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Gabriel Bennett
Emma Goodall
Editors

The Palgrave Encyclopedia of Disability

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With 294 Figures and 291 Tables

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Preface

Disability is a fundamental part of the human condition. Whether we are born with a disability, acquire it through injury or illness, or witness its effects through the lives of others, disability is something that will touch nearly all of us in some form. According to the World Health Organisation (2023), an estimated 1.3 billion people live with a disability. Thus, it is not a marginal or isolated experience, but rather a deeply human one—complex, nuanced, and intimately tied to how we understand ourselves, our bodies, our relationships, and our societies. Across time, disability has been understood through various lenses—from the medical model, which focuses on impairment and cure, to the social model, which emphasizes structural barriers and societal attitudes. More recently, cultural and intersectional approaches have offered new ways to reimagine disability as a dynamic and context-dependent experience. This Encyclopedia draws from and contributes to this evolving intellectual tradition.

When we embarked on *The Palgrave Encyclopedia of Disability*, we were immediately struck by the remarkable diversity and intellectual complexity of the contributions. Far from being confined to clinical or diagnostic categories, the entries reveal disability as a multidimensional concept—one that intersects with the environment, ethics, legislation, arts and culture, etc. For example, entries like *Disabilities and Global Warming* (Sen et al., 2024b) and *Climate Change and Its Effect on Ageing and Disability* (Holland et al., 2024) examine the entanglement of disability with ecological shifts. Others—such as *Diabetes and Disability: Medical, Social, and Legal Perspectives* (Sen et al., 2024a) and *Clinical Ethics in Disability: The Role of Decision-Making Competence* (Grignoli & Livoti, 2025)—offer rich, multidisciplinary analyses of contemporary challenges in medicine and bioethics. Cultural and literary perspectives also feature prominently, as seen in *Ableism and Modern Disability Attitudes* (Friedman, 2024), *Representation of "Disability" in Cultural Narratives* (Srivastava, 2025), and *Disability in Slovenian Literature: From Fables to Autobiographies* (Wang, 2025). Entries like *The Bible and Disability* (Swai, 2025), *Disability History* (Dinu, 2025), and *History of Dyspraxia* (Kirby, 2024) explore how disability has been understood across religious, historical, and philosophical traditions—from ancient scriptures to modern-day policy debates. Finally, the role war plays in the creation of disability has been captured in the entry *Disability in Humanitarian and Conflict Settings* (Shah et al., 2025). Together, these contributions reveal a powerful truth: that

disability is not peripheral to society, but central to understanding the human condition across nations, time, cultures, and disciplines.

Arguably, as of June 2026, the COVID-19 pandemic and the advent of Artificial Intelligence (AI) have been two of the most significant global events. The COVID-19 pandemic highlighted and intensified existing inequalities faced by people with disabilities, revealing critical gaps in healthcare access, support services, and inclusive emergency planning. Three notable entries that describe the impact of the COVID-19 pandemic for people with disabilities are *COVID-19's Impact on Disability Access to Medical Imaging* (Makanjee, 2025), *Inclusive Innovation for Autism in the Post-COVID Workforce* (García-Iglesias et al., 2025), and *COVID-19, Invisible Disabilities, and Political Discourse* (Ningrum, 2025). AI is a rapidly advancing technological field that leverages machine learning, neural networks, and data analysis to solve complex problems and enhance human capabilities. In the context of disability, AI is becoming increasingly relevant since it can suggest innovative solutions for accessibility, mobility, and independence. This is evident in three entries *Applications of Artificial Intelligence for Developing Exoskeletons and Prosthetics* (Tsutsumi et al., 2025), *Artificial Intelligence and the Intersectionality of Disability* (Dieker & Zaugg, 2024), and *Innovative Deep Learning Approaches in Autism Research* (Amjad & Sokouti, 2025). Yet these advances also raise critical questions about algorithmic bias, data privacy, and whether disabled people are meaningfully involved in the design of these technologies. The Encyclopedia engages with both the promises and perils of AI in disability contexts.

