Hidden on the X:
Psychosocial Implications of
Ornithine Transcarbamylase Deficiency in Female Carriers

Master's Thesis

Presented to

The Faculty of the Graduate School of Arts and Sciences
Brandeis University
Graduate Program in Genetic Counseling

Judith Tsipis, PhD, Advisor

In Partial Fulfillment
of the Requirements for the Degree

Master of Science
in
Genetic Counseling

by

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May 2016

ACKNOWLEDGEMENTS

Many thanks to my wonderful thesis committee members: Cynthia Le Mons, Stephanie Coury, MS, CGC, Susan Waisbren, PhD, and Judith Tsipis, PhD.

Thank you also to the Brandeis Genetic Counseling program and faculty including Judith Tsipis, Gretchen Schneider, Gayun Chan-Smutko, Liz Cross, and Missy Goldberg. Thank you to my classmates for your endless support and kindness. And lastly, my deepest thanks to my family and fiancé for everything you do for me.

ABSTRACT

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Psychosocial Implications of
Ornithine Transcarbamylase Deficiency in Female Carriers

A thesis presented to the Graduate Program in Genetic Counseling

Graduate School of Arts and Sciences
Brandeis University
Waltham, Massachusetts

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Ornithine transcarbamylase deficiency (OTCD) is an inborn error of metabolism and the most common urea cycle disorder. Affected individuals may experience hyperammonemia, which can be associated with headaches, disorientation and nausea. Sustained hyperammonemia can cause neurodevelopmental disability, coma, and even death. OTCD is an X-linked disorder that affects both males and females with a spectrum of severity. Males may present with hyperammonemia as an infant while others develop symptoms later in life. Female carriers may or may not ever have symptoms, and many learn of their carrier status with the birth of an affected infant. Our study aimed to identify the specific needs and concerns of women who are known to be OTCD carriers and to learn how they were initially diagnosed. In this study we used an anonymous online survey with quantitative and qualitative questions. We recruited female OTCD carriers who were 18 years of age or older through the National Urea Cycle Disorders Foundation (NUCDF). Thirty-four women completed the survey. We found that most participants were blindsided by their OTCD carrier diagnosis, and that in 70.6% of respondents,

the diagnosis followed the illness or death of an affected child. Our respondents have had many misconceptions about the diagnosis, the genetics of OTCD, and the risks associated with it. Our study further demonstrates that OTCD carriers have unique emotional and physical challenges, and would benefit from additional resources and support from genetic counselors and other healthcare providers, especially at the time of diagnosis. The findings of this study will promote awareness of OTCD and better inform healthcare providers of its implications for female carriers.

Key Words: Urea cycle disorder, ornithine transcarbamylase deficiency, OTC, OTCD, partial OTCD, carrier, heterozygote, genetic counseling

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INTRODUCTION

Ornithine transcarbamylase deficiency (OTCD) is an X-linked metabolic disease involving disruption of the urea cycle and is the most common of the urea cycle disorders. The major function of the urea cycle is to convert ammonia, a toxic byproduct of protein metabolism, into urea, a less toxic substance which can be excreted in the urine. Ornithine transcarbamylase plays an essential role in the urea cycle, converting ornithine and carbamyl phosphate to citrulline. In OTCD, mutations in the *OTC* gene are associated with a decrease or absence of ornithine transcarbamylase enzyme activity and a disruption of the urea cycle. This leads to a buildup of ammonia in the blood, known as hyperammonemia. Prolonged hyperammonemia has been linked to a range of neurological and physical effects, including brain damage, coma and death. Symptoms can also include headaches, disorientation, nausea and vomiting (Tuchman, 1992).

OTCD can be a life-threatening and unpredictable disease with a wide range of phenotypes, even within the same family. Males with severe mutations in the *OTC* gene typically present with symptoms very early in life and face high mortality rates without prenatal or early neonatal diagnosis. Males with less severe mutations may present with symptoms at any age (McCullough et al., 2000). Female carriers of *OTC* mutations can be asymptomatic their entire lives, or may become symptomatic after many years of being symptom-free. In female carriers, this range of phenotypes can be attributed to differences in X-inactivation, mutation severity, and environmental factors (Batshaw, Msall, Beaudet, & Trojak, 1986).

There are many possible hyperammonemia triggers in female OTCD carriers, including surgery (Chiong, Bennetts, Strasser, & Wilcken, 2007), certain diets and foods (Ben-Ari et al., 2010), pregnancy, and delivery (Mendez-Figueroa, Lamance, Sutton, Aagaard-Tillery, & Van den Veyver, 2010) . Treatment and management to avoid hyperammonemia is therefore challenging, so a team of professionals including a metabolic specialist, a nutritionist, a genetic counselor, and many others, is typically required for both carriers and affected individuals (Urea Cycle Disorders Consortium (UCDC) of the Rare Disease Clinical Research Network (RDCRN)). Longterm management involves close monitoring of blood ammonia levels and regulation of protein anabolism and catabolism by controlling intake of protein to minimize ammonia production, and ensuring adequate calorie intake to avoid breakdown of musculoskeletal tissue (catabolism) and subsequent increased production of ammonia. Most individuals with OTCD require nitrogen scavenging medications such as sodium benzoate and sodium phenylbutyrate. In more severe cases liver transplantation may be considered, which is curative for the condition. Treatment during an acute hyperammonemic episode to reduce ammonia levels requires use of intravenous nitrogen scavengers as well as dextrose and lipids to stop catabolism. Catastrophic ammonia levels require intervention with dialysis or hemofiltration. Quick action in emergency situations leads to more favorable outcomes (Saudubray, Berghe, & Walter, 2012; Urea Cycle Disorders Conference group).

Living as an OTCD carrier, symptomatic or not, presents many unique challenges. Existing literature focuses mostly on the phenotype of OTCD carriers, their clinical presentation as well as on possible treatments and newborn screening for OTCD. A study carried out by Cederbaum *et al* in 2001 investigated the psychosocial issues and coping strategies in families with children with urea cycle disorders. The most significant stressors involved finances, dietary

restrictions and fear of a child's death (Cederbaum et al., 2001). Another study focused on stressors in parents of children with a wide range of biochemical genetic disorders. The results of this study demonstrated that parental stress was impacted positively by social support as well as the higher functioning and health of the child (Waisbren, Rones, Read, Marsden, & Levy, 2004). A study examining reproductive decision-making in parents of children with metabolic disorders found that the majority of respondents were interested in future prenatal diagnosis for the metabolic disorder, and just over 40% had taken measures to prevent another affected pregnancy (Read, 2002). Though the literature contains a few studies highlighting potential issues and concerns for OTCD carriers, there are currently no published studies looking specifically into the psychosocial issues associated with being a female OTCD carrier.

The purpose of this study was to identify and explore the specific needs and concerns of women with OTCD and asymptomatic carriers of OTCD. The study specifically focused on:

- Circumstances surrounding the OTCD carrier diagnosis,
- Symptoms and treatments for OTCD,
- Positive or negative effects on relationships with partners, family, and faith,
- Impacts on reproductive decision making,
- Overall mental and physical health, and
- Social support systems.

Genetic counselors and other healthcare providers who work closely with individuals with metabolic disorders such as OTCD can utilize information from this study to help understand the issues related to being a carrier and to help ensure interdisciplinary support is arranged for those with a new diagnosis. It is important for individuals providing this support to understand the unique and evolving challenges faced by female OTCD carriers. This knowledge

will undoubtedly allow for better counseling, education, and coordination of care. The results of this study will fill a gap in the literature and inform the medical community on the specific needs of this understudied population.

METHODS

Study Design

We invited women who were known carriers of OTCD and members of the National Urea Cycle Disorders Foundation (NUCDF) to participate in an online anonymous survey. We asked open and closed questions about demographics, the respondents' experiences with receiving a diagnosis, and the impacts of the diagnosis on their lives. Our goal was to gain insight into the lives of female carriers of OTCD. It was our hope that the knowledge gained from the study would be valuable to others affected by OTCD, genetic counselors and other healthcare professionals, and would help stimulate more research.

Sample and Recruitment

The Brandeis University Committee for Protection of Human Subjects approved this study. The recruitment notice and survey link were distributed through the National Urea Cycle Disorders Foundation (NUCDF) website and via an email blast to a list of OTCD families and carriers who are members of the NUCDF. Only females who were over the age of 18 and who were known carriers of OTCD were eligible to participate in the survey. See appendix A for a sample survey invitation email and appendix B for the recruitment notice. Refer to appendix C for the letter of support from NUCDF.

