A Letter from the RTG Medical Advisory Board

Dear Colleague,

Females with X-linked conditions are not "just carriers" and may manifest symptoms.

As medical professionals and members of the Medical Advisory Board for the nonprofit organization **Remember The Girls (RTG)**, we write this letter at the request of the patient community to assist them in communicating their needs and preferences with their respective health care teams. We hope the information and resources on the following pages will guide your further exploration of the topics as appropriate to your patient(s) and practice(s).

Sincerely,

Cassandra L. Smith, RN, and members of the **Remember The Girls** Medical Advisory Board

DocuSigned by: Cassandra Smith 0B0AF60229E8423... — 8/1/2023
Cassandra L. Smith, RN — Date

DocuSigned by: Florian Eichler 53594BE2881548C... — 8/1/2023
Florian Eichler, MD — Date

DocuSigned by: Robert Sidonio D0A1D93F877D4C5... — 7/28/2023
Robert Sidonio, MD — Date

DocuSigned by: A06C10F0507F412... — 7/31/2023
Patrick Long, MD — Date

DocuSigned by: Rebecca Spencer 9EA6BE014FAB4D8... — 8/1/2023
Rebecca J. Spencer, MD — Date

DocuSigned by: CAAFDAABF10E44A... — 7/28/2023
Kimberly Zahm, Ph.D., CP — Date

DocuSigned by: Julie Cohen 72C9FE7571E349A... — 7/28/2023
Julie Cohen, ScM, CGC — Date

DocuSigned by: Rebecca McClellan 0017178449F34CE... — 8/1/2023
Rebecca McClellan, MGC, CGC — Date

DocuSigned by: Jamie Kostialik 28281E93C391478... — 7/28/2023
Jamie Kostialik, MS, CGC — Date

DocuSigned by: Taylor Kane 8BB52E10EE054E3... — 7/28/2023
Taylor Kane, RTG Founder — Date

Please note: *This letter is not addressed to a specific individual, medical professional, or entity. It is publicly accessible via the* ***Remember The Girls*** *website as a downloadable, read-only file.*

Females with X-linked conditions are not "just carriers"

OVERVIEW

X-linked inheritance refers to the inheritance pattern of genes located on the X chromosome. Only one X chromosome's genetic code is needed per cell for proper cell function. Since males inherit one X chromosome and one Y chromosome (XY), each male human body cell will use the genetic code from the sole X chromosome present. However, since females have two X chromosomes (XX), each female human body cell uses the genetic code from one X chromosome while the other X chromosome is silenced – or *inactivated*.

X-INACTIVATION

The X chromosome selected for inactivation in each female cell is determined early in embryonic development during cell differentiation. The cells that are first to differentiate are called parent cells. Each cell that is derived from a parent cell will have the same X chromosome inactivated as its parent cell. This process results in cellular mosaicism in females (Migeon, 2020).

Theoretically, because there are two X chromosomes from which to select, each parent cell has a 50% chance of selecting one X chromosome for inactivation versus the other. However, the percentage of cells with one X chromosome inactivated versus the other does not always result in equal distribution (Migeon, 2020). Although it is out of the scope of this letter to detail the factors that influence X-inactivation and the subsequent distribution of cells, we have referenced an article by Migeon (2020) that we believe provides a well-rounded discussion of this topic. It is important to note that some females have a higher percentage of an affected X chromosome active in their body cells than cells with the unaffected X chromosome. This is one of several reasons that females with X-linked conditions may exhibit symptoms.

SYMPTOM EXPRESSION IN FEMALES

When females express symptoms associated with a single gene variant on one X chromosome, they typically have a milder presentation than their male counterparts. However, this is not always the case. In addition to females with a higher distribution of active, affected X chromosomes, there are also X-linked conditions known to result in a more severe disease presentation in females. Unfortunately, misconceptions about symptom expression in females persist both in the medical literature and in practice. This can lead to misattribution of symptoms, delayed treatment, and suboptimal healthcare outcomes (Goka et al., 2021). We believe it is, therefore, prudent to consider the possibility of symptom expression in females due to the myriad factors that influence gene expression.

