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Review paper

ANOS1: a unified nomenclature for Kallmann syndrome 1 gene (*KAL1*) and anosmin-1

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on behalf of Group of HGNC consultants for *KAL1* nomenclature

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Abstract

It is accepted that confusion regarding the description of genetic variants occurs when researchers do not use standard nomenclature. The Human Genome Organization Gene Nomenclature Committee contacted a panel of consultants, all working on the *KAL1* gene, to propose an update of the nomenclature of the gene, as there was a convention in the literature of using the '*KAL1*' symbol, when referring to the gene, but using the name 'anosmin-1' when referring to the protein. The new name, *ANOS1*, reflects protein name and is more transferrable across species.

Key words: Kallmann, anosmin-1; *KAL1*; *ANOS1*; gene; nomenclature

Introduction

An analysis of research and review articles published in international journals has been carried out to briefly summarize both the well established and the most recent knowledge on the *ANOS1* gene and anosmin-1 physiopathology in Kallmann's and other diseases.

This article reports the most relevant information on *ANOS1* and its product anosmin-1, from the identification to its new functions. It addresses a topic of importance to endocrinologists of reproduction, with indications for a better and correct classification of the genetic variants of Kallmann's disease. The authors, together with the panel of consultants, hope that researchers and the scientific community, overall, will use the

new nomenclature *ANOS1* for the gene encoding for anosmin-1 and responsible for the X-linked form of Kallmann syndrome (KS), and *ANOS2P* for the pseudogene on the Y chromosome. The symbol *ANOS1* will be propagated to orthologs in vertebrate species.

The application of a standard genetic nomenclature is fundamental to an accurate scientific communication and a correct classification of disease-related genes. In this regard, the Human Genome Organization (HUGO) Gene Nomenclature Committee (HGNC: www.genenames.org) [1] has recently proposed to the community to standardize the nomenclature of the *KAL1* gene to *ANOS1*. The *ANOS1* gene was first described as responsible for KS, a developmental genetic disease belonging

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to the wide family of congenital idiopathic hypogonadotropic hypogonadism.

KS was described as a genetic heterogeneous association between a lack of olfaction/smelling (anosmia) and hypogonadotropic hypogonadism, as the cause of sterility [2–4], with a prevalence estimated from around 1:8000 in men and 1:40 000 in women [5]. Adult patients typically show normal or low levels of circulating gonadotropins and low serum gonadal hormone levels because of an impairment of the function of gonadotropin-releasing hormone (GnRH) system, the master regulators of the hormonal reproductive axis. The lack of smell results from a developmental defect of the olfactory bulb (OB) [6].

The olfactory and reproductive dysfunctions may be combined with other defects or satellite symptoms, including renal agenesis, mirror movement (synkinesis), syndactyly, craniofacial abnormalities, coloboma and sensorineural deafness.

It took until 1989 to get the evidence that the biological defects observed in one 19 week-old KS-affected human fetus resided in the defective development of the olfactory axons and the arrest of hypothalamic GnRH neurons in their migration from the olfactory placode to the hypothalamus [7]; the results of this pioneering report have been confirmed more later in a 25 week-old KS-affected male fetus and in other fetuses affected by developmental arrhinencephalic disorders [8].

However, it was at the beginning of the 1990s decade that the assignment of a syndrome locus on the X chromosome was made [9], and the detection of a genetic lesion at Xp22.3 led to the definitive identification of the first KS candidate gene [10, 11]. A clinical severe form of hypogonadism is present in patients affected by the X-linked form of KS, which includes an absent or altered pulsatile gonadotropin secretion, low serum testosterone levels and a lack of puberty; however, the gonadotropin response to GnRH stimulation is preserved in these subjects [12]. X-linked KS phenotype is characterized by a severe anosmia, bimanual synkinesia, bilateral cryptorchidism and renal agenesis [13]. MRI analysis reveals aplastic or dysplastic OB and other brain changes associated with mirror movement [14].

The gene causative for the X-linked form of KS was named Kallmann syndrome 1 sequence (KAL1) [15]. The gene escapes X inactivation, has a homolog on the Y chromosome (originally named KALP) and shows an unusual pattern of conservation across species because it has not been so far identified in mouse and rat [15]. Other different modes of KS transmission (autosomal dominant and recessive) have since been described [8], among them the autosomal dominant form caused by mutation of the gene FGFR1, initially defined as KAL2 gene [16]. Interestingly, both KAL1 and FGFR1 have been recently proposed for noninvasive embryonic diagnosis of KS [17]. The contribution of FGFR1 to congenital hypopituitarism has been recently revisited [18]. Of interest, the first report on ANOS1 overexpression, because of a recessive X-chromosome microduplication, in humans reveals a phenotype characterized by hyperosmia, genital anomalies (testicular hydrocele and cryptorchidism), ectrodactyly and additional symptoms like mild intellectual disability, unilateral hearing loss, stocky build and facial dysmorphism, possibly related to a possible interference with the FGFR1 signal [19].

