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# Caregiver Perspectives on the Daily Function of People Living With HNRNPH2-Related Neurodevelopmental Disorder: Developing a Conceptual Model

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# Caregiver Perspectives on the Daily Function of People Living With *HNRNPH2*-Related Neurodevelopmental Disorder: Developing a Conceptual Model

by

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## Abstract

**Introduction:** Neurodevelopmental disorders are a group of conditions that start in childhood and lead to impairments in functioning. HNRNPH2-related neurodevelopmental disorder is an ultra-rare disorder in which individuals present with cognitive, behavioral, language and motor function impairments that often leads to reliance on their caregivers. Existing conceptual models of neurodevelopment are not specific to this ultra rare disorder and do not highlight the caregiver impact of living with HNRNPH2-related neurodevelopmental disorder.

**Purpose:** The purpose of this study is to understand the caregiver perspective on the everyday functioning of people living with HNRNPH2-related neurodevelopmental disorder to generate a person-centered conceptual model.

**Methods:** Semi-structured interviews with twenty caregivers of individuals with HNRNPH2-related neurodevelopmental disorder were conducted. The interviews were transcribed verbatim and analyzed using thematic analysis. An initial conceptual model was developed using an adapted grounded theory framework.

**Results:** Twenty primary caregivers including 14 female caregivers and 6 male caregivers of females with HNRNPH2-related neurodevelopmental disorder living in 9 countries: United Kingdom (35%); United States (30%); Netherlands (10%); Denmark, France, Norway, Portugal, and Switzerland (each 5%) were interviewed. The defining concepts of the condition include cognition, communication, neurological, behavioral, visual, musculoskeletal/orthopedics, vi gastrointestinal and others. Individuals with *HNRNPH2*-related neurodevelopmental disorder have impacts on daily functioning including proximal impacts (activities), distal impacts (participation), and modifiers including personal and external factors. In light of caregiver's major role in supporting the everyday functioning of individuals with *HNRNPH2* a conceptual disease model was developed from the study data diagraming the defining concepts or

symptoms, impacts on people living with *HNRNPH2*-related neurodevelopmental disorder and caregiver impacts.

**Practical Implications:** This study highlights the unique features of *HNRNPH2*-related neurodevelopmental disorder impacting the everyday functioning of those living with the condition and impact on their caregivers. The person-centered conceptual model can be implemented by families to describe key features of the condition and their child's current level of function; by clinicians and advocates to develop practical care consideration guidelines and policies; and by researchers to develop person centered assessments and treatments specifically for relevant and meaningful functions of individuals with *HNRNPH2*-related neurodevelopmental disorder.

**Keywords:** *HNRNPH2*, Neurodevelopmental, Person-Centered Care, Grounded Theory

## Chapter 1: Introduction

Neurodevelopmental disorders are conditions starting in childhood that result in significant lifelong burden (American Psychiatric Association, 2013). Approximately 30% of neurodevelopmental disorders are caused by a genetic variation (Soden et al., 2014). A novel neurodevelopmental disorder caused by an ultrarare genetic variant in the X-linked gene *HNRNPH2* (GenBank: NM_019597.4) was first described in six females presenting with a range of neurodevelopmental features including mild to severe developmental delay, intellectual disability, language and communication impairments, motor dysfunction, seizures, and autism spectrum disorder (ASD) (Bain et al., 2016). Through genetic testing, over 145 individuals living with variants in *HNRNPH2* have been identified across 31 countries in the world (Yellow Brick Road Project, 2023). An ongoing collaboration between clinicians, researchers, and patient/family advocacy organizations is underway to identify, describe, and understand *HNRNPH2*-related neurodevelopmental disorder through a natural history study (ClinicalTrials.gov Identifier: NCT03492060).

The observable clinical features of a condition are typically described through clinical outcome assessments that reflect how a patient feels, functions, or survives (Cagney et al., 2018). Function refers to a person's ability to engage in activities of daily living and social activities in everyday life. Due to limitations in function, people living with neurodevelopmental conditions are highly, and sometimes completely, reliant on their caregivers to perform everyday tasks (Semmel et al., 2019). Caregivers, such as loved ones, parents, family, friends, aides, and nurses, regularly assist individuals with everyday tasks such as bathing, dressing, feeding and mobility. Caregivers are integral in assisting the daily function of people with neurodevelopmental disorders. Caregivers can provide meaningful and relevant insight into the functioning of

individuals living with neurodevelopmental conditions, including *HNRNPH2*-related neurodevelopmental disorder (Davis et al., 2023; Salazar et al., 2020; Semmel et al., 2019).

Traditional healthcare models focus on diseases, symptoms, and disabilities without acknowledging the person, family, and caregivers' lived experiences, their expertise, and abilities (Santana et al., 2018; World Health Assembly, 2016). By shifting to a person-centered care model, we recognize the patient as a person with abilities despite their conditions (Santana et al., 2018; World Health Assembly, 2016). In addition, person-centered care promotes personalized care and recognition of people's strengths and abilities in order to live a fulfilling life (Santana et al., 2018; World Health Assembly, 2016). A person-centered approach is vital in assessing how a person with *HNRNPH2*-related neurodevelopmental disorder feels and functions.

The United States Food and Drug Association (US FDA) guidance endorses a person-centered approach for the development of clinical outcome assessments that measure how a person feels are functions (US FDA, 2022). The guidance recommends the inclusion of the perspectives of patients and caregivers in the generation of conceptual models that inform relevant and meaningful outcome measures (Brod et al., 2009; Lasch et al., 2010; US FDA, 2009, US FDA., 2022). A condition-specific conceptual model is a visual representation that delineates the signs, symptoms and impacts of a condition on the person with the condition, their family, and their community (Brod et al., 2009; Lasch et al., 2010). The conceptual model is developed through an inductive, systematic, and iterative approach using adapted grounded theory (Brod et al., 2009; Lasch et al., 2010; US FDA, 2009, US FDA, 2022). The conceptual model emerges from concepts that person and their caregivers recognize as meaningful and relevant (Brod et al., 2009; Lasch et al., 2010). By integrating the perspectives of the person and

caregiver into the conceptual model, measurement experts will be enabled to apply the model to select, adapt, or develop meaningful and robust measurement tools to assess clinically meaningful functions.

Existing outcome measures were developed based on conceptual models of neurodevelopmental conditions such as ASD, attention deficit hyperactivity disorder (ADHD) or cerebral palsy (CP) (McDougall et al., 2018; Schiariti, Longo et al., 2018; Schiariti, Mahdi et al., 2018). Based on existing neurodevelopmental outcome measures, approximately 90% of individuals living with *HNRNPH2*-related neurodevelopmental disorder score below the 5$^{th}$ percentile for age in cognitive, daily activity, mobility, responsibility, and social function (Bain et al., 2021; Davis et al, 2023; Salazar et al., 2020). In addition, over 20 different outcome measures were used to assess the different functional domains of individuals with *HNRNPH2*-related neurodevelopmental disorder, adding additional burden to the person and caregivers (Bain et al., 2021). While available outcome measures measure the salient delays across function domains, these current measures offer limited insight into the actual functional abilities of an individual with *HNRNPH2*, especially for individuals with severe phenotypes, who are most reliant on their caregivers for everyday functioning. The current measures do not capture the clinical variability of the disorder and the spectrum of functioning of individuals living with *HNRNPH2*-related neurodevelopmental disorder (Bain et al., 2021; Davis et al., 2023; Salazar et al., 2020). The true abilities of individuals living with *HNRNPH2*-related neurodevelopmental disorder are obscured by floor-effects seen across cognitive, social, motor, and daily activity functional domains (Bain et al., 2021; Davis et al., 2023; Salazar et al., 2020). Although existing conceptual models were systematically developed for use in neurodevelopmental conditions, major content gaps exist in current models. The everyday functional abilities of individuals

living with *HNRNPH2*-related neurodevelopmental disorder are not adequately captured or highlighted in current models. At this time, conceptual models of neurodevelopmental disorders are not centered on people with *HNRNPH2*-related neurodevelopmental disorder and were not generated from the perspectives of caregivers of people living with *HNRNPH2*-related neurodevelopmental disorder .

### 1.1 Statement of the Problem

*HNRNPH2*-related neurodevelopmental disorder is a unique, ultra-rare, neurodevelopmental genetic disorder for which no conceptual models exist. The unique combination of signs, symptoms, daily function of individuals, and the impact on caregivers and families of *HNRNPH2*-related neurodevelopmental disorder are not included in current conceptual models of neurodevelopmental conditions. The abilities and relevant needs of people with *HNRNPH2*-related neurodevelopmental disorder and their caregivers have not been systematically and inductively integrated into conceptual models of neurodevelopmental conditions. The main problem is that perspectives of caregivers of people with *HNRNPH2*-related neurodevelopmental disorder have not been included in the development of a person-centered conceptual model specific to *HNRNPH2*-related neurodevelopmental disorder.

### 1.2 Significance of the Problem

A person-centered conceptual model generated from the caregiver perspective is necessary to illustrate the meaningful, relevant, and person-centered everyday functions of individuals living with *HNRNPH2*-related neurodevelopmental disorder and their caregivers. A disease-specific conceptual framework could be used by clinicians and families to recognize and develop the strengths and abilities of people living with *HNRNPH2*-related neurodevelopmental disorder. Integrating the wants, needs and perspectives of the caregiver will enable clinicians to

identify the most meaningful and relevant aspects of the disorder to support and guide treatment. In addition, measurement experts will be able to use the model to select clinically meaningful and relevant measurement tools to assess current function and change in function in a meaningful way. A conceptual model is essential for informing, methods of tracking the function of individuals with *HNRNPH2*-related neurodevelopmental disorder, determine disease trajectory, and potentially identify treatments that improve the lives of individuals living with *HNRNPH2*-related neurodevelopmental disorder.

### 1.3 Qualitative Tradition and Theory Summary

Grounded theory is an inductive process used to generate a theory based on data that is systematically collected and analyzed (Glaser & Strauss, 1967). Charmaz (2006) advocates for a constructivist approach to grounded theory allowing for increased flexibility in the guidelines to develop a model based on existing knowledge, multiple realities, hidden networks, and the perspectives of the individuals interviewed. Principles from grounded theory were adapted to generate and refine disease-specific conceptual models that are used to describe the lives of individuals living with a condition and those who care for them. (Brod et al., 2009; Lasch et al., 2010). An adapted grounded theory approach was selected for this study as it is the accepted practice in the development of disease-specific conceptual models (Brod et al., 2009; Lasch et al., 2010; US FDA, 2009; US FDA., 2022). Existing conceptual models of neurodevelopmental disorders were not developed based on the perspectives from the network of caregivers caring for individuals living with *HNRNPH2*-related neurodevelopmental disorder. Therefore, existing conceptual models are not applicable to *HNRNPH2*-related neurodevelopmental disorder and a conceptual model must be developed specifically for *HNRNPH2*-related neurodevelopmental disorder (McDougall et al., 2018; Schiariti, Mahdi et al., 2018).

Brod et al., (2009) describe the development of disease-specific conceptual models based on adapted grounded theory. First literature reviews and expert opinions are used as the initial basis in the development of the conceptual model (Brod et al., 2009). Next, the patient and caregiver perceptive is gathered and analyzed concurrently using constant comparison (Brod et al., 2009). As emergent concepts are identified, these concepts or themes are integrated into future interviews (Brod et al., 2009). Overarching concepts are grouped into categories and further explored in subcategories. The properties and relationships between categories and subcategories are further explored. The categories are confirmed, and disconfirmed until theoretical saturation is reached while continually building and refining the conceptual model (Brod et al., 2009). As many individuals living with *HNRNPH2*-related neurodevelopmental disorder are reliant on their caregivers, the caregivers are key in developing the conceptual model of daily function in *HNRNPH2*-related neurodevelopmental disorder.

### 1.4 Deficiencies in Relevant Literature

The major deficiency in the literature is that the perspectives of the caregivers on the daily function of individuals with *HNRNPH2*-related neurodevelopmental disorder have not been studied or included the development of a person-centered conceptual model. Therefore, the impact of the health condition on the daily function of a person and those who care for them has not been explored specifically for individuals living with *HNRNPH2*-related neurodevelopmental disorder.

### 1.5 Purpose Statement

The purpose of this study is to understand the caregiver's perspective on the everyday functioning of people living with *HNRNPH2*-related neurodevelopmental disorder to generate a person-centered conceptual model.

### 1.6 Overarching Research Questions (RQ) and Sub-Questions (SQ).

**RQ1:** How do caregivers perceive the functioning of an individual with *HNRNPH2*-related neurodevelopmental disorder?

*SQ1a:* How are the body functions of an individual with *HNRNPH2*-related neurodevelopmental disorder perceived by their caregivers?

*SQ1b:* How are the activities of an individual with *HNRNPH2*-related neurodevelopmental disorder perceived by their caregivers?

*SQ1c:* How is the participation of an individual with *HNRNPH2*-related neurodevelopmental disorder perceived by their caregivers?

*SQ1d:* What aspects of daily functioning do caregivers perceive as meaningful when assessing an individual with *HNRNPH2*-related neurodevelopmental disorder?

**RQ2:** What factors do caregivers perceive impact the daily functioning of an individual with *HNRNPH2*-related neurodevelopmental disorder?

*SQ2a:* How are the personal factors of an individual with *HNRNPH2*-related neurodevelopmental disorder perceived by their caregivers?

*SQ2b:* How are the environmental factors of an individual with *HNRNPH2*-related neurodevelopmental disorder perceived by their caregivers?

**RQ3:** How do caregivers perceive their role in supporting the daily functioning of an individual living with *HNRNPH2*-related neurodevelopmental disorder?

*SQ3a:* How do caregivers perceive their own impact on the daily functioning of individual living with *HNRNPH2*-related neurodevelopmental disorder?

*SQ3b:* What caregiver(s) support the daily functioning of individuals living with *HNRNPH2*-related neurodevelopmental disorder?

### 1.7 Summary.

*HNRNPH2*-related neurodevelopmental disorder is an ultrarare neurodevelopmental condition with clinical features including intellectual disability, language and communication impairments, motor dysfunction, and autism spectrum disorder. Most people with *HNRNPH2*-related neurodevelopmental disorder rely on their caregivers for everyday functioning. A person-centered conceptual model of a condition is a visual representation of the signs, symptoms and impacts of a condition on the person with the condition, their family, and their community, typically generated using adapted grounded theory. Existing conceptual models of neurodevelopment are based on other conditions, such as CP, ADHD, and ASD. Unfortunately, the existing conceptual models of neurodevelopment are not inclusive of all the specific features of this ultrarare disorder, and these models are not grounded in the perspectives of the caregivers who support individuals living with *HNRNPH2*-related neurodevelopmental disorder in everyday life. Therefore, there is a need to identify and describe the meaningful and relevant domains of functioning specific to *HNRNPH2*-related neurodevelopmental disorder and create a person-centered conceptual model of this unique disorder. A disease-specific conceptual model based on the perspectives of the caregiver will help identify the meaningful, relevant, and person-centered everyday functions of people living with *HNRNPH2*-related neurodevelopmental disorder as well as inform how clinicians should best track and treat individuals and families living with this condition.

# Chapter 2: Review of Literature

## 2.1 Historical Background

Neurodevelopment is the structural formation of the brain, neuropathways, and structural components of the central nervous. The result of neurodevelopment is the ability to function in everyday life including the ability to learn, move, grow, and socialize. An insult to neurodevelopment may cause a neurodevelopmental disorder. The American Psychiatric Association (2013) define a neurodevelopmental disorder as a complex group of disorders that affects the growth and development of the brain or central nervous system leading to a disorder starting in childhood with significant lifelong burden. The consequences of a neurodevelopmental disorder span a wide range of symptoms and severity that may include intellectual disability, communication disorders, autism spectrum disorder, learning disorder, motor disorder or others.

### *2.1a Genetics of neurodevelopmental conditions*

Genetic variants cause about 30% of neurodevelopmental disorders (Lai et al., 2014; Soden et al., 2014). Genetic variants can be inherited or occur spontaneously. Inside the nucleus of our cells, there are chromosomes that package the human genome. Human cells contain two sets of chromosomes, one set inherited from each parent. Each cell normally contains 23 pairs of chromosomes, which consist of 22 autosomes (numbered 1 through 22) and one pair of sex chromosomes (XX or XY). Inside of each chromosome is deoxyribonucleic acid (DNA) the molecule that holds the genetic information for a cell and an organism. A specific segment of a DNA molecule that holds the information for producing a specific protein is called a gene. The human genome has ~25,000 genes. The X-chromosome contains only about 5% of the human genome but accounts for about 15% of the genes currently known to be associated with

intellectual disability (Neri et al., 2018). As of the 2017, X-linked intellectual disability (XLID) update, 141 genes have been associated with XLID (Neri et al., 2018). One gene that causes XLID is the *HNRNPH2* (GenBank: NM_019597.4) gene (Bain et al., 2016).

*HNRNPH2* gene is contained on the X Chromosome (Xq22.1) and is responsible for producing a protein which is part of a family of ubiquitous heterogeneous nuclear ribonucleoproteins (HNRNP), specifically Heterogeneous Nuclear Ribonucleoprotein H2 (*HNRNPH2* [MIM: 300610]) (Bain et al., 2016). The HNRNPs are a ubiquitously expressed family of RNA binding proteins termed alphabetically from A1 to U (Geuens, Bouhy, & Timmerman, 2016). Together, the HNRNPs have both nuclear and cytoplasmic functions and are implicated in several of the steps of mRNA splicing, metabolism, and gene transcription (Honore et al., 1995). Specifically, *HNRNPH2* primarily functions to regulate the alternative splicing of pre-mRNA (Choi et al., 1986). The *HNRNPH2* protein has been found throughout the body and is highly co-localized to the nuclear compartments in the brain, gastrointestinal tract, lung, skin, spleen, and testes (Bain et al., 2016). A variant or mutation in the *HNRNPH2* gene can disrupt neurodevelopment and present with multi-system involvement (Bain et al, 2016).

*2.1b HNRNPH2-related neurodevelopmental disorder phenotype*

Bain et al. (2016) first described *HNRNPH2*-related X-linked intellectual disability in 6 females ages 2 to 34 years old with a common neurodevelopmental clinical presentation including developmental delay and intellectual disability. Notable tone abnormalities were reported in all 6 participants with all having hypotonia and one also presenting with hypertonia. Developmental regressions, when a child develops skills in mobility, speech, or social abilities, but then progressively loses these milestones, were reported in 3 participants. Diagnosis of ASD and seizures were reported in 50% of the participants. Behavioral disturbances including

attention deficit hyperactivity disorder, obsessive compulsive disorder, aggressive behavior, self-injurious and repetitive stereotypic behavior were described in 3 participants. Skeletal disturbances were noted such as short-stature, microcephaly, scoliosis, pectus carinatum and/or pes planus in 4 participants. In addition, all participants exhibited one or more gastrointestinal symptoms, such as feeding difficulties (n = 2), failure to thrive (n = 2), gastroesophageal reflux disease (GERD) (n =2), and/or constipation (n = 1). As only females were initially identified, Bain, et al. (2016) hypothesized that these variants were lethal in males and only heterozygous females would survive.

Since the original identification of the gene, several male patients have been identified *HNRNPH2* gene variants. In 2019, the first male children with *HNRNPH2*-related neurodevelopmental disorder were identified (Harmson et al., 2019; Jepsen et al., 2019). Harmson et al. (2019) described a 3-year-old boy with a hemizygous missense change c.617G>A, p.Arg206Gln in the *HNRNPH2*-gene who presented with profound developmental delay, progressive microcephaly and muscular hypotonia noted in his first year of life. By 3-years-old, he presented with developmental disabilities, profound hypotonia, inability to move independently, flexion contractures of his knees, scoliosis, feeding difficulties and lack of speech development. Jepsen et al., (2019) described two additional boys with a similar clinical presentation. Patient A, a 5-year-old boy with a hemizygous missense variant c.616C>T, p.Arg206Trp within the NLS, presented with normal development until 3-months old when he exhibited a lack of head control and unusual posturing of his extremities (Jepsen et al., 2019). At 2 years old, he had gastrostomy tube placed as his primary source of nutrition. At 5 years old, he required total support of his head and assistance to keep his mouth closed. He rotated while lying on his back, moved his hands and fingers, however had extreme hypotonia in his extremities and

trunk and was unable to sit or crawl (Jepsen et al., 2019). The child was nonverbal and appeared to have some comprehension with a happy and social disposition (Jepsen et al., 2019). Patient B, described by Jespen et al. (2019), was hemizygous in the second RNA recognition motif (RRM2) of *HNRNPH2* (c.340C>T, p.Arg114Trp) outside of the NLS. Patient B presented with a global developmental delay, microcephaly, failure to thrive, intractable epilepsy, hypotonia, and cortical visual impairment. At times in his life, he had over 10 generalized tonic clonic and dozens of myoclonic seizures each day. At time of publication, Jespsen et al. (2019) reported that the boy was 8 years old, non-verbal and did not follow commands. He presented with athetoid movements of his upper extremities and dyskinetic movements of his face and tongue. Due to feeding difficulties, he had a gastrostomy tube placed. These cases support the finding that *HNRNPH2* variants are not embryonically lethal in boys and other gene variants can produce a range of similar clinical presentation.

Peron et al. (2020) provided evidence to expand the clinical phenotype of *HNRNPH2*-related neurodevelopmental disorder based on a case study of a 35-year-old woman with at pathogenic variant within the mutational hotspot (NLS). Developmental history reported included hypotonia within the first months of life, global developmental delays as she sat unsupported at age 10 months, crawled at age 20 months, and started to walk at age 26 months, with an ataxic and wide-based gait. Speech was absent, except for a few single words and echolalia. Hand stereotypies were reported since infancy, for which she had been diagnosed with Rett syndrome, which was subsequently ruled out by molecular and clinical assessment. She demonstrated progressive regression in adulthood with decreased ability to walk independently starting at age 19 years old and head and upper limb tremors noted from age 31 years old. She also experienced daytime hyperventilation, frequent night waking, hypersensitivity to noise,

gastro-esophageal reflux (GERD), and dysphagia, initially for solid food and later for liquids. She was severely underweight. She had severe intellectual disability, absent speech, but could understand simple commands. She was able to walk with a wide-based gait for only short distances. She demonstrated upper and lower extremity rigidity with tremors in her upper limbs as well as stereotypic movements such as hand flapping and hand washing. Peron et al. (2019) urged for the inclusion of tremors, breathing, sleep and movement disorders, cerebellar vermis hypoplasia, stereotypies, and hypersensitivity to noise to the clinical phenotype of *HNRNPH2*-related neurodevelopmental disorder based on this case study.

