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Commentary

Bringing Kallmann Syndrome into Focus

David P. Bick[1] and Andrea Ballabio[2]

Three articles (1–3) in this issue of *AJNR* bring the power of magnetic resonance (MR) to bear on the problem of neuroimaging in Kallmann syndrome (KS). These investigators provide the most detailed views of KS olfactory pathology that can be obtained outside of the anatomy laboratory, opening a new window on the study of this disease.

The principle phenotypic features of KS, anosmia and hypogonadism, were first reported at autopsy almost 150 years ago (4). When Franz Kallmann demonstrated the association in a living individual, he also showed that the disorder can be inherited in an X-linked fashion (5). Although a rare disorder, affecting about 1 in 10,000 men and 1 in 50,000 women (6), evidence appeared that KS can be inherited as an autosomal recessive (7) or autosomal dominant (8) as well. The three patterns of inheritance imply that mutations in different genes can result in hypogonadism with anosmia. Many genes are known to have pleiotropic effects during development; therefore, it is not surprising that the two principle features of KS are associated with several other defects. Some of the defects are associated with a particular pattern of inheritance, probably reflecting the function of that gene in development. For example, renal abnormalities are seen in patients with the X-linked form (9), whereas midline defects, such as cleft lip and palate, are seen in autosomal recessive pedigrees (7). Some of the associated abnormalities reported in KS patients are likely to be chance associations unrelated to the underlying gene defect. For all of these reasons, correlating the genotype with the phenotype has been difficult in KS.

Nevertheless, the basis of the central features of the disease was clear: anatomic studies showed that the olfactory disturbance was caused by hypoplasia or aplasia of the olfactory bulbs and tracts (10), and physiological studies showed that the hypogonadism was caused by gonadotropin-releasing hormone (GnRH) deficiency (11). The latter studies led to hormonal therapies that restore fertility (12).

Neuroanatomic studies showed that the GnRH-secreting neurons of the hypothalamus originate in the olfactory placode and migrate into the brain along with olfactory, terminalis, and vomeronasal nerves (13, 14). A study of a fetus with X-linked KS showed that the cells and nerves of the olfactory placode develop normally, but fail to migrate to their proper position in the brain, instead stopping prematurely at the meninges (15), suggesting that the X-linked KS gene product is involved in this movement.

Despite these insights, little else was known about KS genes and how mutations in these genes related to the phenotype until recently. In 1991, the gene for X-linked KS (KAL) was isolated (16, 17). Using the cloned KAL gene, investigators have demonstrated mutations in KS patients (18, 19). The KAL-predicted protein sequence proved to have homology to a number of neural cell adhesion molecules involved in axonal pathfinding consistent with a migration defect. Therefore, it was surprising when in situ hybridization studies in the chick showed that KAL messenger RNA (mRNA) is expressed in the mitral cells of the olfactory bulb, the target of olfactory axons. No expression was found in the olfactory placode or its derivatives (20). These data suggest that the KAL protein may be involved in neural target recognition by mediating the interactions between olfactory axons and the mitral cells of the olfactory bulb. The KAL mRNA is found in other areas of the chick brain, providing a clue to the other neurodevelopmental abnormalities in KS. For the clinician, the availability of the cloned KAL gene will allow molecular diagnosis and, therefore, an unambiguous assignment of KS patients into those with a detectable mutation in

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the KAL gene and those with other forms. This is an important step in the delineation of one of the KS genotypes.

The work described in this journal (1–3) allows a more precise definition of the phenotype in KS. Extending the work of Klingmuller (21), each team obtained a series of 3-mm thick coronal MR images through the region of the olfactory bulbs and tracts. These papers demonstrate a small, often absent olfactory sulcus as well as small or absent olfactory bulbs and tracts in the KS patients studied. The findings of each team are remarkably similar despite the use of somewhat different techniques to acquire, display, and analyze the data. Naturally, close inspection of the images does show patient to patient variability. While some variability can be attributed to technical details, clearly this is not a homogeneous group of patients. For example, patient 6 described by Knorr et al (2) has normal olfactory sulci. Is this a phenotypic difference reflecting a genotypic difference among the patients studied?

MR's window to the brain provides a unique opportunity (and challenge) to reassess the classification of KS patients by studying all aspects of phenotype and genotype. A correlation of genotype with phenotype will benefit both the patient and our understanding of KS. For example, it is known that X-linked ichthyosis is caused by a mutation in the steroid sulfatase (STS) gene. STS is found next to the KAL gene on the X chromosome (22). Male patients with a deletion of the X chromosome removing both genes will have both diseases. Patients with larger deletions involving more genes will have more diseases. These are called *contiguous gene syndromes* (23). A DNA analysis using the STS and the KAL probes on Knorr et al's patient 3, a KS patient with ichthyosis, might show that a deletion in this region of the X chromosome is the cause of his disease. Counseling the family about X-linked disease, searching for carriers in the family, and looking for renal abnormalities in the affected family members would follow.

MR opens a number of research opportunities with respect to the phenotype in KS. For example, it is known that some KS patients have neurologic deficits reflecting abnormalities outside the olfactory and hypothalamic regions, including hereditary mirror movements (synkinesia), spastic paraplegia, cerebellar dysfunction, spatial attentional abnormalities, gaze-evoked horizontal nystagmus, color vision disturbance, mental retardation, pes cavus, and hearing loss (18). For some of these, MR imaging of appropriate areas of the brain may yield clues to the underlying brain pathology.

It is important to note that these studies have applicability beyond the study of this rare disease. Coronal MR imaging of the olfactory region can help in the diagnostic evaluation of certain young children with hypogonadism and older individuals with delayed puberty (2, 3), particularly when endocrinologic testing cannot or does not help.

Just as MR imaging is bringing the brain into focus, molecular cloning is bringing human genetics into focus. As these two fields further define the phenotype and genotype of the human brain, there is no doubt that these two imaging techniques will find themselves together in the pages of *AJNR* many times in the future.

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