Spring 2022

Examining Parental Disclosure to Unaffected Siblings of Children Diagnosed With Rett Syndrome

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EXAMINING PARENTAL DISCLOSURE TO UNAFFECTED SIBLINGS OF CHILDREN DIAGNOSED WITH RETT SYNDROME

by

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Bachelor of Science
Virginia Commonwealth University, 2018

Submitted in Partial Fulfillment of the Requirements

For the Degree of Master of Science in

Genetic Counseling

School of Medicine

University of South Carolina

2022

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DEDICATION

This project is dedicated to all of the families affected by Rett syndrome. Your strength, resiliency, and advocacy for your children is profoundly moving. I am eternally grateful for you welcoming me into your community. Thank you for all of the lifelong lessons. I hope to continue working tirelessly for the betterment of your girls and boys affected by Rett syndrome.

ACKNOWLEDGEMENTS

I would like to thank my thesis advisor, Amy Wardyn, as well as my committee members, Hannah Warren Moore and Fran Annese. Thank you all for your continuous patience, guidance, and expertise throughout the entirety of this project. I am so grateful for all of you, and honored to have experienced this project alongside such outstanding clinicians. I'd like to thank the faculty of the USC Genetic Counseling Program. This idea would not have come to fruition without the countless discussions and your unconditional support. I'd like to thank my classmates for being my inspiration and the most helpful teachers throughout the entirety of my graduate training. I am so proud of the genetic counselors we have developed into, and know that our patients will receive a standard of care unlike any other. I want to say a special thank you to Romy Fawaz for being there on my happiest days and my hardest days. I am so incredibly grateful for your love and support these past two years and couldn't imagine being at this point without you as a best friend. I'd like to thank Daniel Monteith for being a listening ear and one of my biggest supporters. You have been my rock through the tumultuousness of graduate school. Most importantly, I would like to thank my family for their unwavering support. Mom and Dad, you have sacrificed so much to allow me to be where I am today. I wouldn't have been able to pursue my dreams without you. Thank you all.

ABSTRACT

Rett syndrome is a neurodevelopmental disorder that is inherited in an X-linked dominant manner due to pathogenic variants in the *MECP2* gene that are almost always *de novo*. It is one of the most common causes of developmental delay and intellectual disability in females and occurs in about 1 in 10,000 females. While there is valuable literature surrounding the impact of a neurodevelopmental diagnosis on unaffected siblings, there are no articles about the impact of a disclosure of Rett syndrome to unaffected siblings and the needs of parents during this disclosure. This study aimed to examine the disclosure process from parent to unaffected sibling(s) about the diagnosis of Rett syndrome in their sister. Semi-structured interviews were used to explore the experiences of these families and needs of parents when discussing Rett syndrome with their unaffected children. We interviewed a parent from five different families and analyzed the conversations for prevalent themes. Four primary themes emerged: the diagnostic odyssey, the ongoing nature of conversations, the emotional nature of the disclosure process, and the significance of support and informational resources. While these parents expressed a difficult journey to the diagnosis of Rett syndrome, most of their unaffected children took the diagnosis in stride as they had always understood their sister had difficulties unlike themselves. There were a variety of emotions expressed by the unaffected siblings and a few resources were helpful in the families' discussions, although there was little that directly addressed the nature of the condition related to the unaffected siblings. The results of this study were consistent with previous literature

exploring the challenges that parents of children with neurodevelopmental disorders face and provided new insight into families specifically affected by Rett syndrome. These findings can begin to aid providers in facilitating familial conversations about the diagnosis of Rett syndrome.

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INTRODUCTION

1.1 History of Rett Syndrome

Rett syndrome is a neurodevelopmental disorder that is inherited in an X-linked dominant manner. It occurs in about 1 in 10,000 females and, in rare cases, affects males. Individuals with Rett syndrome typically have normal development for the first 7-18 months, followed by a period of regression. During this period, children will lose previously acquired skills, such as purposeful hand movements and speech. Additional features that individuals often present with include repetitive hand motions (hand stereotypies), loss of ambulation, acquired microcephaly, seizures, and impaired control of voluntary movements (Neul et al., 2010).

Rett syndrome was first characterized by Dr. Andreas Rett, an Austrian pediatrician who specialized in neurodevelopmental disorders (Rett, 1966). In his literature, Dr. Rett described females making similar repetitive hand-washing motions. When he noticed these motions, he further compared the developmental and clinical history of the girls and found striking similarities. He took it upon himself to find more children with similar behavior and study the condition further. He was able to publish his findings in several German medical journals in 1966 but, at the time, associated these findings with hyperammonemia (Rett, 1977). Unfortunately, his work was not widely circulated, and mostly went unnoticed by the medical community.

In 1970, a Swedish pediatric neurologist by the name of Dr. Bengt Hagberg also noted that some of his patients had a similar clinical presentation which he reviewed at a conference. There, he was informed of Dr. Rett's prior publications and the similarities in these patients. He moved forward to write a paper describing girls with similar features and successfully published an article in 1982 on the condition. This publication was the first to raise widespread awareness of Rett syndrome and served as a breakthrough of communication about the condition. After further investigation, Dr. Hagberg discovered that the hyperammonemia that Dr. Rett's patients experienced happened to be an incidental finding and confirmed that he and Dr. Rett had been studying the same disorder all along. Aware that Dr. Rett had been the pioneer to have first described the condition, Dr. Hagberg and his team honored Dr. Rett by naming the syndrome after him (Hagberg et al., 1983).

Nearly a decade after this publication, a major breakthrough occurred in 1999 when a research fellow, Dr. Ruthie Amir, discovered the *MECP2* gene. Through the usage of mapping studies and data provided by families, she and her team were able to successfully map the locus of interest in girls with Rett syndrome to Xq28. This study provided an explanation for previous findings and proved an X-linked dominant inheritance pattern for Rett syndrome (Amir et al., 1999).

1.2 Rett Syndrome Diagnostic Criteria

As clinical recognition of Rett syndrome increased, Hagberg et al. (2002) sought to establish the first diagnostic criteria. The first diagnostic criteria had eight necessary criteria, five exclusion criteria, and eight supportive criteria. Three of the requirements for these criteria were never explicitly stated and one of the necessary criteria

(deceleration of head growth) was not necessary, leading to much confusion surrounding the diagnosis. Additionally, these diagnostic criteria did not distinguish between classic Rett syndrome and atypical Rett syndrome.

In 2010, a revision of the original 2002 criteria was published to make clinical diagnosis more efficient, add required criteria, and distinguish between forms of Rett syndrome. Diagnosis is primarily clinical and can be divided into two separate types: classic/typical Rett syndrome and atypical Rett syndrome. A diagnosis of classic Rett syndrome is made when patients meet all diagnostic criteria for classic Rett syndrome, which includes a period of regression followed by recovery or stabilization, and all main criteria (Neul et al., 2010).