All previously reported cases of *HNRNPH2*-related were due to de novo or spontaneous gene variants. Somashekar et al. (2019) were the first to describe a family with two affected siblings, a girl and a boy, with a pathogenic variant in the *HNRNPH2* gene possibly due to maternal germline mosaicism. The boy was evaluated at 8 years and 9 months old. He presented with developmental delay, intellectual disability, and seizures. Developmentally, he achieved head control at 10 months, rolling over at 12 months, and sitting with support at 18 months. He reached out to objects at age 12 months and transferred objects at 18 months. He had generalized tonic–clonic seizures at 18 months of age following which he lost all his previously attained milestones. He presented with facial dysmorphia, mild scoliosis, skin hyperextensibility, joint hypermobility, hand flapping, tremors, generalized hypotonia with deep tendon reflexes preserved. His younger sister was 5 years and 9 months at the time of evaluation. She presented with global developmental delay, intellectual disability, and developmental regression after 2 years of age. She achieved head control at 5 months, sat with support at 7 months, and spoke monosyllables at 2 years. She did not have seizures. She had skin hyperextensibility and joint hypermobility, but of less severity when compared to her brother. She had generalized hypotonia

and normal deep tendon reflexes. She also had involuntary movements of her hands. Formal assessment for autism was not carried out for the siblings. As both siblings presented with the condition, the authors hypothesized that the cause could be gonadal mosaicism of the variant in the mother (Somashekar et al., 2019).

White-Brown et al. (2021) also reported a case of an inherited disease-causing variant in the *HNRNPH2* gene in a 22-year affected daughter as her biological mother is asymptomatic biological mother who has markedly skewed X-inactivation. As such, it is important to offer genetic counseling to families with apparent de novo variants in *HNRNPH2* as cases of maternally inherited *HNRNPH2* exist (White-Brown et al., 2021).

Bain et al. (2021) described the clinical and psychological phenotype of 33 individuals living with X-linked *HNRNPH2*-related neurodevelopmental disorder. Participants included 29 females and 4 males ages 2-38 years old. The major features of the phenotype include developmental delay/intellectual disability (100%), severe language impairment (20% verbal), motor problems (37% ambulatory), growth, and musculoskeletal disturbances (70% orthopedics). Minor features include dysmorphic features, epilepsy (36%), neuropsychiatric diagnoses such as autism spectrum disorder (44%), and cortical visual impairment (86% vision problems). Of note, one participant died in her sleep at 23 years old and her genetic diagnosis was returned postmortem, after the seminal manuscript.

*2.1c Outcome measures used in HNRNPH2-related neurodevelopmental disorder studies*

The 33 study participants were enrolled in a natural history study of *HNRNPH2*-related neurodevelopmental disorder (NCT0349060) which included prospective data collection and retrospective chart reviews (Bain et al., 2021). Prospective data collection included parent and

caregiver reported standardized measure of functioning using various online platforms including all outcome measures listed on Table 1.

**Table 1**

*Summary of Caregiver Reported Outcome Measures Utilized in Prospective Natural History Study of HNRNPH2-Related Neurodevelopmental Disorder*

| **Caregiver Reported Outcome Measures in Prospective *HNRNPH2* Studies** | **Purpose** | **Publication** |
|---|---|---|
| Vineland Adaptive Behavior Scales, Third Edition (VABSIII) | Outcome measure used to diagnose intellectual disabilities. | Sparrow et al., 2016 |
| Social Communication Questionnaire (SCQ) | Outcome measure used to evaluate communication skills and social functioning in children who may have ASD. | Rutter et al., 2003 |
| Social Responsiveness Scale, Second edition (SRS) | Outcome measure used to identify and quantify social impairment associated with ASD. | Constantino, 2005 |
| Sensory Profile 2 (SP2) | Outcome measure used to evaluate a child's sensory processing in the home, school and community. | Dunn, 2014 |
| Short Sensory Profile 2 (SSP) | A screening tool to identify children with sensory processing difficulties. | Dunn, 2014 |
| Behavior Assessment System for Children, third edition (BASC-3) | Outcome measure used to evaluate a child's behavior or emotional status. | Reynolds & Kamphaus, 2015 |
| The Pediatric Evaluation of Disability Inventory Computer Adaptive Test (PEDI-CAT) | Outcome measure used to evaluate domains of daily activity, mobility, social/cognitive and responsibility . | Haley et al., 2006 |

*Note*. Adapted from "Detailed Clinical and Psychological Phenotype of the X-linked *HNRNPH2*-Related Neurodevelopmental Disorder" by J. M. Bain, O. Thornburg, C. Pan, D. Rome-Martin, L. Boyle, X. Fan, O. Devinsky, R. Frye, S. Hamp, C. G. Keator, N. M. LaMarca, A. B. R. Maddocks, M. Madruga-Garrido, K. Y. Niederhoffer, F. Novara, A. Peron, E. Poole-Di Salvo, R. Salazar, S. A. Skinner, G. Soares, … W. K. Chung, 2021, *Neurology. Genetics*, *7*(1), e551.

Based on the parent-reported outcome measures, most individuals living with *HNRNPH2*-related neurodevelopmental disorder had elevated scores in social communication questionnaire and social responsiveness scale suggestive of a diagnosis of ASD (Bain et al., 2021). Nineteen caregivers completed the Vineland Adaptive Behavior Scale, third edition (VABS-III) including the Adaptive Behavior Composite (ABC) score and individual domains scales Communication, Daily Living Skills, Socialization and Motor Skills. Using scores normalized to age, most individuals score two standard deviations below the mean, and all scored in the below average to low range. The few participants with higher scores, in the below average range, had genotypes outside the NLS region (Bain et al., 2021).

Retrospective data analysis was performed using a heuristic clinical severity score based on the clinician reported common clinical signs and symptoms including autism spectrum disorder, anxiety, vision, seizures, and tone abnormalities (Bain et al., 2021). Retrospective chart review revealed that previous cognitive, behavioral, and/or other psychological testing was available for 9 participants (27.3%). These 9 participants all had one or more tests completed, with a total of 20 different tests performed. The retrospective chart review illustrated that currently there is no consensus on the type of scale used when clinically assessing a child with a neurodevelopmental condition. In addition, the method of reporting scores varied between participants including a mix of scaled scores, normative scores, age equivalent, percentile, or a qualitative assessment of function.

Although participants with *HNRPH2*-related disorder demonstrated delays across functional domains, there is a lack of consistency on the test performed, methods in reporting scores, variety of tests and low number of participants performing the tests. Therefore, there is currently no consensus on a clinical test or battery of tests for the assessment of function in

children and adults living with *HNRNPH2*-related neurodevelopmental disorder. Table 2 includes the variety of clinical assessments and frequencies reported in the retrospective chart review.

**Table 2**

*Summary of Outcome Measures Reported in Retrospective Chart Reviews of HNRNPH2-Related Neurodevelopmental Disorder*

| **Name of Test** (Bain et al., 2021) | **Purpose of Assessment** | **n (% total)** | **Score on tests** |
|---|---|---|---|
| Autism Diagnostic observation Schedule (ADOS) | Standardized behavior observational test scored by clinicians used to diagnose ASD (Gotham et al., 2006) | 3 (9.1%) | 1. No concern for social disorder<br>2. Met criteria for ASD<br>3. Reported numerical scores and high level of ASD-related symptoms |
| Childhood Autism Rating Scale, 2nd edition, standard version (CARS2-ST) | Behavioral rating scale scored by clinicians to identify children with autism (Schopler et al., 1980) | 2 (6.1%) | 1. At age 7 yo: Total score 34.5<br>2. At age 3 yo: Total score 52 |
| Developmental Assessment of Young Children, 2nd edition (DAYC-2) | Clinician administered test to identify delays in cognition, communication, social-emotional development, physical development, and adaptive behavior (Voress & Maddox, 2013) | 3 (9.1%) | 1. At age 7 yo: domain score age equivalents ranged from 10 month to 13 months old across dimensions.<br>2. At age 2y 2mo age equivalent: 10 months<br>3. At age 4 yo: standard score ranged from 71 - 84 points across dimensions |
| Asperger Syndrome Diagnostic Scale (ASDS) | Scaled designed to identify Asperger's Syndrome with 5 subscales: Language, Social, Maladaptive, Cognitive, and Sensorimotor (Myles et al., 2001) | 1 (3.0%) | Asperger's Syndrome Quotient 107, 68th% (likely Asperger's Syndrome) |

| | | | |
|---|---|---|---|
| Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) | A clinician administered test of intelligence with 5 primary index scales: Verbal Comprehension Index, Visual Spatial Index, Fluid Reasoning Index, Working Memory Index, and Processing Speed Index. (Flanagan et al., 2011) | 2 (6.1%) | WISC-IV (11 yo)<br>Full scale IQ 75<br>Verbal comprehension 87<br>Perceptual Reasoning 79<br>Working Memory 68<br>Processing Speed 85 |
| Goldman-Fristoe Test of Articulation, 2nd Edition | A measure of articulation of consonant sounds for children and young adults (Goldman & Fristoe, 2000). | 1 (3.0%) | Performed at 5y8m - Standard Score 86, 9% |
| The Capute Scales Set | A pediatric assessment tool for the early detection of mental retardation and communicative disorders including the Clinical Adaptive Test/Clinical Linguistic and Auditory Milestone Scale (CAT/CLAMS) (Accardo & Capute, 2005) | 2 (6.1%) | 1. Performed at 2y3m: Language skills (CLAMS) = 10.3-month level Visual-motor / problem-solving skills (CAT) 9.3 month level<br>2. Performed at 4 years old: Language skills (CLAMS) = 9.3-month level, DQ=19 Visual-motor / problem-solving skills (CAT) 12.1 month level, DQ = 25 |
| Peabody Developmental Motor Scales | Standardized assessment intended to measure interrelated motor skills of young children including six subtests: reflexes, stationary, locomotion, object manipulation, grasping and visual-motor integration (Folio, 2000). | 1 (3.0%) | Peabody Test of Fine motor skills – 1st percentile |
| ADD-H Comprehensive Teacher's Rating Scale (ACTeRS) | A teacher reported questionnaire measuring attention deficit, hyperactivity, oppositional behavior and social skills (Ullmann, 1985) | 1 (3.0%) | Significant for attention, hyperactivity, social skills |

| | | | |
|---|---|---|---|
| Child Behavioral Checklist – teacher | A checklist for teachers used to assess a child's behavioral competency and behavioral problems (Achenbach, 1991). | 1 (3.0%) | Significant for attention and though problems, borderline on aggressive scale |
| Child Behavioral Checklist – parent | A checklist for parents used to assess a child's behavioral competency and behavioral problems (Achenbach, 1991). | 1 (3.0%) | Highly significant for attention and borderline for thought problems |
| Bayley Scales of Infant and Toddler Development, Third Edition | Clinician administered test used to assess the cognitive, language and motor function (Bayley, 2006) | 1 (3.0%) | At 17 months old - overall 10.5-11.5 month; Fine motor skills at 10-11-month level; Gross motor skills at 11-12-month level |
| Stanford-Binet Intelligence Scale | Clinician administered intelligence test assessing knowledge, quantitative reasoning, visual-spatial processing, working memory, and fluid reasoning (Terman & Merrill, 1960). | 1 (3.0%) | At 3 years: Form L-M – 18-22-month range; in keeping with significant delay (moderate mental handicap) |
| Receptive expressive emergent language scale (REEL) | Test to help identify infant and toddlers with language impairments (Bzoch & League, 1970). | 1 (3.0%) | Moderate delay in language development with receptive language age of 9-10 months, expressive language development 11-12 months. |
| Mullen Scales of Early Learning | Test of infants and children used evaluate Gross Motor, Visual Reception, Fine Motor, Expressive Language, and Receptive Language function (Mullen, 1995) | 1 (3.0%) | At 3 years old:<br>Visual Reception Scale T-score 20, 1st percentile, Age Equiv. 11 mo, Very Low<br>Fine Motor Scale T-score 20, 1st percentile, Age Equiv. 15 mo, Very Low<br>Receptive Language Scale T-score 20, 1st percentile, Age Equiv. 9 mo, Very Low<br>Early Learning Composite Standard Score 49, 1st percentile, Very Low |
| Level of Activity in Profound/Severe Mental Retardation (LAMPER) scale | A measure of the severity mental retardation of adults (Tesio et al., 2002) | 1 (3.0%) | Profound/Severe Mental Retardation (36yo): 4 |

| | | | |
|---|---|---|---|
| Battelle Developmental Inventory, Second Edition | A clinician administered assessment of a child's developmental skills including adaptive, personal-social, communication, motor, and cognitive (Newborg, 2005). | 1 (3.0%) | At 4y8m - Attention and Memory: Scaled Score 1, SS=55, <1%, Extremely low; Perception and Concepts: Scaled Score 1, SS=55, <1%, Extremely low |
| Adaptive Behavior Assessment System-Second Edition (ABAS-II) | A measure of an individual's adaptive behavior measured through parent-report, teacher-report, or an adult form (Harrison & Oakland, 2003). | 1 (3.0%) | At 4y8m: Teacher Report General Adaptive Composite - SS=46, Extremely Low (noted in all domains, including Social-Emotional Domain) |
| Preschool Language Scales, Fifth Edition (PLS-5) | Instrument used to evaluate the early stages of language development (Zimmerman et al., 2011). | 1 (3.0%) | At 4y8m: Auditory Comprehension: SS=50 Expressive Communication: SS=50 Total Language Score: SS=50 |

*Note*. Adapted from "Detailed Clinical and Psychological Phenotype of the X-linked *HNRNPH2*-Related Neurodevelopmental Disorder" by J. M. Bain, O. Thornburg, C. Pan, D. Rome-Martin, L. Boyle, X. Fan, O. Devinsky, R. Frye, S. Hamp, C. G. Keator, N. M. LaMarca, A. B. R. Maddocks, M. Madruga-Garrido, K. Y. Niederhoffer, F. Novara, A. Peron, E. Poole-Di Salvo, R. Salazar, S. A. Skinner, G. Soares, … W. K. Chung, 2021, *Neurology. Genetics*, *7*(1), e551. 

The Pediatric Evaluation of Disability Inventory-Computer Adaptive Test (PEDI-CAT) is an observer-reported outcome measure that evaluates functional domains including daily activities, mobility, social/cognitive and responsibility (Haley et al., 2006). The test was designed to evaluate individuals ages birth to 21 years old with all clinical diagnoses. Convergent validity was demonstrated between an observational measure of motor function and

the parent reported PEDI-CAT mobility domain in 10 individuals living with *HNRNPH2*-related neurodevelopmental disorder (Salazar, 2019).

Caregivers of 16 individuals living with *HNRNPH2*-related neurodevelopmental disorder completed the 4 domains of the PEDI-CAT. All participants had normative scores less than age-matched peers across domains of functioning – daily activities, mobility, social/cognitive and responsibility. Of the 16 participants, 87.5% scored below the 5$^{th}$ percentile for age in each domain demonstrating the limited ability for the scale to capture the clinical spectrum of the disorder. Mean domain scores at baseline (20 – 80 scale metric) were: daily activities 47.9 (SD 5.1), mobility 57.5 (SD 5.5), social/cognitive 56.8 (SD 5.2) and responsibility 36.4 (SD 8.3). Domain scores are better able to capture the clinical variability in the daily activities, mobility, and social/cognitive domains; however, the responsibility domains are statistically significantly lower than the other domains (Salazar et al., 2020).

In a longitudinal study by Davis et al. (2023), 33 participants (baseline mean age: 14.73 years, range: 2.89-42.04 years, median 11.34 years, 87.9% female) performed Vineland Adaptive Behavior Scale (VABS) measuring communication, daily living skills, socialization and motor skills and the Pediatric Evaluation of Disability Inventory Computer Adaptive Test (PEDI-CAT) measuring daily activities, social/cognitive, mobility and responsibility. Individuals with *HNRNPH2*-related neurodevelopmental disorder had mean normative scores less than age-matched peers across all domains, with 91% participants <5$^{th}$ percentile on the PEDI-CAT and VABS. Moderate positive correlations were demonstrated between the VABS Adaptive Behavior Composite and the following PEDI-CAT domain scaled scores: Daily Activities; Social/Cognitive; and Responsibility, but not the Mobility domain. PEDI-CAT and VABS normative scores do not capture the clinical variability of the individuals with *HNRNPH2*-related

neurodevelopmental disorder. Scaled scores may be able to capture functional variability within the spectrum of individuals with *HNRNPH2*. Although the VABS and PEDI-CAT measure similar constructs, convergent validity was not found across all domains (Davis et al., 2023).

Salazar et al. (2021) studied the motor function of 17 females with *HNRNPH2*-related neurodevelopmental disorder ages 2.7–37.1 years. Out of the 17 females, 88.2 % were able to sit without support, 70.6 % achieved walking independently, and only six participants 35.3 % were able to climb stairs using a railing. The average age at achievement for these milestones was delayed, with sitting without support achieved on average at 1.4 years of age (range 0.4–3.0 years) and walking independently achieved on average at 3.8 years of age (range 1.1–9.7 years). Ten participants walked before the age of 5 and the remaining two ambulatory participants first walked independently at age ages 7 and 9 years, respectively. The five children who were non-ambulatory at time of evaluation were ages: 2.7, 2.8, 3.3, 7.9 and 9.4 years old. As one child did not learn to walk until 9 years old, we expect that children with *HNRNPH2*-related neurodevelopmental disorder can potentially continue to develop motor skills beyond the typical milestone windows (Salazar et al., 2021).

Since the seminal work from Bain et al. (2016) describing the first 6 females with *HNRNPH2*-related, over 145 individuals living with variants in *HNRNPH2* have been identified including at least 16 males across 31 countries in the world (Yellow Brick Road Project, 2023). An observational natural history study began in 2018 with the purpose of understanding the initial presentation of the disorder, patterns and trajectories in development, and the overall prognosis of individuals with a variant in the *HNRNPH2* gene (ClinicalTrials.gov Identifier: NCT03492060). Data for the study is collected retrospectively and prospectively using clinical

outcome measures including caregiver-reported outcome measures, questionnaires, and observational assessments.

A major limitation of the standardized outcome measures used in the current natural history study is that they are not disease specific to *HNRNPH2*-disorder. In addition, caregiver-reported meaningfulness of these scores or items on these scales were not explored in this study. Lastly and most importantly, the best practice guidelines for clinical outcome assessments highlight that instruments must be based on conceptual models that are condition-specific (Brod et al., 2009; Lasch et al., 2010). Caregivers of individuals living with *HNRNPH2*-related neurodevelopmental disorder have not been provided the opportunity to develop a conceptual model of the functioning of the individuals that they care for on an everyday basis. To be person-centered, the conceptual model must include the perspectives of the person and caregivers.

**2.2 Empirical Research**

Children and adults with neurodevelopmental conditions receive frequent clinical outcome assessments across a variety of clinical, medical, and educational settings (Kelleher et al., 2020). Standardized functional outcome measures are used to assess an individual's current functional status. Functional outcome measures are tools used to categorize a patient, map changes over time and in some cases predict functional trajectories. Clinicians use the measures to describe and assess an individual's status, diagnose, categorize, and track changes over time, predict functional trajectories, as well as identify the needs of patients and make recommendations and interventions as per the clinical picture. A person-centered outcome measures places patients, their families, and caregivers at the heart of decisions concerning the most valuable criteria in health assessment, rather than leaving assessments solely to clinicians (Morel & Cano, 2017). FDA-NIH Biomarker Working Group (2016) outlines the four types of

outcome measures: 1) Patient-reported outcome measures (PRO) a measure based on a report that comes from the patient about the status of their health condition without the influences of the clinician or anyone else; 2) Observer-reported outcome measures (ObsRO): a measure based on the report of someone other than the patient or a health professional i.e.: a parent or caregiver on the of observable signs or behaviors related to a patient's health condition; 3) Clinician reported outcome measures (ClinRO): A measure based on the results from a trained health-care professional after observation of a patient's health condition; and 4) Performance outcome measures (PerfO) are types of clinical outcome assessments: A measure based on task(s) performed by a patient according to directions administered by a health care professional.

PROs and PerfOs are very difficult to perform in most patients with *HNRNPH2*-related neurodevelopmental disorder due to lack of cooperation, poor cognition, and lack of communication skills (Salazar et al., 2019; Wilson et al., 2018). ClinRO assessments are currently being evaluated by a team of clinicians studying *HNRNPH2*-related neurodevelopmental disorder (ClinicalTrials.gov Identifier: NCT03492060). Observer-reported outcome measures such as caregiver-reported outcome measures have been developed specifically for neurodevelopmental disorders, reduce the burden on the patient, and can better reflect day-to-day function (McConachie et al., 2015). Optimizing measurement of functioning will facilitate the quantification of meaningful change in skills and the identification of efficacious interventions aimed at improving outcomes and quality of life.

*2.2a Standardized outcome measures used in neurodevelopmental conditions*

Standardized outcome measures are used to assess current functional status and changes over time. Normative scores are used when comparing how individuals perform in comparison to individuals of their same age and gender. The normative scores of standardized outcome

measures have limited utility as most individuals living with neurodevelopmental disorders score < 5$^{th}$ percentile for norms (Bain et al., 2021, Farmer et al., 2020; Salazar et al, 2020). A relative advantage of ability scores, raw scores and scaled scores exists in capturing the functional abilities of individuals who are lower functioning (Bain et al., 2021, Farmer et al., 2020; Salazar et al, 2020).

Clinicians must take a comprehensive approach to treat complex rare disorders addressing all facets of function and quality of life, including functional, physical, psychological, and social wellbeing and provide referrals to the appropriate specialists (Karimi & Brazier, 2016). The ability to accurately capture the best performance and functional abilities is limited in children with intellectual and behavioral disabilities (Wilson et al., 2018). A standardized assessment performed in a novel environment, such as a clinic or hospital, may not reflect how a child performs in the comfort of their home (Darragh et al., 1998). Clinician-reported assessments of function or performance measures may not accurately reflect the true functioning of an individual with a neurodevelopmental disorder. As the clinician-reported assessments are limited, the true needs of people with conditions may not be identified in the evaluation and therefore the clinician may have difficulty making recommendations and implementing interventions.