Data Collection

Using Qualtrics®, we created and distributed an anonymous online survey. The survey was available from January 22, 2015 through February 10, 2015. The survey contained several types of questions, including multiple choice, Likert scale, and open-response. The first question of the survey asked the respondent if she was a known carrier of OTCD, and only those who indicated that they were carriers were allowed to continue with the survey. The remaining questions were organized into sections. These sections covered the carrier diagnosis, symptoms (if any), family structure and family history, perceived impacts of being a carrier, support systems, and demographics. Participants also were asked to answer questions from the Patient Reported Outcomes Measure Information System (PROMIS) Adult Global Health Short Form questionnaire, a validated questionnaire originally developed by the National Institutes of Health (NIH), which focused on mental and physical health (Hays, Bjorner, Revicki, Spritzer, & Cella, 2009). The full survey tool is included in appendix D.

Data Analysis

A total of 46 respondents began our survey. Thirty-four surveys were completed or mostly completed. The data were uploaded to IBM SPSS Statistics Version 22 and Microsoft Excel and analyzed. Microsoft Excel was used to analyze open-ended responses. This analysis involved identifying key words and coding, then sorting quotes into themes. The relationships between variables were explored using univariate, bivariate and multivariate statistical analyses. We used the established scoring system for the NIH PROMIS questions to calculate mental and physical health scores for each respondent. Instructions for scoring PROMIS are included in appendix E.

Raw and analyzed data were stored on a password-protected personal computer and on an encrypted, password-protected external hard drive. The Genetic Counseling Program at Brandeis University keeps consent documents for 5 years in a locked filing cabinet.

RESULTS

Demographics

The survey was emailed to 141 individuals through the National Urea Cycle Disorders Foundation (NUCDF). In total, 46 participants began the survey and 34 completed a majority of the survey questions, resulting in a response rate of approximately 24.1% (34/141). A total of 33 answered the demographic questions. All respondents were assumed to be female due to the inclusion criteria.

Respondents were between the ages of 27 and 70 years, with an average age of 44 years. Approximately 94% of participants reported that they were Caucasian. Only 2 individuals stated that they were a different ethnicity; one respondent indicated that she was Asian, and one indicated that she was from Argentina.

The majority of participants, 63.6%, reported that they had not gone beyond receiving an Associate's degree. Approximately 18.2% had a Bachelor's degree, 18.2% had a Master's degree, and none of the respondents reported having education above Master's level.

Table 1 - Highest education level

Education level (n=33)	Respondents	Percent
Some high school or below	1	3.0%
High school degree or GED	4	12.1%
Some college	11	33.3%
Associate's degree	5	15.2%
Bachelor's degree	6	18.2%
Master's degree	6	18.2%
Professional degree	0	0.0%
Doctorate degree	0	0.0%

When asked about relationship status, the majority of respondents indicated that they were currently married, 72.7%, and 12.1% said that they were divorced.

Table 2 - Current relationship status

Relationship (n=33)	**Respondents**	**Percent**
Divorced	4	12.1%
In a relationship	1	3.0%
Never married	1	3.0%
Now married	24	72.7%
Separated	1	3.0%
Single	2	6.1%
Widowed	0	0.0%

We inquired about where participants lived and asked them to select the corresponding time zone. Respondents lived in areas throughout the country and around the world, but the majority of participants reside in the United States, 75.8% (n=33). Of the 25 individuals in the United States, 36.0% reported living within the Eastern time zone (EST), and 32.0% reporting living in the Pacific time zone (PST). Two participants lived in Canada (6.1%), one lived in Australia (3.0%), and five reported that they lived in Argentina (15.2%).

Table 3 - Location

Location (n=33)	**Respondents**	**Percent**
Eastern time zone (US)	9	27.3%
Central time zone (US)	5	15.2%
Mountain time zone (US)	3	9.1%
Pacific time zone (US)	8	24.2%
Alaska	0	0.0%
Hawaii	0	0.0%
Canada	2	6.1%
Australia	1	3.0%
Argentina	5	15.2%

Carrier Diagnosis

The average age of carrier diagnosis for respondents was 34 years, with a range of 5 to 63 years of age. Participants learned of the diagnosis in a variety of ways, but most were told by a physician (26.5%) or a geneticist (58.8%) (n=34). One participant reported that she was told by her mother.

Twenty-five women, or 73.5% of the total respondents (n=32), indicated that they were diagnosed after one of their children became ill or passed away. Four said that they were

diagnosed following the diagnosis of another family member, and only three were the first in the family to be diagnosed. Most participants explained that the diagnosis came as an overwhelming shock.

Respondent #12, a woman who was diagnosed after her newborn son became sick, wrote, “We were overwhelmed, scared, anxious. Not only were we new young parents, our son was very ill, in need of a liver transplant... and we just found out I was a carrier.”

Respondent #31, whose son suddenly became hyperammonemic in his 20s, wrote, “[We had] genetic testing done after my son had hyerammonia [*sic*] and now has a brain injury. He had 24 years of no problems. OTC reared its ugly head and ruined my son and I feel I have let him down.”

Respondent #29’s diagnosis came after a sudden and intense illness in one of her siblings. She wrote, “When my younger brother was admitted to hospital with an 'illness' we had no idea what was install [*sic*] for us for the next 12 months. My brother was admitted to ICU, and after a lot of testing it was confirmed that he had OTC. He was getting th [*sic*] best treatment but he was in a coma for a month and ha [*sic*] about 7 head/brain operations, he was moved to a ward and was there for 6 months. He is now in a rehab center and is getting daily rehab from his brain injury.”

The majority of participants indicated that the person informing them of the diagnosis delivered the news with a supportive attitude. Having compassion (32.4%) and kindness (44.1%), delivering good advice on how to manage symptoms (32.4%), having optimism or hope about future quality of life (11.8%), and using easy language (52.9%) were considered positive approaches. Responses are shown in Table 4.

When learning of the diagnosis of being a carrier of OTCD, respondents indicated that they felt many different emotions, the majority of which were negative. These responses are illustrated in Table 5.

TABLE 4: How would you describe how the news was first given to you?

	Respondents (n=34)	Percent
In terms that were difficult for me to understand	0	0.0%
With no advice about how to manage the possible symptoms	6	17.6%
With pessimism about my future quality of life	1	2.9%
With pity	0	0.0%
Without any emotion	4	11.8%
With compassion	11	32.4%
With good advice about how to manage the possible symptoms	11	32.4%
With kindness	15	44.1%
With language and terminology I was able to understand	18	52.9%
With optimism and hope about my future quality of life	4	11.8%
With sympathy	3	8.8%
	Negative approach	
	Positive approach	

TABLE 5: How did you feel when you first received the news that you are a carrier?

	Respondents (n=34)	Percent
Afraid	6	17.6
Angry	8	23.5
Anxious	8	23.5
Confused	6	17.6
Depressed	8	23.5
Guilty	10	29.4
Helpless	2	5.9
Isolated	7	20.6
Overwhelmed	11	32.4
Pessimistic about my future quality of life	3	8.8
Sad	9	26.5
Grateful	4	11.8
Optimistic about my future quality of life	0	0
Relieved	3	8.8
Supported	2	5.9
Understood	3	8.8
Well-advised	6	17.6
Other	*8*	*23.5*
	Negative emotion	
	Positive emotion	

Symptoms of OTCD

Thirteen participants (38.2%) indicated that they have experienced symptoms associated with being an OTCD carrier, while nine (26.5%) said that they had not and twelve (35.3%) were unsure (n=34). For the women who indicated that they have experienced symptoms (n=13), average age of onset was 12 years, with a range of 5 years of age to 22 years of age. Participants described a wide variety of symptoms, but most commonly reported having headaches (92.3%).

TABLE 6: Symptoms of OTCD in Carriers

Symptom (n=13)	Respondents	Percent
Confusion	7	53.8
Difficulty remembering some things	8	61.5
Disorientation	5	38.5
Elevated ammonia level	6	46.2
Feeling tired	9	69.2
Headaches	12	92.3
Irritability	7	53.8
Nausea	9	69.2
Protein aversion	8	61.5
Vomiting	8	61.5
Other	4	30.8

Respondent #18 shared a story about the severity of her symptoms, “I started having grand mal seizures during my pregnancy and was put on seizure meds. I became lethargic and was that way for almost a week when my husband drove me to th [*sic*] ER. They had to do an emergency C-section and I slipped into a coma. I went into liver and kidney failure in the coma. I was in the coma for 8 days”

While 25% of symptomatic participants reported that they had not had any treatment for their symptoms, the remainder reported receiving numerous treatments for the manifestations of OTCD. The majority relied on low protein diet (58.3%) and/or L-citrulline supplementation (50.0%).