Supportive criteria are not required to make a diagnosis but are frequently seen in typical Rett syndrome. When a child presents with Rett-like symptoms but does not fulfill all diagnostic criteria, they may be diagnosed with atypical Rett syndrome. A diagnosis of atypical Rett syndrome is made when the child meets two of the four main criteria in addition to five of eleven supportive criteria. In order to make a diagnosis of either typical/classic Rett syndrome or atypical Rett syndrome, exclusion criteria must not be met (Neul et al., 2010). Main, supportive, and exclusion criteria are listed in Table 1.1. Criteria are continuing to be evaluated and may evolve as researchers uncover more about this condition.

Table 1.1. Rett Syndrome Diagnostic Criteria

Main Criteria
1. Partial or complete loss of acquired purposeful hand skills 2. Partial or complete loss of acquired spoken language 3. Gait abnormalities: Impaired (dyspraxic) or absence of ability 4. Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing, and washing rubbing automatisms
Supportive Criteria
1. Breathing disturbances when awake 2. Bruxism when awake 3. Impaired sleep pattern 4. Abnormal muscle tone 5. Peripheral vasomotor disturbances 6. Scoliosis/kyphosis 7. Growth retardation 8. Small cold hands and feet 9. Inappropriate laughing/screaming spells 10. Diminished response to pain 11. Intense eye communication
Exclusion Criteria
1. Brain injury secondary to trauma (peri- or postnatally, neurometabolic disease, or severe infection that causes neurological problems 2. Grossly abnormal psychomotor development in first 6 months of life

1.3 Natural History

The clinical features seen in individuals with Rett syndrome are typically age-dependent and involve both regression and static periods. Individuals with Rett syndrome generally have normal development up to 7-18 months of life, followed by a distinct period of regression of learned developmental skills. Symptoms typically become stabilized in the period spanning from childhood to adulthood (Nomura & Segawa, 2005).

A longitudinal referral-to-treatment study showed that the average age at which Rett syndrome is diagnosed has been steadily decreasing. According to Tarquinio et al. (2019), the average age at which diagnosis occurs is around 30-36 months for classic Rett syndrome, and about 3-6 years for atypical forms of Rett syndrome. Although there is variability in the clinical spectrum of Rett, it more commonly presents in the classic form and leads to lifelong disability.

The quality of life for individuals with Rett syndrome continues to evolve as well. Survival for classic and atypical Rett syndrome is greater than 70% at 45 years, and survival into the 5th decade of life has become increasingly common. Individuals with movement issues are at an increased risk of accidents and falls, which can have an impact on mortality rates. With continuous surveillance and monitoring for seizures, pneumonia, scoliosis, and accidental falls, the life expectancy and quality of life is expected to improve (Tarquinio et al., 2015).

1.4 Causes of Rett Syndrome

Rett syndrome is typically caused by one of more than 300 known loss-of-function pathogenic variants in the methyl-CpG-binding protein 2 (*MECP2*) gene on the X chromosome. A few other genes, including *FOXG1* and *CDKL5*, have also been indicated less commonly in atypical and, rarely, in classic Rett syndrome. Presence of a pathogenic variant in one of these genes is typically supportive of a Rett syndrome clinical diagnosis; however, it is not confirmatory due to limited genotype-phenotype data being available (Neul et al., 2014). In other instances of Rett syndrome where a pathogenic variant in *MECP2*, *FOXG1*, or *CDKL5* genes cannot be detected, a not yet identifiable genetic etiology may be the cause (Sajan et al., 2017).

De novo, or sporadic, pathogenic variants account for 99.5% of the variants in *MECP2*, and about 70% of these are C > T substitutions due to the hypermutability of the *MECP2* gene, which contains numerous methylated CpG sites, which are areas prone to mutability (Banerjee et al., 2019). Instances of gonadal mosaicism or asymptomatic carrier mothers have been reported; however, these are rare (Zhang et al., 2012). While limited data exist, certain known pathogenic variants in the *MECP2* gene confer differing clinical severities (Neul et al., 2008). Additionally, the clinical presentation of Rett syndrome in females is variable. Some of this variability may be explained by X-inactivation. Either the paternally inherited or maternally inherited X chromosome is inactivated and, in some instances, skewed X-inactivation may occur. Skewed X-inactivation is the preferential expression of either the maternal or paternal X chromosome. The potential for this phenomenon further complicates diagnosis and prognostic guidance and provides some explanation for instances of asymptomatic carrier mothers (Knudsen et al., 2006). Despite the mounting research and scientific progress since its discovery, the pathophysiology in which *MECP2* mutations cause Rett syndrome has not been fully elucidated. Due to these factors, treatment options are still currently limited and centered on relieving symptoms.

1.5 Familial Communication

Family systems theory is one of the main theories that attempts to explain familial interconnectedness and make sense of familial communication. It defines the family unit as a social system in which its members interact with each other and are impacted by the emotional condition of the family as a whole. Familial communication is one of the major family processes that affects how the family functions as said social system (Broderick,

1993). Genetic conditions affect the entire family, whether the condition is inherited or not. Regardless of the situation, familial communication typically occurs in-line with pre-existing family communication patterns and has the potential to impact short-term and long-term communication between its members (Galvin et al., 2015).

From a clinical standpoint, one of the most important communication functions within a family that is affected by a genetic condition is to accurately communicate health risk and disease information to its members (Peterson, 2005). Many factors affect the disclosure of these messages, including interpersonal histories, family structures, members' roles, gender, privacy rules, nature of the disorder, and cultural patterns (Forrest et al., 2003). Talking about genetic conditions to children, particularly young children, has been a task that many parents find difficult, with many parents instinctually wanting to protect their child from potentially difficult information. Providing information to a child about a genetic condition at a level that is appropriate to their developmental maturity has been shown to be more beneficial to the child than attempting to protect the child by withholding information (Hern et al., 2006; Metcalfe et al., 2011).

During the disclosure process of a genetic diagnosis to unaffected siblings, parents report feelings of anxiety, worry, and concern. Parents often struggle with when and what to tell their other children after one child has been diagnosed with a genetic condition (Metcalfe et al., 2008). Not only do parents struggle with conversations, but it is known that parents of children with disabilities tend to experience more adverse physical and mental health outcomes (Yamaoka et al., 2015). More specifically, caregivers of individuals with Rett syndrome typically have poorer emotional and mental

wellbeing than population norms (Mulroy et al., 2008). Not only are parents impacted, but other children are as well. Having a brother or sister affected by a genetic condition, specifically a neurodevelopmental disorder, has been shown to affect quality of life in unaffected siblings (Lamsal & Ungar, 2021). Studies have shown that information and support needs go largely unmet and unrecognized by healthcare professionals in these families affected by genetic conditions (Plumridge et al., 2011).