A pronounced theme throughout this Encyclopedia is the emphasis on research *with*, rather than *on*, people with disabilities. For much of history, knowledge about disability was produced by nondisabled researchers—often without the involvement, insight, or consent of disabled individuals themselves. This imbalance has shaped not only what we know about disability but how that knowledge has been used. In response, participatory and community-led research approaches have gained significant momentum within Disability studies. These methodologies challenge the traditional researcher–researched hierarchy and instead position disabled people as co-creators and leaders in the research process. Five entries in this Encyclopedia speak directly to this important epistemological shift. *Co-creation and Co-production in Research with People with Intellectual Disabilities* (Petropoulou et al., 2025) explores inclusive models of research design and collaboration. *Community-Based Participatory Research* (Miller, 2024a) and *Youth Participatory Action Research* (Miller, 2024b) highlight the role of community and youth voices in shaping agendas and outcomes. Meanwhile, *Open and Reproducible Special Education Research* (Kalandadze, 2025) underscores the need for transparency and replicability in inclusive inquiry, and *Making Survey Research Accessible for People with Intellectual and Developmental Disabilities* (Friedman & Spassiani, 2024) addresses the practical barriers that often exclude disabled people from participating in data collection.

Another defining feature of this Encyclopedia is the notion of intersectionality. Intersectionality has become a vital framework in Disability studies, recognizing that disabled people are not a monolithic group but are

shaped by other factors such as race, gender, sexuality, class, and age. This approach moves beyond seeing disability as a singular experience and acknowledges that people with disabilities often face multiple layers of disadvantage or privilege. By embracing this lens, the Encyclopedia highlights how overlapping identities can compound disadvantage or shape unique experiences of access, discrimination, and resilience. The entries *Disability and Intersectionality* (Flynn, 2024) and *Ageing with an Intellectual Disability* (Wark, 2025) exemplify this intersectional insight. Rather than simplifying these issues, this Encyclopedia offers space for multiple perspectives to coexist—recognizing that context, culture, and personal features all matter.

Much of the foundational literature in Disability studies has emerged from Western, Educated, Industrialized, Rich, and Democratic nations in the Global North. However, nations in the Global South and Indigenous communities are starting to produce more contributions to the discipline of Disability studies. Reflecting this trend, this Encyclopedia contains entries titled *Indigenous Disability in Australia* (Cooms & Muurlink, 2025), *Blindness and Vision Loss in Central Asian Countries* (Rahim et al., 2025), *Disability in State Socialist Eastern Europe* (Dinu & Zdrodowska, 2025), *The Stigma Associated with Speech Delay in the Middle East and North Africa* (Ghazy et al., 2025), and *Disability Stigma in the Middle East* (Javaid, 2024). These contributions offer not only new regional insights but alternative conceptual frameworks—from collectivist understandings of care to spiritual or religious interpretations of disability. Such perspectives challenge dominant Global North paradigms and broaden the field's epistemic horizons.

Creating *The Palgrave Encyclopedia of Disability* has been both a deeply humbling and energizing experience. Across hundreds of entries, written by hundreds of leading international scholars and grounded in a range of disciplinary traditions, this Encyclopedia reflects an incredible pool of intellectual richness and competing insights. Yet even with its comprehensive scope, it can only ever be a beginning—a prompt for further exploration, deeper dialogue, and more inclusive practice.

Understanding disability and its impacts is not confined to activists or academics. It is the work of all of us. It is found in the design of a waiting room, in the language of a research grant, and in the assumptions behind a diagnosis. The future of disability knowledge depends on the next generation of scholars, activists, practitioners, and community leaders and people living with disabilities. This Encyclopedia is dedicated to them. May it serve not only as a repository of what we know but as a provocation—to ask better questions, build deeper alliances, and imagine more liberatory futures.

This Encyclopedia was made possible by the contributions of more than 400 scholars from 58 nations. We are grateful beyond words for their generosity and expertise. We also wish to acknowledge the scholars who came before us. This Encyclopedia stands on their shoulders.

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References

Amjad, E., & Sokouti, B. (2025). Innovative deep learning approaches in autism research. In G. Bennett & E. Goodall (Eds.), *The Palgrave encyclopedia of disability*. Palgrave Macmillan. https://doi.org/10.1007/978-3-031-40858-8_388-1

Cooms, S., & Muurlink, O. (2025). Indigenous disability in Australia. In G. Bennett & E. Goodall (Eds.), *The Palgrave encyclopedia of disability*. Palgrave Macmillan. https://doi.org/10.1007/978-3-031-40858-8_477-1

Dieker, L., & Zaugg, T. (2024). Artificial intelligence and the intersectionality of disability. In G. Bennett & E. Goodall (Eds.), *The Palgrave encyclopedia of disability*. Palgrave Macmillan. https://doi.org/10.1007/978-3-031-40858-8_121-1