TABLE 7: Treatments for symptoms of OTCD

Treamtent (n=12)	Frequency	Percent
Ammonia scavengers	3	25.0%
Arginine	3	25.0%
Citrulline	6	50.0%
Low protein diet	7	58.3%
Specialty foods/ formula	0	0.0%
I have not had any treatments	3	25.0%

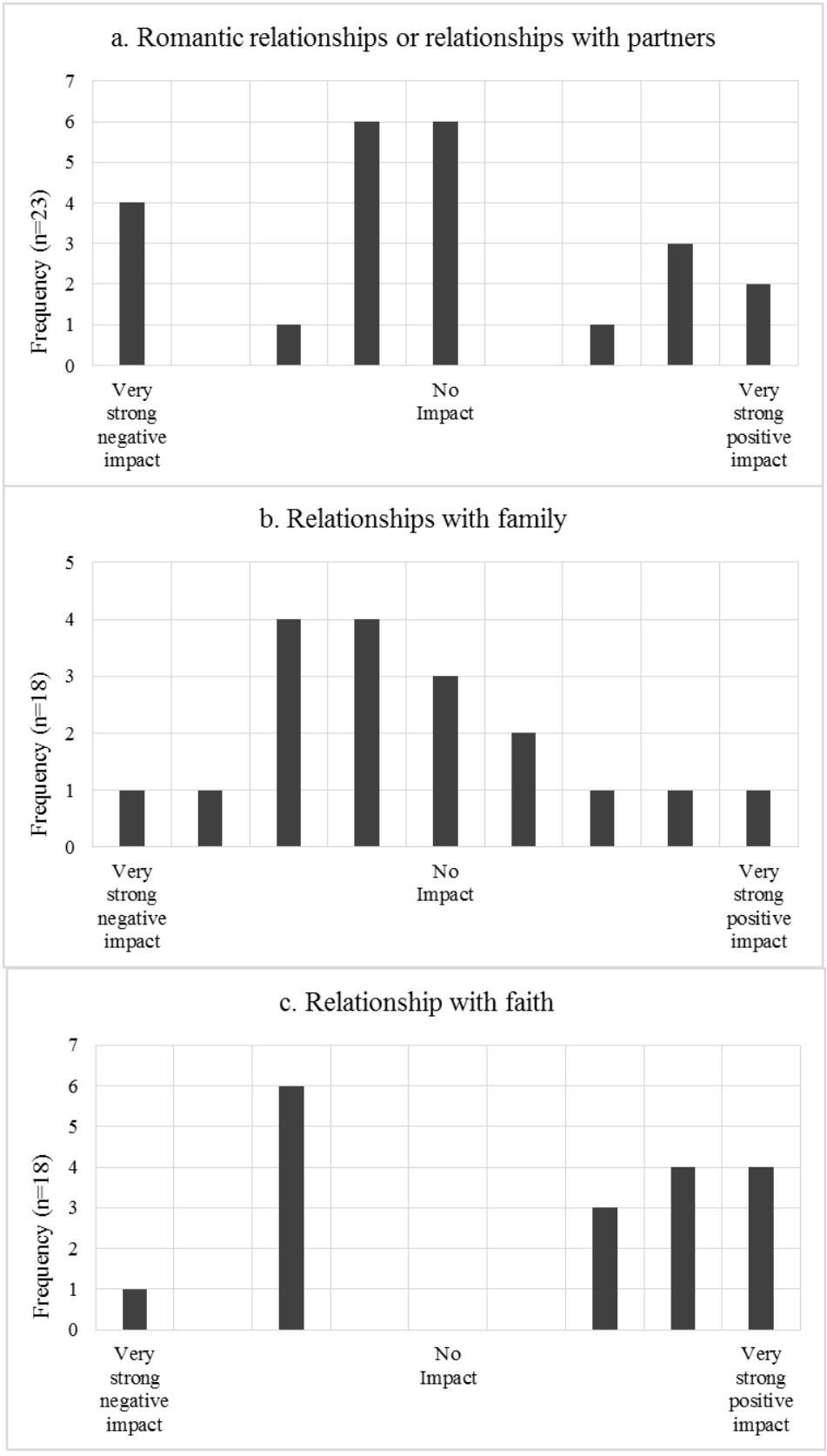
Impacts of Being a Carrier

Survey participants showed that being a carrier of OTCD impacts many aspects of life. Respondents indicated that romantic relationships or relationships with partners were impacted variably by the diagnosis (n=23); some respondents experienced little to no impact, while some respondents experienced a strong positive effect, and others experienced a strong negative effect. Respondent #31 wrote, “I know that I am to blame for the damage it has done to my son, I just don't have any more love to give to my husband [*sic*] I need all my strength for my son and my daughter who also has OTC.”

Relationships with family members also were impacted variably. Respondents reported a wide range of effects on these relationships (n=18), but the majority experienced a slight negative impact or no impact at all. Respondent #20 wrote about issues with her family members, “Everyone seems to thik [*sic*] I'm the only one who's a carrier, and they think I'm being overly-cautious for wanting everyone else to get tested. The death of my son has also made friends and family hesitant to share their pregnancies with me. This only made me feel worse about my situation to realze [*sic*] that others feel uncomfortable.”

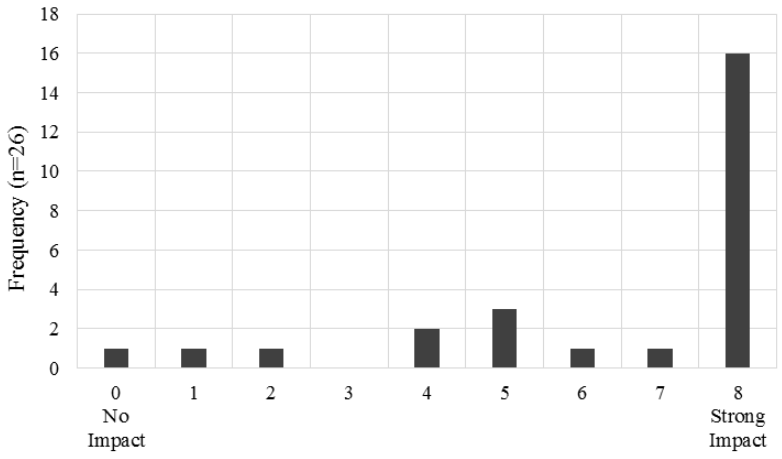
All respondents experienced an effect on relationships with faith or religion (n=18), and most indicated that the impact was either strongly negative or strongly positive. Respondent #31 wrote, “My religion has become my strength, I don't blame God for doing this to my son, but I just can't understand why he thinks I am strong enough to keep going everyday [*sic*].” Respondent #20 had an opposite experience, writing, “At first, it caused me to question everything I believe in, but now a year later after burying my son, I find myself seeking a relationship with God and a desire to understand the life after this one. After all, it's my only chance at being with my son agin [*sic*]. I HAVE to beleive [*sic*] in order to keep my sanity.”

FIGURE 1: Impacts of being a carrier



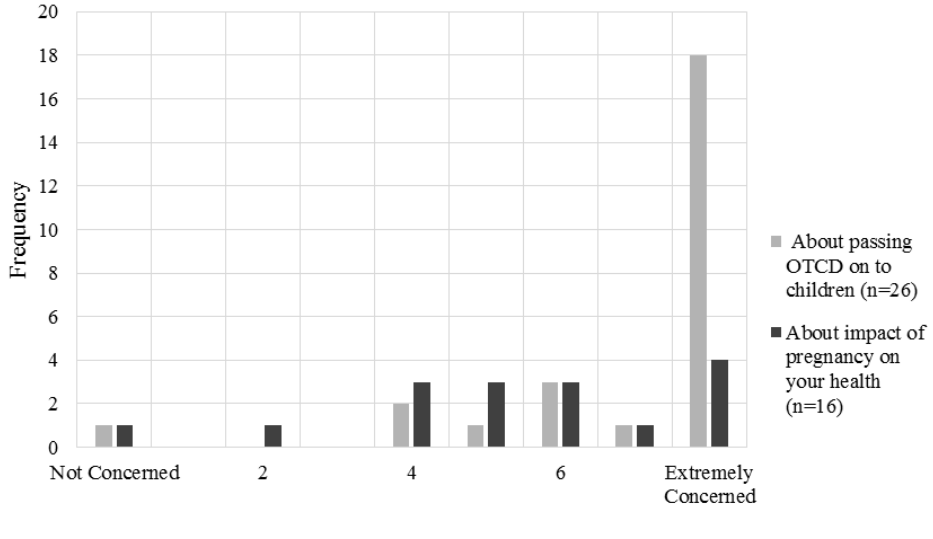
The data showed that being an OTCD carrier very strongly impacted the participants' decisions to have children. Respondent #30 said, "It didn't stop me, I just wanted to know if my child was gene positive so we could prepare accordingly." The diagnosis seemed to be a greater burden for Respondent #20, who wrote, "The whole talk of getting pregnant has lost it's [*sic*] joy, fun, excitement. It feels stressful and it's a source of anxiety and tension."