Open intrafamilial communication surrounding genetic conditions and diagnoses has been shown to ameliorate some of these difficulties and allows both children and parents to better cope with the diagnosis of a genetic condition (Metcalfe et al., 2011; Mori et al., 2019). In the instance of Rett syndrome, families with high coherence and levels of adaptation have also reported having strong relationships and open intrafamilial communication. Specifically, in the case of Rett syndrome, families with high coherence and levels of adaptation also report having access to information and professional experts, strong relationships, and open intrafamilial communication (Retzlaff, 2007).

Recent review literature has shown that there is a growing need for more resources to help clinicians facilitate parent-to-child communication regarding genetic diagnoses (Keenan et al., 2020). While there is literature that assesses quality of life of unaffected siblings of children with Rett syndrome and generalized publications about parental experiences discussing genetic diagnoses to unaffected siblings, there is no apparent literature specifically studying the Rett syndrome community and parental disclosure to unaffected siblings. Our study aimed to fill these gaps in knowledge surrounding disclosure and guide approaches to aiding these families in parent-child communication.

It has been established that poor communication within families can lead to decreased family cohesion and, as a result, diminish support and care for individuals long-term and into adulthood. When siblings are fully informed about genetic conditions and are included in family discussions, they have a better understanding of their role and family relationships are reported to be more harmonious (Plumridge et al., 2011). Considering the prevalence of this condition in addition to concerns regarding the quality of life for families of these individuals, it is beneficial to characterize and explore the complexities surrounding the disclosure process to lay foundational work to meet the informational and support needs of these families. Based on the current literature surrounding intrafamilial communication about a genetic diagnosis of a neurodevelopmental disorder, we predicted that there are many challenges, regarding both the process and emotions experienced, that parents face when disclosing their child's diagnosis of Rett syndrome to the child's unaffected siblings.

This study aimed to identify the experiences and needs of parents disclosing a diagnosis of Rett syndrome to their unaffected children by interviewing parents of females diagnosed with classic Rett syndrome. Examining the disclosure process between parents and children can produce valuable insights into emotional and procedural challenges parents face during the disclosure process of a diagnosis of Rett syndrome. An integral part of helping parents cope and overcome feelings of panic, fear, and guilt when a child is affected by a genetic condition is access to information and greater access to informal support (Metcalfe et al., 2008).

Additionally, this study aimed to provide further exploration into the perspectives and dialogues of these families. It has recently been reported that genetics professionals

struggle with providing guidance on and facilitating parent-child communication, and many express a need for resources to aid them in the process (Keenan et al., 2020). Through this study, we hoped to gather themes and identify challenges that can lay the groundwork for future studies surrounding the disclosure process and aid in the production of educational materials that can help genetic counselors and clinicians meet the informational needs of these parents. The ultimate goal of this study was to identify these challenges and highlight the informational needs of parents during this disclosure process.

CHAPTER 2

EXAMINING PARENTAL DISCLOSURE TO UNAFFECTED SIBLINGS OF CHILDREN DIAGNOSED WITH RETT SYNDROME[1]

[1] Nicely, R. M., Wardyn, A., Moore, H., Annese, F. To be submitted to *Journal of Genetic Counseling*

2.1 Abstract

Rett syndrome is a neurodevelopmental disorder that is inherited in an X-linked dominant manner and occurs in about 1 in 10,000 females. It is caused by pathogenic variants in the *MECP2* gene located on the X chromosome. It is one of the most common causes of developmental and intellectual disability in females. While there is valuable literature surrounding the impact of a neurodevelopmental diagnosis on unaffected siblings, there are no specific articles about the impact of a disclosure of Rett syndrome to unaffected siblings and the informational needs of parents during this disclosure process. The purpose of this study was to examine the disclosure process from parent to unaffected siblings about the diagnosis of Rett syndrome in hopes of identifying the experiences and needs of parents of daughters with Rett syndrome. We interviewed a parent from five different families and examined the conversations for prevalent themes. Four themes emerged from the semi-structured interviews: the diagnostic odyssey, the ongoing nature of conversations, the emotional nature of the disclosure process, and the significance of support and informational resources. The results of this study were consistent with previous literature exploring the challenges that parents of children with neurodevelopmental disorders face, with all parents having faced the difficulty of a diagnostic odyssey. The results of this study can begin to aid providers in facilitating familial conversations about the diagnosis of Rett syndrome.

2.2 Introduction

Rett syndrome is an X-linked dominant neurodevelopmental condition that primarily affects females and is characterized by developmental regression and hand stereotypies, but may present with a wide clinical spectrum. Diagnosis is primarily

clinical and can be divided into two separate types: classic/typical Rett syndrome and atypical Rett syndrome. A diagnosis of classic Rett syndrome is made when patients meet all diagnostic criteria for classic Rett syndrome, which includes a period of regression followed by recovery or stabilization, and all main criteria. Supportive criteria are not required to make a diagnosis but are frequently seen in classic Rett syndrome. When a child presents with Rett-like symptoms but does not fulfill all diagnostic criteria, they may be diagnosed with atypical Rett syndrome. A diagnosis of atypical Rett syndrome is made when the child meets two of the four main criteria in addition to five of eleven supportive criteria. In order to make a diagnosis of either classic/typical Rett syndrome or atypical Rett syndrome, exclusion criteria (brain injury second to trauma and/or grossly abnormal psychomotor development in the first 6 months of life) must not be met (Neul et al., 2010).

It has been established that poor communication within families can lead to decreased family cohesion and, as a result, diminish support and care for individuals long-term and into adulthood. When siblings are fully informed about genetic conditions and are included in family discussions, they have a better understanding of their role, and family relationships are reported to be more harmonious (Plumridge et al., 2011). Considering the prevalence of this condition in addition to concerns regarding the quality of life for families of these individuals, it is beneficial to characterize and explore the complexities surrounding the disclosure process to lay foundational work to meet the informational and support needs of these families.

Based on the current literature surrounding intrafamilial communication about a genetic diagnosis of a neurodevelopmental disorder, we predicted that there are many

challenges, procedural and emotional, that parents face when disclosing their child's diagnosis of Rett syndrome to the child's unaffected siblings. Results from this study aimed to identify these challenges and highlight the informational needs of parents during this process.

2.3 Methods

2.3.1 Participants

Approval for this study was obtained from the University of South Carolina Institutional Review Board (Pro00114365). Parents of females diagnosed with classic Rett syndrome were identified through national, local, and online organizations affiliated with Rett syndrome, including the International Rett Syndrome Foundation (IRSF) and the Greenwood Genetic Center (GGC). This study was limited to parents of females diagnosed with classic Rett syndrome, as experiences may differ based on the various clinical presentations of atypical Rett syndrome. The selection process of parent participants included individuals who are at least18 years of age, live in the United States, can read, write, and speak in English, have a daughter with classic Rett syndrome and have other unaffected children that were between the ages of 5 and 17 years old at the time of their affected sibling's diagnosis. Only one parent per family was eligible to take the survey and be interviewed. Parents of children with variant or atypical forms of Rett syndrome or parents of children with classic Rett syndrome who have no other unaffected children were excluded from participation. Our study aimed to interview 15 randomly selected parents. Participation in our study was voluntary; therefore, completing the preliminary survey served as their consent to be contacted for an interview. Participants who were recruited online were provided the link directly to the preliminary survey on an

online recruitment flyer (Figure 2.1). Parents of children who were seen in person at GGC were given a paper recruitment flyer (Figure 2.2) with the link to the preliminary survey.