Dinu, R. H. (2025). Disability history. In G. Bennett & E. Goodall (Eds.), *The Palgrave encyclopedia of disability*. Palgrave Macmillan. https://doi.org/10.1007/978-3-031-40858-8_236-1

Dinu, R. H., & Zdrodowska, M. (2025). Disability in state socialist Eastern Europe. In G. Bennett & E. Goodall (Eds.), *The Palgrave encyclopedia of disability*. Palgrave Macmillan. https://doi.org/10.1007/978-3-031-40858-8_237-1

Flynn, S. (2024). Disability and intersectionality. In G. Bennett & E. Goodall (Eds.), *The Palgrave encyclopedia of disability*. Palgrave Macmillan. https://doi.org/10.1007/978-3-031-40858-8_221-1

Friedman, C. (2024). Ableism and modern disability attitudes. In G. Bennett & E. Goodall (Eds.), *The Palgrave encyclopedia of disability*. Palgrave Macmillan. https://doi.org/10.1007/978-3-031-40858-8_29-1

Friedman, C., & Spassiani, N. A. (2024). Making survey research accessible for people with intellectual and developmental disabilities. In G. Bennett & E. Goodall (Eds.), *The Palgrave encyclopedia of disability*. Palgrave Macmillan. https://doi.org/10.1007/978-3-031-40858-8_77-1

García-Iglesias, J. J., Ávila-Gutiérrez, M. J., & Gómez-Salgado, J. (2025). Inclusive innovation for autism in the post-COVID workforce. In G. Bennett & E. Goodall (Eds.), *The Palgrave encyclopedia of disability*. Palgrave Macmillan. https://doi.org/10.1007/978-3-031-40858-8_461-1

Ghazy, R. M., Ali Ahmed Shiba, H., & Alsaleem, S. A. (2025). The stigma associated with speech delay in the Middle East and North Africa. In G. Bennett & E. Goodall (Eds.), *The Palgrave encyclopedia of disability*. Palgrave Macmillan. https://doi.org/10.1007/978-3-031-40858-8_344-1

Grignoli, N., & Livoti, S. (2025). Clinical ethics in disability: The role of decision-making competence. In G. Bennett & E. Goodall (Eds.), *The Palgrave encyclopedia of disability*. Palgrave Macmillan. https://doi.org/10.1007/978-3-031-40858-8_253-1

Holland, A. B., Markides, K. S., & Milani, S. A. (2024). Climate change and its effect on aging and disability. In G. Bennett & E. Goodall (Eds.), *The Palgrave encyclopedia of disability*. Palgrave Macmillan. https://doi.org/10.1007/978-3-031-40858-8_132-1

Javaid, S. F. (2024). Disability stigma in the Middle East. In G. Bennett & E. Goodall (Eds.), *The Palgrave encyclopedia of disability*. Palgrave Macmillan. https://doi.org/10.1007/978-3-031-40858-8_72-1

Kalandadze, T. (2025). Open and reproducible special education research. In G. Bennett & E. Goodall (Eds.), *The Palgrave encyclopedia of disability*. Palgrave Macmillan. https://doi.org/10.1007/978-3-031-40858-8_24-1

Kirby, P. (2024). History of dyspraxia. In G. Bennett & E. Goodall (Eds.), *The Palgrave encyclopedia of disability*. Palgrave Macmillan. https://doi.org/10.1007/978-3-031-40858-8_227-1

Makanjee, C. (2025). COVID-19's impact on disability access to medical imaging. In G. Bennett & E. Goodall (Eds.), *The Palgrave encyclopedia of disability*. Palgrave Macmillan. https://doi.org/10.1007/978-3-031-40858-8_423-1

Miller, A. L. (2024a). Community-based participatory research. In G. Bennett & E. Goodall (Eds.), *The Palgrave encyclopedia of disability*. Palgrave Macmillan. https://doi.org/10.1007/978-3-031-40858-8_60-1

Miller, A. L. (2024b). Youth participatory action research. In G. Bennett & E. Goodall (Eds.), *The Palgrave encyclopedia of disability*. Palgrave Macmillan. https://doi.org/10.1007/978-3-031-40858-8_59-1

Ningrum, A. P. (2025). COVID-19, Invisible disabilities, and political discourse. In G. Bennett & E. Goodall (Eds.), *The Palgrave encyclopedia of disability*. Palgrave Macmillan. https://doi.org/10.1007/978-3-031-40858-8_450-1