FIGURE 2: Impact of OTCD diagnosis on decisions to have children

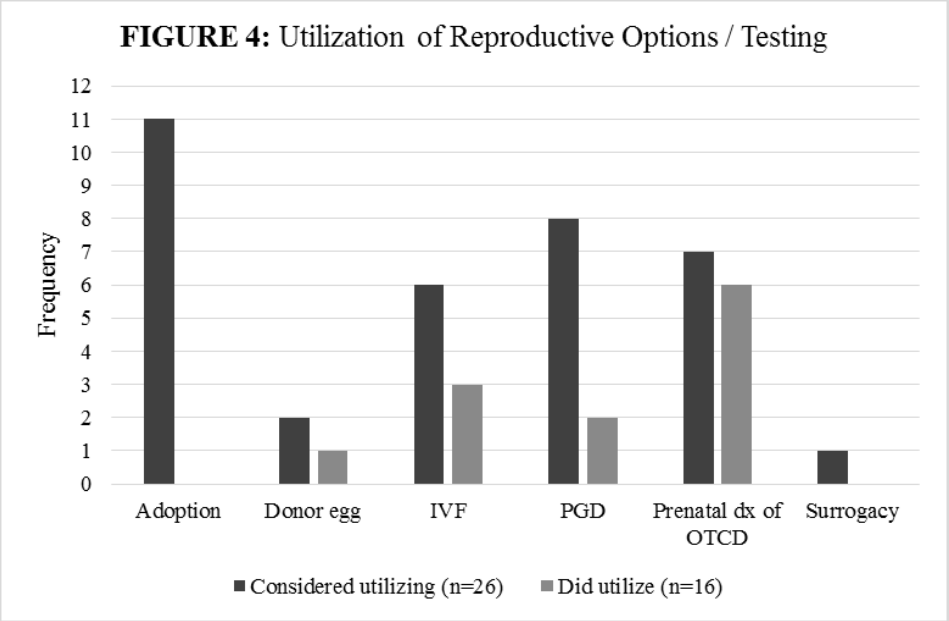


Participants then ranked individual concerns according to impact on reproductive decision-making. Overall, respondents' concerns about passing OTCD on to children had the greatest impact on reproduction. Respondents also were concerned, but not as strongly, about the possible impacts of pregnancy on their own health.

FIGURE 3: Concerns Impacting Decisions to have Children



Nearly 94% of respondents indicated that they have children. Out of 34 participants, there were a total of 25 sons with OTCD, 10 of whom were deceased, and 15 daughters who were known carriers, 1 of whom was deceased. Many of the respondents indicated that they considered pursuing alternative reproductive methods or considered different options for testing, but few actually chose to utilize these options.



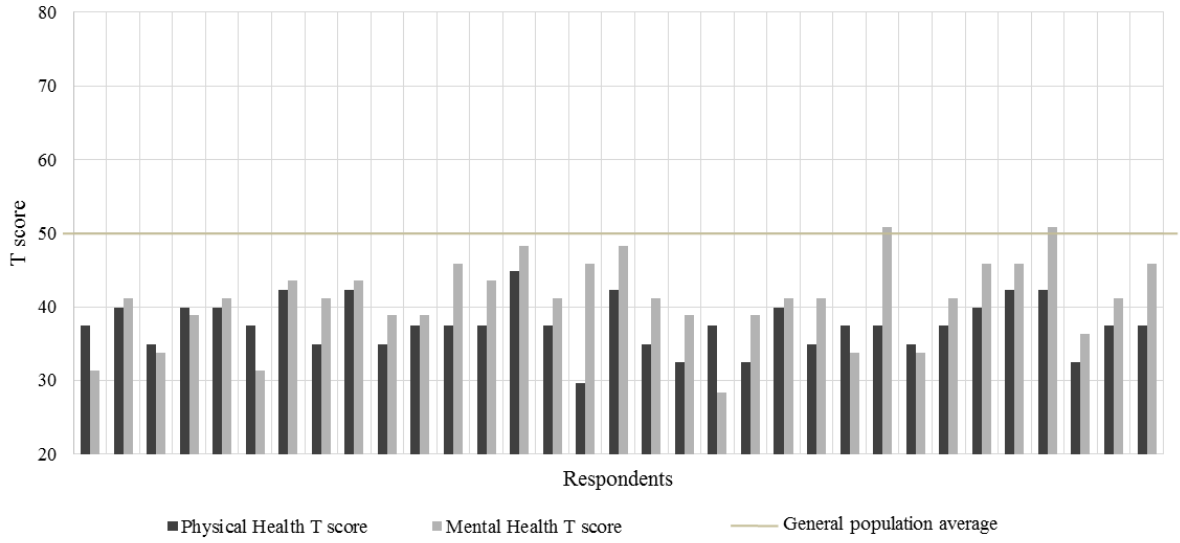
When asked about relatives (besides children), 30.3% of respondents (n=33) indicated that they had at least one relative either affected with or a carrier of OTCD. The number of affected or carrier relatives ranged from one to five. In total, within the families of 33 respondents, there were 10 affected males reported, 6 of whom were deceased, and 22 known carrier females, 2 of whom were deceased. It is unknown if any of the respondents are from the same families.

PROMIS Adult Global Health

In order to score the NIH PROMIS Adult Global Health survey for each respondent, every question within this section had to have been answered. A total of 33 respondents completed all questions in this section. The average Mental Health T score and Physical Health T score for the general population according to the NIH are each 50.0 with standard deviations of

10.0, and a higher score indicates better functioning (Hays et al., 2009). The mean Physical Health T score for our participants was 37.6 with a range of 29.6 to 44.9 and a standard deviation of 3.4. The mean Mental Health T score was 40.9 with a range of 28.4 to 50.8 and a standard deviation of 5.5. Physical and Mental Health T scores were significantly different (p=0.0049).

FIGURE 5: Physical and Mental Health T Scores



Support Systems

Exploration of participants' emotional and social support systems revealed that all but one participant (97%) felt that they received support from at least one source. Friends (57.6%) and spouses/ partners (57.6%) provided support to the greatest proportion of respondents. Social workers (9.1%) appeared to provide the least amount of support to these individuals. A small percentage (6.1%) indicated that they wish not to discuss being a carrier with others.

