c3 nonprofit charitable organization in the United States (EIN: 86-1930096). With a team including medical and genetic experts, we are dedicated to raising awareness, supporting families and driving research into HUWE1-related genetic conditions. Medical information here was reviewed by our Scientific Advisor, Kristin W. Barañano, M.D., Ph.D.

Your support means a lot! To help us continue to fund research and produce information guides please consider donating to Louie's HUWE at **www.huwe1.org/louieshuwe**.

LOUIE'S HUWE
FOR HUWE1-RELATED GENETIC CONDITIONS