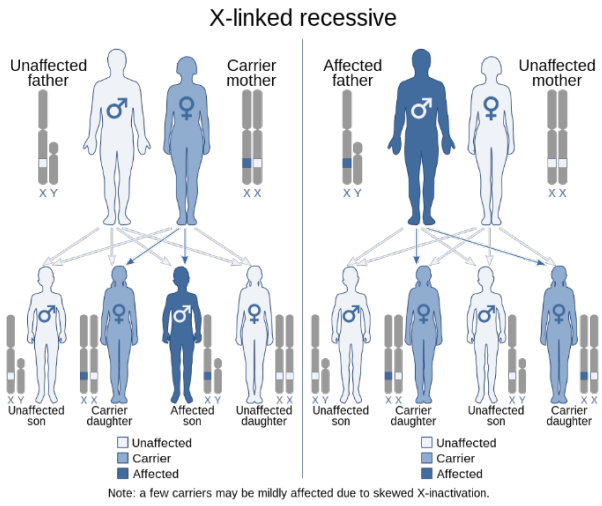
KD and Female Carriers

Introduction: Kennedy's Disease (KD) or Spinal and Bulbar Muscular Atrophy (SBMA) is a rare, X-linked neuromuscular disease. In men, symptoms usually begin in the 3rd-4th decade of life and disease slowly progresses with age, resulting in weakness of proximal limbs (arms and legs) and bulbar musculature (speech and swallowing). Patients may note muscle fatigue, fasciculations, tremors, and cramps, leading to reduced mobility. They may also suffer difficulty speaking (dysarthria) and swallowing (dysphagia). SBMA female carriers may experience some neuromuscular symptoms, but with less severity than male patients, and some medical providers may have limited knowledge about symptoms among X-linked disorders. [1,2] Additional research on female carriers is needed to better determine the frequency and severity of KD symptoms, as well as to establish medical management guidelines for symptomatic carriers.

Genetics and Inheritance: SBMA is caused by an expansion mutation in the androgen receptor (AR) gene on the X-chromosome. In unaffected men and women, the AR gene contains 9 to 34 CAG repeats. However, in men diagnosed with SBMA, CAG repeat numbers vary from 38 to 68 with an average of 46 [2]. The CAG translates to a glutamine tract in the protein, making SBMA one in a family of polyglutamine expansion disorders.



The AR gene is passed on to children through the X-chromosome in the egg or the sperm cell. Men have one X- and one Y-chromosome, while women have two X-chromosomes. If a man has more than 38 CAG repeats in the AR gene on their single X-chromosome, they have Kennedy's Disease or SBMA. If a woman has more than 38 CAG repeats on at least one of their two X-chromosomes, they are carriers [2].

Sons of men with SBMA will not have SBMA because they receive a Y-chromosome from their father, and the Y-chromosome does not carry the AR gene. Daughters of men with SBMA will always be carriers (obligate carriers), because women always receive one X-chromosome from their father (carrying the AR expansion mutation) and one X-chromosome from their mother. Sons and daughters of female carriers have a 50% chance of inheriting the X-chromosome with the AR expansion mutation from their mother.

CAG Repeat Stability: In some CAG repeat disorders, a phenomenon called Genetic Anticipation occurs where the number of CAG repeats increases from one generation to the next, resulting in earlier symptom onset. However, Genetic Anticipation does **NOT** appear to occur in SBMA. In SBMA, CAG repeat numbers appear to be relatively stable from one generation to the next, sometimes increasing, sometimes decreasing [2,3,4].

Carrier Symptoms: In many X-linked diseases, carriers can experience a wide range of symptoms, from undetectable to severe [1]. Female carriers of the mutant AR gene often report muscle cramping and occasionally tremor [5]. Carriers may exhibit mild muscle weakness in the

neck or reduced walking speed [6]. Carriers with cramps or tremor may also have abnormal electromyography (EMG) results and decreased motor unit number estimation (MUNE) [6,7]. The reasons that female carriers are spared the most severe symptoms are not fully understood but are likely related to skewed inactivation of the affected X chromosome [8] and their low levels of circulating androgens (e.g., testosterone) [3].

Genetic Testing: Genetic testing is the standard method for diagnosis of SBMA (see reference sheet "KD Diagnosis and DNA Testing") and is important for diagnostic and medical management of symptomatic carriers. Often, however, carriers only find out they have an X-linked condition when a male relative is diagnosed [1]. For family planning purposes genetic determination of carrier status is required before any preconception (preimplantation genetic screening-PGS) or post conception screening procedures (chorionic villus sampling or amniocentesis). Genetic testing is a very personal choice based on many factors--such as a person's risk status, health status (symptomatic), age, timing/family planning status, as well as lifestyle/personal and religious beliefs. A genetic counselor can help individuals make an informed decision about genetic testing.

Genetic Counseling: Genetic counselors work as members of health care teams providing information and support to individuals or families who have genetic disorders or may be at risk for inherited conditions. A genetic counselor will provide a risk assessment based on one's family history, discuss pros and cons of genetic testing, test costs, and insurance coverage, discuss family planning, and help individuals make an informed decision that is best for them. In the United Kingdom, in-person and Telehealth counseling is available through the National Society of Genetic Counselors.

References:

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