PATHOPROFILE

Kallmann syndroMe

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INTRODUCTION

Kallmann syndrome (KS) is a form of hypogonadotropic hypogonadism characterized by a combination of both an inability to smell and properly regulate hypothalamic gonadotropin-releasing hormone (GnRH) pulses.[1] This, as a result, affects the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary gland, which in turn influences the secretion of endocrine hormones, such as estrogen and progesterone. It is found fairly infrequently, at a rate of approximately 1 in every 125,000 females and 1 in every 30 000 males.[2] The inability to regulate GnRH secretion from the hypothalamus leads to a variety of consequences, including reduced sex hormone levels and the delayed onset of puberty.[2]

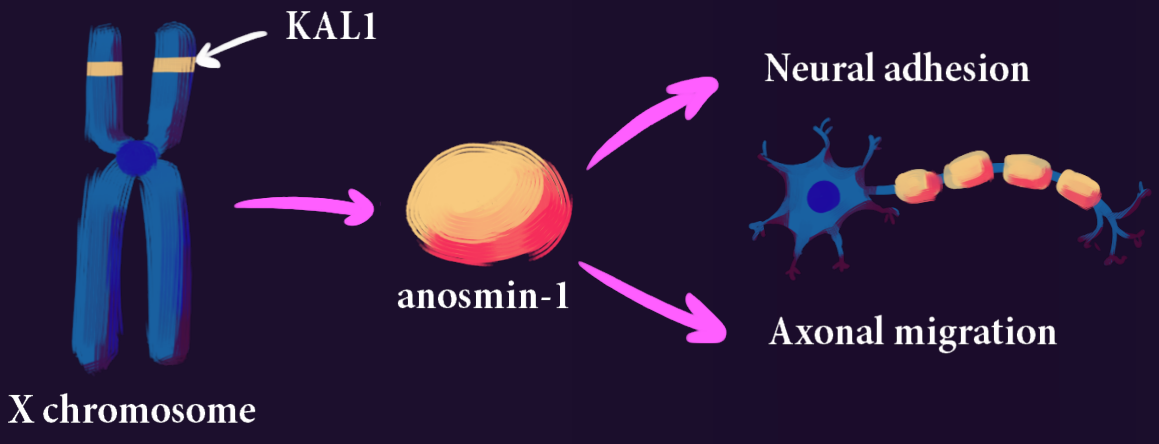
PRESENTATION AND DIAGNOSIS

The pattern of GnRH secretions from the hypothalamus continually changes throughout the stages of sexual development.[3] As such, diagnosis of KS solely on the basis of GnRH levels requires an understanding of normal developmental timing. Although occasionally diagnosed during the neonatal stage, the most common period of diagnoses occurs during adolescence due to the disease's characteristic inhibitory effects on puberty and sexual development.[4] Notably, KS patients often experience stunted growth due to a lack of hormonal stimulation.[1,4]

Additionally, pituitary dysfunction as a result of KS often differs between males and females during sexual development, resulting in sex-specific clinical presentations.[5] A study completed by Seminara et al. recruited a group of 50 males with GnRH deficiency observed that approximately 84% of patients exhibited no detectable GnRH pulses.[4] Other minority groups exhibited different pulse frequencies, including abberant patterns during sleep or diminished pulse amplitudes.[2,3] In contrast, the most common female GnRH secretion abnormality was a decrease in pulse frequency, occurring in approximately 40% of subjects.[3] The study also observed that abnormal pulse patterns were extremely consistent within families with KS, indicating that genetic factors may also influence GnRH secretion.[3]

RISK FACTORS AND HERITABIILITY

The mechanism of genetic inheritance varies significantly for KS.[6] GnRH pulse deficiencies have been shown to be inherited through X-linked recessive, autosomal dominant, and autosomal recessive manners.[6] To this date, over 35 genes have been identified whose mutations are associated with GnRH pulse deficiencies.[3] KS development has also been closely associated with other reproductive disorders, such as hypothalamic amenorrhea and constitutional delay of puberty, making these particular disorders comorbidities for the development of KS.[1]