Petropoulou, E., Bak-Klimek, A., & O'Leary, L. (2025). Co-creation and co-production in research with people with intellectual disabilities. In G. Bennett & E. Goodall (Eds.), *The Palgrave encyclopedia of disability*. Palgrave Macmillan. https://doi.org/10.1007/978-3-031-40858-8_242-1

Rahim, F., Toguzbaeva, K., & Dzhusupov, K. (2025). Blindness and vision loss in central Asian countries. In G. Bennett & E. Goodall (Eds.), *The Palgrave encyclopedia of disability*. Palgrave Macmillan. https://doi.org/10.1007/978-3-031-40858-8_418-2

Sen, A., Saxena, I., & Kaur, A. P. (2024a). Diabetes and disability: Medical, social, and legal perspectives. In G. Bennett & E. Goodall (Eds.), *The Palgrave encyclopedia of disability*. Palgrave Macmillan. https://doi.org/10.1007/978-3-031-40858-8_378-1

Sen, A., Vasudeva, A., & Dwivedi, S. (2024b). Disabilities and global warming. In G. Bennett & E. Goodall (Eds.), *The Palgrave encyclopedia of disability*. Palgrave Macmillan. https://doi.org/10.1007/978-3-031-40858-8_330-1

Shah, M. H., Wayn, D. K., & Ali, N. (2025). Disability in humanitarian and conflict settings. In G. Bennett & E. Goodall (Eds.), *The Palgrave encyclopedia of disability*. Palgrave Macmillan. https://doi.org/10.1007/978-3-031-40858-8_460-1

Srivastava, S. (2025). Representation of "disability" in cultural narratives. In G. Bennett & E. Goodall (Eds.), *The Palgrave encyclopedia of disability*. Palgrave Macmillan. https://doi.org/10.1007/978-3-031-40858-8_490-1

Swai, E. (2025). The bible and disability. In G. Bennett & E. Goodall (Eds.), *The Palgrave encyclopedia of disability*. Palgrave Macmillan. https://doi.org/10.1007/978-3-031-40858-8_182-1

Wang, A. (2024). Disability in Slovenian literature: From fables to autobiographies. In G. Bennett & E. Goodall (Eds.), *The Palgrave encyclopedia of*

disability. Palgrave Macmillan. https://doi.org/10.1007/978-3-031-40858-8_139-1

Wark, S. (2025). Ageing with an intellectual disability. In G. Bennett & E. Goodall (Eds.), *The Palgrave encyclopedia of disability*. Palgrave Macmillan. https://doi.org/10.1007/978-3-031-40858-8_274-1

World Health Organisation. (WHO). (2023). Disability. https://www.who.int/news-room/fact-sheets/detail/disability-and-health#:~:text=Key%20facts,than%20for%20those%20without%20disabilities. Accessed 21 Apr 2025.

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Dr. Gabriel Bennett, Ph.D., formerly Dr. Matthew Bennett, is an Australian scholar whose work spans disability studies and emerging biotechnologies. He holds a Ph.D. in Disability Studies from Flinders University, and he has lectured in Disability Studies at Griffith University, Queensland. He has advised the Australian government's Autism Cooperative Research Centre (Autism CRC) and has published several peer-reviewed books about autism, senotheraputics, and metascience/research methods.

In the future, he intends to examine xenobiological research, in particular its potential applications, benefits, and limitations in biomedical science. Synthetic biology uses principles of genetic modification and engineering to create new biological functions. In contrast, xenobiology—derived from the Greek word *xénos*, meaning "*strange*" or "*alien*"—extends this approach by altering biological systems at a fundamental level. Rather than relying solely on naturally occurring biological components, it introduces nonnatural elements into molecular biology, such as novel genetic building blocks (i.e., Xeno Nucleic Acids). These systems operate alongside, but remain distinct from, natural life. This separation enables both conceptual and practical advances, such as providing new tools for understanding the basic principles of life while also supporting innovation in areas such as personalized medicine and therapeutics.

Dr. Emma Goodall, PhD is an autistic author and industry researcher at the Queensland University of Technology working on a national guideline for the teaching of autistic children and young people in preschools and schools across Australia. She is also a consultant specializing in autism, disability, and education who works across Australia and internationally to improve outcomes for neurodivergent people in learning and community settings. She has a background as a qualified teacher and specialist educator, and has held senior roles in education systems, where she has focused on inclusive practice, behavior support, and creating environments that enable autistic and disabled children and young people to thrive. She is also a Co-Principal at Dara School for gifted students and an education and disability consultant. She holds a Ph.D. in the teaching of autistic students from University of Canterbury in Aotearoa, New Zealand. Widely published, she writes for academic and mainstream audiences on autism, disability, interoception, and educational practice, and is a sought-after keynote speaker at conferences and professional learning events.