Figure 2.1 Online Recruitment Flyer

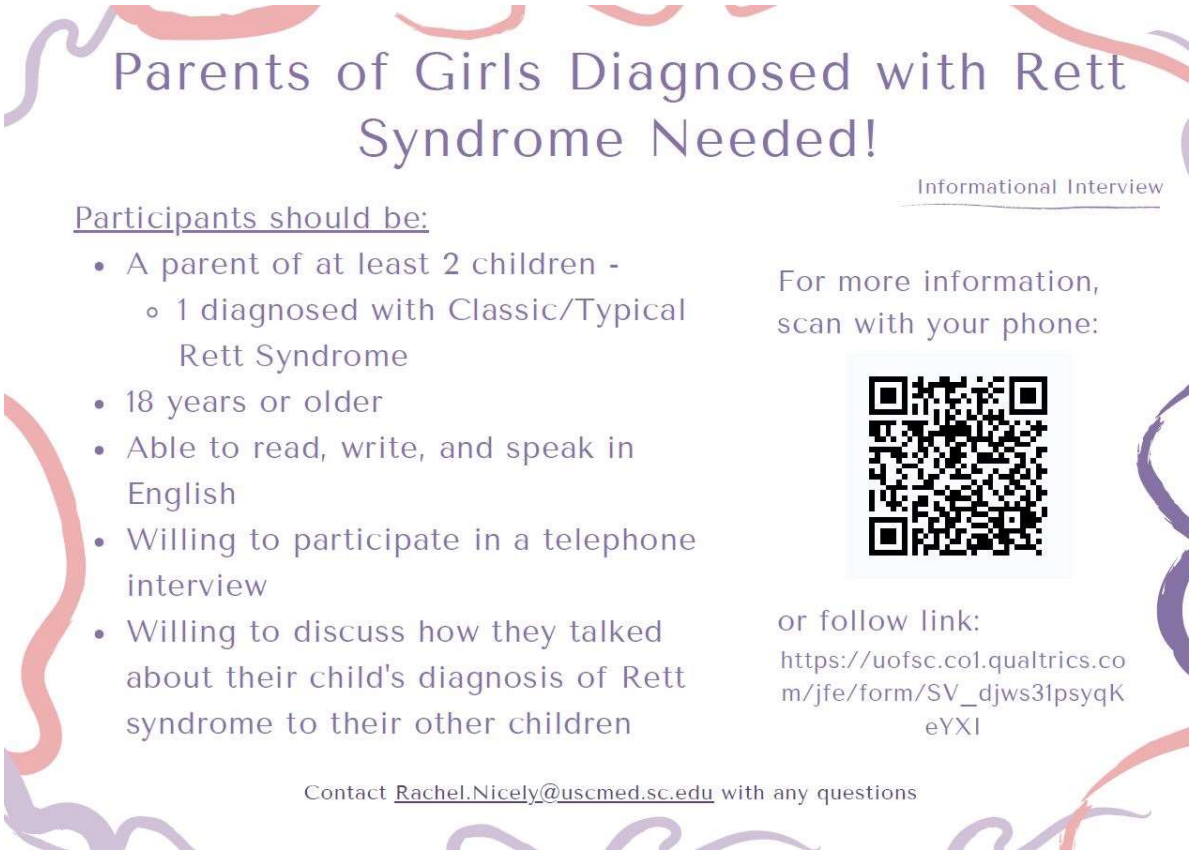

Figure 2.2 Paper Recruitment Flyer

2.3.2 Questionnaire and Interview Design

We employed the use of a preliminary questionnaire for recruitment and eligibility identification followed by a semi-structured telephone interview. Preliminary questionnaires were administered through Qualtrics and were utilized to ensure participants met inclusion criteria in addition to gathering basic demographic data of participants. Upon completion of the online questionnaire, respondents were asked to provide their contact information (first name, email, and phone number) to schedule a semi-structured telephone interview. The online questionnaire took approximately 10 minutes to complete.

Participants who provided their contact information were contacted via telephone by the principal investigator (RN) to determine a time for an interview. Interview

questions explored the emotional and procedural process of disclosing the diagnosis of Rett syndrome of the affected child to their other unaffected children. The interview questions explored if inheritance was discussed, perception of preparedness to disclose, and informational needs of parents. Interviews lasted up to an hour and a half in duration. Verbal consent for participation and recording was obtained at the beginning of each interview. Interviews were recorded on the interviewer's password-protected computer via Windows Voice Recorder and were transcribed verbatim. Audio recordings were destroyed following transcription.

Responses were collected from September 2021 to January 2022. Of the 17 individuals who began the preliminary questionnaire, seven respondents were eligible for interview. Of the seven eligible respondents, six were contacted via telephone once. If the respondent did not answer, a voice message was left requesting a call back. One international respondent was contacted via SMS text message to schedule an interview via an alternate platform but did not respond. Of the seven eligible respondents, five ultimately completed the interview (Table 2.1).

Table 2.1 Participant Demographics

	Participants				
	R_001	**R_002**	**R_003**	**R_004**	**R_005**
Age of daughter at diagnosis (years)	3	1	2	1	2
Diagnosed by	Geneticist	Geneticist	Geneticist	Neurologist	Neurologist
Age of siblings at diagnosis (years)	1, 3, 5	7	3, 11	6	10,8
Age of parent at diagnosis (years)	35	28	32	37	30
Current age of parent (years)	35	38	33	39	35
Race/Ethnicity	Caucasian	Caucasian	Hispanic or Latino	Caucasian	Caucasian
Highest degree of education	Professional degree	Some college	Professional degree	Professional degree	Some college
Occupational status	Stay-at-home parent	Student	Employed	Employed	Employed
Marital status	Married	Married	Married	Married	In a relationship

2.3.3 Data Analysis

Semi-structured interviews were chosen to explore the complexity of disclosure and gather unique parental experiences to be examined for themes. A grounded theory approach was implemented to analyze qualitative data gathered from interviews. Derived themes were coded based on participant responses, and thematic frequency was recorded.