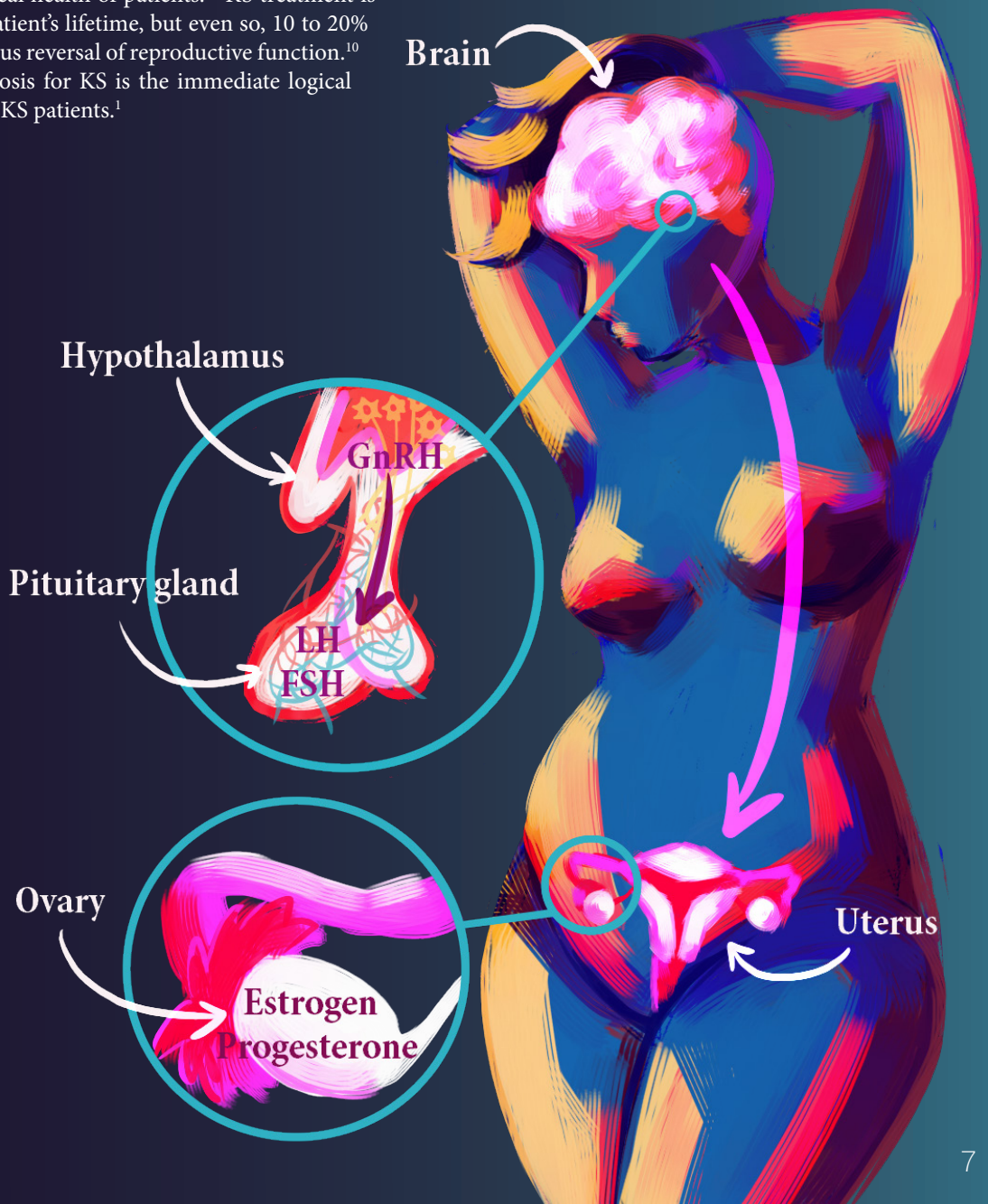


One of the first genes found to be associated with KS was the Kallmann 1 gene (*KAL1*), located on the X chromosome.[3,7] A sequencing approach conducted by Georgopoulos et al. on KS patients found nine different point mutations occurring within the exons of the *KAL1* gene, which acted as a precursor to KS.[3,8] The *KAL1* gene is responsible for the production of anosmin-1, a protein that plays a vital role in the processes of neural adhesion and axonal migration.[7] The loss of function of this protein associated with the aforementioned genetic mutations is speculated to contribute to the aberrant GnRH secretion patterns found in KS patients.

Finally, it is worth noting that only about 40% of KS patients have an identifiable genetic mutation.[3,7] This indicates that there are either additional genes not identified by researchers whose mutations give rise to KS, or other factors besides heritability that promote the presentation of KS.

TREATMENT

The median age to begin effective KS treatment is 18 to 19 years of age in Europe.[9] Although advances have been made in the field, this median age has remained unchanged for the past three decades, with timely clinical diagnosis and overall quality of patient care having barely improved.[9] Receiving an early diagnosis and treatment for KS is ideal as it can prevent disease-related complications, particularly during adolescence —a critical period for secondary sexual maturation and psychological development.[9,10] Genetic interruption is one solution to prevent vertical transmission of KS and can be used after detection via preimplantation genetic testing.[10] For a newborn diagnosed with KS and presenting with cryptorchidism, surgical operation is the first choice at 6 to 12 months of age.[10] In addition, KS patients can develop secondary sexual characteristics, maintain normal sex hormone levels, lead a healthy sexual life, and achieve fertility if provided with timely and appropriate hormone replacement therapy (HRT).[10] Depending on the main goals and age of a KS patient, different HRT prescriptions support different treatment objectives.[10] These treatments for physiological and biological presentations of KS can also improve the psychological health of patients.[10] KS treatment is usually required for the entirety of a patient's lifetime, but even so, 10 to 20% of patients may still undergo spontaneous reversal of reproductive function.[10] Further research on a definitive diagnosis for KS is the immediate logical step in improving the quality of life for KS patients.[1]



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