Systematic reviews of the tools used in neurodevelopmental disorders, such as autism spectrum disorder, demonstrate that there is a limited scope of the outcome measures and there was not enough supportive evidence to recommend a battery or combination of scales to be used (McConachie et al., 2015). In addition, there is limited evidence that available outcome measures are useful in identifying change from an intervention. Families and caregivers need to be included in the process of outcome measure development to determine the items and domains of

function that are important when monitoring the progress of their children (McConachie et al., 2015).

A challenge with patient-reported outcome measures and performance-based outcome measures of function are that these measures rely on individuals to follow verbal commands, reading skills, task attention and cognition to measure function (Wilson et al., 2018). Children with intellectual and motor delays have difficulty performing standardized functional assessments (Wilson et al., 2018). Performing a standardized test increases stress and anxiety in some patients (Wilson et al.,2018). Solutions are to include the performance of a functional outcome measure in the home, such as using a pedometer or accelerometer to measure step count or movement throughout the day (Hauck et al., 2016). However, as only 37% of individuals with *HNRNPH2* are ambulatory, step count and gait analysis would not be able to capture the function of all individuals with *HNRNPH2* gene variants (Bain et al., 2021). Video recording a play session and coding the videos to quantify observed functional movements based on several behavioral or functional categories based a disease-specific framework has been performed in other neurodevelopmental disorders (Baranek, 1999; McConachie et al., 2015). Remote assessments, video analysis of movements such as gait and motor function, and telehealth clinical evaluations are currently being explored, implemented, and validated in individuals with *HNRNPH2*-related neurodevelopmental disorder (Yellow Brick Road Project, 2023). Regardless of the assessment being used, patients and families prefer assessments that were minimally burdensome (McConachie et al., 2015). As individuals living with neurodevelopmental disorders have difficulty performing patient-reported and performance-based measures due to verbal, cognitive and motor challenges, caregiver-reported measures may be used to determine the everyday functioning of these individuals (Semmel et al., 2019).

*2.2b Caregiver Experience with Outcome Measures*

Kelleher et al. (2020) describe the caregiver's perception and suggestions for improvement of outcome assessment experience for children with neurogenetic syndromes, including 75 caregivers (mothers: n = 69; fathers: n = 4; grandparents: n = 2). Genetic syndromes included Down Syndrome (n = 29); fragile X (n = 12); Angelman Syndrome (n = 11); Prader-Willi Syndrome (n = 8); Williams Syndrome (n = 5); Rett Syndrome (n = 4); Turner Syndrome (n = 2); 22q11.2 Duplication (n =2); 15q Duplication (n=1); Bainbridge-Roper Syndrome (n=1); 22q deletion (n = 1); and Klinefelter's Syndrome (n=1). Caregivers reported neutral or negative experiences with functional assessments. Importantly, caregivers prefer individualized testing and results with actionable next steps based not only on the child, but also the caregiver. Caregivers perceived that interactive and checklist-based assessment tools adequately detected their child's needs and weakness. Caregivers reported sometimes reported dissatisfaction with the content of assessment materials, with one participant stating, "stop handing me a paper asking questions that have nothing to do with him…I am going to be hurt by the end." (Kelleher et al. 2020, Page 1449). The quote highlights the demoralization and hurt of providing a caregiver a clinical checklist or scale in which the child is unable to do anything on the list. By using a person-centered approach and intentionally capturing the child's abilities, rather than limitations or disabilities, the unique traits of the individuals can be highlighted, especially in individuals with unique and ultrarare conditions.

*2.2c Caregiver-Reported Outcome Measures*

Families and caregivers of individuals living with neurodevelopmental disorders are instrumental in caring for and assisting with the daily functioning of individuals living with neurodevelopmental disorders. An observer-reported measure is an assessment performed by

someone other than the patient or health professional, typically a parent or caregiver who observes the person in daily life (FDA-NIH Biomarker Working Group, 2016). Caregiver-reported outcome measures reduce the burden on the person and may better reflect day-to-day function of an individual who is highly reliant on their caregiver due to limited verbal, motor, and cognitive abilities (McConachie et al., 2015).

Available caregiver-reported measures such as the Vineland Adaptive Behavior Scale (VABS) and the Pediatric Evaluation of Disability Inventory, Computer Adaptive Test (PEDI-CAT) were unable to capture the clinical variation and broad scope of functioning of individuals living with *HNRNPH2*-related neurodevelopmental disorder (Bain et al., 2021; Salazar et al., 2020). In addition, the caregiver perspective of the content, material, and adequacy of the scales has not been explored in caregivers of individuals living with *HNRNPH2* related disorder. As such, the meaningfulness and relevance of the scores from these outcome measures are limited in interpretation due to both floor effects as well as the fact that the caregivers have not provided insight into the relevance of the scales or items on each instrument. Therefore, future studies must first implement a person-centered approach and gather insight from the families and caregivers to determine meaningful and relevant aspects of daily functioning as it pertains to individuals with *HNRNPH2*-related neurodevelopmental disorder.

**2.3 Theoretical Literature.**

Grounded theory framework is used to develop a conceptual model generated from the lived experiences of the participants. The goal of classic grounded theory is to generate a theory based on data that is systematically collected and analyzed (Glaser & Strauss, 1967). Constructivist grounded theory allows the researcher and the participants to collaborate in constructing the theory (Charmaz, 2006). In addition, the constructivist approach allows for

review of previous literature of the topic, before starting data collection, while still encouraging the researcher to be open to emergent concepts gathered from the participants (Charmaz, 2006). Adapted grounded theory is fundamentally based on grounded theory principles, however adapted specifically to the development of condition-specific conceptual models (Brod et al., 2009; Lasch et al., 2010). In adapted grounded theory, data collection and analysis are concurrent, not linear. As emergent themes are identified during data collection and analysis, then these themes are incorporated in future interviews and observations. Data collected by participants are labeled and categorized as concepts. Related concepts are grouped into categories. Categories are further developed by interviewing more participants and examining the relationship between categories to develop the conceptual model. Data is analyzed through the constant comparative method. The model is continually assessed based on ongoing interviews that confirm or disconfirm the model. Theoretical saturation must be reached through sufficient data collection and is defined as the point where interviews are no longer added new insights. An adapted grounded theory approach is selected as currently available conceptual models of function in neurodevelopmental disorders are not specific to *HNRNPH2*-related neurodevelopmental disorder and are not based on the perspectives from the network of caregivers caring for these individuals daily.

The US FDA (2009) published the draft guidance for industry for the development of patient-reported outcome measures used in medical product development for the purpose of supporting product labeling claims. The process described by the FDA draft guidance was circular where the first step is to identify concepts and domains that support each claim, second to create an instrument and based on the framework; third to assess the measurement properties and identify the meaningful differences in scores; fourth to modify the instrument-based

concepts, populations, and method of administration. The FDA guidance has a narrow focus as the sole purpose of the conceptual models developed under the FDA guidance are exclusively to support labeling claims for medical products. In contrast, a theoretical model can serve a broader purpose in outlining the relationships between domains, concepts and potential modifiers when describing a condition.

In addition, the US FDA (2022) published the draft guidance for patient-focused drug development: selecting, developing, or modifying fit-for-purpose clinical outcome assessments which provided additional granularity in the steps used to improve the relevance across the types of outcome measures used in clinical trials. The first step of the roadmap to patient-focused outcome measurement is the understanding the disease or condition accomplished by gathering the patient/caregiver perspective, establishing a natural history study of the condition; and defining patient subpopulations. The patient/caregiver perspectives gathered include the definition of treatment benefit, benefit-risk trade off and impact of the disease. Key stakeholder groups (including clinicians, patients, carers, and policy makers) inform the development of what to measure in the clinical assessment. In the case of *HNRNPH2*-related neurodevelopmental disorder, the patient/caregiver perspective is needed to better understand the condition.

Specific to the process of gathering the patient and caregiver perspective, Brod et al., (2009) describe the adapted grounded theory framework for the development of outcome measures. In the content validity phase, literature reviews and expert opinion are used as the initial basis in the development of the domains for the conceptual model. Next, the patient perceptive is gathered through an iterative process of qualitative interviewing to further refine the conceptual model. The specific process to generate a conceptual model for *HNRNPH2*-Related Neurodevelopmental Disorder will require the voice of the caregivers to be integrated

into the model as people with *HNRNPH2* have developmental delays include communication impairments and intellectual disability. The grounded theory approach includes constant comparison and temporary suspension of prior existing theories to elicit emerging concepts and themes from the participants (Boateng et al., 2021; Brod et al., 2009; Charmaz, 2006; Glaser and Strauss, 1967). Once the conceptual model is developed and functional domains are identified, future studies are implemented to develop a disease specific instrument using a similar rigorous and iterative approach.

Existing conceptual models of neurodevelopmental disorders are specific to certain conditions such as ASD, ADHD, and CP (McDougall et al., 2018; Schiariti, Longo et al., 2018; Schiariti, Mahdi et al., 2018). A conceptual model of individuals living with neurodevelopmental disorders was integrated using the International Classification of Functioning, Disability and Health (ICF) Core Sets for Cerebral Palsy, Autism Spectrum Disorder and Attention Deficit Disorders (Schiariti, Mahdi et al., 2018). The ICF provides a model for describing a health condition and for neurodevelopmental disorders. The ICF has focused on ASD, ADHD, or CP (World Health Organization, 2002). The ICF structures functional abilities of an individual or condition into three aspects of human functioning: 1) the body structure or body part or impairment; 2) the whole person or activity level; 3) the whole person in the context of society or participation; and 2 contextual factors that influence function: 1) personal factors and 2) environmental factors (World Health Organization, 2002). The ICF consists of a comprehensive list of 1685 categories in total to describe functioning which may not be fully applicable to a certain condition or group.

Shorter versions of the ICF have been developed into core sets for certain disorders such as CP (135 ICF categories), ASD (111 ICF Categories) and ADHD (72 ICF Categories). Core

sets are used to guide clinicians on areas of functioning unique and relevant to the specific neurodevelopmental disorder. Schiariti, Mahdi et al., (2018) used comparative content analysis to compare the ASD, ADHD, and CP Core Sets. Although commonalities existed between the 3 core sets, the sets capture unique functional information demonstrating the importance of creating condition-specific ICF-based tools. Schiariti, Mahdi et al., (2018) highlighted the need to apply condition-specific ICF-based tools as well as to generate functional profiles for unique conditions based on the features of the specific population with the condition. Existing ICF models are not specific to *HNRNPH2*-related neurodevelopmental disorder and the existing framework does not allow for the flexibility to include the impact of the disease on the caregiver and family that cares for these individuals every day.

McDougall et al. (2018) generated a patient-centered conceptual model of the impact of living with ASD with the purpose of supporting the selection of outcome measures used in clinical trials. An initial literature review of 29 articles was used to identify preliminary concepts to inform the semi-structured interview guide. Based on modified grounded theory, in-depth interviews were conducted with adolescents and adults with ASD (IQ $\geqslant$ 70) (n = 10), as well as parents of children, adolescents, and adults with ASD (IQ $\geqslant$ 70) (n = 26). A conceptual model was generated containing three interrelated domains reflecting core symptoms of ASD (communication deficits, socialization deficits, and restrictive, repetitive patterns of behavior), three domains reflecting associated symptoms of ASD (physical, cognitive, and emotional/behavioral), and three domains representing the impacts of living with ASD (impacts on activities of daily living, school/work, and social life). The comprehensive conceptual model of living with ASD includes some aspects of the ICF model including symptoms, activities, and participation level functioning, however the model adds an additional layer of the interaction

between symptoms, associated symptoms and specifically the impact of these symptoms in their daily functioning. In addition, the model highlights the caregiver's perspective and the impact on the caregivers and family. Although 44% of individuals living with *HNRNPH2*-related neurodevelopmental disorder also have a diagnosis of ASD, the conceptual model of ASD is not specific to *HNRNPH2*-related neurodevelopmental disorder and would not be relevant in selecting an outcome measure specifically for *HNRNPH2*-related neurodevelopmental disorder . The person-centered conceptual model of the impact of living with ASD does offer insight into the relationships between core and associated symptoms of autism spectrum disorder on the person with ASD and the impacts on caregivers and families.

Several domains of function that are pertinent to *HNRNPH2*-related neurodevelopmental disorder are not included in the current ICF model of neurodevelopmental disorders and the conceptual model of autism spectrum disorder including: cognitive function: cognition, attention, cortical visual impairment, seizures; language function: expressive language, comprehension, and receptive language; behavioral function: self-injurious, stereotypic, anxiety; and mobility and extremity movement (Bain et al., 2016; Bain et al, 2021; Davis et al., 202; Harmsen et al., 2019; Jepsen et al., 2019; Peron et al., 2020; Salazar et al., 2019; Salazar et al., 2020; Salazar et al., 2021; Somashekar et al., 2020). A limitation of the ICF categories is that the ICF framework is rigid and does not provide an opportunity to map the interactions between the specific categories of functioning and other factors that emerge from the perspectives of the caregiver. As individuals living with *HNRNPH2*-related neurodevelopmental disorder are highly reliant on their caregivers, the inclusion of bidirectional interactions and impact of the condition and functioning on the caregiver and family would be included. The benefit of the condition-specific conceptual model of ASD is that it includes the impact on the caregiver and family. However,

the major limitation of the existing conceptual model of the impact of living with autism spectrum disorders is that the model does not include patients with IQ < 70 or intellectual disability, and therefore would not be applicable to most individuals living with *HNRNPH2*-related neurodevelopmental disorder. Upon review of available literature, a conceptual framework that is specific to *HNRNPH2*-related neurodevelopmental disorder has not been developed, and therefore, there is a need to develop a person-centered and condition specific conceptual model.

To develop a conceptual model, adapted grounded theory is used to determine the impact of a health condition on function in disorders such as cerebral palsy, Rett syndrome, neonatal conditions, achondroplasia, and ASD (Davis et al., 2017; Epstein et al., 2016; McDougal et al., 2018; Murphy et al., 2017; Neul et al., 2010; Oliveria, 2019; Pfeiffer et al., 2020; Rios & Benson, 2020; Strugnell et al., 2020). Although some conceptual models are based on the ICF model to describe the health and function, a limitation of using a pre-existing model such as the ICF is that there is a potential to omit concepts and interactions highlighted by the patients and caregivers, such as the interaction and reliance on the caregiver for daily functioning. Existing conceptual models of function of neurodevelopmental disorders may have some overlap with the clinical phenotype of individuals with *HNRNPH2*-related neurodevelopmental disorder; however, the patients and caregivers have not yet been included in the development of a disease-specific conceptual model. Generating a person-centered and disease specific conceptual based on the perspectives of the caregivers of individuals living with *HNRNPH2*-related neurodevelopmental disorder will allow the caregivers to describe the most relevant and meaningful concepts specific to their child and to the condition.

## 2.4 Research Design

Condition-specific conceptual models are generated using qualitative studies, with most studies relying on principles based in phenomenology and grounded theory (Brod et al., 2009; Lasch et al., 2010). For concept elicitation and validity, principles of phenomenology are used to ensure the essence of the patient and caregiver-centered lived experiences are included in the model. Grounded theory principles are used to develop a meaningful and relevant conceptual framework based on the person-centered lived experience (Brod et al., 2009; Lasch et al., 2010). The generation of disease-specific conceptual frameworks have included semi-structured interviews and focus groups with patients, caregivers, and clinicians. Disease-specific conceptual models have been developed based on as few as twelve caregivers or as large as 142 healthcare provider assessments (Oliveira et al., 2020, Schiariti, Mahdi et al., 2018). Adapted grounded theory is the accepted approach to develop conceptual frameworks. Table 3 summarizes the methods used to develop conceptual models used in neurodevelopmental conditions and other developmental disorders.

**Table 3**

*Disease-specific conceptual models of neurodevelopmental conditions and other conditions*

| **Author/Year** | **Purpose/Methods** | **Results** |
|---|---|---|
| McDougall et al., 2018 | Ten adolescents/adults with ASD and twenty-six parents of adolescents/adults with ASD interviewed | Conceptual Model Daily life with autism |
| Grieco et al., 2019 | Thirty-four primary caregivers and four clinicians participated in concept elicitation. | Conceptual Model of Angelman Syndrome |

| | | |
|---|---|---|
| Schiariti, Longo et al., 2018 | Brazil: Physical Therapist administered the ICF coreset set to 34 children with ZIKV-associated microcephaly<br>Russia: Interdisciplinary team of specialists (neurologists, pediatrician orthopedist, ophthalmologist etc.) conducted ICF corset on 142 children with CP<br>Malawi: Healthcare provider assessed eighteen children with CP | ICF Coreset for CP |
| Tangarorang et al., 2018 | 25 parents of individuals registered in the International CDKL5 Disorder Database participated in semi-structured telephone | Framework of QOL of CDKL5 Deficiency Disorder |
| Ash et al., 2020 | Qualitative, grounded theory study of twelve mother's understanding of a language disorder | Lack of understanding of the disorder causes mothers' long-lasting psychological harm. |
| Belkin & Swigris, 2013 | Qualitative, study of fourteen informal caregivers' perspectives on the effects of idiopathic pulmonary fibrosis – modified grounded theory approach | Developed a conceptual framework for person's journey as informal caregiver patient-loved one. |
| Carlozzi et al., 2015 | Nine focus groups with fifty-five caregivers of individuals living with traumatic Brain Injury – grounded theory approach. | Although PROs capture relevant Health-related quality of life (HRQOL) for caregivers, there are HRQOL domains that are not addressed. |
| Oliveira et al., 2020 | Focus group with 6 caregivers and 6 healthcare providers<br>Interview with two caregivers and 3 healthcare providers | A conceptual framework of HRQOL in neonates and infants |
| Murphy et al., 2017 | Semi-structured interviews with seventeen primary caregivers of children with Down Syndrome using grounded theory. | A conceptual framework of QOL in children with Down Syndrome |
| Epstein et al., 2016 | Semi-structured interview with nineteen mothers and 2 fathers using grounded theory approach. | QOL of children with Rett Syndrome |
| Davis et al., 2017 | Semi-structured interviews with eighteen parents using grounded theory approach | QOL of children with Cerebral Palsy and intellectual disability |
| Epstein et al., 2019 | Semi-structured interviews with nineteen mothers and 2 fathers with children with ASD and intellectual disability | QOL of children with ASD and intellectual disability |
| Nabbout et al., 2018 | Twenty caregivers of children with Dravet syndrome in four countries | Impact of Dravet Syndrome |

| | | |
|---|---|---|
| | (Australia, USA, UK, and Italy) using grounded theory | |
| Rios & Benson, 2020 | Semi-structured interviews with seventeen caregivers of children with ASD based on ICF framework and constant comparative methodology | Social and motor impact on participation in ASD |
| Strugnell et al., 2020 | Parents and/or primary caregivers of twenty adults with Rett Syndrome directed-content analysis based on Epstein, 2016 framework | Framework for QOL of adults with Rett |
| Pfeiffer et al., 2020 | Parents of thirty-six children with achondroplasia participated in interviews based on adapted grounded theory approach. | Physical symptoms, daily functioning and well-being in achondroplasia |
| Roborel de Climens et al., 2021 | Twenty-one patients and seven parents were interviewed, thematic analysis led to identification of concepts organized to generate a disease model | Disease Model of living with Stargardt disease |
| Johnston et al., 2023 | Twenty-three individuals with LGMD with (n = 5) or without (n = 18) a caregiver participated in 60-minute semi-structured video interviews analyzed using thematic analysis and grounded theory | Conceptual Model to Understand the Patient Experience of Limb Girdle Muscular Dystrophy |
| Goodspeed et al., 2023 | Open ended interviews with two patient advocate key opinion leaders, analysis of de-identified conversations between families of people with SLC6A1-NDD on social media using FDA framework based on adaptive grounded theory | Draft conceptual model of SLC6A1 neurodevelopmental disorder |



Once the conceptual model is developed, the next series of studies include the selection, adaptation and/or development of an outcome measure with items based directly from the model, validation studies as well as studies to determine the responsiveness and clinical meaningfulness of the measure. Table 4 includes a review of available literature in which authors used disease specific conceptual frameworks for the development of person-centered outcome measures across different conditions and diseases.

**Table 4**

*Use of Conceptual Models for the Development of PROs*

| Author/Year | Purpose/Methods | Results |
|---|---|---|
| Bhatia, 2021 | Validity and relevance of PROs based on the developed conceptual framework of Hypospadias-Specific Health-Related Quality of Life. | Current generalized measures for PROs lack relevance to the experience of hypospadias patients. |
| Braun, Yeung & Chen, 2020 | Review of the Skindex and ItchyQoL instruments as examples of the process in development of PROs including instrument and conceptual framework development based on review of literature and patients, items and conceptual framework refinement, psychometric property testing, and (iv) clinical meaning and interpretation. | QOL Outcome Measures for Skin diseases should shift from development to refinement through iterative processes. |
| Aber et al, 2020 | Describe the stages undertaken to generate the items and conceptual framework of a electronic personal assessment questionnaire for vascular condition. | Multidimensional electronic PRO for vascular conditions |
| Hu et al., 2020 | Develop a disease-specific instrument to assess patient-reported outcomes for Chinese patients with gastric cancer following the FDA's draft guidance for PROs. | Gastric Cancer PROM |
| Twohig et al., 2017 | Based on initial literature review and established conceptual framework developed, items for a patient-completed questionnaire were established. | PROM for polymyalgia rheumatica |
| Aggarwal et al., 2016 | Experts, patients, caregivers, and clinicians interviewed to construct conceptual framework and definition of HRQoL. | HRQOL Parkinson's |
| Singer et al., 2015 | Patient-centered outcome measure development of a shortened lung transplant specific valued life activities scale. | Lung transplant-specific disability questionnaire |
| Scholzel-Dorenbos et al., 2012 | Conceptual framework developed based on review of literature, qualitative interviews of people with dementia and their carers, expert opinion, and team discussion. Validity of survey based on dementia professionals, people with dementia and their caregivers. | HRQOL of dementia |
| Lasch, 2012 | Develop a disease-specific questionnaire to assess symptoms important and relevant to adult Major Depressive Disorder patients. | Major depressive disorder outcome measure |
| Jolly, 2012 | Beginning with a conceptual framework, items for Lupus PRO were generated using feedback from people with SLE. | Systemic lupus erythematosus PRO |

## 2.5 Summation

Individuals living with *HNRNPH2*-related neurodevelopmental disorder present with common neurodevelopmental features including global function impairments and high reliance on their caregivers. Due to their developmental disabilities, individuals living with *HNRNPH2*-related neurodevelopmental disorder have difficulty performing standard functional tests that rely on verbal commands, task attention and cognition to measure function. In addition, individuals living with *HNRNPH2* demonstrate floor effects on normative caregiver-reported outcome measures and questionnaires. The broad phenotype and clinical variability of *HNRNPH2* has not been captured using the existing clinical outcome measures for neurodevelopmental disorders due to extensive floor-effects.