2.4 Results

While the aim of this study was to characterize the disclosure process of a diagnosis of Rett syndrome to unaffected siblings, the overall impact that the diagnosis made on the family was undeniably intertwined with the sibling disclosure process and

many parents shared much information about the diagnosis and experiences of their families. Results were divided into two major categories – the experience surrounding the initial diagnosis and subsequent experiences and conversations with siblings. While unrelated to our initial research question, a major theme of a diagnostic odyssey emerged from the discussion surrounding the diagnosis.

Regarding the conversation with unaffected siblings, three major themes were prevalent after analysis of the conversations: the ongoing nature of these discussions with unaffected siblings, the overwhelmingly emotional nature of the conversations, and the importance of having access to resources.

2.4.1 Diagnostic Odyssey

Participants were asked to discuss the process of receiving their daughter's diagnosis of Rett syndrome. All individuals described initially noticing delays and developmental regression in their daughter, which then prompted a long diagnostic process leading up to the official diagnosis of Rett syndrome. All participants cited having visited numerous providers, including neurologists, geneticists, and developmental pediatricians, and going through a barrage of testing before arriving at the diagnosis of Rett syndrome:

- *That also led us to go to the geneticist, and then after all of these tests, because, we did not hit the spot on the first, second, third, on all of these tests. Later, she told us.. "Let's do this test. It's a bit, you know, expensive but this will lead us to the right diagnosis." - [R_003]*
- *We were just kind of waiting for the diagnosis and then I guess getting the diagnosis earlier would have saved us a lot of time and money. - [R_002]*

- *And so all the while we were seeing a neurologist, developmental pediatrician, and they were all saying like, you know, let's wait and see kind of approach which I'm not- I didn't love. – [R_004]*
- *I also had just met with [PHYSICIAN] at [RETT SYNDROME CLINIC] here in New York and she was kind of the first one to even say ever like "Wow, I'm really surprised [DAUGHTER] wasn't diagnosed earlier because she presents as, you know, fairly standard Rett."- [R_001]*

Many of the daughters began experiencing a variety of symptoms, which prompted a number of parents to begin doing their own research. Of note, one participant had come across the diagnosis of Rett syndrome and advocated for testing, but was met with doubt from the medical community: "*The very first doctor that we mentioned it to said to me 'I would stake my career that your child doesn't have Rett syndrome'." -* [R_002]

Additionally, many parents expressed experiencing a variety of reactions and intense emotions after receiving the diagnosis. Most parents noted the shock and disbelief they experienced:

- *After she started explaining it to us, it was like.. I don't know how to describe it, but it was crushing… I was thinking "Why me? Why her?" She's, you know, just a child. - [R_003]*
- *.. I was like "Oh my god". So I get in the car and we get halfway to the highway. I had pulled my car over on the side of the highway because I couldn't breathe because at that point, like, it hit me. Like I didn't know*

what I was getting into. I come home and I'm like totally flipped out about it. - [R_005]

Another participant noted the gravity of the stress she experienced and the struggle to cope with the emotions after receiving the diagnosis:

- *Since the stress that I went through, during getting her diagnosis, I wasn't equipped for that level of stress- I don't think anybody is- but especially a person with lots of childhood trauma and lots of unhealed wounds this time and I didn't have the coping mechanisms necessary to process all what was happening. - [R_002]*

Another participant expressed that the diagnosis was a relief, but if the diagnosis would have been delivered earlier, a different reaction would have been experienced:

- *It was actually like, it was a huge relief. So I think if [DAUGHTER] had been diagnosed with Rett syndrome at two, it would have been a tremendous emotional blow for her outlook. - [R_001]*

2.4.2 Ongoing Conversations with Unaffected Siblings

Respondents who were interviewed were asked to share their experience regarding the discussion they had with their unaffected children about their daughter's diagnosis of Rett syndrome. Many respondents explained that these conversations happened overtime and were ongoing:

- *I know we had talked a lot about Rett syndrome because at that point we were learning so much. We were talking about it to other people for that whole three years prior, so [SIBLING 1] really just had this understanding that his sister was different. - [R_002]*

A majority of participants felt as though they were prepared to disclose the diagnosis of Rett syndrome to their unaffected children. Participants were asked if there was information they would have liked to have known before discussing the diagnosis with their their unaffected children. Individuals described the desire for accurate and realistic expectations for development before these conversations:

- *So when I'm explaining this to them, I'm like "She's going to require a feeding tube. She's going to have seizures, she's going to pass out from holding her breath." Like I was under the assumption those things were going to happen as soon as the book said that they were going to happen and I wish I could have known that each Rett diagnosis is not the same, really. - [R_005]*
- *I would feel more prepared if I had a specific explanation of, you know, the specific mutation she has or what to expect from her, what to do. - [R_003]*

Two individuals suggested the idea of age-appropriate conversation guides or scripts:

- *Yeah I guess maybe some more structured age-appropriate guides. You know, like where a kid is developmentally and what's reasonable to expect at each developmental stage of the child to understand. Because the kid who's, you know, 16 is going to have a very different understanding than a kid who's seven. - [R_002]*
- *I would have looked into more of a script or more of a way to put it if I felt like I was struggling. I just didn't feel like I needed to but perhaps if I was someone else maybe I would. I work with children for a living, so I kind of*

understand developmentally delayed to put it so, like, I didn't really need that but I could see others who aren't. - [R_004]

Parents also shared their own thoughts on what is most helpful during these discussions:

- *Each kid is different when you're going to tell him to because with some kids you just lay the truth out to them and some of you have to be sensitive with but I think you also have to like judge your other children's character before. - [R_005]*

2.4.4 Sibling Emotions and Reactions

When asked about the emotions that they felt during the disclosure process, negative emotions and feelings were experienced by all participants. Emotions and feelings varied, and included sadness, pity, and guilt:

- *Most of the time, what I feel is pity. - [R_003]*
- *I know, you know, [HUSBAND] felt sad and all the other emotions, but I think I was a little bit immediately more upset and then just sort of.. you know, dealt with it through talking to others, taking a lot of time for myself processing it. - [R_004]*

One participant noted the overwhelming nature of the discussion was due to the challenge of making the discussion understandable for their unaffected children:

- *And pretty overwhelmed too by the whole concept and trying to make it understandable and digestible was really overwhelming. - [R_002]*

Two participants discussed that the source of some of these emotions experienced was due to the idea of a loss of a normal expected life lived with their sibling:

- *So like I just felt.. I did cry when I told both of them separately because I felt bad for them because I knew that their life wasn't going to be the same. Because it's doctor's, appointments and therapy appointments. And if she's screaming and having a bad day our plans are canceled, and we can't leave the house... - [R_005]*
- *I remember feeling very sad for him. So I have younger siblings and I think having younger siblings is pretty cool. I was just really sad he was never going to get to experience that- the solidary you can get in those relationships. - [R_002]*

While some individuals expressed intensely negative emotions during the disclosure process, one participant noted that she felt as though she were empowering her other children with knowledge:

- *Honestly excitement because I felt like it was empowering them with information that we did not have before as a family.. Well I mean as much as I'm saying it was a positive experience, getting the diagnosis, it was also incredibly scary because we had never thought about [DAUGHTER] like, not outliving me and my husband and the Rett syndrome diagnosis kind of put that into question. - [R_001]*

Parents cited a variety of emotions and responses that they perceived their children felt. When appropriate, they were asked to expand upon how they knew their unaffected child was feeling said emotion, such as if their behavior changed or if they were explicitly verbal about their emotions. The unaffected siblings' reactions appeared

to be dependent upon age. Younger children seemed to express indifference and even acceptance of their sister's diagnosis:

- *...the youngest boy.. He kind of more was like "Okay, cool". He took it more in strides. I think, like, "It'll all work out. We'll figure it out", but didn't seem to be too concerning to him that his sister was different. - [R_005]*
- *My youngest son.. he would have been three at the time. He was definitely indifferent. - [R_001]*

However, the older the child was, the more concerned and involved in their care they seemed to be.