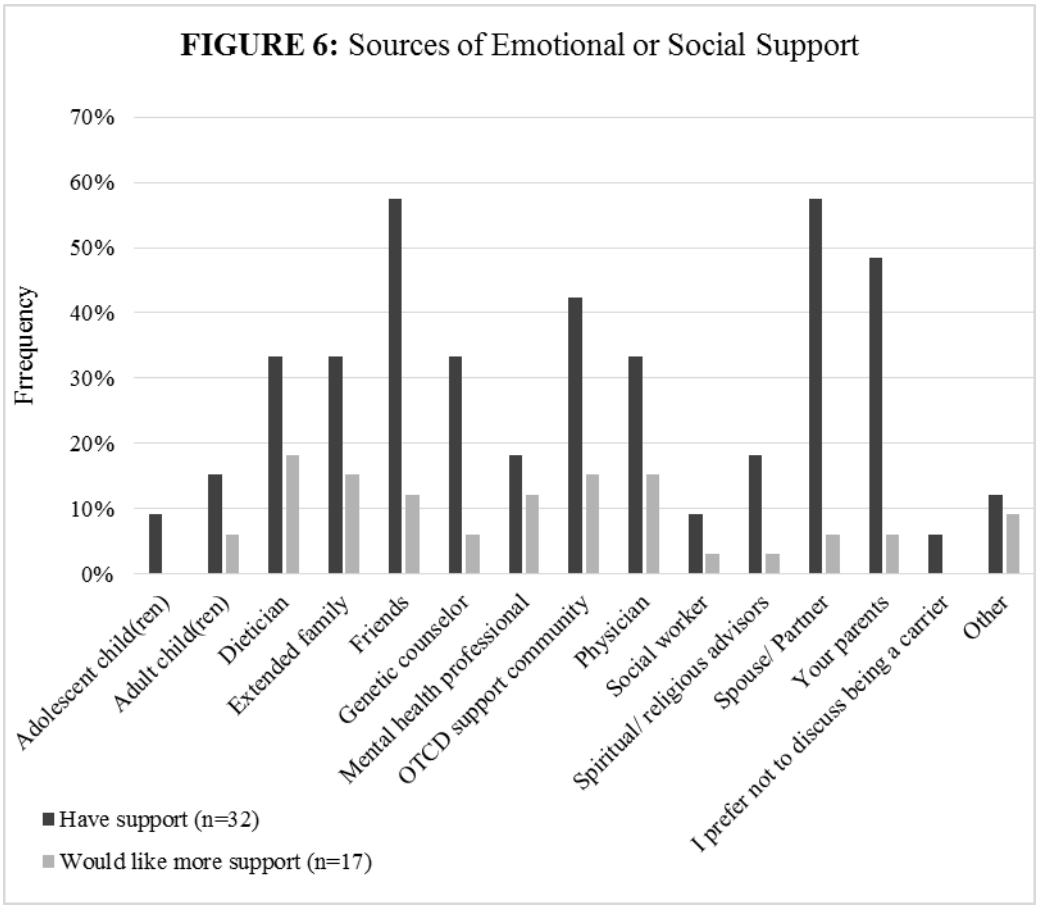


FIGURE 6: Sources of Emotional or Social Support
Frrequency
70%
60%
50%
40%
30%
20%
10%
0%
Adolescent child(ren)
Adult child(ren)
Dietician
Extended family
Friends
Genetic counselor
Mental health professional
OTCD support community
Physician
Social worker
Spiritual/ religious advisors
Spouse/ Partner
Your parents
I prefer not to discuss being a carrier
Other
Have support (n=32)
Would like more support (n=17)

DISCUSSION

Carrier Diagnosis

Our study participants had many different stories about how they were diagnosed as OTCD carriers and who gave them this news. The age at diagnosis varied widely, from elementary school age to postmenopausal age. All but one respondent reported that the diagnosis was disclosed by a healthcare provider, which included physicians, geneticists and genetic counselors. These results indicate that the majority of individuals are given the news by educated professionals. Three participants shared that they had been given the diagnosis by a genetic counselor.

Overall, participants indicated that the person who gave them the diagnosis did so with a positive attitude or supportive approach, although there was no statistically significant relationship between the approach and the individual disclosing the diagnosis. Respondent #35, who was given the diagnosis by her mother, did not report the use of any positive approaches, and indicated that the diagnosis was disclosed without any emotion. Respondent #35 wrote, "My mother told me and it was on the way to school. I had to ask her if my results were back in. She was not very emotionally supportive, understanding or sympathetic to my feelings at the time."

Even though most respondents indicated that they had been given the carrier diagnosis in a supportive manner, most reported feeling negative emotions when they received the news. Respondents most commonly reported feeling guilty and overwhelmed. Although overall the respondents felt negative emotions, 11.8% also felt grateful, and 17.6% felt well-advised (n=34).

There was no statistically significant relationship between who disclosed the diagnosis and how the individual felt. In intense situations, we expect individuals to experience many different emotions all at once, and our results reflect this expectation. In addition, the length of time since initial diagnosis in our participants varied widely, and there was no significant difference between the feelings in those who learned their diagnosis after the death or diagnosis of their child compared to those who were the first diagnosed or were diagnosed after another family member. This lack of statistical significance may be due to the small sample size and lack of power, since the overwhelming majority of respondents were diagnosed after an affected child, while very few were diagnosed in an alternative situation.

Symptoms of OTCD

Previous reports in the literature stated that only about 15% of carrier females were symptomatic (Batshaw et al., 1986). Articles published more recently rarely cite specific statistics. However, many do present evidence that female heterozygotes are at risk for hyperammonemia and the symptoms of OTCD, including coma (Arn et al., 1990), and brain, biochemical and cognitive changes have been observed in seemingly asymptomatic female carriers (A. L. Gropman et al., 2008; A.L. Gropman et al., 2010; Sprouse et al., 2014). Less than half of our participants, 38.2% (13/34), indicated that they had definitely experienced symptoms of OTCD, suggesting that the majority of female carriers do not have clinical manifestations but that the proportion of symptomatic carriers may be higher than previously reported. However, nearly the same proportion of respondents, 35.3% (12/34), was unsure if they had had symptoms or not. Many of these women may truly be asymptomatic, but it is concerning that such a large number of participants were unable to give a definitive answer. It is important to note that many

symptoms of OTCD can be non-specific; for example, it is difficult to discern whether a participant has experienced regular, ordinary headaches, or headaches specifically caused by hyperammonemia.

One overwhelming theme we observed was lack of knowledge about OTCD. Respondents expressed feelings of being uninformed and unaware of what symptoms are associated with being an OTCD carrier. Respondent #19 said, “I would like to know more about how to manage this disease and what to look for if I become symptomatic. And I would like to know how often to do blood tests to check my ammonia and amino acids.”

Others were worried about the risks to their children and to themselves during pregnancy, but felt that they were lacking necessary support and accurate information or guidance. Respondent #12 wrote, “I am very very anxcious [*sic*] about our second pregnancy. The doctors and dietician a know [*sic*] very little about OTC carriers going through pregnancies, my current dietician believes my Arginine is a supplement and not a medication. I have been given no advice on i [*sic*] I can even have a natural birth or if cesarean is our only option. I don't know where to go or what to do, I don't want to risk having a hyper ammonia [*sic*] case during labour, I'm not sure if that is a risk. To be honest I have no idea what to expect during tis [*sic*] pregnancy or what to look out for and it is making me very nervous and anxcious [*sic*].”

Among the participants who did indicate that they were symptomatic, many different symptoms of varying severity were reported. Due to differences in X-inactivation patterns in females, it is difficult to predict the clinical phenotype for any one individual. One woman may experience the most severe symptoms, while her sister or mother has no symptoms at all.

Impacts of Being a Carrier

Our survey attempted to identify the impacts of being an OTCD carrier on many different aspects of life. Respondents reported highly variable effects on romantic relationships and relationships with partners, although we did not ask participants if the relationships in questions were established before or after the diagnosis. Relationships with family members also were variably impacted. For both questions, some respondents stated that there was no effect, some said the effect was negative, and some said the effect was positive. In difficult circumstances, we expect to observe strengthening of some existing relationships while others weaken (Randall & Bodenmann, 2009), and our responses showed a definite mix of these two scenarios. Age at carrier diagnosis did not have a statistically significant correlation with impacts on relationships with partners or with family members. In general, individuals who were the first in the family diagnosed as an OTCD carrier reported more difficulty with relationships, but this correlation did not reach statistical significance.

Overall the data showed that OTCD has a stronger impact on faith than on relationships with partners or family members. All 18 responses showed some impact on relationships with faith or religion. The effect was negative for 38.9% of respondents, and many questioned their beliefs after illness or after receiving the diagnosis. However, 61.1% believe that the effects on faith were positive. Those who reported a positive impact said that they looked toward religion for an explanation and for guidance. It is important to note that these data are somewhat skewed because only 18 of 34 total participants answered this question. Perhaps participants without strong feelings about religion skipped this question completely. We may have only received responses from women who felt strongly one way or another.

As expected, respondents indicated that being diagnosed as a carrier had a very strong impact on decisions to have children. The majority expressed that the diagnosis made them less likely to have children in the future. Only a few said that the impact was small or none, and these respondents were mostly women who were diagnosed later in life after they had finished having children. When asked about specific child-bearing concerns, most were much more worried about passing on OTCD to a child than the effects of pregnancy on themselves, but again this could be partially due to the fact that many said that they are uninformed about their own health risks.

The impact of carrier status on childbearing and reproductive decision-making was the strongest we observed, but it is difficult to assess whether the effects are due to the women's own carrier diagnoses or due to the diagnoses in children. The majority of participants had children, and most were diagnosed as carriers following the death or illness of a child. This was a very important consideration when examining the data from our study. A number of participants said that they will not have any additional children as a result of OTCD, or that they would not have had children if they had known of the diagnosis in the past. Few utilized any alternative reproductive technologies for subsequent children, but many of our participants considered utilizing these technologies.

PROMIS Adult Global Health

The PROMIS survey questions were used to assess both physical and mental health of our respondents quickly and easily. None of the participants had physical health T scores equal to or above the general population mean score of 50.0, but only one respondent was significantly below the general population (greater than two standard deviations below). The mean physical

health T score for our respondents was 37.6 with a standard deviation of 3.4, which suggests that OTCD carriers generally have lower physical health than the general population, but the mean score does fall within two standard deviations (20.0 points) of the general population average.

Only two individuals had mental health T scores at or above the normative mean, and only one respondent received a score greater than two standard deviations below this mean. This individual was not the same as the participant with the lowest physical health T score. The mean mental health T score for our participants was 40.9 with a standard deviation of 5.5, which indicates that OTCD carriers generally have poorer mental health than the general population, but the mean score for the group falls within one standard deviation of the general population mean.