The outcome measures used in current studies of *HNRNPH2*-related neurodevelopmental disorder are based on conceptual models of neurodevelopmental conditions. However, the major limitation of available conceptual models of neurodevelopmental conditions are that they are not based on the perspectives of caregivers of individuals living with *HNRNPH2*-related neurodevelopmental disorder. Based on adapted grounded theory, a disease-specific conceptual model must first be developed from the literature review, expert opinion, and the patient/caregiver perspective. The caregivers of individuals living with *HNRNPH2*-related neurodevelopmental disorder have not been included in the generation of the conceptual model for this specific condition. The meaningful and relevant concepts and categories specific to the functional abilities of individuals living with *HNRNPH2*-related neurodevelopmental disorder and those who care for them are not known. Therefore, there is a need to develop a person-centered, condition-specific conceptual model of the functioning of individuals of *HNRNPH2*-related neurodevelopmental disorder based on the perspective of the caregivers.

# Chapter 3: Methods

The goal of this study was to understand the caregiver perspective on the everyday functioning of individuals with *HNRNPH2*-related neurodevelopmental disorder through a qualitative adapted grounded theory approach to develop a conceptual model based upon the following research questions:

## 3.1 Research Questions

**RQ1:** How do caregivers perceive the functioning of an individual with *HNRNPH2*-related neurodevelopmental disorder?

*SQ1a:* How are the body functions of an individual with *HNRNPH2* perceived by their caregivers?

*SQ 1b:* How are the activities of an individual with *HNRNPH2* perceived by their caregivers?

*SQ 1c:* How is the participation of an individual with *HNRNPH2* perceived by their caregivers?

*SQ 1d:* What aspects of daily functioning do caregivers perceive as meaningful when assessing an individual with *HNRNPH2*-related neurodevelopmental disorder?

**RQ2:** What factors do caregivers perceive impact the daily functioning of an individual with *HNRNPH2*-related neurodevelopmental disorder?

*SQ2a:* How are the personal factors of an individual with *HNRNPH2* perceived by their caregivers?

*SQ2b:* How are the environmental factors of an individual with *HNRNPH2* perceived by their caregivers?

**RQ3:** How do caregivers perceive their role in supporting the daily functioning of an individual living with *HNRNPH2*-related neurodevelopmental disorder?

*SQ3a:* How do caregivers perceive their own impact on the daily functioning of individuals living with *HNRNPH2*?

*SQ3b:* What caregiver(s) support the daily functioning of individuals living with *HNRNPH2*?

## 3.2 Type of Study

The study methodology implemented was a qualitative exploratory study based on adapted grounded theory. A qualitative study design was selected as there is a need to understand and explore the caregiver perspective of individuals with *HNRNPH2*. Specifically, an adapted grounded theory approach was selected to create a framework of the daily function of individuals with *HNRNPH2*-related neurodevelopmental disorder including the concepts of functioning and the relationships between concepts that impact the daily functioning of an individual with *HNRNPH2*-related neurodevelopmental disorder.

### *3.2a Overview of the qualitative tradition*

Grounded theory, is an inductive process, used to construct conceptual models generated from the perspectives of the participants who have had the lived experience (Glaser & Strauss, 1967). Charmaz (2006) advocated for a constructivist approach to grounded theory allowing for increased flexibility in design and methodology to develop a theory from the perspectives of the individuals interviewed. A rigorous and iterative approach rooted in adapted grounded theory was used to develop condition-specific and person-centered conceptual models (Brod et al., 2009; Lasch et al., 2010; US FDA, 2009).

Brod et al., (2009) described adapted grounded theory for the development of caregiver reported outcome measures. In the content validity phase, literature reviews and expert opinion were used as the initial basis in the development of the domains for the conceptual model. Next, the perspectives of the people with the lived experience were gathered through an iterative process of qualitative interviewing and comparative analysis to further refine the conceptual model. After the conceptual model was developed, future studies include the selection, adaptation or creation of an instrument based on the conceptual model. The first step in the process and the aim of this study is to develop a person-centered, condition-specific conceptual model of the everyday functioning of individuals with *HNRNPH2*-related neurodevelopmental disorder generated from the perspectives of their primary caregiver(s), informal caregiver(s) and/or formal caregiver(s).

### 3.3 Operational Definitions

**Neurodevelopmental Disorders:** a complex group of disorders that affect the growth and development of the brain or central nervous system starting in childhood leading to significant lifelong burdens (American Psychiatric Association, 2013).

**Intellectual Disability:** Significant limitations in both intellectual functioning and adaptive behavior.

- ***Intellectual Functioning:*** General mental capability and involves the ability to reason, plan, solve problems, think abstractly, comprehend complex ideas, learn quickly, and learn from experience.
- ***Adaptive Behavior:*** collection of conceptual, social, and practical skills that are learned and performed by people in their everyday lives.

**Functioning:** Ability to engage in everyday life including activities of daily living and social activities.

**Caregiver:** Paid and/or unpaid adults who regularly assist an individual with activities of daily living and/or medical tasks, such as parents, family, friends, aides, and nurses.

- ***Primary caregiver:*** Person who provides most of the care for the individual (i.e.: parent, guardian).
- ***Informal caregiver:*** Family or friends who provide care usually without payment (i.e.: aunt, friend).
- ***Formal caregiver:*** A person who is trained and educated to be a caregiver and typically paid for their services (i.e.: nurse, aide, paraprofessional).

### 3.4 Participant Recruitment

Since 2018, I have volunteered as a physical therapist for the Yellow Brick Road Project (*HNRNPH2*-Related Neurodevelopmental Disorder Family Advocacy Group) and collaborated with the *HNRNPH2* Natural History Study registry. I have established rapport with the *HNRNPH2* families and caregivers through my ongoing volunteer work. In addition, I have collaborated with Dr. Jennifer Bain, MD, PhD, the Principal Investigator for the *HNRNPH2* Natural History Study.

For this study, I relied on the Yellow Brick Road Project and the *HNRNPH2* Natural History Study registry to distribute an email with a link to the introduction to the study and pre-screening survey.

#### *3.4a Participants*

Adult caregivers who regularly assist with the activities of daily living and/or medical tasks of an individual with *HNRNPH2*-related neurodevelopmental disorder (care recipient) were

recruited to participate in this study. A caregiver could be a primary caregiver (i.e.: parent, guardian); informal caregiver (i.e.:  relative); or a formal caregiver (i.e.: nurse, paraprofessional). Caregivers must have personally cared for the care recipient within the last week. Caregivers were at least 18 years old and sufficiently able to speak and understand English.

Exclusion criteria included a caregiver who had not recently, within the last 7 days, cared for a person living with *HNRNPH2*-related neurodevelopmental disorder; a caregiver of a deceased child or adult with *HNRNPH2*-related neurodevelopmental disorder; a caregiver < 18 years old; and/or caregivers who are unable to sufficiently speak or understand English.

*3.4b Sample Size*

Consistent with the estimated sample sizes of grounded theory studies, 20 adult caregivers currently caring for individuals with *HNRNPH2*-related neurodevelopmental disorder were recruited (Charmaz, 2006).

*3.4c Sampling*

Purposeful theoretical sampling method including criterion sampling of caregivers of individuals with *HNRPNH2*-related disorder was implemented. Snowball sampling of the primary caregivers/guardians of children/adults with this condition was used as participants were asked to distribute the letter of solicitation (Appendix C) and pre-screening survey link (Appendix D) to their child's other caregivers (family, friends, nurses, aides etc.) and other known caregivers of individuals with *HNRNPH2*-related neurodevelopmental disorder. Maximal variability sampling was implemented as to include participants who care for people with the most severe *HNRNPH2* phenotype including people who are non-ambulatory, non-verbal and tube-fed as well as people with a milder phenotype who are higher functioning (ambulatory and verbal). Maximal variation sampling was confirmed by including pre-screening survey questions

on the ambulation status, verbal status and feeding status of the person with *HNRNPH2*. Confirming/disconfirming sampling was implemented to include participants with children that are similar or different than the initial participant(s) selected.

*3.4d Level of Analysis*

The level of analysis was at the level of individual. The caregivers interviewed were all primary caregivers who have had the lived experience of caring for and assisting the everyday functioning of an individual with *HNRNPH2*-related neurodevelopmental disorder.

**3.5 Instruments**

Qualitative interviews based on semi-structured interview guides were conducted based on the adapted grounded theory framework. Interview questions were funneled, beginning with broad general questions to gain the unbiased caregiver-perspective i.e.: "Tell me about your child," then to specific concepts based on the literature, and finally to probes within a domain to develop specificity and deeper understanding. The temporary suspension of prior theories allowed for the emergence of new concepts based on the caregiver's perspectives (Charmaz, 2006; Glaser and Strauss, 1967). The semi-structured guide was modified and adapted between interviews as new concepts or themes were gathered from the interviews (Appendix E).

The semi-structured interview guide questions were developed based on the adapted grounded theory and previously developed conceptual models of individuals with neurodevelopmental conditions.

**3.6 Study Procedures**

Upon Seton Hall University Institutional Review Board (IRB) approval (Appendix A), recruitment of primary caregivers through the Yellow Brick Road Project and the *HNRNPH2* Natural History Study Registry commenced. A Letter of Solicitation (Appendix C) with a

hyperlink including the pre-screening survey (Appendix D) and Informed Consent Form (Appendix B) was emailed to the Yellow Brick Road Project and the *HNRNPH2* Natural History Study Registry. Primary caregivers were asked to snowball the pre-screening survey link with their child's other caregivers including other primary caregiver(s), informal caregiver(s) and/or formal caregiver(s). The pre-screening survey includes demographic questions related to the caregivers as well as questions related to the person with *HNRNPH2* (Appendix D). Once screened, a formal Letter of Informed Consent (Appendix B) was sent via email to potential participants by the PI.

Once consent was obtained, participant names were de-identified using coded pseudonyms for confidentiality purposes by the PI. Microsoft Teams video conference calls were planned to conduct virtual interviews with the PI. Data was collected using in-depth, semi-structured interviews conducted virtually using Microsoft Teams. The semi-structured interview guide questions rooted in adapted grounded theory and based on the research questions were used to facilitate the discussion along with the use of probing questions, as needed. The semi-structured interview format facilitated the emergence of new concepts, domains, and subdomains. All interviews were audio recorded and transcribed verbatim by the principal investigator. Using a constant-comparative method, the interview guide and probes were modified and refined as the data are collected. The interviews were approximately 60 minutes in length. After the interview, participants were asked if they had any additional questions related to the study or their involvement in the study. In addition, participants were asked if they would be interested in a follow-up debrief interview to review results and conceptual model.

**3.7 Data Analysis.**

The adaptive grounded theory framework provided by Brod et al. (2009) served as a blueprint for inductive data analysis including transcription, coding, building a conceptual model and cognitive debriefing to establish content validity.

*3.7a Transcription*

The first step of data analysis was thorough transcription (Charmaz, 2006). Interviews were transcribed verbatim including what was said, heard and seen during the interview. The verbatim transcriptions allowed the inclusion of expressions of emotion, including laughter or signs; pauses including length of pause; emphasized words; and instances when the speaker was quoting someone else to be captured and clearly indicated in the transcript. The transcription-maintained confidentiality of the participant in accordance with the IRB protocols.

*3.7b Coding*

Coding was performed using inductive reasoning through the review and coding of full transcripts. Hand coding was used and led to pattern recognition, emergence of categories, and theoretical conceptualization. Coding was the basis of analysis. As outlined in grounded theory, the three basic types of coding are open, axial, and selective coding were used.

Coding of data was performed by hand. Computer software programs are helpful in assisting in analysis, particularly when coding large amounts of data and identifying complex relationships and links in the data. Software can be helpful in preparing data; however, the researcher still needs to identify and define conceptual categories and meaningfulness of the codes. Reliance on computer analysis alone has the potential to produce inherently flawed results. Reading and re-reading transcripts is essential in data analysis. Therefore, for this project

hand coding was selected to lead to better understanding of the data. Committee chair review of transcripts and coding was used to determine intercoder agreement.

The three types of coding, open, axial, and selective coding, were used, as outlined in grounded theory. Open coding is the conceptual labeling of all statements, actions, interactions, and emotions that can be compared and grouped into categories and subcategories. Some subcategories were pre-established by previous literature and included in the interview guide (e.g.: cognition and mobility); however, those that emerged from the data which were not labeled in the interview guide. Charmaz (2006) recommended that the researcher remains open to the data, construct simple and short codes, and remains active and analytical throughout the process to compare the collected data. Using line-by-line open coding, the transcripts were first read and re-read for descriptive codes and in-vivo codes and were highlighted in distinct colors.

After open coding, the purpose of axial coding was to sort and organize data (Strauss & Corbin, 1998). In axial coding categories are mapped in relationship to subcategories either pre-determined by the interview guide (e.g.: walking and stair climbing are categorized as motor function) or newly emerging codes (Brod et al., 2009). The pre-determined provisional coding structure for concepts, categories and codes is summarized in Table 5. For axial coding, the transcript was read again and coded using the comment feature on Microsoft Word. Codes were grouped into categories and subcategories using provisional coding structure in Table 5.

Third, selective coding, all categories are then united around an overarching core concept and defines or names what the conceptual model is intending to capture (Brod et al., 2009). In this step, the comments in Microsoft Word were transferred to Microsoft Excel. Selective coding was done in Microsoft Excel as categories were combined around a core concept. To further

explore the relationships and links between categories, memo writing was used to explore the relatedness and interconnection of concepts.

**Table 5**

*PI Developed Provisional Concepts, Categories, Codes*

| **Provisional Concepts** | **Categories** | **Codes** |
|---|---|---|
| 1a. Body Function | Mental | Intellectual Disability, Developmental Delay |
| | Speech | Language impairment |
| | Neurological | Epilepsy, Tone, Balance, Coordination, Behavioral |
| | GI | Growth, Nutrition, GTT, Incontinence, diarrhea, constipation |
| | Musculoskeletal | Orthopedic, scoliosis, feet |
| | Behavior | Autism, Anxiety |
| | Vision | CVI, Strabismus |
| 1b. Activities | Proximal Impact: Activities | Learning, communication, mobility, self-care, relationships, selfcare, responsibility, ADLs |
| 1c. Participation | Distal Impact: Participation | School, Work, Community, Socialization, Friends, Family |
| 1d. Meaningful measurements | emerging | emerging |
| 2a. Personal Factors | 2a. Modifiers: Personal factors | Personal factors: coping, disposition, psychosocial |
| 2b. Environmental Factors | 2b. Modifiers: External factors | External factors: environment, access, services, policies |
| 3. Caregivers Role | Caregiver Role / Burden | Family dynamics, Relationships, Finances, Support system |
| 3a. Caregiver Impact | 3a. Personal factors<br>3b. External factors | Personal factors: coping, disposition<br>External factors: environment, access, caregiver network, policies |
| 3b. Caregiver network | emerging | emerging |



*3.7c Memo-writing*

During the coding process, memo writing allowed for early and active analysis of data and codes. Memo-writing is an informal process in which the PI defines categories, compares data, identify gaps and critically analyzes categories for personal use (Charmaz, 2006). Memo-

writing is used as a preliminary analysis to explore ideas, demonstrate connections between categories, and find new connections and concepts from the collected data to explore in future interviews (Charmaz, 2006). Memos were written to explore categories and themes. Memos were integral to sketching the thematic analysis and attempting to develop and evaluate the categories and relationships between them (Charmaz, 2006).

*3.7d Theoretical Saturation*

Through theoretical sampling, categories were developed until theoretical saturation was reached. Glaser (2001) notes that theoretical saturation is more than repetition of patterns, but more so, when new properties of categories or patterns emerge from interviews. Theoretical saturation was used to justify the final sample size. Once saturation was reached, it was not likely that additional interviews would generate new information and thus recruitment ceased (Charmaz, 2006). In summary, theoretical saturation is the point that no additional emergent properties or relationships are found; additional interviews are unlikely to generate new knowledge; and therefore, no further interviews are needed.

*3.7e Conceptual model building*

A conceptual model outlines the relationship between the overarching core concept, categories, and subcategories as modifiers and/or consequences (Charmaz, 2006). A preliminary model was generated prior to the data analysis; however, the final model was based on the conceptual development and findings of the interviews.

Through review of coded concepts, categories, subcategories and memos, the conceptual model was sorted, diagramed, and integrated. Theoretical sorting is an analytical method to determine theoretical links and comparisons between categories (Charmaz, 2006). As memos were written and developed for each category, the memos were sorted, compared, and integrated

to develop theoretical links between the data (Charmaz, 2006). Diagramming allows for a visual representation of the categories including the extent and direction of the relationships and connections between categories (Charmaz, 2006). Integrating memos is a method of logically ordering and determining how concepts fit or do not fit together. Collectively sorting, diagramming, and integrating memos and codes led to the draft of the conceptual model.

*3.7f Confirmability of Conceptual Model*

To further confirm the conceptual model, debrief interviews were held with participants. Debriefing interviews were used to establish content validity. Whereas the purpose of initial caregiver interviews was to generate new ideas, the debriefing interviews were used to confirm that the model is relevant, meaningful, and inoffensive (Brod et al., 2009). Debriefing is an iterative process in which issues with the model can be revised and refined for future debrief interviews. The questions asked during the debrief included:

- Please tell me what you thought about the model.
- Is the category in any way offensive to you?
- Is the category relevant to you?
- Is there something else you would like to comment on?
- Is there something missing?

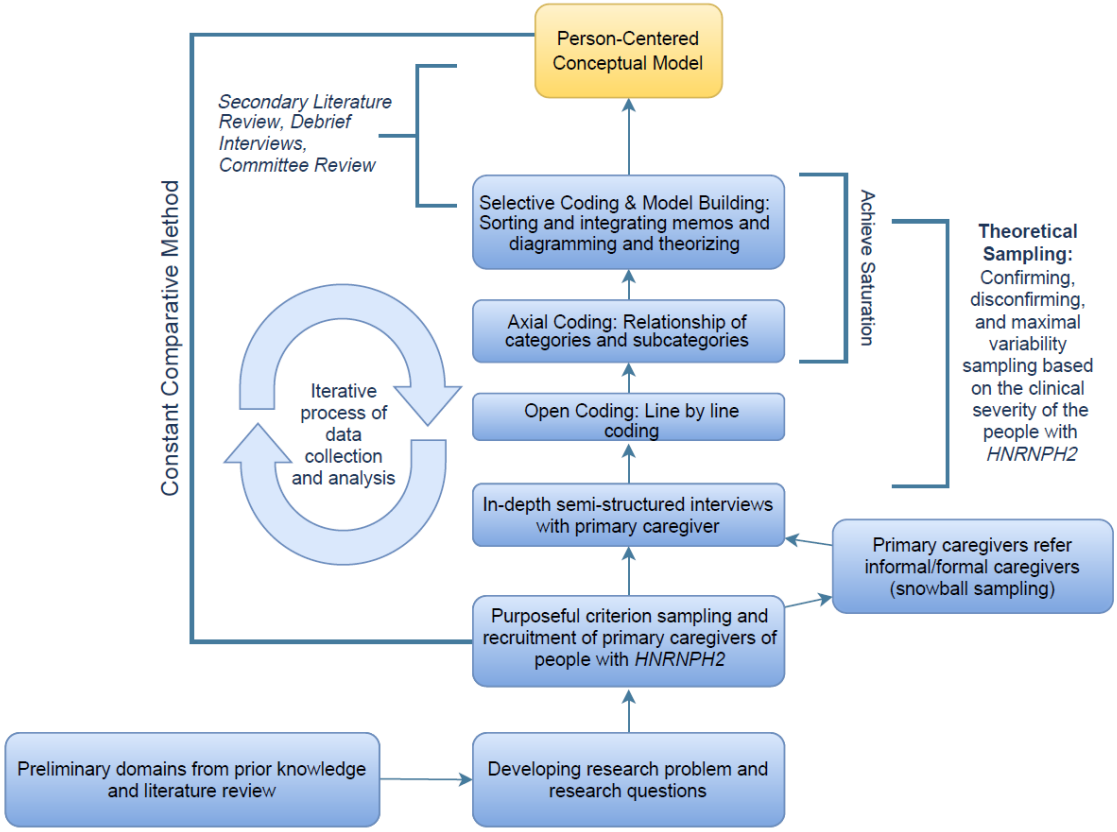
After each question, the PI probed for the reason or explanation for the response and alternatives. After debriefing interviews with caregivers, the model was reviewed and compared to the primary and secondary literature review. Lastly, the model was reviewed by dissertation committee members.

*3.7g Summary of Data Analysis*

Data analysis was conducted using a constant comparative method using an iterative process of data collection and analysis as outlined in Figure 1. Interviews were transcribed, coded and memos were developed by the PI. As emergent themes or issues were identified in ongoing data analysis, they were incorporated into the next set of interviews. Analysis was achieved through confirming and disconfirming data and refinement of the categories, subcategories, and core concept. The conceptual model was built through sorting, diagraming, and integrating categories, subcategories, and memos. The finalized conceptual model was confirmed through debrief interviews with caregivers, secondary literature review and consensus with dissertation committee members.