Through her consultancy work, including Healthy Possibilities, she supports schools, preschools, residential services, government and community organizations to design and implement practical, evidence-informed strategies that center neurodivergent voices and rights. She provides policy advice, staff training, coaching, and program design, with particular emphasis on interoception, self-regulation, and person-centered support for autistic people across the lifespan. Her work bridges research, policy, and practice, helping systems move toward genuinely inclusive education and disability support that recognizes the strengths, needs, and lived experiences of autistic and other disabled people.

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bind to methylated DNA, while the latter are able to confer enzymatic activity effecting chromosome conformation changes. Except for CHD5, all human CHD proteins are known to be ubiquitously expressed. Mutations in all *CHD* genes except for *CHD6* and *CHD9* have been found to cause several different neurodevelopmental disorders (Yasin & Zahir, 2020), attesting to the important role the CHD genes products play in development.

CHD8 in particular has been shown to be a "master regulator" that acts upon a number of downstream target genes. CHD8 is a regulator of the consequential Wnt signaling pathway (Durak et al., 2016), significant in several primary developmental pathways including in cortical neurogenesis. The Wnt signaling pathway plays a critical role in embryonic development as well as homeostasis in adult tissues, thus making it important in various forms of diseases including cancers (Durak et al., 2016; Sawada et al., 2013; Shingleton & Hemann, 2015; Suetterlin et al., 2018; Wang et al., 2015). In human tissue models, CHD8 has been shown to be involved in the regulation of thousands of downstream target genes, notably those involved in brain development and cancer pathways (Sugathan et al., 2014; Wang et al., 2015, 2017). It is also known to interact with the chromatin insulator protein CTCF (Damaschke et al., 2014a, b; Ishihara et al., 2006). CTCF binding to DNA causes chromatin looping and plays a role in gene promoter-enhancer interaction. A number of other important "master regulator" activities for CHD8 has been proven (reviewed by Basson, 2024). These include both activation and repression activities. Some examples of prominent protein complexes CHD8 is involved with are COMPASS (associated with ID, epilepsy, ASD among other diseases), BAF, and NURD complexes (associated with ASD, ID, and a number of neurodevelopmental syndromes). Thus, CHD8 is known to be a critical protein for correct development. *CHD8* sequence defects have been particularly noted to cause ASD, explaining approximately 0.5% of cases in some series, leading it to be termed a "master driver" of autism (Bernier et al., 2014).

SUPT16H

The *SUPT16H* gene encodes the Spt16 protein, one of two subunits of the FACT complex (Huang et al., 2015; Liu et al., 2020). It is highly conserved as is the other subunit of FACT, SSRP1. FACT has suggested roles in DNA transcription, replication, and repair, via effects on the nucleosome (Liu et al., 2020). No disease has yet been identified for SSRP1. The specific role of the Spt16 subunit is to interact with the histone dimer H2A-H2B of the nucleosome, allowing RNA polymerase access to DNA for transcription (Liu et al., 2020). In fact, reports of disease caused by *SUPT16H* gene variants were only recently reported, with the first and thus far only publication appearing in 2020, in contrast to CHD8 disease associations which were identified with the first high-resolution genome screening methods such as chromosomal microarray in the early noughties. Bina et al. reported four patients with de novo missense variants and one with a de novo deletion in *SUPT16H*, identified by whole exome screening of patients with corpus callosum anomalies (Bina et al., 2020). Protein products for all five variants are reported to be damaging. The fact that disease causing variants in *SUPT16H* have been so rarely identified likely indicates that severe variants in this gene likely are lethal prior to live birth (this is in contrast to *CHD8* disease causing variants recognized frequently from the very first high-resolution genome screening studies). This hypothesis is supported by the fact that the probability of loss-of-function intolerance for *SUPT16H* calculated based on normal variation reported from the EXAC database of normal human variation is extremely high (pLI = 1.0). Interestingly, one of the ZFS patients was reported to have hypoplasia of the corpus callosum (Yasin et al., 2019). Screening for corpus callosum defects has not been done as a routine assessment for other ZFS patients to our knowledge, so there could be other ZFS patients with this phenotype. Alternatively, the presence of *CHD8* deletions may mitigate the more severe phenotype caused by *SUPT16H* deleterious variants. Notably all five patients with *SUPT16H* deleterious variants reported by Bina et al. had developmental delay, speech, and cognitive

delay, and some went on to present with ID- and ASD-like presentations (Bina et al., 2020). Features reported for the patients include those characteristics for ZFS, such as down slanting palpebral fissures, ear anomalies, and sleeping difficulties. Unfortunately, Bina et al. have not included patient photographs in their publication precluding a more meaningful facial assessment.