CARRIER TERMINOLOGY

Some individuals in the community have expressed displeasure with the use of the term *carrier* in reference to their status as individuals with X-linked genetic variants. Use of the term began in the medical literature when females were largely considered to have no or minimal possibility of symptom expression. It has also been used to compare symptom severity in females to males, which may contribute to female symptoms being minimized or dismissed (Goka et al., 2021). For these reasons, we encourage you to explore the terminology preferences of your patients with X-linked variants.

MENTAL HEALTH AND WELLBEING

The impact of an X-linked diagnosis on female mental health and well-being has been described in the literature. Implications such as uncertainty, guilt, grief, stigma, and chronic sorrow have all been described (Kay & Kingston, 2002; Goldman et al., 2018; Sheridan et al., 2023). Ineffective coping and impaired psychosocial well-being and quality of life have also been demonstrated in some females with X-linked conditions (von der Lippe, 2018). We find these congruent with our professional practices and in our collective work with the organization. For this reason, we encourage you to assess the presence and efficacy of coping processes and the mental health and well-being of females with X-linked conditions.

CONCLUSION

In conclusion, we hope this letter has provided you with a brief overview of X-linked inheritance and symptom expression in females. We also hope you will consider the terminology preferences of your patients and employ a holistic approach to care. Last, we invite you to remain abreast of the evolving research on X-inactivation and its impact on female symptom expression.

We hope to update the organization's website in the coming months to include a section for medical professionals. In the meantime, we expect the resources below will guide your further exploration of the topic. Thank you for your time and commitment to providing high-quality care to your patients. If the organization can assist you in any way, please contact the organization's executive director at taylor@rememberthegirls.org.

remember the girls NOT JUST CARRIERS.

Remember The Girls *is a nonprofit that aims to break the stigma facing females impacted by X-linked conditions by providing them with tools to seek support, engage with research, and access family planning options, as well as by advocating for increased attention of medical professionals to the physical, emotional, and reproductive needs of this community. Visit rememberthegirls.org for more.*

Resources

Basta, M. & Pandya, A. M. (2022, May 8). Genetics, X-linked inheritance. Stat Pearls. https://www.ncbi.nlm.nih.gov/books/NBK557383/

Goka, S., Copelovitch, L., & Levy Erez, D. (2021). Long-term outcome among females with Alport syndrome from a single pediatric center. *Pediatric Nephrology*, *36*, 945—951. https://doi.org/10.1007/s00467-020-04748-4

Goldman, A., Metcalfe, A., & MacLeod, R. (2018). The process of disclosure: Mothers' experiences of communicating X-linked carrier risk information to at-risk daughters. *Journal of Genetic Counseling*, *27*(5), 1265—1274. https://doi.org/10.1007/s10897-018-0251-7

Migeon, B. R. (2020). X-linked diseases: Susceptible females. *Genetics in Medicine*, *22*, 1156-1174. https://doi.org/10.1038/s41436-020-0779-4

James, C. A., Hadley, D. W., Holtzman, N. A., & Winkelstein, J. A. (2006). How does the mode of inheritance of a genetic condition influence families? A study of guilt, blame, stigma, and understanding of inheritance and reproductive risks in families with X-linked and autosomal recessive diseases. *Genetics in Medicine*, *8*(4), 234—242. https://doi.org/10.1097/01.gim.0000215177.28010.6e

Kay, E., & Kingston, H. (2002). Feelings associated with being a carrier and characteristics of reproductive decision making in women known to be carriers of x-linked conditions. *Journal of Health Psychology*, *7*(2), 169—181.

Sheridan, N., Thompson, B., Lichten, L., Coleman, K., & Sidonio, R. (2023). The emotional experience of mothers of children with haemophilia: Maternal guilt, effective coping strategies and resilience within the haeomophilia community. *Haemophilia, 29*, 513--520. https://doi.org/10.1111/hae.14746

von der Lippe, C. (2018). *Not just a carrier – a qualitative study of psychosocial aspects of women's experiences of living with an X-linked disorder* [Unpublished doctoral thesis]. University of Oslo. http://urn.nb.no/URN:NBN:no-68489