**Figure 1**

*Framework for Conceptual Model Development for HNRNPH2*

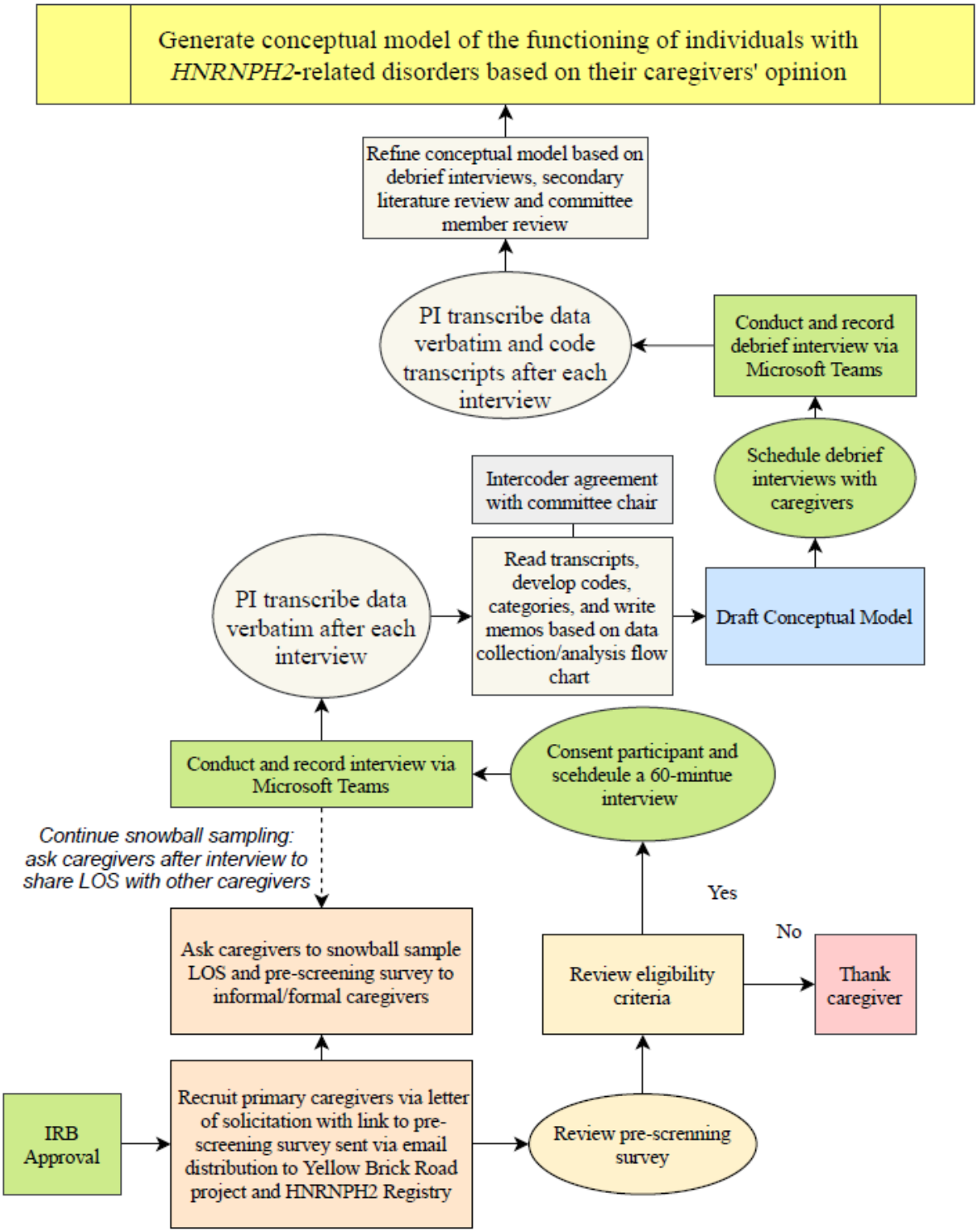


### 3.8 Summary of Methods

The primary goal of this study was to develop a conceptual model of the functioning of individuals with *HNRNPH2* specifically based on the views of the caregivers. After IRB approval, purposeful criterion sampling was used to identify primary caregivers and snowball sampling was used to recruit informal and formal caregivers. In-depth semi-structured interviews with caregivers were transcribed, coded and memos were generated. An adapted grounded theory approach was used to iteratively collect and analyze data until theoretical saturation. The conceptual model was developed based on the data, codes and memos and further refined after debriefing interviews with caregivers and a secondary literature review. Finally, consensus and review with the dissertation committee was used to finalize the conceptual model. Figure 2 provides a summary of the procedures employed.

**Figure 2**

*Inductive procedural flow chart for study*



# Chapter 4: Results

In the results section, the participant demographics, results for each research question, thematic analysis, and initial conceptual model of the functioning of individuals with *HNRNPH2* are presented based on the perspectives of the caregivers.

## 4.1 Setting

Twenty caregiver interviews were conducted over a 1-year period from April 2022 to April 2023. The semi-structured interviews took place via Microsoft TEAMS and were audio recorded. Interviews lasted between 35 minutes to 2 hours. The average length of interviews was 54 minutes.

## 4.2 Participant Demographics

All participants were recruited via the Yellow Brick Road Project's outreach to families in their registry. Table 6 provides a summary of the twenty primary caregivers (14 females, 6 males) with an average age of 44.65 years (range: 33 – 71) that completed interviews. Most participants were from Europe (70%) followed by North America (30%). Most participants identified their ethnicity as White British (30%, n = 6), followed by White (25%, n = 5). Caregivers reported their highest level of education as Doctorate/PhD (15%, n = 3), Masters/Postgraduate Professional Qualification (20%, n=4), Bachelors/College/University (35%, n=7), Vocational training/applied university (20%, n=2), Associate level/some college (10%, n=2), with the least at a high school/GCSEs level (10%, n=2).

**Table 6**

*Demographics*

| Caregiver | | | | | | | Individual with HNRNPH2 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Participant** | **Age** | **Caregiver Role** | **Gender** | **Location** | **Ethnicity** | **Highest Level of Education** | **Age** | **Gender** | **Country** | **Mobility** | **Communication** | **Feeding** |
| Vivi | 55 | Primary | Female | North America | Caucasian | Masters | 19 | Female | USA | Walk Alone | Verbal | Oral |
| Jaime | 37 | Primary | Female | Europe | White British | GCSE's | 4 | Female | UK | Pushed in a wheelchair | Nonverbal | Oral |
| Laurie | 71 | Primary | Female | North America | - | Masters OT | 40 | Female | USA | Walk alone | Limited verbal | Oral |
| Elena | 39 | Primary | Female | North America | White | Bachelor | 3 | Female | USA | Walk with support | Sign language | Oral |
| Julia | 37 | Primary | Female | North America | White | College | 5 | Female | USA | Walks with walker | Sign Language | Oral |
| Carol | 38 | Primary | Female | North America | White/ Native American | Doctorate | 5 | Female | USA | Walk alone | Gestures | Oral |
| Dane | 44 | Primary | Male | North America | White | Some College | 8 | Female | USA | Walk alone | Verbal | Oral |
| Bonjour | 55 | Primary | Male | Europe | White | University | 22 | Female | Netherlands | Scoot on the floor | Verbal | Oral |
| Juan | 40 | Primary | Male | Europe | Portuguese | University | 9 | Female | Portugal | Walk Alone | Verbal | Oral |
| Agrippine | 40 | Primary | Female | Europe | French | 4 years at university | 11 | Female | France | Walk Alone | Verbal | Oral |
| Doris | 33 | Primary | Female | Europe | Dutch | Applied university | 2.5 | Female | Netherlands | Walk with walker | Nonverbal | Tube fed |
| Dora | 49 | Primary | Female | Europe | Scottish | University | 22 | Female | Scotland | Pushed in a wheelchair | Pre-verbal, acc user | Tube fed |
| Noire | 38 | Primary | Female | Europe | Bulgarian | High school | 5 | Female | Denmark | Walk alone | Nonverbal, makes sounds | Oral |
| Bob | 46 | Primary | Male | Europe | Italian Swiss | Trade School | 8 | Female | Switzerland | Walk alone | Signs, noises | Oral |
| Leonard | 53 | Primary | Male | Europe | White British | Graduate | 13 | Female | UK | Pushed in a wheelchair | Nonverbal | Oral |
| Amie | 40 | Primary | Female | Europe | White British | A level | 5 | Female | UK | Pushed in a wheelchair | With her eyes mainly | Oral & tube fed |
| Emma | 36 | Primary | Female | Europe | White British | Doctorate | 3.5 | Female | UK | Walk alone | Verbal | Oral |
| Dinah | 42 | Primary | Female | Europe | British | College | 11 | Female | UK | Walk with support | Eyes, pointing and reaching, noises | Oral |
| Simone | 45 | Primary | Male | Europe | European | PhD | 11 | Female | Norway | Walk alone | Verbal | Oral |
| Juliette | 55 | Primary | Female | Europe | White British | Postgraduate | 21 | Female | UK | Walk alone | Noises and gestures | Oral & tube fed |

In addition, each caregiver provided a summary of the person they care for with *HNRNPH2*. Each caregiver was a parent of a daughter with *HNRNPH2*. The mean age of their daughters was 11.35 years (range 2.5 – 40 years), with 75% (n=15) being < 18 years old. Descriptive statistics of the demographics and a summary of the mobility, communication and feeding ability of the individuals with *HNRNPH2* are provided in Table 7.

**Table 7**

*Descriptive Statistics – Individual with HNRNPH2*

| Individual with *HNRNPH2* Demographics | | |
|---|---|---|
| **Age** | | |
| | Age, mean (range), years | 11.35 (2.5 – 40) |
| | Child < 18, % (n) | 75 (15) |
| | Adult ≥ 18 years, % (n) | 25 (5) |
| **Location** | | |
| | Europe, % (n) | 70 (14) |
| | North America, % (n) | 30 (6) |
| **Gender** | | |
| | Female, % (n) | 100 (20) |
| **Mobility** | | |
| | Pushed in wheelchair, % (n) | 20 (4) |
| | Walk with Support, % (n) | 20 (4) |
| | Scoot on Floor, % (n) | 5 (1) |
| | Walk Alone, % (n) | 55 (11) |
| **Communication** | | |
| | Nonverbal, % (n) | 15 (3) |
| | Preverbal*, % (n) | 45 (9) |
| | Verbal, % (n) | 40 (8) |
| **Feeding** | | |
| | Oral, % (n) | 80 (16) |
| | Oral & Tube Fed, % (n) | 10 (2) |
| | Tube fed only, % (n) | 10 (2) |

Note. *Preverbal defined as use of eyes, gestures, noises, and/or sign language for communication

### 4.3 Research Question 1 – Function

Research question 1 explored *How do caregivers perceive the functioning of an individual with HNRNPH2*-related neurodevelopmental disorder? Caregiver interviews included semi-structured open-ended interview questions including “Tell me about your child’s daily functioning.” Research question 1 sub questions a, b and c explore the overall domain of

functioning as per the ICF criteria including body function, activity, and participation levels, respectively.

*4.3a Research Question 1a Body Function*

Responses addressing Research Question 1a: *How are the body functions of an individual with HNRNPH2 perceived by their caregivers?* resulted in the development of twenty-eight codes across 8 categories. All caregiver reported categories of ***cognition*** and ***communication*** impacting function; ***neurological*** behavior by 90% (18 / 20 caregivers); ***visual***, ***musculoskeletal/orthopedic***, ***gastrointestinal*** 80% (16 / 20 caregivers); and ≤ 50% had other features including ***puberty-related*** by 50% (10 / 20 caregivers); ***cardiac abnormalities*** and ***sleep problems*** 10% (2 / 10 caregivers) and hearing impairment in 1 / 20 (5% caregivers). Results of Research Question 1a are summarized in Table 8 including descriptive codes, in vivo codes organized into categories.

**Table 8**

*Results Research Question 1a*

| **RQ1: How do caregivers perceive the functioning of an individual with *HNRNPH2*-related neurodevelopmental disorder?**<br>*RQ1a: How are the body functions of an individual with HNRNPH2 perceived by their caregivers?* | | |
|---|---|---|
| **Descriptive Codes** | **In Vivo Codes** | **Categories** |
| Intellectual Disability<br>Developmental Delay<br>Planning<br>Processing | "Cognitively, even though she's coming up to five, she's about nine months, so she can't do anything herself." – **Jaime**<br>"It's very hard to foster the fact that she's very independent, but also sort of incapable of working through like the motor planning pieces missing. So she's very independent. She knows what she wants. But getting to the point that she knows to what she wants is, the steps are not there. They're very not consistent. She understands the steps, but the processing piece of those steps are very difficult for her." – **Julia** | Cognitive |

| | | |
|---|---|---|
| Severe Language Impairment<br>Expressive language delay<br>Language regression | “We have hope that's why we say pre-verbal. She is not silent and the older she becomes the more vocal she is with different noises dependent on pitch and speed.” **- Dora**<br>"She's nonverbal. She says some syllables and she kind of tries to communicate. She has some sign language just, just few basic signs. Uh, but also the same with regression where you know she used to be able to pronounce something, let's say apple or horse. And now when you ask her to say that word does not sound the same anymore.” – **Elena** | Communication |
| Epilepsy/Seizures<br>Tone<br>Balance/Coordination<br>Regressions | “Seizures leading to developmental regressions…she used to be able to pull herself up, but she's regressed quite a lot in the last year, and she can't, she can't do that anymore” –**Jaime**<br>“There's a group of kids running around and they'll run past her. She loses her balance, falls, like sits down to the ground.” – **Elena** | Neurological |
| Anxiety<br>Repetitive Behaviors<br>Autism traits | “ She bites her arm. She's got quite a scar on her arm. Just one arm, her left arm. She bites.”- **Laurie**<br>“…bite her wrist if she's really anxious“ – **Dane**<br>“Oh, she's had some mild hand flapping in her life. She stims on her fingers and I've never been able to turn her towards anything else….sometimes she'll get all four of them in there and be chewing on them.” - **Vivi** | Behavior |
| Visual perception<br>Cortical Visual Impairment<br>Strabismus | “And once she figures out the height, she can do it The perception of height and even light and then dark is different.” – **Agripine**<br>"when we found out that with the CVI diagnosis, that when she's more anxious, her field of vision essentially is is going down to nothing and so when she's completely overwhelmed it's, she's blind - the connection between brain input and vision is gone. So essentially, she's blind“ – **Dane** | Vison |
| Growth<br>Musculoskeletal Disturbance<br>Scoliosis<br>Hip dysplasia<br>Foot Deformities<br>Microcephaly | “So she has special shoes, her feet curl in. She has the inward facing feet. She had bilateral hip surgery when she was 7. So then they were concerned about hips dislocating. And so they went through the surgery, and she was in a, the spica and all that kind of thing. And. But hips are fine now. The hardware came out as well, so it was two surgeries right middle of locked down.” - **Leonard** | Musculoskeletal/ Orthopedic |
| Constipation<br>Incontinence<br>Failure to thrive<br>GERD | “Constipation, she does get that. So she's on a daily. Umm, what's it called in America? Miralax. Yes, that's it. Two sachets a day. Unfortunately, it's very hard to get a | Gastrointestinal |

| | | |
|---|---|---|
| | balance between Constipation and sort of horrendous flood.” **- Juliette**<br>“So that's kind of how we knew something was wrong because feeding was always an issue. It would take her well over an hour to finish one ounce of milk and then just as we finished, we'd have to start again.” - **Amie**<br>“It took her forever to be toilet trained and a t about 23 I just said, you know, screw this and we started using incontinence pads and she has a pull up that night. But I have to say that most of the time she is she goes to the bathroom independently.” - **Laurie** | |
| Structural Cardiac Defect<br>Hearing impairment<br>Sleep Problems<br>Puberty | “she has a small ASD in her heart as well, but they keep an eye on it, there's no problem.” **-Aime**<br>“And when she's born, they make the test. And she said she can only hear out of the left ear.” - **Bob**<br>“She has very good moments. Yeah, that she can sleep all night. Yeah, without waking up. Yeah, but lately she has like, long period before she has, like, 2-3 weeks. She's waking up in the nighttime. 2/3 times.” - **Noire** | Other |

*4.3b Thematic analysis for Defining Concepts: Symptoms*

The categories of ***Cognitive, Communication, Neurological, Behavior, Vison, Musculoskeletal/Orthopedic, Gastrointestinal*** and ***Other*** were unified into **Defining Concepts: Symptoms.** *HNRNPH2*-related neurodevelopmental disorder is a multisystemic complex condition with core, hallmark symptoms including intellectual disability, developmental delay, communication impairments, neurological symptoms, behavioral traits such as anxiety, biting or chewing wrists/hands, visual perception impairments, orthopedic concerns (hip dysplasia, foot deformities), and gastrointestinal disturbance including constipation impacting the lives of those with the condition and those who care for them.

*4.3c Research Question 1b Activities*

Responses addressing Research Question 1b: *How are the activities of an individual with HNRNPH2 perceived by their caregivers?* resulted in the development of six codes grouped into

the category of ***Proximal Impact: Activities***. Results of Research Question 1b are summarized in Table 9 including descriptive codes, in vivo codes and category.

**Table 9**

*Results Research Question 1b*

| **RQ1: How do caregivers perceive the functioning of an individual with *HNRNPH2*-related neurodevelopmental disorder?**<br>RQ1b: How are the activities of an individual with *HNRNPH2* perceived by their caregivers? | | |
|---|---|---|
| Descriptive Codes | In Vivo Codes | Categories |
| Mobility<br>Daily Activities<br>Responsibility<br>Communication<br>Learning<br>Self-care | "She can't walk, crawl, she can't free stand, she can just about feed herself, but she has difficulty with chewing and swallowing. She can't speak, she can't sign…She can press things so like she'll play with toys that have got like cause and effect. So she'll press the button and it'll flash her and start dancing or play music or stuff like that. She can do that herself. But that's that is about it, really, that she can do.“ – **Jaime**<br>“She can't go out and play soccer that's she can’ she can't run, you know. But we found the things that she was able to do that she enjoyed doing and you know kept her active in that stuff.” **- Vivi**<br>"As far as math, reading things like that, that's, you know, we can, we're doing some counting, some colors, some letters trying to work on phonics, things like that” - **Dane** | Proximal Impact: Activities |

*4.3d Research Question 1c Participation*

Responses addressing Research Question 1c: *How is the participation of an individual with HNRNPH2 perceived by their caregivers?* resulted in five codes grouped into the category of ***Distal Impact: Participation***. Results of Research Question 1c are summarized in Table 10 including descriptive codes, in vivo codes organized into the category.

**Table 10**

*Results Research Question 1c*

| **RQ1: How do caregivers perceive the functioning of an individual with *HNRNPH2*-related neurodevelopmental disorder?**<br>RQ1c: How is the participation of an individual with *HNRNPH2* perceived by their caregivers**?** | | |
|---|---|---|
| Descriptive Codes | In Vivo Codes | Categories |
| Socialization<br>Play<br>School<br>Community<br>Work | "She's very, very sociable, very affectionate to really with people she likes to give them hugs. Very sweet. And she's friendly with other the other young people that she sees every most days as well. She likes to hug and she'll communicate by mostly touching and gesturing towards go over them and get and put our arms around people. I mean, in some ways it can be a bit inappropriate if she doesn't really know the person." – **Juliette**<br>"Yeah, she she's very happy at school. She likes people. She likes being middle. Yeah, the people that she likes, the journey to and from, probably because of the people on the. Yeah, she likes people watching. Just sit so looking through the window. She has a lovely time in the car. She'll go on a long journey. No problem. Yeah. She just looked through the window." - **Dinah**<br>"So if you're doing something that she enjoys, she'll laugh, and then if you're singing to her, she'll and you stop she'll put her hand on your mouth to obviously get you to do, to carry on and to do more. And she loves the praise. So after after she's done something really well, she will clap herself." - **Jaime**<br>"Last year, she actually did the last two years, she actually worked in the community. She worked at a pizza place and assisted in making the boxes and getting them ready for lunch and then stacking them so that everybody is ready…she's very social, so she'll enjoy practically anything that she does. I could really see her like maybe a Hostess in a grocery store or Walmart." – **Vivi** | Distal Impact: Participation |

*4.3e Thematic Analysis: Impact Concept on the individual with HNRNPH2*

***Proximal Impacts: Activities*** and ***Distal Impacts: Participation*** were unified into **Impact Concept for the individual with *HNRNPH2***. Individuals with *HNRNPH2* experience multiple impacts on activities of daily living, communication, mobility, socialization, school, and community-related interactions. There is a broad range of activities and participation impacts with some individuals with *HNRNPH2* relying entirely on their caregivers for assistance to

complete all basic activities of daily living and others having more independence, responsibility and preparing to work in the community.

### 4.4 Research Question 2 Factors Impacting Function

Research question 2 explored: *What factors do caregivers perceive impact daily functioning of an individual with HNRNPH2*-related neurodevelopmental disorder? Interview questions included: "What factors impact your child's daily functioning?" Factors were divided according to the ICF criteria of personal factors and environmental factors. Research question 2 sub questions a and b explore the personal factors and environmental factors, respectively.

#### *4.4a Research Question 2a Personal Factors*

Responses addressing Research question 2a, *how are the personal factors of an individual with HNRNPH2-related neurodevelopmental disorder perceived by their caregivers?* resulted in six codes grouped into the category of ***Modifiers: Personal Factors***. Results of Research Question 2a are summarized in Table 11 including descriptive codes, in vivo codes organized into categories.