- *The oldest one was very concerned. He wanted to make sure that she was going to be all right. He did ask a lot of like, 'Is she going to die? Is she going to be able to talk?' Like he did have a lot of questions about her well-being, like he wanted to make sure she was going to be okay. - [R_005]*

2.4.3. Importance of Support Groups, Families, and Informational Resources

Participants were asked if any informational resources were given to them by their providers about how to talk to their unaffected children about the diagnosis of Rett syndrome. Some participants mentioned receiving a number of resources during the initial diagnosis, including contact information to the International Rett Syndrome Foundation (IRSF) website (International Rett Syndrome Foundation, n.d.) as well as a copy of the Rett Syndrome Handbook written by Kathy Hunter (Hunter, 1999), which includes information on how to talk to children about the diagnosis. No individuals

recalled having an explicit conversation with healthcare providers regarding how to talk to their unaffected child or children.

Participants were asked what information they found most helpful to have these conversations with their unaffected children. Participants reported utilizing a variety of support groups and resources to aid in these conversations. The two main sources of information parents reported utilizing were the IRSF website as well as the Rett Syndrome Handbook.

- *So like, I found it (the Rett Syndrome Handbook) helpful in the way of explaining to them. Like I said, like she was born fine. And then she's going to lose those abilities, but we do have to make sure that we watch for this because seizures could start and, you know, there's a thing called breath-holding and she holds her breath. She could pass out and we can't leave her alone. We need to make sure that somebody is with her all the time in case those things happen. We need to be with her and they were definitely understanding of that she's going to require more attention. - [R_005]*
- *I feel like that of everything that I have received, that book was… was so, so, so helpful. - [R_001]*
- *Most of my information came from rettsyndrome.org (International Rett Syndrome Foundation). And I had got in contact with a lady named [NAME] and she sent me this giant Rett syndrome book – the Rett Syndrome Handbook. - [R_005]*

However, one participant found that reading through the Rett syndrome handbook evoked difficult emotions:

- *I told myself that whatever I could read like 12 pages.. Sometimes I read more because it's so interesting. But I start crying again because they quote parents saying stuff that I .. I feel that I'm there with them.. and that that those words are my words. And I start crying again, and I know I cannot keep going. - [R_003]*

In addition to the IRSF website as well as the Rett Syndrome Handbook, participants cited social media support groups as being important sources of information regarding Rett syndrome:

- *The Facebook group where you posted.. parents experiencing it firsthand is probably the most helpful information you will find. - [R_005]*

One individual expressed a desire to be connected to other families with Rett syndrome in close physical proximity, but was limited due to geographic location:

- *I'm from Puerto Rico, right? And in here, I don't know anybody that has Rett. I know there are kids, you know children that have sisters and brothers. I don't know anybody. I did look on Facebook or Instagram or something for like a group. - [R_003]*

2.5 Discussion

Through these interviews with parents of children diagnosed with Rett syndrome, it was shown that parents experienced a range of emotions and conveyed a variety of informational needs during the disclosure process to their unaffected children. There was also an undeniable impact of the diagnostic odyssey that all families endured. As shown

in our research, these conversations with unaffected siblings were ongoing and varied in nature.

2.5.1 Diagnostic Odyssey

It was apparent that parents face many challenges once learning of a diagnosis of Rett syndrome and the time leading up to the diagnosis being identified. All families interviewed described seeing a number of specialists before arriving at the diagnosis. Some were met with doubt and difficult interactions with healthcare providers, which contributed another layer to the challenges these families endured. These challenges and obstacles are consistent with what other families with rare diseases have experienced. It is well established in the literature that the diagnosis of a rare disorder is dependent on the clinician's particular knowledge and experience, and can prove to be a particular challenge when the clinical presentation is variable (Fehr et al., 2010). As with many rare disorders, families often experience a variety of emotions, such as frustration, during the process of reaching a diagnosis, particularly in the case of Rett syndrome (Lim et al., 2011).

These complex emotions were apparent during the course of these interviews, which adds to the emotional complexity of disclosure conversations with unaffected siblings. It is important for providers to be aware of the nuances of the diagnostic odyssey when providing care for families diagnosed with Rett syndrome and facilitating these conversations. Awareness of Rett syndrome and additional training in neurodevelopmental disorders may help to expedite these diagnostic processes and help to ameliorate some of the emotional challenges faced by these families.

2.5.2 Ongoing Conversations with Siblings

As mentioned previously, many participants had ongoing conversations with their unaffected children about the diagnosis of Rett syndrome. Many stated that these conversations about Rett syndrome have been continuing within the family, and as younger children age, more information is shared. This can be a key point when providing a new diagnosis of Rett syndrome to a family in order to set realistic expectations of these conversations with unaffected children. It can be important for families to know that they may frequently have these conversations and they may benefit from being provided information deemed to be age-appropriate for children, as has been suggested as a strategy employed by other parents with similar experiences (Hunter, 1999).

Many participants stated feeling adequately prepared to have these conversations with their unaffected children. However, when participants were asked what information they would have liked to have known before disclosing the diagnosis to their unaffected children, many stated they would have liked to have a more accurate depiction of the clinical features of Rett syndrome and the variability of the condition. This may possibly identify a crucial informational need at the time of diagnosis. Without this information, the conversations that are had with siblings and the delivery of the diagnosis may be impacted. It is important for providers to emphasize that even within the typical Rett syndrome clinical spectrum, not all individuals will exhibit every feature. This finding echoes previous literature that establishes the need for accurate information during initial disclosure of a diagnosis. When parents have greater access to information, they are

better equipped to cope and handle negative feelings they may experience, such as guilt and fear, when a child is affected by a genetic condition (Metcalfe et al., 2008).

Ultimately, the conversations between parents and unaffected children varied from family to family. Some children had numerous questions and concerns for the well-being of their sister. Other children were indifferent when hearing the news of the diagnosis and were quick to accept the information. There is no doubt that age plays a role in the understanding and processing of the diagnosis, but providers and parents must keep in mind that parents know their children best and know what is appropriate for their children and what they are able to handle.