ANOS1 loss-of-function mutations are associated with the X-linked KS phenotype, but they have not so far been linked with other developmental defects (midline abnormality, cleft palate) found in other forms of KS [13].

Moreover, in recent years, the identification of a large proportion of oligogenic forms of the disease has changed the whole view of the genetic basis of KS [20].

The ANOS1 gene is largely conserved from invertebrates to primates including some rodents (Table 1). It is peculiar to note that although human ANOS1 gene product has been found to be functional in mice cells and tissues [21, 22], its immunoreactivity has been detected in rat tissue, using an antibody for the human protein, and human and mice share about 99% of genes; no KAL1 ortholog in mouse and rat has been so far identified [23], making a more complete genetic analysis of the role of ANOS1 in biological processes using classical rodent models not possible.

Anosmin-1

The ANOS1 gene contains 14 exons and encodes for the protein anosmin-1 whose lack or mutation is responsible for the main symptoms characterizing the X-linked form of this disease [24]. Anosmin-1 is a 680 amino acid glycoprotein of the extracellular matrix [25], with a high degree of sequence identity among species, that contains: (i) a cysteine-rich region (CR domain), (ii) a whey acidic protein (WAP)-like domain similar (like serine protease inhibitors), (iii) four consecutive fibronectin type III domains (FNIII, like many cell-adhesion molecules) and (iv) a C-terminal region rich in basic histidines and prolines [26] (Figure 1). The WAP domain is present in protease inhibitors and was found to play a role in axonogenesis and neuron migration. FnIII domains are present in proteins involved in cell adhesion, in tyrosine kinases and in phosphatases, implicated in neuronal migration and in axon guidance. In this sense, along this sequence, it is noteworthy that there are five potential heparan sulphate-binding sites as well as six sites for possible N-glycosylation.

The expression of ANOS1 messenger RNA (mRNA) and anosmin-1 protein extends from the embryonic development to adulthood, and it should be remarked that both mRNA and protein are largely more present in the different structures of the central nervous system (CNS, including cerebral cortex, OB and other components of the olfactory system, retina, cerebellum, spinal cord) than in other body organs and structures (inner ear, kidney, testis, skin and vascular endothelial cells), and overall explains the main and satellite symptoms in KS patients (for a comprehensive review on the subject, see [27]).

Table 1. Orthologs of human KAL1 gene with updated nomenclature to ANOS1 and similarities in different species

Organism	Gene name	Human gene similarity (%)
Chimpanzee	ANOS1	97
Cow	ANOS1	79
Dog	ANOS1	82
Chicken	ANOS1	74
Guinea Pig	ANOS1	84
Rabbit	ANOS1	74
Squirrel	Anos1	87
Rat	No ANOS1 ortholog so far identified	–
Mouse	No ANOS1 ortholog so far identified	–
Zebrafish	anos1a, anos1b	61
C. elegans	kal-1	42
Drosophila	Anos1	38

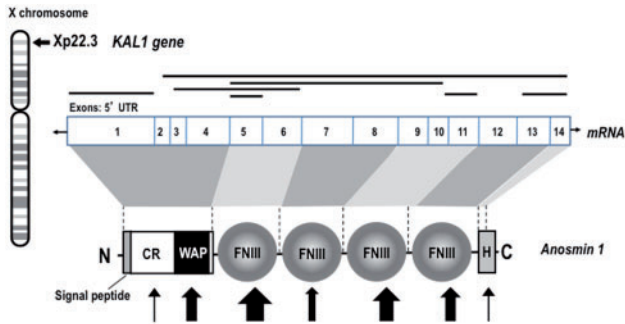


Figure 1. Structure of ANOS1 gene and of anosmin-1 protein. Schematic representation of the ANOS1 gene location on the short arm of X chromosome, of anosmin-1 mRNA and protein structures and mutations. The number on the mRNA structure indicates the exons covering the ORF of the protein anosmin-1; shaded area indicates the exons involved in the coding of the different protein domains. The position of the CR domain, the WAP-like domain, the four FNIII repeats and the histidine-rich domain of anosmin-1 are also indicated. Main exon deletions are shown with black lines, and point mutations are indicated by the arrows; the size of the arrows indicates approximately the frequency of the identified mutations (adapted from [31]).