**Table 11**

*Results Research Question 2a*

| **RQ2: What factors do caregivers perceive impact the daily functioning of an individual with *HNRNPH2*-related neurodevelopmental disorder?**<br>*RQ2a: How are the personal factors of an individual with HNRNPH2*-related neurodevelopmental disorder *perceived by their caregivers?* | | |
|---|---|---|
| Descriptive Codes | In Vivo Codes | Categories |
| Fatigue<br>Emotions<br>Coping<br>Disposition<br>Autonomy<br>Fear | "Eating is hard for her and I think it takes a lot out of her, eating and an then just physically. Everything is just that little bit more effort for her and I think sometimes she just gets so tired. And she and and she does have absent seizures as well. And I think if she's had an occasion where during breakfast, she's had two or three absent seizures. It just completely wipes her out" - **Julia** | Modifiers: Personal Factors |

| | | |
|---|---|---|
| | “She's very happy, loves music, adores Disney” - **Dora**<br>“Very, very, very much aware of emotions. Emotions, even when they're not discussed or if there's some tension or grief or something. She she noticed that.” - **Bonjour**<br>"We'll go to the park and things, but she gets a bit frightened of a lot of the stuff at the park so we don't tend to do that very often.“ - **Jaime**<br>“She kind of doesn't need a whole lot to to stay happy. As long as you kind of follow her, her routine and patterns and and, you know, kind of feed her, make sure she's not hungry.” – **Elena** | |

*4.4b Research Question 2b External Factors*

Responses addressing Research question 2b, *how are the environmental factors of an individual with HNRNPH2*-related neurodevelopmental disorder *perceived by their caregivers?* resulted in 8 codes grouped into the category of ***Modifiers: External Factors***. Results of Research Question 2b are summarized in Table 12, including descriptive codes, in vivo codes organized into categories.

**Table 12**

*Results Research Question 2b*

| **RQ2: What factors do caregivers perceive impact the daily functioning of an individual with *HNRNPH2*-related neurodevelopmental disorder?**<br>*RQ2b: How are the environmental factors of an individual with HNRNPH2-related neurodevelopmental disorder perceived by their caregivers?* | | |
|---|---|---|
| Descriptive Codes | In Vivo Codes | Categories |
| Environment<br>Access<br>Services<br>DME<br>Routine<br>Policies<br>Technology<br>Siblings | “We try to black out the room, so we'll put a black tablecloth over the table so whatever puzzle pieces or playdough whatever she is using, she can focus on“ - **Dane**<br>"Every time we go into the developmental team, they reassess for autism and she's not been considered on spectrum. Actually, we were kind of hoping she was because it opens up it makes because there's an ICD10 code for autism that makes everything with insurance easy and comparably most of the things resources we need in insurance, I mean therapy, some things line up. So so that would have made things a lot easier“ – **Dane** | Modifiers: External Factors |

| | | |
|---|---|---|
| | "We give our choice of what she wants to do after school. On most days she likes her computer a lot. She's able to navigate quite a bit to the things that she likes, like she understands to type into the address bar like Y, O, U to get it to fill out YouTube and then she'll go and and watch her videos on YouTube." - **Vivi**<br>"She has older siblings, younger siblings, which we really feel like is a great benefit to her both for support and challenge for development" – **Dane** | |

*4.4c Thematic Analysis: Modifiers of impact concept for the individual with HNRNPH2*

***Modifiers: Personal Factors*** and ***Modifiers: External Factors*** were unified under the **Modifiers of Impact Concept for the individual with *HNRNPH2*.** Overall, caregivers describe their daughters as happy social girls when in a familiar environment. Often new environments, new people, or being tired or hungry produce fear and agitation that could impact and limit functioning. Policies, accessibility, services, and access to a medical care team can modify the functioning of an individual with *HNRNPH2*.

**4.5 Research Question 3 Caregiver Role**

Research question 3: *How do caregivers perceive their role in supporting the daily functioning of an individual living with HNRNPH2*-related neurodevelopmental disorder? was explored through interview questions such as "What is your role in supporting the daily function of your child?" Responses addressing Research Question 3 resulted in six descriptive codes, in vivo codes organized into the category of ***Caregiver Role,*** summarized in Table 13.

**Table 13**

*Research Question 3*

| **RQ3: How do caregivers perceive their role in supporting the daily functioning of an individual living with *HNRNPH2*-related neurodevelopmental disorder?** | | |
|---|---|---|
| Descriptive Codes | In Vivo Codes | Categories |
| Advocate<br>ADLs<br>Support<br>Total Care<br>Routine<br>Plan for future | "Certainly as a caregiver doing a lot for her and feel like you'll continue to do this for all the foreseeable future" - **Jaime**<br>"pursuing diagnosis was a full-time job" - **Dane**<br>"And I didn't learn about it from my school district, and I became very active in advocacy, and I was a span resource parent and I was one of the founding members of the New Jersey Coalition for Inclusive Education" - **Laurie**<br>"She can't stand or anything like that. She can't physically get herself out of bed so we physically lift her out of bed, put her on to her changing table, and then we dress her, her brush her and then carry her down the stairs…obviously we we have to do everything for her So she's limited in in quite a bit. She's she's like having a baby." - **Elena**<br>"We are fine now we don't we. Of course we are afraid of what's coming. I think, what's gonna be her life and and adult age. And now we are in a project that we are going to make a a place for us to stay. We have people with similar situations. We are going to do an association and when she's 18, we will stay as a community" – **Juan** | Caregiver Role |

*4.5a Research Question 3a Caregiver Factors*

Research question 3: *How do caregivers perceive their impact on the daily functioning of individuals living with HNRNPH2*-related neurodevelopmental disorder? was explored through interview questions such as *"How has your [child] impacted your life?"* Results of Research Question 3a are summarized in Table 13 including seven descriptive codes, in vivo codes organized into the category of ***Modifiers: Personal Factors***. In addition, table 14 includes six descriptive codes, in vivo codes organized into the category of ***Modifiers: External Factors***.

**Table 14**

*Research Question 3a*

| **RQ3: How do caregivers perceive their role in supporting the daily functioning of an individual living with *HNRNPH2*-related neurodevelopmental disorder?**<br>SQ3a: How do caregivers perceive their impact on the daily functioning of individual living with *HNRNPH2*-related neurodevelopmental disorder? | | |
|---|---|---|
| Descriptive Codes | In Vivo Codes | Categories |
| Coping<br>Health/aging<br>Family dynamics<br>Relationships<br>Finances<br>Career<br>Isolation | "Uh well, hugely because when you when you choose to have a a child, you don't. You wouldn't choose to obviously have a child that's got additional needs or any disabilities. So when we chose to have a baby, we didn't think that our life would be the way it is and that, you know, we'd have a nearly five year old that can't walk or talk and can't do the normal in brackets, things that she should. To be able to do and where we should, what we should be able to do with her. So it's quite sad really obviously how much it's impacted our lives as well, cause we've had to adapt." - **Jaime**<br>"I have got quite a bad back…but you have to pick her up sometimes. And I can't change her on the floor…one of my knees is titanium. So I can't actually kneel down to change her on the floor. So, for example, I've gotta change her on a bed because I literally can't kneel to change her. The physicality of dealing with her is getting harder and harder." - **Juliette**<br>"Pay for private physiotherapist, adapted bike, running pushchair and will be moving to a new house, so financial, obviously it is quite a lot on us" - **Jaime**<br>"She'll never have a cognitive understanding of stuff, so there's lots of stuff that we can't go to because her peers of the same age are obviously far different to her, so there's a lot of stuff we can no longer attend because obviously she's not able bodied. We can't do a lot of stuff" – **Jaime** | Modifiers: Personal Factors |

*4.5b Research Question 3b Caregiver Support*

Research question 3b: *What caregiver(s) support the daily functioning of individuals living with HNRNPH2?* was explored through interview questions such as *"*Describe the other adult caregivers, if any, that help you take care of your [child]." Results of Research Question 3b are summarized above in Table 14 including descriptive code "caregiver network," in vivo codes and organized into the category of ***Modifiers: External Factors***.

**Table 15**

*Research Question 3b*

| **RQ3: How do caregivers perceive their role in supporting the daily functioning of an individual living with *HNRNPH2*-related neurodevelopmental disorder?**<br>SQ3b: What caregiver(s) support the daily functioning of individuals living with *HNRNPH2* | | |
|---|---|---|
| Descriptive Codes | In Vivo Codes | Categories |
| Caregiver network<br>Siblings<br>Environment<br>Medical care<br>Access<br>Policies | "..both still work full time, but then when it comes to childcare, we can't leave her with anybody other than grandparents" – **Jaime**<br>"her mother and I, we're a good team. We really try. There's a lot of dividing and conquering." - **Dane**<br>"We physically can't really adapt our house, so we need to move house" – **Jaime**<br>"Accessible vehicle only just arrived the day before. Yeah. It's been a godsend" - **Leonard**<br>"We tried to get that, insurance denied it multiple times, kept going back and forth, got a case manager and we really pushed hard - finally got it approved" – **Dane** | Modifiers: External Factors |

*4.5c Thematic Analysis: Caregiver Impacts and Modifiers*

The categories of ***Caregiver Role***, ***Modifiers: Personal Factors*** and ***Modifiers: External Factors*** were unified around the concept of **Caregiver Impacts and Modifiers**. Caregivers primarily saw their role as being an advocate and supporting their child's wants and needs. From advocating for the diagnosis to physically supporting all activities of daily living, maintaining a routine for their child, and planning for the future, particularly adulthood.

Caregiving had a major impact on the lives, health (mental and physical), family dynamics, relationships, finances, and career of the caregivers. In addition, many felt isolated from others who were unable to understand their situation.

Caregivers did rely on additional external and caregiver support. The caregiver network caring for an individual with *HNRNPH2* was at least two people, with additional caregivers for

respite care. A general concern from caregivers was the future and developing a plan for when they as caregivers are no longer capable or alive to take care of their daughter with *HNRNPH2*.

Caregivers highlighted the impact on siblings and parenting style. In addition, many needed to modify their home environment for accessibility and discussed issues with policies impacting access to medical care and respite care.

### 4.6 Research Question 1d: Meaningfulness

Research question 1d: *What aspects of daily functioning do caregivers perceive as meaningful when assessing an individual with HNRNPH2*-related neurodevelopmental disorder? was explored through interview questions such as "What would be meaningful to you to include in an assessment of your [child]'s daily functioning?" Results of Research Question 1d are summarized in Table 15 including six descriptive codes, in vivo codes organized into the category of **I*ndividualized Approach***.

**Table 16**

*Results Research Question 1d*

| **RQ1: How do caregivers perceive the functioning of an individual with *HNRNPH2*-related neurodevelopmental disorder?**<br>RQ1d: What aspects of daily functioning do caregivers perceive as meaningful when assessing an individual with *HNRNPH2*-related neurodevelopmental disorder? | | |
|---|---|---|
| **Descriptive Codes** | **In Vivo Codes** | **Categories** |
| Communication<br>Anxiety<br>Epilepsy<br>Daily Social Life<br>Plan for future<br>Optimal care | "Probably for her to talk, yeah. To say if she wants something or if something hurts, if you know." - **Elena**<br>"So I'd say the for me the most, yeah, the most sort of key issues for her is anxiety and and lack of confidence" – Juliette<br>"well, at the at this very moment, we're we're most worried about the epilepsy like potential for epilepsy just because we don't know" - **Leonard**<br>"It's not rocket science to work with her, but other parents, they don't know what to expect and what to do so they keep their distance. So as a result you are a bit like socially a little | Individualized Approach |

| | | |
|---|---|---|
| | bit isolated I think. And so it is a bit of problem there. So it would be good if she would be able to be in that direction. To work and act normal socially in a way to participate in the daily social life." – **Simone**<br>"Rather than always needing somebody by her side, I mean reality is she's probably going to need to to it. But if we can improve that, you know, that would be the ideal. Like I think we've come to terms with the fact that you know she's going to have. She doesn't have a disability diagnosis yet, but she's going to. But if we can, you know, at least give her some level of independence so that you know whether it she can live in a, you know, supported housing or something like that when she's older and that would be a good outcome, I think." - **Emma**<br>"Even if it doesn't work, some guidance feels good. Instead of feeling like, you're just stumbling around in the dark trying to grasp for whatever might happen to to fall within reach…following up and giving people hope that OK, it's it's it's years. It is years and these are the methods that we tried. This didn't work, but what did work for us was." - **Dane** | |

*4.6a Thematic Analysis: Meaningfulness*

The aspects of daily functioning that caregivers perceived as meaningful were quite individualized depending on the caregiver and the status of their child (mild to severely affected) and certain symptoms. The most common meaningful functions included communication and the wish for their child "To say if she wants something or if something hurts." This was most mentioned by caregivers of individuals who were nonverbal or preverbal. Second most common was anxiety as it impacts function in the community spanned across the spectrum of the disorder. Worries surrounding epilepsy and trauma surrounding having a seizure were mentioned most by those who cared for girls with seizures and some caregivers with newly diagnosed children who had not had a seizure. For higher functioning girls and women who are verbal and ambulatory, meaningful work and participation in daily social life was noted as most meaningful. In addition,

the idea of having guidelines and practical care considerations would be meaningful as guidance, instead of relying on trial and error, and providing hope for the future.

## 4.7 Conceptual Model

A conceptual model, or disease concept map, is a comprehensive description of the lived experience of people with a disorder. The conceptual model outlining the features of *HNRNPH2* and capturing its complexity and heterogeneity in relation to daily functioning, from the caregiver perspective was built by diagramming, sorting, and integrating categories, concepts, and their relationships.

### *4.7a Apriori HNRNPH2 Conceptual Model based on Initial Literature Review*

The apriori conceptual model was developed from the review of published literature. Concepts were organized into the WHO ICF domains: 1) Disease Defining Concepts, 2) Proximal and Distal Individual Impact Concepts and 3) Caregiver impact concepts and modifying factors. Figure 3 is the diagram of the apriori *HNRNPH2* Conceptual Model based on Initial Literature Review (January 2022). Based on the literature, defining concepts and symptoms including major features of the disorder being developmental delay, intellectual disability, language impairment, and musculoskeletal disturbances were previously reported. In addition, impacts to activities including mobility, daily activities, and responsibility; as well as participation and socialization were previously reported. However, based upon the available evidence  an effective understanding of the functional impacts on the person with *HNRNPH2* and the impacts on the caregivers was absent in the model.

**Figure 3**

*Apriori HNRNPH2 Conceptual Model based on Initial Literature Review*

*Apriori HNRNPH2* Conceptual Model based on Initial Literature Review*

| Defining Concepts / Symptoms of *HNRNPH2*<br>WHO: Body Functions / Structures | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Cognition** | **Communication** | **Neurological** | **Behavior** | **Visual** | **Musculoskeletal** | | | |
| Intellectual Disability | Severe Language Impairment | Epilepsy / seizures | Neuropsychiatric diagnoses | Vison Problems | Growth | | | |
| Developmental Delay | | | Autism | | Musculoskeletal Disturbances | | | |
| | | | | | Dysmorphic Features | | | |

| Individual with *HNRNPH2* Impact Concepts | | | |
|---|---|---|---|
| **Impact Concepts** | | **Modifiers** | |
| **Proximal Impacts**<br>WHO: Activities | **Distal Impacts**<br>WHO: Participation | **Personal Factors**<br>WHO: Personal Factors | **External Factors**<br>WHO: External Factors |
| Mobility | Socialization | | |
| Daily Activities | | | |
| Responsibility | | | |

| Caregiver Impact Concepts | | |
|---|---|---|
| **Caregiver Impact** | **Modifiers** | |
| **Caregiver Role** | **Personal Factors** | **External Factors** |

**Literature as of January 2022*

**Literature as of January 2022*

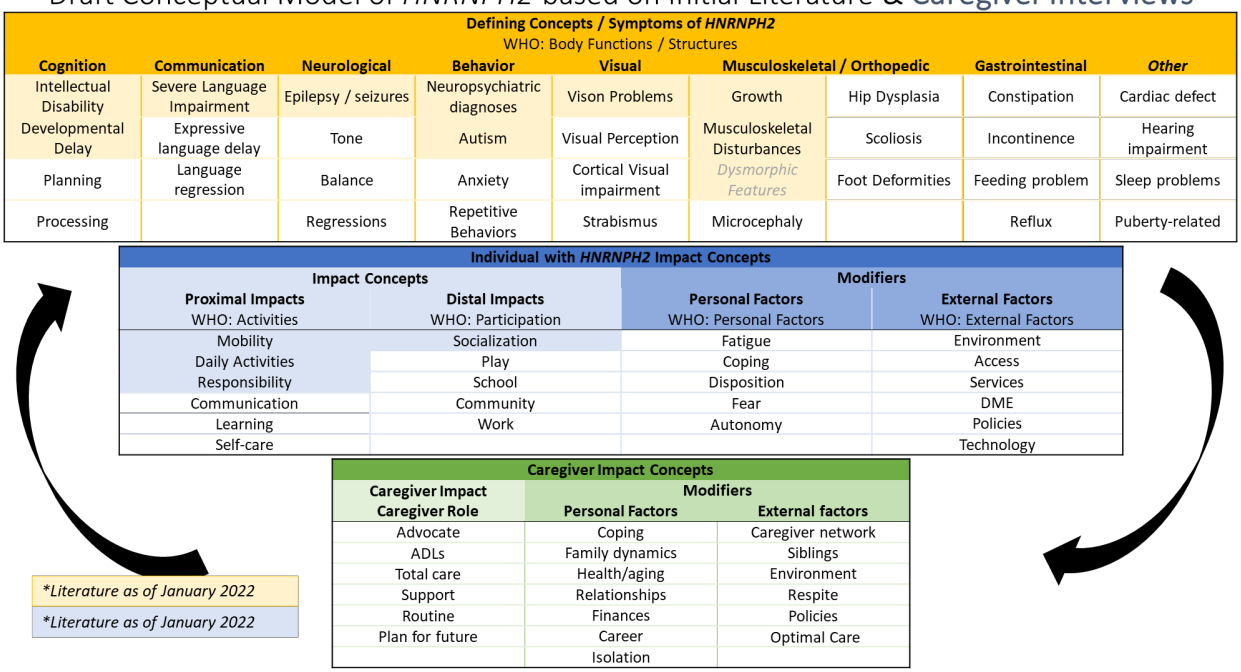
*4.7b Draft Conceptual Model of HNRNPH2 Integrating Caregiver Interviews*

The conceptual model developed from the review of published literature as of January 2021 was updated to reflect the caregivers voice extrapolated from the interviews and is illustrated in Figure 4. In white are the concepts, categories and properties of categories emerging from the interviews including **Defining Concepts / Symptoms of *HNRNPH2***, **Individual with *HNRNPH2* Impact Concept** and **Caregiver Impact Concept**. Key changes to the initial model include recategorization of symptoms to disease defining concepts. In the literature review, some symptoms were categorized as minor features, however caregivers reported these features as major features impacting function.

The caregiver reported **Defining Concept /Symptoms of *HNRNPH2*** include seven key categories: ***Cognition, Communication, Neurological, Behavior, Visual, Musculoskeletal/Orthopedic, Gastrointestinal,*** and ***Other*.** The **Individual with *HNRNPH2* Impact Concept** including, ***Proximal Impact Concept***: Activities, and ***Distal Impact Concept: Participation*** were expanded to include additional impacts on activities including communication, learning and self-care. Participation was expanded to include play, school, community, and work. In addition, ***Modifiers*** including personal and external factors emerged from the interviews. Personal factors of the individual with *HNRNPH2* included fatigue, coping, disposition, fear, and autonomy. External factors included the environment, access, service, durable medical equipment (DME), policies, and technology. Finally, the **Caregiver Impact Concepts** include **C*aregiver Impact*** and ***Modifiers.*** The Caregiver Role is to be an advocate, support activities of daily living, total care in some cases, support, routine, and develop a plan for the future. Modifying factors including personal factors such as coping, family dynamics, health and aging, relationships, finances, career, and isolation as well as external factors including having a caregiver network, sibling impact, environment, respite care, polices and optimal care.

**Figure 4**

*Draft Conceptual Model of HNRNPH2 Integrating Caregiver Interviews*

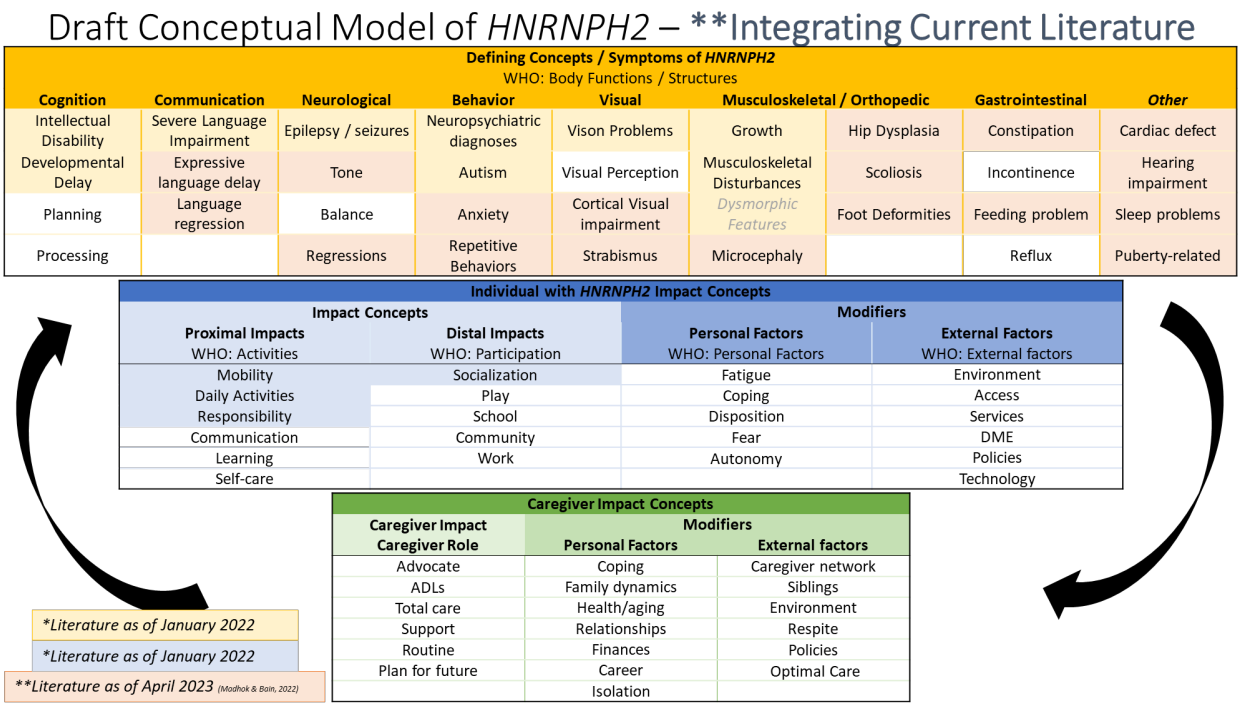



*4.7c Draft Conceptual Model of HNRNPH2 Integrating Current Literature*

After reaching saturation across the interviews, current literature was reviewed and integrated in orange in Figure 5 to the conceptual model. Madhok & Bain (2022) described 49 individuals from 45 families living with *HNRNPH2*. Although the findings from the Madhok & Bain 2022 study did not add any additional features to the model, it further informed and reinforced what was heard in the caregiver interviews. Importantly, there have been no specific studies exploring the caregiver impact of living with *HNRNPH2* found in the literature to date.