We expected both the physical and mental health T scores to be generally lower than the general population because female carriers of OTCD likely face some physical challenges if they are symptomatic, as well as complex mental or emotional issues. But, there was no significant correlation between younger age at diagnosis and lower T scores, nor between being symptomatic and having lower T scores.

Support Systems

Almost all participants indicated they received emotional or social support from at least one source, which may explain why mental health T scores were significantly higher than physical health T scores. As expected, close family and friends provide support to the most individuals. Responses showed that participants receive more support from the OTCD community than from genetic counselors, mental health professionals, physicians, dieticians or social workers, however our cohort was recruited from an OTCD support group, NUCDF, so this

data may not be generalizable. Our respondents showed that support groups are extremely valuable, but the data also suggests that healthcare professionals may have the opportunity to provide more emotional or social support to their patients who are OTCD carriers.

Study Limitations

Most limitations of this study are due to the small sample size. OTCD is a relatively rare disease, but with only 34 completed surveys, and only 18 fully completed surveys, our results are not generalizable and few of our comparisons were able to reach statistical significance.

This study also may have been limited by biases, including selection bias, self-selection, and recall bias. For example, selection bias could be related to the tendency for individuals to seek help from support groups if they are having difficulties; studies have shown that support groups are beneficial to families coping with genetic disorders (Plumridge, Metcalfe, Coad, & Gill, 2012). Since we recruited participants through a support network (NUCDF), our respondents could have more severe health issues, or could have a difficult situation surrounding the diagnosis. Alternatively, our respondents could be in better health, physically or mentally, than the general OTCD carrier population because they have accessed NUCDF's informational and support resources. This selection bias could skew our results toward either more mild or more severe cases in OTCD carriers. We were only able to survey individuals who have access to a computer and the internet, which limits the generalizability of our results as well. Our data also could be skewed due to self-selection; we likely captured only individuals who felt comfortable or strong enough to share their stories. In addition, some of our survey questions asked participants to comment on their feelings or thoughts during past events, making it difficult to avoid potential recall bias.

Most of our respondents were Caucasian and lived in the United States so there was little ethnic diversity among our participants. We did observe a wide range of education levels, but because we did not ask about income, socioeconomic status, or whether the respondents lived in rural or urban locations, we do not know what services, medicines or treatments our respondents have access to.

Our study also is difficult to generalize because of the varying ages at diagnosis, the differing circumstances surrounding the diagnosis, and different levels of affectedness. For example, it is nearly impossible to compare the life of a woman who was diagnosed as a symptomatic OTCD carrier at age 5 to that of an asymptomatic woman who was diagnosed at age 63 after her adult son passed away. These scenarios match those from two of our respondents, and nearly every participant had a different situation.

Because there is currently a gap in the literature concerning carriers of OTCD, an anonymous online survey was the best way to reach the most participants and gather as much information as possible for a pilot study. However, this data collection method does not allow us to ask follow-up questions or expand upon certain ideas. Additional information from any one of our participants would help the medical community, including genetic counselors, gain a better understanding of the needs and experiences of female OTCD carriers.

CONCLUSION

Our survey respondents shared compelling, heartbreaking stories, and information about being a female OTCD carrier that has never been formally collected previously. Most were diagnosed after a child or a relative was sick or passed away. Many of our participants described feeling overwhelmed, guilty and anxious, no matter how or who delivered the news of the diagnosis. On average, both physical and mental health T scores were lower in our participants than in the general population, indicating a need for physical and mental health remedies of some kind.

We observed great individual variability in responses from our participants, from diagnosis to symptom management to making decisions about having children and everything in between. Our study presents evidence that being an OTCD carrier can strongly impact social relationships and faith. Many aspects of life can change in an instant when a woman finds out she is an OTCD carrier.

Carriers of OTCD could benefit from increased involvement of genetic counselors, physicians, and dieticians, who are familiar with the phenotype and who possess the skills necessary to help address negative emotions. Genetic counselors can make a difference by creating trusting and long-lasting relationships with OTCD families to provide them with support and information. Support groups for OTCD and other urea cycle disorders, such as NUCDF, are also important. Introducing families affected by OTCD to reliable sources of information like NUCDF is crucial, especially because so many of our participants expressed feelings of

helplessness and confusion about what their diagnosis meant in terms of symptoms to watch for, circumstances to avoid, risks to family members, and reproductive options.

Future Research Suggestions

Future studies could involve distributing the survey to a larger sample of women who are OTCD carriers. Recruitment criteria could be made less stringent, allowing women to participate who have not had their carrier diagnosis confirmed but who live with the assumption that they are carriers. Future surveys with additional participants may distinguish experiences in the United States from experiences in other countries. Age at diagnosis or the circumstance surrounding the diagnosis could be analyzed in relationship to physical, social and emotional outcomes as well.

This pilot study that used an anonymous survey could also be used to develop a qualitative study involving in-depth interviews. Because we now have evidence of what specific issues and struggles that female carriers of OTCD encounter, it would be interesting to have more detailed conversations with some of the participants.

We observed that many participants felt uninformed or confused about aspects of their OTCD diagnoses. The data collected in this study could be used to create information packets for newly diagnosed carriers, or to help create or enhance support websites specifically for women who are carriers.

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APPENDIX A: Sample Participation Invitation Email

[Dear <person's name>,]

We are contacting you to invite you to participate in an online survey designed to report the experiences of female carriers of ornithine transcarbamylase (OTC) deficiency. If you are a woman who is a carrier of OTC deficiency, aged 18 years or older, you are eligible to participate in this important survey. The online survey is anonymous, and will take about 15 minutes to complete. You may skip questions you do not feel comfortable answering, and may exit the survey at any point.

The goal of this study is to gain insights into the experiences, needs and concerns of women who are carriers of OTC deficiency. There is currently very little research about the life experiences and health status of OTC carriers. It is our hope that the knowledge gained from this survey will be valuable to other families and patients affected by OTC deficiency, as well as UCD researchers, genetic counselors and other healthcare professionals.

It is very easy to participate in the survey. Please use the link below to access the survey introduction and questionnaire.
(INSERT LINK)

Thank you for considering participating in this important study.

[Organizational signature and address block, National Urea Cycle Disorders Foundation]

APPENDIX B: Recruitment Notice

As a carrier of OTC deficiency (OTCD), your experiences and opinions are valuable to understanding more about the condition. Some carriers may experience symptoms (symptomatic) and others may not experience any identifiable symptoms (asymptomatic). The goal of this study is to gain insight into the lives of female carriers of OTCD. It is our hope that the knowledge gained from this study will be valuable to others affected by OTC deficiency, genetic counselors and other healthcare professionals, and will help stimulate more research.

Participation in this study is voluntary and open to women who meet all of the following criteria:

- 18 years of age or older
- Known carrier of OTCD
- Read and write English

If you meet the criteria above, you have the option to take an anonymous online survey that can be completed in about 15 minutes. Please respond to all of the survey questions to the best of your knowledge, but feel free to skip any questions that you do not feel comfortable answering. You may exit the survey at any time.

There is no cost to you to participate in the study. We do not anticipate any risk to survey participants, but some respondents may feel discomfort or stress due to the sensitive nature of some questions. If you feel you need additional support, contact the Brandeis Genetic Counseling program faculty member and psychologist Dr. David Rintell at rintell@brandeis.edu.

If you have questions about the study or survey, please contact the student researcher, Chelsea Thompson, at cathomps@brandeis.edu or the Principal Investigator, Judith Tsipis, at 781-736-3165 or tsipis@brandeis.edu.
If you have questions about your rights as a research participant, please contact the Brandeis Institutional Review Board at 781-736-8133 or irb@brandeis.edu.

By clicking **Next**, you acknowledge that you have read the information above and voluntarily consent to participation in this survey.

Thank you!

APPENDIX C: Letter of Support

NUCDF

National Urea Cycle Disorders Foundation

Saving Lives through Awareness, Education, Research & Support.

75 South Grand Ave.
Pasadena, CA 91105

Website: www.nucdf.org

Phone: 800-38-NUCDF
Fax: 626-578-0823
Email: info@nucdf.org

December 12, 2014

Chelsea Thompson
193 Strathmore Road, Apt 4
Brighton, MA 02135

Re: Thesis Project titled Psychosocial Implications in Female Carriers of Ornithine Transcarbamylase Deficiency

Dear Chelsea,

Thank you for inviting the National Urea Cycle Disorders Foundation (NUCDF) to collaborate on your proposed thesis project. We understand that the involvement of our patient advocacy organization is critical to the accomplishment of this project, and are pleased to assist you in achieving its important goals.