Effect of Heterozygous Loss of both Critical Genes

While studies probing the combined molecular impact of heterozygous deleterious variation in both *CHD8* and *SUPT16H* have not been extensively undertaken, selected relevant studies overviewed below provide valuable insights.

FACT and CTCF

A recent report by Wang et al. shows that in mice inhibition of FACT by knock down of the Ssrp1 FACT subunit leads to enhanced CTCF binding, causing a remarkable wide-reaching change in gene expression dynamism (Wang et al., 2024). It may be hypothesized that the same effect would result from the knock down of the Spt16 subunit of FACT as well, though this is supposition.

Transcriptomic Profile of ZFS Patients

In an interesting study, Yasin et al. conducted the first transcriptomic profiling for a ZFS patient (Yasin et al., 2020). They used high-resolution whole transcriptomic RNA sequencing on peripheral blood mononuclear cells from patient "Vancouver 4444." This patient is notable for having the smallest reported deletion that spans the critical region. Furthermore, the patient was an adult at the time of blood draw, and thus the results are expected to show how the gene expression profile of this lesion presents at adulthood. However, the age of the patient may also have unfavorable consequences in that it could be supposed the gene expression profile may be influenced by tissue specific alterations acquired later in life. The patient's transcriptome was compared to that of his sex-matched brother as a normal control—a strong choice for control as this is expected to mitigate effects of genomic background-dependent gene expression profiling. While the study is underpowered, in that only one patient has been assessed, nevertheless the authors' finding that over 40% of all 13,002 detected expressed genes were significantly differently expressed between the patient and his brother is remarkable (Yasin et al., 2020). This finding proves that the genetic lesion in ZFS has wide-ranging consequences, affecting a very high number of other genes.

The authors also analyzed their data in comparison to five published gene expression data sets from *CHD8*+/− model studies of human-induced pluripotent stem cells derived organoids and cell lines. As expected, several important downstream target genes were commonly differentially expressed across the patient sample and model studies, reiterating the complex and wide-ranging effect on molecular pathophysiology this lesion causes. While the authors do not contrast the difference in gene expression between their sample and those of the cellular models from the perspective of what addition effects could be surmised to be caused by haploinsufficiency of *SUPT16H*, it can be seen that the vast majority of the most differentially expressed genes in the patient are not found in the cellular models. Of the 23 genes that were found to have + or − threefold differential expression between the patient and his brother, only 3 were also found as differential expressed genes in any of the 5 *CHD8*+/− iPSC models. Thus, it is possible that the other 20 genes' regulation change was caused by either the combined effect of *CHD8* and *SUPT16H* haploinsufficiency or only by *SUPT16H* haploinsufficiency (Yasin et al., 2020).

Epigenomic Profile of ZFS Patients

Given that both the causative genes for ZFS have notable functions in epigenomic regulation, it is disappointing that to date no methylation or any other rigorous targeted epigenomic profiling study has been carried out on a patient sample. Nevertheless, the gene expression data between patient and control being so divergent in the one transcriptomic study thus far published (Yasin et al., 2020) indicates that significant epigenomic changes are expected to be caused by the haploinsufficiency of the causative genes.

Treatment and Management

There is no reported treatment to date for ZFS. Patients are identified by genetic testing either due to suspicion of the syndrome due to facial gestalt and other symptoms, or as is more often the case, via routine genomic or exomic screening conducted on children with DD. Patients once identified are managed by symptom-specific clinical interventions. Issues during infancy such as sleep and feeding difficulties may be resolved by a specialized remedial interventionist. In terms of the child's cognitive development, patients are reported to respond well to individualized special learning needs and education plans. Children are able to attend school but may not be able to keep up with their age-matched peers except with intensive remedial learning interventions. The mild and gentle disposition of children with ZFS is conducive to implementing personalized educational and other developmental aids. These children are often reported as being a "pleasure to be around."

An important concern is the reported involvement of CHD8 in cancer development. Therefore, it is advised that ZFS patients be routinely screened for cancer, especially as they enter adulthood. To date no ZFS patient has reported a childhood cancer.