**Figure 5**

*Draft Conceptual Model of HNRNPH2 Integrating Current Literature*

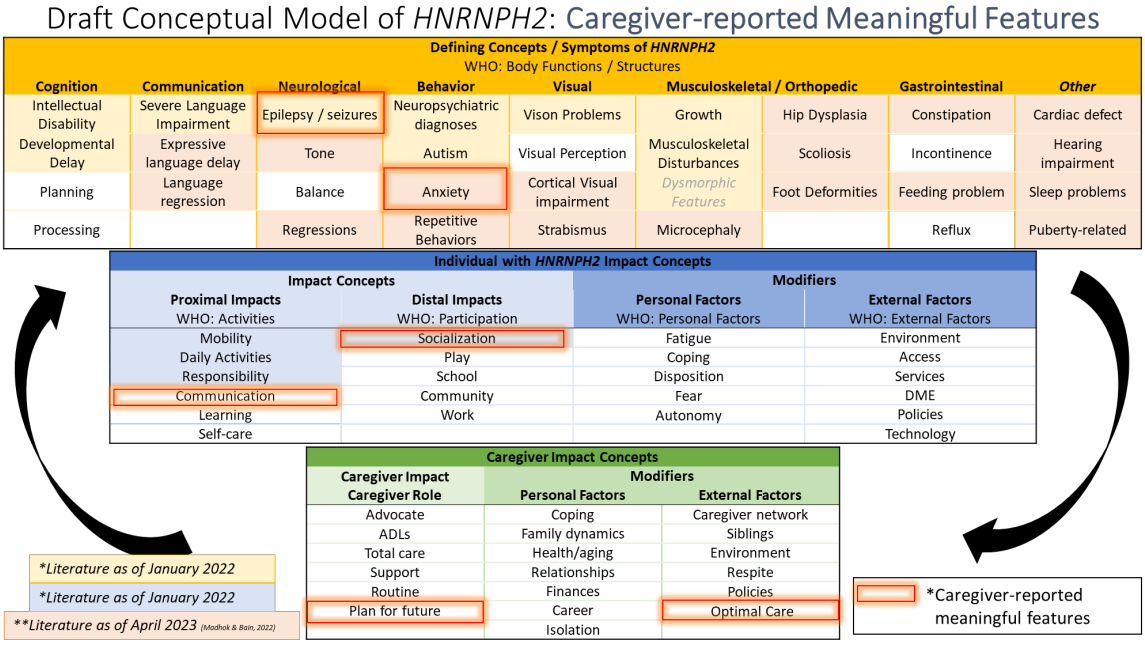



*4.8d Draft Conceptual Model of HNRNPH2 Caregiver-Reported Meaningful Features*

Finally, the features that caregivers most reported as meaningful based on research question 1d are highlighted in red in Figure 6. These meaningful features span across all aspects of functioning from symptoms, impact on the individual, and the impact on the caregiver. The meaningful features provide us with a roadmap to identify potential assessments, guidelines and treatments for anxiety, seizures, or communication. In addition, caregivers noted that they were most concerned with having a plan for when they were unable to care for their child as well as need for guidelines for optimal care.

**Figure 6**

*Draft Conceptual Model of HNRNPH2 Caregiver-Reported Meaningful Features*



# Chapter 5: Discussion and Conclusion

*HNRNPH2*-related neurodevelopmental disorder is caused by variants in the X-linked gene *HNRNPH2* affecting females and less commonly in males worldwide (Madhok & Bain, 2022). There have been 49 individuals with *HNRNPH2* described in the literature with at least 16 affected males reported (Bain et al., 2021; Gillentine et al., 2021;Harmsen et al., 2019; Jepsen et al., 2019; Kreienkamp et al., 2022; Madhok & Bain, 2022; Somashekar et al., 2020).

This study expands our current understanding of the lived experience of 20 primary caregivers including female caregivers (n=14, 70%) and male caregivers (n=6, 30%) of females with *HNRNPH2* living in 9 countries: United Kingdom, n=7, 35%; United States, n=6, 30%; Netherlands (n=2, 10%); Denmark, France, Norway, Portugal, and Switzerland (each n=1, 5%)). This chapter will discuss the implications of each of the concepts emerging from the caregiver interviews including defining concepts, individual with *HNRNPH2* concepts, caregiver impact concepts, meaningfulness, as well as implications for practice and research, limitations, suggestions for future research and conclusions.

## 5.1 Defining Concepts

*HNRNPH2*-related neurodevelopmental disorder is a unique condition with defining core features previously reported in the literature confirmed through caregiver interviews and included in the conceptual model. Key features of the condition were reported by caregivers in similar frequency than what was reported in the current literature (Table 17). There may be slightly higher reports of behavior, because caregivers reported their daughters had anxiety or anxious features, however some were not formally diagnosed. Another example is for vision, caregivers may have reported visual perception issues, although not formally diagnosed as visual impairment or cortical visual impairment. For puberty-related, in the literature only diagnoses of

delayed or precocious puberty were included, whereas caregivers reported puberty-related concerns including how growth spurts impacted scoliosis, or menses impacting fatigue, function, mood, and daily life. Overall, this illustrates the difference in perspectives from health professionals focusing on medical diagnosis, which may not highlight the lived experience of people with the condition and their caregivers. Although facial dysmorphisms are noted in 70% (31 out of 44 individuals) in the literature, caregivers did not mention facial dysmorphisms during interviews.

**Table 17**

*Caregiver Interview Defining Concepts and Symptom Frequency Compared to Frequencies Reported in the Literature*

| Defining Concepts / Symptoms of *HNRNPH2* (Caregiver Interviews) | # of Caregivers reporting feature (%) | *Feature in the literature (Madhok & Bain, 2022)* | *# of Persons w/Feature (%)* |
|---|---|---|---|
| **Cognition** | **20/20 (100%)** | *Developmental delay / Intellectual disability* | *46/46 (100%)* |
| **Communication** | **20/20 (100%)** | *Severe language impairment* | *37/45 (82%)* |
| **Neurological** | **18/20 (90%)** | *Abnormal tone* | *41/46 (89%)* |
| | | *Seizures* | *18/46 (39%)* |
| **Behavior** | **18/20 (90%)** | *Psychiatric disorders (Anxiety, ASD, & ADHD)* | *32/42 (76%)* |
| **Visual** | **16/20 (80%)** | *Visual defects* | *29/43 (67%)* |
| **Musculoskeletal** | **16/20 (80%)** | *Microcephaly* | *16/44 (36%)* |
| **Orthopedic** | **16/20 (80%)** | *Orthopedic problems* | *25/37 (68%)* |
| **Gastrointestinal** | **16/20 (80%)** | *Feeding problems* | *28/41 (68%)* |
| **Puberty-related** | **10/20 (50%)** | *Delayed / precocious puberty* | *4/41 (10%)* |
| **Cardiac abnormalities** | **2/20 (10%)** | *Nonspecific cardiac abnormalities* | *4/41 (10%)* |

| | | | |
|---|---|---|---|
| **Sleep Problems** | **2/20 (10%)** | *Sleep problems* | *16/41 (39%)* |
| **Hearing Impairment** | **1/20 (5%)** | *Hearing loss* | *~25%* |

### 5.2 Individuals with *HNRNPH2*

All caregivers reported that individuals with *HNRNPH2* had proximal impacts (activities), distal impacts (participation), and modifiers (personal and external factors). Previous studies have described the daily activities, mobility, social/cognitive and responsibility limitations when compared to age matched peers on normative outcome measures. (Bain et al., 2021; Davies et al., 2023; Salazar et al., 2021) Elicited through the caregiver perspective, the wide spectrum of relevant activities and abilities of individuals with *HNRNPH2* were gathered (i.e.: pushing buttons on cause-and-effect toys, listening to music, dancing, people watching, reading, math, archery, and working in the community). Modifiers to functioning include personal factors (fatigue, coping, disposition, fear, and autonomy) and external factors (environment, access, services, durable medical equipment, polices, and technology) warrant consideration for optimal daily functioning. Due to the wide spectrum of functioning, there is a need for an individualized approach to care, assessments and treatment of individuals with *HNRNPH2*-related neurodevelopmental disorder.

### 5.3 Caregiver Impact Concepts

The role of the caregiver of people living with *HNRNPH2* has not been previously reported in the literature. Caregivers have a significant role in supporting the everyday function of individuals with *HNRNPH2*. Caregivers reported providing total support (physically lifting, changing, dressing, and doing all daily activities), planning and maintaining routines, advocating, and planning for the future. Impacts on family dynamics, siblings, relationships, finances and/or careers were reported more often in caregivers of individuals who were non-ambulant and

nonverbal. Overall, isolation was noted throughout the spectrum of the disorder as well as awareness that it was difficult for others to understand their situation. Environmental modifications for accessibility to optimize daily functioning were reported by most caregivers from adding railings to stairs, to blacking out work/play spaces, to complete remodels of homes for wheelchair accessibility.

Attention to caregiver wellbeing (mental and physical health) and policies to support caregivers should be considered and explored. Some caregivers from European countries had access to adult day programs, standard respite care and a slow transition to care homes for adults with developmental conditions whereas in the US, caregivers have generally adapted independent spaces their homes for their adult daughters. All caregivers relied on additional support from at least one additional caregiver and discussed the need for caregiver networks, aides, and respite care, adding to the need for societal involvement and structure to caring for someone with a neurodevelopmental disorder.

**5.4 Meaningfulness**

Communication, anxiety, seizures/epilepsy, daily social life, plans for the future, and assessment for optimal care were the most frequently reported meaningful features impacting daily functioning. Communication and anxiety impacted daily functioning, education, participation in daily life and caregiver coping/emotion. Although seizures were only reported in 35% (7 / 20) of the interviews, caregivers of individuals who had not had seizures still worried about them in the future, fears of not noticing a seizure, and leading to one caregiver to consult with a naturopath for supplements and foods to prevent seizures. For caregivers of girls and women who were ambulant and verbal, the ability to function and participate in daily social life, have some independence, and role in the community was noted as most meaningful. Across the

spectrum from childhood to adulthood, caregivers reported that planning for the future including having a living will and developing a plan for supportive housing when transitioning to adulthood as well as having an optimal care team was most important. Trends of meaningful features of the condition among and between groups of the spectrum of *HNRNPH2* (sex, age, comorbidities) warrant further exploration in larger samples.

### 5.5 Conceptual Model

Traditional healthcare models focus on diseases, symptoms, and disabilities without acknowledging the person, family, and caregivers' lived experiences, their expertise, and abilities (Santana et al., 2018; World Health Assembly, 2016). This initial conceptual model includes the unique lived experience of caregivers of individuals living with *HNRNPH2* within the disease description. The model was developed using a person-centered approach through adaptive grounded theory and following regulatory guidance. Further work to include perceptions of caregivers of males with *HNRNPH2,* other stakeholders not included (individuals living with the condition, health care providers, educators, researchers etc.) is warranted to further refine the model.

### 5.6 Implications for Practice and Research

The conceptual model of *HNRNPH2*-related neurodevelopmental disorder has utility and implications for clinical practice and future research. In clinical practice, the conceptual model can be used as the basis of organization of interdisciplinary care teams to optimize functioning of people living with *HNRNPH2* and their caregivers. The conceptual model can serve as the basis of the standards of care as each concept will need to be addressed to optimize care recommendations and guidelines for clinicians and families. The conceptual model has implications in natural history study design, specifically exploring the meaningful concepts that

emerged from caregiver interviews as well as further research on caregiver impact. These meaningful concepts can be used as a guide for disease modifying therapy development, biomarker research, development of person-centered outcome measures, and meaningful and relevant endpoints for clinical trials.

### 5.7 Suggestions for Future Research

The next step in this research is to further refine the model in order to develop a person-centered outcome measure that can potentially be used as an endpoint in clinical trials. Brod et al., (2009) outline the best practice guidelines for the development of a caregiver reported outcome measure for *HNRNPH2*-related neurodevelopmental disorder including the expert opinion. Future research will include interviews with experts including healthcare providers and advocacy leaders, item generation based on concepts and features, cognitive debriefing of items, and validation studies for the outcome measure to develop a person-focused outcome measure to be implemented in natural history studies, clinical practice, and future clinical trials. Therefore, we will continue to work on further conceptualizing treatment benefit as well as selection and development of outcome measures specific to the meaningful functions affecting the lives of the people with *HNRNPH2* and those who care for them every day. In addition, further work is needed to explore trends and relationships between concepts in larger samples of individuals with *HNRNPH2*, quality of life of caregivers and individual with *HNRNPH2*, and the impact on siblings. In addition, the overall societal impact can be explored in the future in health economic models.

## 5.8 Limitations

Limitations to this study are that perceptions of other stakeholders such as individuals living with the condition, informal/formal caregivers, health care providers, educators, researchers, and advocacy leaders were not included. As only caregivers of females living with *HNRNPH2* were interviewed, the perspectives of caregivers of males living with the condition were not included and thus cannot be accounted for. While over 145 individuals with *HNRNPH2* variants have been identified in from 31 countries worldwide, (Yellow Brick Road Project, 2023) this study only included English-speaking caregivers from 9 out of 31 countries including only perspectives primarily of the United Kingdom, United States of America, and a limited spread of European countries. Therefore, there is a major limitation in our understanding of the lived experiences of caregivers in Latin America, Africa, Middle East, and the Asia Pacific region. An overarching limitation in this study is that there may be limited access to genetic testing, reginal health disparities, and socioeconomic disparities that were not explored specifically in this study. Therefore, limiting our ability to understand the full spectrum of those living with *HNRNPH2* but who have not been able to be diagnosed due to disparities in access to genetic testing and care.

Although a non-random sample was utilized results cannot be generalized beyond the caregivers included within this study. There is a possibility for selection bias or failing to ensure that the sample obtained is completely representative of the spectrum of caregivers and families living with this condition. Researcher bias or preconceived notions could also be a potential limitation; however, the PI did try to suspend all biases and notions during the caregiver interviews to allow for the free emergence of concepts directly from the caregivers' voice.

Finally, there always exists inherent limitations in data interpretation and potential response bias from the caregivers themselves that might have impact the results.

### 5.9 Conclusions

Overall, this study expands our current understanding of the experience of living with *HNRNPH2* and their caregivers. *HNRNPH2*-related neurodevelopmental disorder is a unique multisystemic condition impacting the everyday living with the condition and those who care for them. This study is the first to describe the impact of symptoms on the activities, participation, and potential modifiers specific to people with *HNRNPH2* as well as the major role caregivers have in the everyday functioning from total support, planning routines, advocating for, and planning for their future.

Caregivers highlighted the meaningful and relevant features of the condition. Due to the wide spectrum of functioning, there is a need for an individualized approach to care, assessments and treatment of individuals with *HNRNPH2*-related neurodevelopmental disorder. There is a highly unmet need for attention to caregiver well-being including mental and physical health, programs, and policies to ensure caregiver support.

The developed disease conceptual model of *HNRNPH2*-related neurodevelopmental disorder developed based upon this study's findings can serve as the basis for organization of interdisciplinary care teams, particularly as caregivers expressed the need for an optimal medical and educational care team. Standards of care and practical care guidelines addressing the need for optimal care at home, school, and the community will be explored in the future. In addition, natural history study design can be reassessed to ensure inclusion of all features of the conceptual model. Person centered outcome measures based on meaningful and relevant features can be developed or adapted for use in natural history studies. As we move forward with

symptomatic treatment and precision genetic therapies for *HNRNPH2*, the disease conceptual model can be used as a guide for developing or implementing therapies for key feature of the condition and the outcomes of therapeutic trials could be based on the meaningful functions described in the disease conceptual model.

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## Appendix A: Seton Hall University IRB Approval

### IRB Approval Letter 2022 – 2023

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SETON HALL UNIVERSITY
1 8 5 6

03/23/2022

Rachel Salazar
Seton Hall University

Re: Study ID# 2022-304

Dear Rachel,

The Research Ethics Committee of the Seton Hall University Institutional Review Board reviewed and approved your research proposal entitled "Caregiver perspectives on the daily functioning of people living with HNRNPH2-related disorder: Generating a conceptual model" as resubmitted. This memo serves as official notice of the aforementioned study's approval as exempt. Enclosed for your records are the stamped original Consent Form and recruitment flyer. You can make copies of these forms for your use.

The Institutional Review Board approval of your research is valid for a one-year period from the date of this letter. During this time, any changes to the research protocol, informed consent form or study team must be reviewed and approved by the IRB prior to their implementation.

You will receive a communication from the Institutional Review Board at least 1 month prior to your expiration date requesting that you submit an Annual Progress Report to keep the study active, or a Final Review of Human Subjects Research form to close the study. In all future correspondence with the Institutional Review Board, please reference the ID# listed above.

Thank you for your cooperation.

Sincerely,

Mara C. Podvey, PhD, OTR
Associate Professor
Co-Chair, Institutional Review Board

Phyllis Hansell, EdD, RN, DNAP, FAAN
Professor
Co-Chair, Institutional Review Board

Office of the Institutional Review Board
Presidents Hall · 400 South Orange Avenue · South Orange, New Jersey 07079 · Tel: 973.275.4654 · Fax 973.275.2978 ·
www.shu.edu

**IRB Approval Letter 2023 – 2024**

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SETON HALL UNIVERSITY
1 8 5 6

March 28,2023

Rachel Salazar
Seton Hall University

Re: IRB # 2022-304

Dear Rachel,

The Research Ethics Committee of the Seton Hall University Institutional Review Board reviewed your Annual Progress Report for the research proposal entitled "Caregiver perspectives on the daily functioning of people living with HNRNPH2-related disorder: Generating a conceptual model" This memo serves as official notice of the Institutional Review Board's acceptance of this report.

The Institutional Review Board approval of your research is extended for a one-year period from the date of this letter. During this time, any changes to the research protocol, informed consent form or study team must be reviewed and approved by the Institutional Review Board prior to their implementation.

You will receive a communication from the Institutional Review Board at least 1 month prior to your expiration date requesting that you submit an Annual Progress Report to keep the study active, or a Final Review of Human Subjects Research form to close the study. In all future correspondence with the Institutional Review Board, please reference the ID# listed above.

Thank you for your cooperation.

Phyllis Hansell, EdD, RN, DNAP, FAAN
Professor
Co-Chair, Institutional Review Board

Office of the Institutional Review Board
Presidents Hall · 400 South Orange Avenue · South Orange, New Jersey 07079 · Tel: 973.275.4654 · Fax 973.275.2978 ·
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## Appendix B: Informed Consent Form

## Informed Consent Form 2022 – 2023


**Informed Consent Form**



**Title of Research Study:** Caregiver perspectives on the daily functioning of people living with *HNRNPH2*-related disorder: Generating a conceptual model

**Principal Investigator:** Rachel Salazar, PT, DPT, PCS (doctoral student)

**Department Affiliation:** Department of Interprofessional Health Sciences and Health Administration, School of Health and Medical Sciences

**Sponsor:** This research is supported by the Department of Interprofessional Health Sciences and Health Administration, School of Health and Medical Sciences. This research is not externally funded or supported.

**Brief summary about this research study:**
The following summary of this research study is to help you decide whether or not you want to participate in the study. You have the right to ask questions at any time.

The purpose of this study is to create a conceptual model of the everyday function of individuals living with *HNRNPH2*-related disorder based on the views of their caregivers.

You will be asked to complete a survey and virtual interview. You will have the option to complete a debrief interview.

We expect that you will be in this research study for 10-minutes for the demographics survey, 60-minutes for primary interview, and the option to participate in a 60-minute debrief interview to review results, on dates of your choosing.

There are minimal foreseeable risk or discomfort anticipated by your participation in this research study.

The main benefit of participation for yourself is the potential to learn more about and identify your views of the daily functioning of people living with *HNRNPH2*-related disorder. The main benefit of participation for us is to identify the meaningful and relevant everyday functions specific to individuals living with *HNRNPH2*-related disorder and their caregivers.

**Purpose of the research study:**
The purpose of this study is to generate a conceptual model of the everyday function of individuals living with *HNRNPH2*-related disorder based on the views of their caregivers.

You are being asked to take part in this research study because you are a caregiver for a person living with *HNRNPH2*-related disorder, at least 18 years old, and able to speak and understand English.

Your participation in this research study is expected to be for 10-minutes for the demographics survey, 60-minutes for primary interview, and an optional 60-minute debrief interview to review results, on dates of your choosing.

You will be one of approximately 20 people who are expected to participate in this research study.

**What you will be asked to do:**
Your participation in this research study will include:

First, you will be asked to first complete a survey. The survey includes questions about yourself and the person you care for.

Afterwards, you will be asked to schedule a date/time for the interview.

Then, you will be asked to participate in an audio-recorded virtual interview through Microsoft Teams on your computer or phone in a quiet location. The audio will be recorded for transcription purposes. A sample of the open-ended question that may be asked of you is the following: *How would you describe the daily functioning of the person that you care for living with HNRNPH2-related disorder?*

If you choose to participate in a follow-up debrief interview to review results, then it is expected that the interview will take 60-minutes on a day of your choosing. The audio will be recorded for transcription purposes. A sample question that may be asked of you is the following: *Please tell me what you think about this category. Is the category meaningful to you?*

**Your rights to participate, say no or withdraw:**
Participation in research is voluntary. You can decide to participate or not to participate. You can choose to participate in the research study now and then decide to leave the research at any time. Your choice will not be held against you.

The person in charge of the research study can remove you from the research study without your approval. Possible reasons for removal include missing study visits, non-compliance with the study procedures.

**Potential benefits:**
There may be no direct benefit to you from this study. You may obtain personal satisfaction from knowing that you are participating in a project that contributes to new information.

**Potential risks:**
The risks associated with this study are minimal in nature.

Your participation in this research may include collecting of audio recordings. Appropriate steps will be taken to ensure the privacy of the audio recordings from the interview.