In addition to my role as a member of your thesis committee, our organization will assist by distributing an invitation to participate in the survey with a link to the thesis survey instrument via email and our online discussion groups to families of NUCDF who are affected with OTC deficiency and may have a family member who is a female carrier, and additionally to our list of known female carriers for OTC deficiency. We will be at your disposal to provide advisory support throughout the duration of the project.

I have thoroughly reviewed your research proposal and the survey instrument, and enthusiastically support the involvement of our organization in this project. I look forward to working with you.

Sincerely,

Cynthia Le Mons

Cynthia Le Mons
Executive Director, NUCDF
Co-Primary Investigator, NIH Rare Diseases Clinical Research Network UCD Consortium

APPENDIX D: Survey Instrument

1. Are you a known carrier for OTC deficiency (OTCD)?
   - ❍ Yes
   - ❍ No

   (If no, end of survey; If yes, survey continues to question 2)

2. At what age did you find out that you are a carrier of OTCD? ___ ___ years

3. Who first told you that you are a carrier? Please select one.
   - ❍ Physician
   - ❍ Geneticist
   - ❍ Genetic counselor
   - ❍ My parent
   - ❍ Other _____

4. How would you describe **how** the news was first given to you? Please check all that apply.
   - □ With pity
   - □ With compassion
   - □ With sympathy
   - □ With language and terminology I was able to understand
   - □ In terms that were difficult for me to understand
   - □ Without any emotion
   - □ With kindness
   - □ With optimism and hope about my future quality of life
   - ☐ With pessimism about my future quality of life
   - ☐ With good advice about how to manage the possible symptoms
   - ☐ With no advice about how to manage the possible symptoms
   - ☐ Other _____

5. How did you feel when you **first** received the news that you are a carrier?
   - ☐Sad
   - ☐Relieved
   - ☐Isolated
   - □Helpless
   - □Guilty
   - ☐Depressed

□Confused

☐Anxious

☐Angry

☐Afraid

☐ Well-advised

☐ Understood

☐ Supported

☐ Pessimistic about my future quality of life

☐ Overwhelmed

☐ Optimistic about my future quality of life

☐ Grateful

6. We would be interested in learning more about this experience in your own words. If you feel comfortable telling us more, please share your thoughts in the space provided below.

   _____

7. What could have made receiving the diagnosis better or easier for you? If you feel comfortable, please tell us in your own words using the space below. (For example, additional resources about the condition, referral for a support group, more support from family or a spouse, etc.)

   _____

SYMPTOMS

8. Have you experienced symptoms associated with being an OTCD carrier?
   - ❍ Yes
   - ❍ No
   - ❍ Not sure

   (If no or not sure, continue to question 12; If yes, continue to question 9)

9. At what age did your symptoms begin? ___ ___ years

10. What symptoms have you experienced over your lifetime associated with being an OTCD carrier? Please select all you have experienced.

    ☐ Elevated ammonia level

    ☐ Protein aversion

    ☐ Headaches

    ☐ Nausea

    ☐ Vomiting

    ☐ Difficulty remembering some things

    □ Feeling tired

☐ Irritability

☐ Disorientation

☐ Confusion

☐ Other (fill in) _____

☐I have not experienced symptoms

11. What treatments have you received as a carrier of OTCD? Please select all that apply.

☐ Citrulline

☐ Arginine

☐ Ammonia scavengers

☐ Special foods/formula

☐ Low protein diet

☐ Other (fill in) _____

☐ I have not had any treatments

FAMILY AND OTC DEFICIENCY

In this section we would like to learn more about any members of your family who have OTCD or who are carriers of OTCD.

12. Do you have children (living or deceased)?

❍ Yes

❍ No

(If no, continue to question 20; If yes, continue to question 13)

13. Please fill in the information below about your children.

	Male or Female?	Biologically related?	Living or deceased?	Select one	Symptomatic?	If deceased, was cause of death related to OTCD?
Child #1	M/F	Y/N	L/D	(Affected with OTCD, carrier of OTCD, neither)	Y/N	Y/N
Child #2	M/F	Y/N	L/D	(Affected with OTCD, carrier of OTCD, neither)	Y/N	Y/N
Child #3	M/F	Y/N	L/D	(Affected with OTCD, carrier of OTCD, neither)	Y/N	Y/N

Child #4	M/F	Y/N	L/D	(Affected with OTCD, carrier of OTCD, neither)	Y/N	Y/N
Child #5	M/F	Y/N	L/D	(Affected with OTCD, carrier of OTCD, neither)	Y/N	Y/N

14. (If respondent selected that they have a child **with OTCD**) **How** was the news that your child had OTCD first delivered to you? Please check all that apply.

□ With pity

□ With compassion

□ With sympathy

□ With language and terminology I was able to understand

□ In terms that were difficult for me to understand

□ Without any emotion

□ With kindness

□ With optimism and hope about my child's future quality of life

☐ With pessimism about my child's future quality of life

☐ With good advice about how to manage the possible symptoms

☐ With no advice about how to manage the possible symptoms

☐I don't remember

☐ Other _____

15. (If respondent selected that they have a child **with OTCD**) What was your initial reaction when your first child was diagnosed with OTCD?

□Sadness

☐Confusion

☐Guilt

☐Helplessness

☐Relief

☐Anger

☐Fear

☐Anxiety

☐Depression

☐Sense of isolation

☐I don't remember

☐Other _____

16. (If respondent selected that they have a child **with OTCD**) We would be interested in learning more about this experience in your own words. If you feel comfortable telling us more, please share your thoughts in the space provided below.

_____

17. (If respondent selected that they have a child who is **carrier of OTCD**) **How** was the news that your child is a carrier first delivered to you? Please check all that apply.

□ With pity

□ With compassion

□ With sympathy

□ With language and terminology I was able to understand

□ In terms that were difficult for me to understand

□ Without any emotion

□ With kindness

□ With optimism and hope about my child's future quality of life

☐ With pessimism about my child's future quality of life

☐ With good advice about how to manage the possible symptoms

☐ With no advice about how to manage the possible symptoms

☐I don't remember

☐ Other _____

18. (If respondent selected that they have a child who is a **carrier of OTCD**) What was your initial reaction when your first child was found to be a carrier of OTCD?

□Sadness

☐Confusion

☐Guilt

☐Helplessness

☐Relief

☐Anger

☐Fear

☐Anxiety

☐Depression

☐Sense of isolation

☐I don't remember

☐Other _____

19. (If respondent selected that they have a child who is a **carrier of OTCD**) We would be interested in learning more about this experience in your own words. If you feel comfortable telling us more, please share your thoughts in the space provided below.

20. Do you have family members (besides your children) who have OTCD or who are carriers of OTCD?
    - ❍ Yes
    - ❍ No
    - ❍ Not sure

    (If no or not sure, continue to question 22; If yes, continue to question 21)

21. To the best of your knowledge, please fill in the table below about your relatives with OTCD and relatives who are carriers of OTCD.

	Male or Female?	Living or deceased?	Relation to you? (drop down- pick one)	OTCD or carrier of OTCD? (pick one)	Symptomatic?	If deceased, was cause of death related to OTCD?
Relative #1	M/F	L/D			Y/N	Y/N
Relative #2	M/F	L/D			Y/N	Y/N
Relative #3	M/F	L/D			Y/N	Y/N
Relative #4	M/F	L/D			Y/N	Y/N
Relative #5	M/F	L/D			Y/N	Y/N

—Questions below are for every respondent—

IMPACTS OF BEING A CARRIER

22. Each carrier of OTCD experiences its impact on her everyday life differently. For each of the areas below, please use the sliding scales to indicate the impact on your life. Please feel free to elaborate in the spaces provided.

    a. Romantic relationships/ relationships with partners

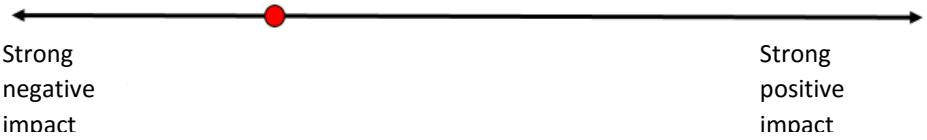
    b. If you wish, in the space provided please describe briefly how your romantic relationship/relationships with partners were affected:

    c. Relationships with family members

d. If you wish, in the space provided please describe briefly how you relationship with family members were affected.