Conclusion

ZFS is a neurodevelopmental disorder characterized by a distinctive yet subtle facial gestalt, DD, ID, and/or ASD in addition to feeding and sleep difficulties. Macrocephaly is also commonly found, and there has been some debate as to whether ZFS may be characterized as an overgrowth syndrome, especially due to the suggestion that *CHD8*+/− sequence variation causes a subtype of autism with overgrowth. However, ZFS patients cannot be said to have overgrowth as a distinguishing characteristic.

Confusion had arisen as to whether ZFS and the syndromic autism caused by *CHD8*+/− were the same, especially in the early years when the contribution of SUPT16H was not able to be assessed well. The latter disorder, termed CHD8-NDD, is caused primarily by sequence variation in the *CHD8* gene that is deleterious. The variants may be loss of function or gain of function due to missense mutations and thus present a complex picture. Some features in children with ZFS and CHD8-NDD were commonly found (see Yasin et al., for a thorough comparison (Yasin et al., 2019)) including in some cases a facial presentation that could be easily mistaken for either syndrome. At that time, it was not known if the ancillary deletion of *SUPT16H* was being involved simply due to its physical location as the gene adjacent to *CHD8* or whether its loss also played an active role in syndrome pathophysiology. In contrast we now know that *SUPT16H* is a highly conserved gene with an extremely low probability of intolerance in the general population and that its heterozygous loss of function causes corpus callosum anomalies. This suggests that not only is *SUPT16H* haploinsufficiency contributory to the ZFS presentation but that the additional presence of the *CHD8* heterozygous deletion may actually mitigate the severity of a *SUPT16H* heterozygous loss-of-function outcome. Indeed, the great number of differentially expressed genes found in the ZFS patient transcriptome profile not found in CHD8+/− cellular models (Yasin et al., 2020) supports this notion.

Given that both causative genes for ZFS are involved in epigenomic regulation, it is possible continued precision medicine research and multiomics studies could lead to identification of mitigative treatment modalities to counter the effects of the *CHD8* and *SUPT16H* loss of function. However, the management of ZFS has proven to be effective with remedial measures able to counteract the severity of disease progression especially in the cognitive domain. This necessitates that the syndrome is detected and confirmed via genetic testing early in the child's life. ZFS remains a rare neurodevelopmental syndrome that is mostly mild to moderate in its impact, which can be effectively managed with a suite of specialized interventions and minimal medication.

Cross-References

- Ageing with an Intellectual Disability
- Friendship and Persons with an Intellectual Disability
- Genetic Etiology of Neurodevelopmental Disorders
- Genomic Research About Autism
- Maltreatment of Children with Disability

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References

Basson, M. A. (2024). Neurodevelopmental functions of CHD8: New insights and questions. *Biochemical Society Transactions, 52*(1), 15. https://doi.org/10.1042/BST20220926

Bernier, R., Golzio, C., Xiong, B., Stessman, H. A., Coe, B. P., Penn, O., Witherspoon, K., Gerdts, J., Baker, C., Vulto-van Silfhout, A. T., Schuurs-Hoeijmakers, J. H., Fichera, M., Bosco, P., Buono, S., Alberti, A., Failla, P., Peeters, H., Steyaert, J., Vissers, L. E. L. M., … Eichler, E. E. (2014). Disruptive CHD8 mutations define a subtype of autism early in development. *Cell, 158*(2), 263–276. https://doi.org/10.1016/j.cell.2014.06.017

Bina, R., Matalon, D., Fregeau, B., Tarsitano, J. J., Aukrust, I., Houge, G., Bend, R., Warren, H., Stevenson, R. E., Stuurman, K. E., Barkovich, A. J., & Sherr, E. H. (2020). De novo variants in SUPT16H cause neurodevelopmental disorders associated with corpus callosum abnormalities. *Journal of Medical Genetics, 57*(7), 461. https://doi.org/10.1136/jmedgenet-2019-106193

Damaschke, N., Huang, W., Lin, C. P., Lee, J. H., & Jarrard, D. (2014a). MP52-03 DISRUPTION of CHD8-CTCF chromatin complex in PROSTATE cancer alters DNA methylation patterns. *Journal of Urology, 191*(4S). https://doi.org/10.1016/j.juro.2014.02.1613