2.5.3 Parent and Sibling Emotions

As shown in the excerpts from the interviews, both parents and siblings expressed a variety of emotions. Participants stated feeling negative emotions during the disclosure process, including pity, sadness, and guilt. Many of the conversations explored these emotions in the context of the unaffected sibling with a number of parents alluding to the concept of the loss of a "normal life" for the unaffected siblings.

A number of participants struggled emotionally due to the challenging nature of making the information understandable and digestible to the unaffected sibling. Parents noted that they wanted to make the diagnosis understandable to their children. This finding is suggestive that ameliorating some of the conversational challenges parents may face may alleviate some of these emotional burdens felt during the conversation.

When considering the sibling's emotions and reaction to the diagnosis of Rett syndrome for their sister, it is important to keep in mind that these reported emotions and reactions are the participant's recollections and own perception of these feelings. This

study did not explore the unaffected children's direct recollection of these conversations and their reactions to their sister's diagnosis. The findings of this study were consistent with literature showing that having a sibling affected with a neurodevelopmental disorder can affect quality of life (Lamsal & Ungar, 2021).

2.5.4 The Importance of Support Groups and Informational Resources

Considering that all participants cited the utility and helpfulness of three key resources, healthcare providers delivering a new diagnosis of Rett syndrome should consider including IRSF, the Rett Syndrome Handbook, and links to parent support groups to facilitate a smoother parental disclosure to unaffected siblings.

The emotional nature of the diagnostic odyssey is also deeply intertwined with the significance of these support resources, particularly social media. Our participants emphasized the utility of social media support groups as a way to aid in not only the facilitation of the disclosure conversations, but as a source of emotional reprieve and information surrounding the diagnosis. Studies of families coping with a rare disease have shown that there are benefits of connecting with other individuals and families that share similar medical experiences (Deuitch et al., 2021). These findings further emphasize the significance of social media support groups as a valuable tool within the Rett syndrome community.

As the landscape for Rett syndrome and available treatments evolves, it is important to be cognizant of how these treatments may affect these experiences, conversations, and family dynamics moving forward. However, these narratives can serve as a basis of facilitation if asked the question "How do I tell my other children?". This study also serves as a reminder of the care we should be providing for each family

with a new Rett syndrome diagnosis while characterizing some of the conversations had with unaffected siblings of children with Rett syndrome.

2.5.5 Limitations

Our study involved a relatively small sample size, with only five individuals being interviewed. All individuals interviewed had at least some education beyond high school, which may suggest that all parents had some health literacy. Information obtained and experiences may differ between individuals who may have lower health literacy. Additionally, it is significant to note that these interviews recorded the participants' perceptions and interpretations of their unaffected children's reactions. Assessing these conversations by interviewing the unaffected sibling directly regarding their experiences might capture more accurate data surrounding the unaffected sibling's experience.

2.5.6 Suggestions for further research

Through our research, we attempted to identify the emotions and reactions of unaffected siblings through the perspectives of parents. However, there is no specific literature exploring siblings' preferences and needs during a Rett syndrome diagnosis. Our findings could serve as potential insight and as a model for future questions exploring those children's reactions. Additionally, further assessing these conversations over time may further explore how these conversations naturally evolve as many parents cited having ongoing conversations and may capture these experiences as they unfold. Another potential suggestion for future research is repeating this study with assessing the disclosure process for unaffected siblings of children diagnosed with atypical Rett syndrome. As the phenotype differs between atypical Rett and classic Rett syndrome, it is

important to assess similarities and differences within conversations had between parents and unaffected siblings of children with Rett syndrome.

CHAPTER 3

CONCLUSION

This study aimed to assess some of the procedural and emotional challenges parents face when discussing a diagnosis of Rett syndrome for their child with their unaffected children and identify informational and emotional needs of these parents. Four themes emerged as a result of our semi-structured interviews: the diagnostic odyssey, the ongoing nature of conversations, the emotional nature of the disclosure process, and the significance of support and informational resources. The results of this study were consistent with previous literature exploring the challenges that parents of children with neurodevelopmental diseases face, with all parents having faced the difficulty of a diagnostic odyssey. Many described the conversations as ongoing, with many disclosing the diagnosis while the unaffected child was young, and continuing to discuss more information as the unaffected sibling got older. Considering the emotional nature of these conversations and prior research illustrating that access to information better equips parents to cope with various negative emotions surrounding a genetic diagnosis, we suggest that providers making diagnoses of Rett syndrome provide access to support resources such as IRSF, the Rett Syndrome Handbook, and online patient support groups, most specifically those found on social media. Not only will this potentially alleviate some emotional burden faced during the diagnostic odyssey, but these resources can aid in facilitating these discussions with other family members. This study provided personal experiences explored by parents of daughters diagnosed with Rett syndrome and their

unaffected siblings, which providers can use to help families navigate this nuanced communication.

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APPPENDIX A

INVITATION TO PARTICIPATE: ONLINE QUESTIONNAIRE

Dear Parent of a Child with Rett Syndrome,

My name is Rachel Nicely and I am a graduate student in the Genetic Counseling Training Program at the University of South Carolina. I am conducting a research study as part of the requirements of my degree in Genetic Counseling, and I would like to invite you to participate.
I am examining the parental disclosure process to unaffected siblings of children with Rett syndrome. If you decide to participate, you will be asked to complete a preliminary online survey with questions about your background, your first name, a telephone number that you may be contacted, and the hours in which I may contact you to schedule an interview. Interviews will be conducted via telephone and then will be recorded and transcribed. Audio recordings will remain private and confidential.

During the interviews, I hope to gather information about your child's diagnosis of Rett syndrome and how you discussed this with your other child or children. All responses gathered from both the preliminary survey and interviews will be kept confidential. The results of this study might be published or presented at academic meetings; however, participants will not be identified.

Those eligible to participate include parents of at least two children, with one being diagnosed with Classic Rett Syndrome, and at least one unaffected child. Those eligible must be 18 years or older, live in the United States, and must be able to read, write, and speak English. Please note that we aim to interview only one parent/guardian per family. If you believe that your child's other parent/guardian has taken this survey, we ask that you do not complete this survey.

Your participation in this research is voluntary. By completing the survey, you are consenting that you have read and understood this information. At any time, you may withdraw from the study by exiting the survey.

Thank you for your time and consideration to participate in this survey and interview. Your responses may help healthcare providers better facilitate parent-child

communication within the Rett Syndrome community. If you have any questions regarding this research, you may contact either myself or my faculty advisor, Amy Wardyn, MS, CGC, using the contact information below. If you have any questions about your rights as a research participant, you may contact the Office of Research Compliance at the University of South Carolina at (803)-777-7095.