There are minimal risks to psychological welfare, legal, social, economic or other privacy that the participant may encounter as part of their participation. This study prompts discussion about potentially psychologically sensitive topics, such as the health status and functioning of the person you care for, and implications for the person and the caregiver. In the event of emotional distress or discomfort, you have the right to take a break, skip a question, terminate the interview, or withdraw from the study, at any point.

## Informed Consent Form

**Confidentiality and privacy:**
Efforts will be made to limit the use or disclosure of your personal information. This information may include the research study documents or other source documents used for the purpose of conducting the study. We cannot promise complete secrecy. Organizations that oversee research safety may inspect and copy your information. This includes the Seton Hall University Institutional Review Board who oversees the safe and ethical conduct of research at this institution.
The pre-screening demographics survey is being hosted by Microsoft Forms. Interviews will be hosted by Microsoft Teams and involve a secure connection. Microsoft terms of service, addressing confidentiality, may be viewed at https://www.microsoft.com/en-us/servicesagreement

Your email address, which may be used to schedule your interview(s), will be stored on a password protected USB memory key, and kept in a locked drawer in the PI's private home office.

Upon receiving results of your survey and interview(s), any possible identifiers will be deleted by the investigator. You will be identified only by a unique pseudonym (a fictious name). Your email address, which may be used to contact you to schedule a study visit will be stored separately from your survey and interview data. All information will be a stored on a password protected USB memory key only accessible by the research team. The results of the research study may be published, but your name and the name of the person you care for will not be used.

By signing below, you are granting permission for the PI to audio record the interview. The recorded interview will only be listened to by the PI and/or PI's faculty advisor. The recording will be stored on a password protected USB memory key and kept in a locked drawer in the PI's private home office and will be destroyed within three years after the completion of data collection.

**Data sharing:**
Data collected from this study will not be shared with anyone outside of the study team.

**Cost and compensation:**
You will not be responsible for any of the costs or expenses associated with your participation in this study.

There is no payment for your time to participate in this study.

**Conflict of interest disclosure:**
The principal investigator and members of the study team have no financial conflicts of interest to report.

**Contact information:**
If you have questions, concerns, or complaints about this research project, you can contact the principal investigator Rachel Salazar at rachel.salazar@student.shu.edu, the PI's faculty advisor Genevieve Zipp at Genevieve.zipp@shu.edu or the Seton Hall University Institutional Review Board ("IRB") at (973) 761-9334 or irb@shu.edu.


## Informed Consent Form

**Other Elements:**

1) Audio recordings will be performed as part of the research study. Please indicate your permission to participate in these activities by placing your initials next to each activity.

| I agree | I disagree | |
|---|---|---|
| _____ | _____ | The researcher may record my audio interview. I understand that this is done to help with data collection and analysis. The researcher will not share these recordings with anyone outside of the study team. |

2) Optional Debrief Interviews will be performed with interested participants. Please indicate if you wish to be contacted for an additional 60-minute interview to review the preliminary findings of this study:

| I agree | I disagree | |
|---|---|---|
| _____ | _____ | The researcher may contact me for an optional debrief interview to review the preliminary results from this study. The researcher will need to collect my email address to schedule this additional interview. |

If you agree to be contacted to schedule the debrief interview, please enter your preferred contact method and sign below:

Email Address: _____

I hereby consent to participate in this research study.

_____ _____

Signature of participant Date

_____

Printed name of participant

_____ _____

Signature of person obtaining consent Date

_____

Printed name of person obtaining consent

**Informed Consent Form 2023 – 2024**

## Informed Consent Form

Seton Hall University
Institutional Review Board
MARCH 23, 2023
Approval Date
Expiration Date
MARCH 23, 2024

**Title of Research Study:** Caregiver perspectives on the daily functioning of people living *HNRNPH2*-related disorder: Generating a conceptual model

**Principal Investigator:** Rachel Salazar, PT, DPT, PCS (doctoral student)

**Department Affiliation:** Department of Interprofessional Health Sciences and Health Administration, School of Health and Medical Sciences

**Sponsor:** This research is supported by the Department of Interprofessional Health Sciences and Health Administration, School of Health and Medical Sciences. This research is not externally funded or supported.

**Brief summary about this research study:**
The following summary of this research study is to help you decide whether or not you want to participate in the study. You have the right to ask questions at any time.

The purpose of this study is to create a conceptual model of the everyday function of individuals living with *HNRNPH2*-related disorder based on the views of their caregivers.

You will be asked to complete a survey and virtual interview. You will have the option to complete a debrief interview.

We expect that you will be in this research study for 10-minutes for the demographics survey, 60-minutes for primary interview, and the option to participate in a 60-minute debrief interview to review results, on dates of your choosing.

There are minimal foreseeable risk or discomfort anticipated by your participation in this research study.

The main benefit of participation for yourself is the potential to learn more about and identify your views of the daily functioning of people living with *HNRNPH2*-related disorder. The main benefit of participation for us is to identify the meaningful and relevant everyday functions specific to individuals living with *HNRNPH2*-related disorder and their caregivers.

**Purpose of the research study:**
The purpose of this study is to generate a conceptual model of the everyday function of individuals living with *HNRNPH2*-related disorder based on the views of their caregivers.

You are being asked to take part in this research study because you are a caregiver for a person living with *HNRNPH2*-related disorder, at least 18 years old, and able to speak and understand English.

Your participation in this research study is expected to be for 10-minutes for the demographics survey, 60-minutes for primary interview, and an optional 60-minute debrief interview to review results, on dates of your choosing.

You will be one of approximately 20 people who are expected to participate in this research study.

**What you will be asked to do:**
Your participation in this research study will include:

First, you will be asked to first complete a survey. The survey includes questions about yourself and the person you care for.

Afterwards, you will be asked to schedule a date/time for the interview.

Then, you will be asked to participate in an audio-recorded virtual interview through Microsoft Teams on your computer or phone in a quiet location. The audio will be recorded for transcription purposes. A sample of the open-ended question that may be asked of you is the following: *How would you describe the daily functioning of the person that you care for living with HNRNPH2-related disorder?*

If you choose to participate in a follow-up debrief interview to review results, then it is expected that the interview will take 60-minutes on a day of your choosing. The audio will be recorded for transcription purposes. A sample question that may be asked of you is the following: *Please tell me what you think about this category. Is the category meaningful to you?*

**Your rights to participate, say no or withdraw:**
Participation in research is voluntary. You can decide to participate or not to participate. You can choose to participate in the research study now and then decide to leave the research at any time. Your choice will not be held against you.

The person in charge of the research study can remove you from the research study without your approval. Possible reasons for removal include missing study visits, non-compliance with the study procedures.

**Potential benefits:**
There may be no direct benefit to you from this study. You may obtain personal satisfaction from knowing that you are participating in a project that contributes to new information.

**Potential risks:**
The risks associated with this study are minimal in nature.

Your participation in this research may include collecting of audio recordings. Appropriate steps will be taken to ensure the privacy of the audio recordings from the interview.

There are minimal risks to psychological welfare, legal, social, economic or other privacy that the participant may encounter as part of their participation. This study prompts discussion about potentially psychologically sensitive topics, such as the health status and functioning of the person you care for, and implications for the person and the caregiver. In the event of emotional distress or discomfort, you have the right to take a break, skip a question, terminate the interview, or withdraw from the study, at any point.

**Confidentiality and privacy:**
Efforts will be made to limit the use or disclosure of your personal information. This information may include the research study documents or other source documents used for the purpose of conducting the study. We cannot promise complete secrecy. Organizations that oversee research safety may inspect and copy your information. This includes the Seton Hall University Institutional Review Board who oversees the safe and ethical conduct of research at this institution.
The pre-screening demographics survey is being hosted by Microsoft Forms. Interviews will be hosted by Microsoft Teams and involve a secure connection. Microsoft terms of service, addressing confidentiality, may be viewed at https://www.microsoft.com/en-us/servicesagreement

Your email address, which may be used to schedule your interview(s), will be stored on a password protected USB memory key, and kept in a locked drawer in the PI's private home office.

Upon receiving results of your survey and interview(s), any possible identifiers will be deleted by the investigator. You will be identified only by a unique pseudonym (a fictious name). Your email address, which may be used to contact you to schedule a study visit will be stored separately from your survey and interview data. All information will be a stored on a password protected USB memory key only accessible by the research team. The results of the research study may be published, but your name and the name of the person you care for will not be used.

By signing below, you are granting permission for the PI to audio record the interview. The recorded interview will only be listened to by the PI and/or PI's faculty advisor. The recording will be stored on a password protected USB memory key and kept in a locked drawer in the PI's private home office and will be destroyed within three years after the completion of data collection.

**Data sharing:**
Data collected from this study will not be shared with anyone outside of the study team.

**Cost and compensation:**
You will not be responsible for any of the costs or expenses associated with your participation in this study.

There is no payment for your time to participate in this study.

**Conflict of interest disclosure:**
The principal investigator and members of the study team have no financial conflicts of interest to report.

**Contact information:**
If you have questions, concerns, or complaints about this research project, you can contact the principal investigator Rachel Salazar at rachel.salazar@student.shu.edu, the PI's faculty advisor Genevieve Zipp at Genevieve.zipp@shu.edu or the Seton Hall University Institutional Review Board ("IRB") at (973) 761-9334 or irb@shu.edu.

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**Other Elements:**

1) Audio recordings will be performed as part of the research study. Please indicate your permission to participate in these activities by placing your initials next to each activity.

| I agree | I disagree | |
|---|---|---|
| _____ | _____ | The researcher may record my audio interview. I understand that this is done to help with data collection and analysis. The researcher will not share these recordings with anyone outside of the study team. |

2) Optional Debrief Interviews will be performed with interested participants. Please indicate if you wish to be contacted for an additional 60-minute interview to review the preliminary findings of this study:

| I agree | I disagree | |
|---|---|---|
| _____ | _____ | The researcher may contact me for an optional debrief interview to review the preliminary results from this study. The researcher will need to collect my email address to schedule this additional interview. |

If you agree to be contacted to schedule the debrief interview, please enter your preferred contact method and sign below:

Email Address: _____

I hereby consent to participate in this research study.

_____ _____

Signature of participant Date

_____

Printed name of participant

_____ _____

Signature of person obtaining consent Date

_____

Printed name of person obtaining consent

## Appendix C: Letter of Solicitation

Dear Parent(s), Guardian(s) and Caregiver(s) of a person living with *HNRNPH2*-related disorder,

My name is Rachel Salazar. I am a PhD student in Department of Interprofessional Health Sciences, School of Health and Medical Sciences at Seton Hall University.

I am kindly requesting your participation in my doctoral dissertation research study titled: *Caregiver perspectives on the daily functioning of people living with HNRNPH2-related disorder: Generating a conceptual model.* The purpose of this research study is to gather caregiver perspectives on the daily function of individuals living with *HNRNPH2*-related disorder. The study will help us identify the meaningful and relevant daily functions of individuals living with *HNRNPH2*-related disorder and their caregivers. Integrating the caregiver perspective into a comprehensive model specific to *HNRNPH2* is an essential first step in creating a person-centered assessment relevant to the daily lives of individuals with *HNRNPH2*-related disorder and those who care for them every day.

The study will involve completion of a pre-screening demographics survey, a virtual interview (roughly 60 minutes), and the option to have a debrief interview to review the findings. Participation involves completing an audio-recorded interview using the Microsoft Teams conference system on your preferred device, i.e.: computer, tablet, phone in your preferred quiet location.

Participation is completely voluntary, and you may withdraw from the study at any time.

To maintain your anonymity, any possible personal identifiers will be deleted from your survey and interview(s). You will be identified only by a unique pseudonym (a fictious name).

Your data will be securely stored to maintain confidentiality All information will be kept on a password protected USB memory key only accessible by the research team.

If you are interested in participating in this study, please:

1) Email Rachel.salazar@student.shu.edu to set up a day and time for your virtual interview.
2) Complete the pre-screening demographics survey.

Lastly, please share this letter with any of your child's other routine caregivers. Caregivers can be parents, grandparents, siblings, friends, relatives, nurses, aides etc., who are 18 years of age or older, and who speak and understand English. If you have any questions, please do not hesitate to ask. I look forward to hearing from you.

Thank you,

**Rachel Salazar, PT, DPT, PCS**
Doctoral Student, Seton Hall University
Rachel.salazar@student.shu.edu

## Appendix D: Pre-screening Survey

1. Do you regularly care for a person with *HNRNPH2*-related disorder?
    a. Yes
    b. No (stop survey and thank you)
2. What is your age range?
    a. < 18 years (stop survey and thank you)
    b. 18-30
    c. 31-40
    d. 41-50
    e. 51-60
    f. 61-69
    g. 70+
3. Are you able to speak and understand English?
    a. Yes
    b. No (stop survey and thank you)
4. If you have answered **YES** to all the above questions, please read the letter of consent below. If you agree (consent), please sign and upload consent form:
    a. Upload consent form
5. Provide your preferred email address:
    a. (free text)
6. How would you classify caregiver role?
    a. Primary Caregiver (i.e.: parent, guardian)
    b. Informal Caregiver (i.e.: relative, friend)
    c. Formal Caregiver (i.e.: paraprofessional, nurse)
    d. Other (write in)
7. What is your gender?
    a. Male
    b. Female
    c. Prefer not to say
    d. Other (please provide preferred pronouns)
8. What is the highest level of education you have completed?
    a. High School
    b. Associates degree
    c. Bachelor's degree
    d. Master's degree
    e. Graduate or professional school
    f. Other_____
9. What is your ethnicity? (check all that apply)
    a. Caucasian
    b. African-American
    c. Latino or Hispanic
    d. Asian
    e. Native American
    f. Native Hawaiian or Pacific Islander
    g. Other/Unknown

    h. Prefer not to say
10. Where is your home located?
    a. North America
    b. Central America
    c. South America
    d. Europe
    e. Africa
    f. Asia
    g. Australia
    h. Caribbean Islands
    i. Pacific Islands
    j. Other: _____
    k. Prefer not to say
11. A few questions about the person you care for with *HNRNPH2*-related disorder. What is the age range for your child or person you care for with *HNRNPH2*-related disorder?
    a. 0-2 years old
    b. 3-5 years old
    c. 6-10 years old
    d. 11-18 years old
    e. 19+ years old
12. Please describe the mobility of your child/person you care for with *HNRNPH2* (check all that apply)
    a. They can walk alone
    b. They use a walker to walk
    c. They scoot on the floor
    d. They push a wheelchair
    e. I push them in a wheelchair/stroller
    f. Other (please describe)
13. Please describe how your child/person you care for communicates:
    a. (free text)
14. Please describe how your child/person you care for feeds (check all the apply):
    a. Eats food by mouth
    b. Tube feeds
    c. Other
15. Are you interested in scheduling a 60-minute interview to review your perception on the functioning of the person you care for with *HNRNPH2*-related disorder?
    a. Yes
    b. No
16. Please select a date and time below for your interview:

## Appendix E: Interview Guide

### Interview Guide

*Research Purpose Statement:* The purpose of this study is to create a conceptual model of the functioning of individuals with *HNRNPH2*-related disorder based on the perspectives of their network of informal caregiver(s) and/or formal caregiver(s).

**The interview guides are provided in below and are specific to the caregiver status:**

A) Primary Caregiver i.e.: Parent/Guardian
B) Formal Caregiver i.e.: paid or unpaid nurse, personal care aide, paraprofessional
C) Informal caregiver i.e.: paid or unpaid friend, family, relative

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A) <u>Parent/primary caregiver:</u>

1) Tell me about your child. (RQ1)
2) Describe a typical day with your child. (RQ1)
    a. What are your responsibilities when caring for your child on a typical day? (RQ3)
3) What are your child's strengths? (RQ1)
4) What, if any limitations, does your child have? (RQ1, RQ2)
5) How would you describe your child's daily functioning? (RQ1)
    a. How would you describe your child's…?
        i. Body functions? (SQ1a)
            1. General health?
        ii. Activities? (SQ1b)
            1. Social skills?
            2. Mobility and motor function?
            3. Cognition/intellect?
            4. Behavior?
            5. Communication?
            6. Activities of daily living?
        iii. Participation in school, community, with family? (SQ1c)
6) What factors impact the daily functioning of your child? (RQ2)
    a. How do your child's personal factors impact their daily functioning? (SQ2a)
    b. How do environmental factors impact their daily functioning? (SQ2b)
7) What is your role in supporting the daily functioning of your child? (RQ3)
    a. What is your impact on your child's daily functioning? (SQ3a)
    b. How has your child impacted your life? (SQ3a)
        i. Family dynamics? Relationships? Finances? Challenges? Rewards? Support system?

c. Describe the other adult caregivers, if any, that help you take care of your child. (SQ3b)
    i. In the home: Aides, Nurses, Friends, Family?
    ii. At school: paraprofessionals, RNs, aides?
    iii. What is the structure of the caregiver network?
    iv. What are the roles of the other caregivers?

8) Tell me about your experience with parent questionnaires used to assess your child's everyday function. (SQ1d)
    a. Who asked you to fill out the questionnaire? School, Early intervention, doctor's office, research study? (SQ1d)
    b. What was the purpose of the questionnaire? Assess cognition? Communication? Social? Behaviors? (SQ1d)
    c. What sorts of questions were asked? (SQ1d)
9) What would be meaningful to you to include in an assessment of your child's daily functioning? (SQ1d)
    a. What, if any questions, would you like when assessing your child's daily functioning? (SQ1d)
    b. What, if any questions, would you not like when assessing your child's daily functioning? (SQ1d)
10) What other topics related to your child's everyday function you would like to raise?
11) I am interested in gathering the perspectives from other adults who care for your child regularly. Would you be open to sharing a letter of solicitation for this study with your child's other caregivers so that they may contact me if they are interested in potentially scheduling an interview to discuss their perceptions of your child's daily function or to learn more about the project?
12) Can I contact you in the future to schedule a debriefing interview to review your thoughts on the findings and results of the study?

Thank the individual for participating in this interview and potential for connecting again in the future.

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B) <u>Formal Caregiver (aide/nurse – if this with a school paraprofessional or one to one would use "student" instead of "client")</u>

1) Describe your responsibilities as a caregiver for your client with *HNRNPH2*-related disorder (RQ3)
2) Describe a typical shift with your client. (RQ3)
3) What are your client's strengths? (RQ1)
4) What, if any limitations, does your client have? (RQ1)
5) How do you perceive your client' daily functioning? (R1)
    a. How would you describe your client's…?
        i. Body functions? (SQ1a)
            1. General health?
        ii. Activities? (SQ1b)

1. Social skills?
2. Mobility and motor function?
3. Cognition/intellect?
4. Behavior?
5. Communication?
6. Activities of daily living?
7. Participation? ((SQ1c)

6) What factors impact your client's daily functioning? (RQ2)
    a. How do your client's personal factors impact their daily functioning? (SQ2a)
    b. How do environmental factors impact their daily functioning? (SQ2b)
7) What is your role in supporting the daily functioning of your child? (RQ3)
    a. What is your impact on your client's daily functioning? (SQ3a)
    b. How has your client impacted your life? (SQ3a)
        i. Negatives? Positives? Challenges? Rewards?
    c. Tell me about the other caregivers that regularly assist with your client's daily functioning. (SQ3b)
        i. Who is involved?
        ii. How do you collaborate in caring for the child?
8) Tell me about your experience with caregiver-reported questionnaires or assessments used to describe your client's everyday function (SQ1d)
    a. Who asked you to fill out the questionnaire? School, Early intervention, doctor's office, research study? (SQ1d)
    b. What was the purpose of the questionnaire? Assess cognition? Communication? Social? Behaviors? (SQ1d)
    c. What sorts of questions were asked? (SQ1d)
    d. How would you feel about filling out a questionnaire to describe your client's everyday function?
9) What would be meaningful to you to include in an assessment of your client's daily functioning? (SQ1d)
    a. What questions would be relevant to include in a questionnaire to describe your client's everyday functioning? (SQ1d)
    b. What questions would not be relevant to include in a questionnaire to describe your client's everyday functioning? (SQ1d)
10) What other topics related to your client's everyday function you would like to raise?
11) Can I contact you in the future to schedule a debriefing interview to review your thoughts on the findings of the study?

Thank the individual for participating in this interview and potential for connecting again in the future.

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C) <u>Informal Caregiver (friends, family, relatives)</u>

1) Describe your responsibilities as a caregiver for your loved one with *HNRNPH2*-related disorder (RQ3)
2) Describe a typical day when you care for them. (RQ3)
3) What are their strengths? (RQ1)

4) What, if any limitations, do they have? (RQ1)
5) How do you perceive their daily functioning? (R1)
    a. How would you describe their…?
        i. Body functions? (SQ1a)
            1. General health?
        ii. Activities? (SQ1b)
            2. Social skills?
            3. Mobility and motor function?
            4. Cognition/intellect?
            5. Behavior?
            6. Communication?
            7. Activities of daily living?
            8. Participation? ((SQ1c)
6) What factors impact your loved one's daily functioning? (RQ2)
    a. How do their personal factors impact their daily functioning? (SQ2a)
    b. How do environmental factors impact their daily functioning? (SQ2b)
7) What is your role in supporting the daily functioning of your loved one? (RQ3)
    a. What is your impact on their daily functioning? (SQ3a)
    b. How has your loved one's impacted your life? (SQ3a)
        i. Negatives? Positives? Challenges? Rewards?
    c. Tell me about the other caregivers that regularly assist with your loved one's daily functioning. (SQ3b)
        i. Who is involved?
        ii. How do you collaborate in caring for the child?
8) Tell me about your experience with caregiver-reported questionnaires or assessments used to describe your loved one's function, if any. (SQ1d)
    a. How would you feel about filling out a questionnaire to describe your client's everyday function?
9) What would be meaningful to you to include in an assessment of your loved one's daily functioning? (SQ1d)
    a. What questions would be relevant to include in a questionnaire to describe your loved one's everyday functioning? (SQ1d)
    b. What questions would not be relevant to include in a questionnaire to describe your loved one's everyday functioning? (SQ1d)
10) What other topics related to your client's everyday function you would like to raise?
11) Can I contact you in the future to schedule a debriefing interview to review your thoughts on the findings of the study?

Thank the individual for participating in this interview and potential for connecting again in the future.