Damaschke, N. A., Yang, B., Blute, M. L., Lin, C. P., Huang, W., & Jarrard, D. F. (2014b). Frequent disruption of chromodomain helicase DNA-binding protein 8 (CHD8) and functionally associated chromatin regulators in prostate cancer. *Neoplasia, 16*(12), 1018–1027. https://doi.org/10.1016/j.neo.2014.10.003

Drabova, J., Seemanova, E., Hancarova, M., Pourova, R., Horacek, M., Jancuskova, T., Pekova, S., Novotna, D., & Sedlacek, Z. (2015). Long term follow-up in a patient with a de novo microdeletion of 14q11.2 involving CHD8. *American Journal of Medical Genetics Part A, 167*(4), 837–841. https://doi.org/10.1002/ajmg.a.36957

Durak, O., Gao, F., Kaeser-Woo, Y. J., Rueda, R., Martorell, A. J., Nott, A., Liu, C. Y., Watson, L. A., & Tsai, L.-H. (2016). Chd8 mediates cortical neurogenesis via transcriptional regulation of cell cycle and Wnt signaling. *Nature Neuroscience, 19*(11), 1477–1488. https://doi.org/10.1038/nn.4400

Huang, H., Santoso, N., Power, D., Simpson, S., Dieringer, M., Miao, H., Gurova, K., Giam, C. Z., Elledge, S. J., & Zhu, J. (2015). FACT proteins, SUPT16H and SSRP1, are transcriptional suppressors of HIV-1 and HTLV-1 that facilitate viral latency. *Journal of Biological Chemistry, 290*(45), 27297. https://doi.org/10.1074/jbc.M115.652339

Ishihara, K., Oshimura, M., & Nakao, M. (2006). CTCF-dependent chromatin insulator is linked to epigenetic remodeling. *Molecular Cell, 23*(5), 733. https://doi.org/10.1016/j.molcel.2006.08.008

Kari, V., Shchebet, A., Neumann, H., & Johnsen, S. A. (2011). The H2B ubiquitin ligase RNF40 cooperates with SUPT16H to induce dynamic changes in chromatin structure during DNA double-strand break repair. *Cell Cycle, 10*(20), 3495. https://doi.org/10.4161/cc.10.20.17769

Katayama, Y., Nishiyama, M., Shoji, H., Ohkawa, Y., Kawamura, A., Sato, T., Suyama, M., Takumi, T., Miyakawa, T., & Nakayama, K. I. (2016). CHD8 haploinsufficiency results in autistic-like phenotypes in mice. *Nature, 537*(7622), 675–679. https://doi.org/10.1038/nature19357

Liu, Y., Zhou, K., Zhang, N., Wei, H., Tan, Y. Z., Zhang, Z., Carragher, B., Potter, C. S., D'Arcy, S., & Luger, K. (2020). FACT caught in the act of manipulating the nucleosome. *Nature, 577*(7790), 426. https://doi.org/10.1038/s41586-019-1820-0

Ma, M., Zhang, X., Zheng, Y., Lu, S., Pan, X., Mao, X., Pan, H., Chung, H. L., Wang, H., Guo, H., & Bellen, H. J. (2023). The fly homolog of SUPT16H, a gene associated with neurodevelopmental disorders, is required in a cell-autonomous fashion for cell survival. *Human Molecular Genetics, 32*(6), 984. https://doi.org/10.1093/hmg/ddac259

Merner, N., Forgeot d'Arc, B., Bell, S. C., Maussion, G., Peng, H., Gauthier, J., Crapper, L., Hamdan, F. F., Michaud, J. L., Mottron, L., Rouleau, G. A., & Ernst, C. (2016). A de novo frameshift mutation in chromodomain helicase DNA-binding domain 8 (CHD8): A case report and literature review. *American Journal of Medical Genetics. Part A, 170A*(5), 1225–1235. https://doi.org/10.1002/ajmg.a.37566

Platt, R. J., Zhou, Y., Slaymaker, I. M., Shetty, A. S., Weisbach, N. R., Kim, J.-A., Sharma, J., Desai, M., Sood, S., Kempton, H. R., Crabtree, G. R., Feng, G., & Zhang, F. (2017). Chd8 mutation leads to autistic-like behaviors and impaired striatal circuits. *Cell Reports, 19*(2), 335–350. https://doi.org/10.1016/j.celrep.2017.03.052

Prontera, P., Ottaviani, V., Toccaceli, D., Rogaia, D., Ardisia, C., Romani, R., Stangoni, G., Pierini, A., & Donti, E. (2014). Recurrent ~100 kb microdeletion in