Thank you,

Rachel Nicely
Principal Investigator
Genetic Counseling M.S. Candidate
University of South Carolina
703-919-6546

Amy Wardyn, MS, CGC
Faculty Advisor
Genetic Counseling Program
University of South Carolina
Amy.Wardyn@uscmed.sc.edu

APPPENDIX B

ONLINE QUESTIONNAIRE

Do you consent to participate?

- ○ Yes (1)
- ○ No (2)

Skip To: End of Survey if "Do you consent to participate?"= No

End of Block: Introduction

Start of Block: Eligibility Criteria

Q1
What is your relationship to the individual with Rett syndrome?

- ○ Parent (1)
- ○ Other (2) _____

Q2 Do you have other children who are not diagnosed with Rett syndrome?

- ○ Yes (1)
- ○ No (2)

Skip To: End of Survey If "Do you have other children who are not diagnosed with Rett syndrome?" = No

Q3 Please note that we only intend to interview one parent/guardian per family. To your knowledge, has your child's other parent taken this survey?

- ○ No (1)
- ○ Yes (2)

Skip To: End of Survey If "Please note that we only intend to interview one parent/guardian per family. To your knowledge, h..". = Yes

Q4 Is your child with Rett syndrome male or female?

- ○ Female (1)
- ○ Male (2)

Skip To: End of Survey If "Is your child with Rett syndrome male or female?" = Male

Q5 Is your child diagnosed with classic/typical Rett syndrome?

- ○ Yes (1)
- ○ No (2)

Skip To: End of Survey If "Is your child diagnosed with classic/typical Rett syndrome?" = No

Q6 Are you over the age of 18 and can read/speak English?

- ○ Yes (1)
- ○ No (2)

Skip To: End of Survey If "Are you over the age of 18 and can read/speak English?" = No

End of Block: Eligibility Criteria

Start of Block: Block 1

Q7 How old was your child when she was diagnosed with Rett syndrome?

_____

Q8
Who diagnosed your child with Rett syndrome?

- ○ Neurologist (1)
- ○ Geneticist (2)
- ○ Genetic Counselor (3)
- ○ Pediatrician (4)
- ○ Developmental Pediatrician (5)
- ○ Unsure (6)
- ○ Other (Please Specify) (7) _____

Q9 Has your child had genetic testing (i.e. through a laboratory) to diagnose Rett syndrome?

- ○ Yes (1)
- ○ No (2)
- ○ Unsure (3)

Q10 When your child was diagnosed with Rett syndrome, how many other children did you have? (Enter number below)

_____

Q11 What ages were your other children at the time of your child's diagnosis? Please list each child's age separated by a comma (ex. 5,7).

_____

Q12 What age were you at the time of your child's diagnosis?

_____

Q13 What is your current age?

_____

Q14 What is your race/ethnicity? Check all that apply

- [ ] Caucasian (1)
- [ ] African American (2)
- [ ] Hispanic or Latino (3)
- [ ] Native American or American Indian (4)
- [ ] Asian or Pacific Islander (5)
- [ ] Prefer not to respond (6)
- [ ] Other (7) _____

Q15 What is your highest degree of education?

- ○ Less than high school (1)
- ○ High school diploma or equivalent (2)
- ○ Some college (3)
- ○ 2 year degree (4)
- ○ 4 year degree (5)
- ○ Professional degree (6)
- ○ Doctorate (7)
- ○ Prefer not to respond (8)

Q16 What is your occupational status?

- ○ Employed (1)
- ○ Unemployed (2)
- ○ Stay-at-home parent (3)
- ○ Student (4)
- ○ Retired (5)
- ○ Prefer not to respond (6)
- ○ Other (please specify) (7) _____

Q17 What is your marital status?

- ○ Single (1)
- ○ Married (2)
- ○ Divorced/separated (3)
- ○ In a relationship but not married (4)
- ○ Prefer not to respond (5)

End of Block: Block 1

Start of Block: Thank you for your interest in participating in our study!

Q18 Thank you for your interest in participating in our study! Please provide your contact information below so that we may contact you for an interview. The interview will last up to an hour and a half in duration, but may vary. In the interview, you will be asked about how you talked about your child's diagnosis of Rett syndrome with their other sibling(s). Some topics discussed will include your/your child's emotional response, how you explained the diagnosis, and what information aided you in the process. Interviews will be conducted via telephone and will be recorded and transcribed. Audio recordings will remain private and confidential, and will be destroyed upon completion of transcription.

Please provide your first name.

_____

Q19 Please provide a telephone number that we can reach you at to schedule an interview

_____

Q23 Please indicate times and days in which we may call you to schedule an interview

_____

End of Survey: Thank you for your interest in participating in our study!

APPPENDIX C

TELEPHONE INTERVIEW CONSENT

My name is Rachel Nicely and I'm a genetic counseling student at the University of South Carolina. My current study aims to examine the parental disclosure process to unaffected siblings of children with Rett syndrome. During the course of this semi-structured interview, you will be asked to share your experiences about how you talked to your unaffected child or children about your daughter's diagnosis of Rett syndrome. Some questions will ask you to talk about your level of preparedness, the emotions you felt, questions your child asked, and any other topics you wish to share about this process. I expect this interview to last at least 30 minutes, but may be up to an hour and a half depending on our conversation. The entirety of this interview will be recorded and transcribed. The recording will be destroyed immediately following transcription. The results of this study might be published or presented at academic meetings; however, participants will not be identified. Your participation in this research is voluntary. At any time, you may withdraw from this study by informing me that you no longer wish to participate in the study.

Do you have any questions before we begin the interview?

Do you consent to participate?

APPPENDIX D

SEMI-STRUCTURED INTERVIEW QUESTIONS

1. Can you tell me about when your child was first diagnosed with Rett syndrome?
2. Can you tell me about when you talked to XXX's siblings about the diagnosis of Rett syndrome?
3. Did you feel prepared to talk to your child about their sibling's diagnosis?
4. Did you receive information from anyone or any resource on how to talk to your unaffected child about your affected child's diagnosis of Rett syndrome?
5. Did you find the information you were given helpful?
6. What information did you find most helpful to prepare you to talk to your unaffected child about your other child's diagnosis of Rett syndrome?
7. Is there any information you would have liked to know before talking to your other children about your child's diagnosis of Rett syndrome?
8. Please describe the emotions that you felt when you disclosed the diagnosis to your other unaffected children.
9. How did you cope with these emotions?
10. How did your unaffected child react to the diagnosis?
11. How do you know they felt that emotion?
12. Was their behavior affected?
13. How did they cope with these emotions?
14. Did your unaffected children ask questions about your child's diagnosis? If so, what were they?
15. How long after the diagnosis did you wait to tell your unaffected children?
16. Would you have chosen to wait to disclose?
17. Have you discussed the inheritance of Rett syndrome to your unaffected child?
18. Is there anything else that you would like to share that we have not already discussed?