_____

e. Your relationship with faith/ religion

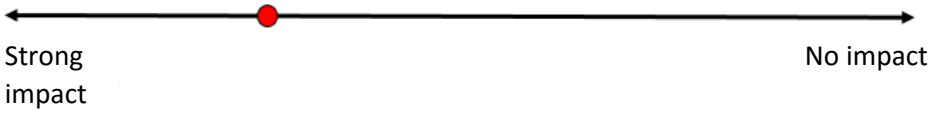


f. If you wish, in the space provided please describe briefly how you relationship with your faith/religion was affected:

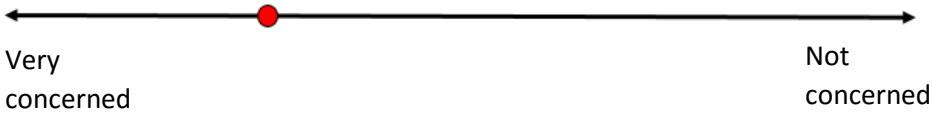
_____

23.

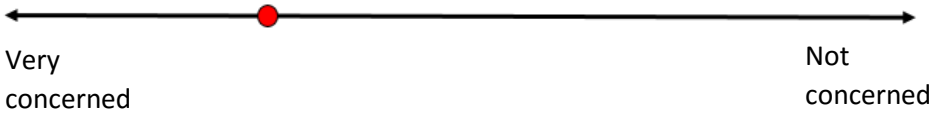
a. To what extent has being a carrier impacted your decisions about having children?



b. To what extent were you concerned about the impact of pregnancy on your health?



c. To what extent were you concerned about passing OTCD on to children?



d. If you wish, in the space provided please describe how being a carrier has affected your thinking and decision-making about having children:

_____

e. Please indicate in the table if you have considered using or have used each of the following:

	Considered utilizing	Did utilize
In vitro fertilization (IVF)	Y/N	Y/N
Preimplantation genetic diagnosis (PGD)	Y/N	Y/N
Prenatal diagnosis for OTCD (CVS or amniocentesis)	Y/N	Y/N
Donor egg	Y/N	Y/N
Surrogacy	Y/N	Y/N
Adoption	Y/N	Y/N

SUPPORT SYSTEMS

We would like to learn about your support systems in order to better serve all carriers of OTCD.

24. What sources of emotional or social support do you have? Please check all that apply.

☐Friends

☐ Adolescent child(ren)

☐ Adult child(ren)

☐ Spouse/Partner

☐ Your parents

☐ Extended family

☐ OTCD support community

☐ Spiritual/religious advisors

☐ Mental health professional

☐ Physician

☐ Social worker

☐ Genetic counselor

☐ Dietician

☐ Other (fill in)

_____

☐ I prefer not to discuss being a carrier with others

25. Please indicate which sources you would like **more** emotional or social support from. Please check all that apply.

☐ Friends

☐ Adolescent child(ren)

☐ Adult child(ren)

☐ Spouse/Partner

☐ Your parents

☐ Extended family

☐ OTCD support community

☐ Spiritual/religious advisors

☐ Mental health professional

☐ Physician

☐ Social worker

☐ Genetic counselor

☐ Dietician

☐ Other (fill in)

_____

YOUR HEALTH
(PROMIS Global Health measure via NIH)

Questions 26 through 35 are from the PROMIS Global Health measure and are designed to get a sense of how your general health is overall.

	Excellent	Very Good	Good	Fair	Poor
26. In general, would you say your health is…	❍	❍	❍	❍	❍
27. In general, would you say your quality of life is…	❍	❍	❍	❍	❍
28. In general, how would you rate your physical health?	❍	❍	❍	❍	❍
29. In general, how would you rate your mental health, including your mood and your ability to think?	❍	❍	❍	❍	❍

30. In general, how would you rate your satisfaction with your social activities and relationships?	❍	❍	❍	❍	❍
31. In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.)	❍	❍	❍	❍	❍

	Completely	Mostly	Moderately	A little	Not at all
32. To what extend are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?	❍	❍	❍	❍	❍

	Never	Rarely	Sometimes	Often	Always
33. In the past 7 days, how often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?	❍	❍	❍	❍	❍

	None	Mild	Moderate	Severe	Very severe
34. In the past 7 days, how would you rate your fatigue on average?	❍	❍	❍	❍	❍

	No pain 0	1	2	3	4	5	6	7	8	9	Worst imaginable pain 10
35. In the past 7 days, how would you rate your pain on average?	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍

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36. Please enter any additional information you wish to share or any comments in the space below.

_____
_____
_____
_____
_____
_____
_____
_____

DEMOGRAPHICS
We would like to collect some additional information about you because it may help us understand your unique needs. Please skip any questions that you do not wish to answer.

37. What is your current age? ___ ___ years

38. What is your ethnicity? Please check all that apply

☐ Black or African American

☐ White

☐ Asian

☐ Hispanic/ Latino

☐ American Indian or Alaskan native

☐ Hawaiian native or Pacific Islander

☐ Other _____

39. Where do you live?

- Pacific time zone (US)
- Mountain time zone (US)
- Central time zone (US)
- Eastern time zone (US)
- Alaska
- Hawaii
- Canada
- Other _____

40. What is your highest completed education level?

- Nursery, kindergarten, elementary school
- Middle school
- High school degree or GED
- Some college (1-4 years, no degree)
- Associate's degree (including occupational or academic degrees)
- Bachelor's degree (BA, BS, AB, etc)
- Master's degree (MA, MS, MENG, MSW, etc)

- ❍ Professional school degree (MD, DVM, DDC JD, etc)
- ❍ Doctorate degree (PhD, EdD, etc)

41. What is your current relationship status? Please select all that apply

- ☐ Now married
- ☐ Widowed
- ☐ Divorced
- ☐ Separated
- ☐ Never married
- ☐ Other (please specify) _____

Thank you for taking the time to complete this survey. Please click the submit button to record your responses.

APPENDIX E: National Institutes of Health PROMIS Global Health Scoring Instructions

Scoring PROMIS Global Short Form

Scoring Global Short Form v1.0 and v1.1

The PROMIS Global Health short form is a 10-item instrument representing multiple domains. It can be scored into a Global Physical Health component and Global Mental Health component using the tables below. Because a scoring table is prepared for a fixed set of items, it can only be used when an examinee responds to all of the items in the set. *One or more missing responses will render such scoring tables unusable*.

The Global scores require re-coding of three items so that high scores reflect better functioning.

Global07	In the past 7 days	How would you rate your pain on average?	5=0 No pain 4=1 4=2 4=3 3=4 3=5 3=6 2=7 2=8 2=9 1=10 Worst pain imaginable
Global08	In the past 7 days	How would you rate your fatigue on average?	5=None 4=Mild 3=Moderate 2=Severe 1=Very severe
Global10	In the past 7 days	How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?	5=Never 4=Rarely 3=Sometimes 2=Often 1=Always

After recoding, the Global Physical Health score is generated by summing responses to Global03, Global06, Global07rescored, and Global08rescored. The Global Mental Health score is generated by summing responses to Global02, Global04, Global05, and Global10rescored.

Raw Score to T Score Conversion Tables

The following conversion tables allow a user to convert simple summed raw scores from PROMIS global into T-score values on an individual respondent or group of respondents. In all cases, these conversions only work accurately when all questions on the short form have been answered. T-Score distributions are standardized such that a 50 represents the average (mean) for the US general population, and the standard deviation around that mean is 10 points. *A high score always represents more of the concept being measured*. Thus, a person who has T-scores of 60 for the Global Physical Health or Global Mental Health scales is one standard deviation better (more healthy) than the general population.

Physical
Short Form Conversion Table

Raw.Score	T.Score	SE*
4	16.2	4.8
5	19.9	4.7
6	23.5	4.5
7	26.7	4.3
8	29.6	4.2
9	32.4	4.2
10	34.9	4.1
11	37.4	4.1
12	39.8	4.1
13	42.3	4.2
14	44.9	4.3
15	47.7	4.4
16	50.8	4.6
17	54.1	4.7
18	57.7	4.9
19	61.9	5.2
20	67.7	5.9

*SE = Standard Error

Mental
Short Form Conversion Table

Raw.Score	T.Score	SE*
4	21.2	4.6
5	25.1	4.1
6	28.4	3.9
7	31.3	3.7
8	33.8	3.7
9	36.3	3.7
10	38.8	3.6
11	41.1	3.6
12	43.5	3.6
13	45.8	3.6
14	48.3	3.7
15	50.8	3.7
16	53.3	3.7
17	56.0	3.8
18	59.0	3.9
19	62.5	4.2
20	67.6	5.3

*SE = Standard Error

- **Conversion Table applies only when ALL questions on the subdomain have been answered**

Hays, R.D., Bjorner, J., Revicki, R.A., Spritzer, K.L., & Cella, D. (2009). Development of physical and mental health summary score from the Patient Reported Outcomes Measure Information System (PROMIS) global items. *Quality of Life Research, 18(7),* 873-80. (PMCID: PMC272.4630)