Although different putative interacting proteins for anosmin-1 have been described to date, the mechanism of action of this protein remains far from completely characterized. FGFR1, heparan sulphates, syndecan, glypicans, as well as different components of the extracellular matrix (uPA, fibronectin, laminin, integrin-beta, anosmin-1 itself—in many of these cases, the activity seems totally independent of FGF2–FGFR1 signaling) are able to interact with anosmin-1 either alone or, occasionally (this is the case of FGFR1 and heparan sulphate), together and with different results [23, 28–30]. Among them, FGFR1 is undoubtedly the most studied because mutations in FGFR1 gene (*KAL2*) are responsible for the autosomal dominant form of KS [16]. In total, >60 mutations of ANOS1 have been described, but clear hot spots have not been identified (Figure 1) [31]. Most of mutations are deletion, frameshift or nonsense; missense mutations in the FNIII domains of ANOS1 are among the most frequent in KS patients, while the real significance of the mutations in the WAP domain on the biological activity of anosmin-1 remains far from clear [21, 29, 32]. More details on the ANOS1 gene mutations underlying KS, including the suggested heterogeneity of effects related to the cell type, their extracellular environment or the combined interaction with different putative receptors, have been widely reported [23, 31]. More recently, a study carried out in *Caenorhabditis elegans* revealed that KAL-1/anosmin-1 may mediate neurite branching by acting as an autocrine cofactor of FGF signaling through a receptor complex consisting of the nematode orthologs of fibroblast growth factor receptor and cell adhesion molecule L1 [33].

Regarding its function in biology, in different *in vitro* models, anosmin-1 has been demonstrated to affect cell adhesion, neurite outgrowth and branching [34–36] and cell migration [21], whereas in *in vivo* models, it appears to regulate several aspects of neurogenesis [22], the motility/migration of different neural cell types during development and, both physiologically and in pathological scenarios in the adult [28, 30, 37], the outgrowth of axons and the genesis of axon collaterals [38, 39] as well as in the differentiation of oligodendrocytes and myelin formation [40]. Finally, the relevance of locally produced anosmin-1 on regulating three major morphogens like FGF8, BMP5 and WNT3a and therefore its crucial role in the formation of the neural crest has been also shown [41].

Other functions of Anosmin-1

Besides KS, anosmin-1 has been described as relevant in the pathogenesis of multiple sclerosis, the most frequent primary demyelinating disease and the most frequent neurological disease in young adults: the protein is upregulated in the core of chronic-active and chronic-inactive demyelinating lesions (in this zone of the lesions, there is no spontaneous remyelination), maybe produced by astrocytes, but not in the periplaque of the former type or in active lesions, the only sites where spontaneous remyelination by endogenous oligodendrocyte precursor cells occurs [37]. Also in samples from human cerebral cortices with multiple sclerosis, anosmin-1 is present in 13–14% of the nude axons crossing demyelinated lesions, but not in their periplaques or in the normal appearing white matter [37]. It is extremely interesting that endogenous oligodendrocyte precursor cells effectively recruited toward demyelinating lesions are mainly positive for FGFR1, which suggests that this lack of potential remyelinating cells would be because of anosmin-1 antagonizing the FGF2 motogenic effect [28, 37] (this scenario has been described more extensively by de Castro and coworkers [23, 42]). Indeed, the relationship between KS and demyelination/multiple sclerosis remains to be fully addressed after recent reports [43, 44, 45]. The real/direct contribution of ANOS1 gene to septo-optic dysplasia and deafness has been recently reevaluated together with the availability of new diagnostic tools [46–48].

Anosmin-1 protein also exerts functions outside the CNS: it modulates the response to immunoglobulin therapy in dermatomyositis [49] and regulates the density of nerve terminals in the epidermis affected by atopic dermatitis [50]. More recently, it has been shown that is concomitant SOX10 mutation the real cause of skin/hair/iris hypopigmentation [48].

Finally, ANOS1 has been involved in migration and metastasis of cancer cells; in particular, its expression was found modified in several tumors including brain, ovarian, colorectal, hepatocellular and oral squamous cancer [30, 51–55], where it may play a role as a possible modulator of the reactivation of developmental signal pathways, and therefore proposed as diagnostic or prognostic tool. In this regard, recently, it has been proposed that while the serum levels of anosmin-1 would be a good biomarker for gastric cancer prognosis and treatment stratification of patients [56], ANOS1 may be a tumor suppressor for hepatocellular cancer [55].

The change of nomenclature

The scientific community has previously used *KAL1*, *KAL-1* and even *ANOS-1* or *ANOS1* (both, with or without hyphen, either in capital letters or not) to refer to the same gene, that encodes anosmin-1. In accordance with the suggestion of HGNC, who supported and encouraged us to write this position statement, we and the other researchers forming the group of consultants recruited by HGNC (see Acknowledgements) agree here to adopt the gene name *anosmin1* (without hyphenation), encoding for anosmin-1 protein, with the approved symbol ANOS1 (Table 2).

The symbol 'KAL' was first approved in 1986 by the HGNC to represent the KS phenotype rather than a specific gene. This was later updated from *KAL* to *KAL1* to distinguish it from the distinct form of KS known as *KAL2*. The causative gene for the X-linked form of KS was identified by two separate groups in 1991 as *KALIG-1* for 'Kallmann's syndrome interval gene 1' [10] and as *ADMLX* for 'adhesion molecule-like from the X

Table 2. Old and new nomenclatures for ANOS1

	Old nomenclature	New nomenclature
Gene name	Kallmann syndrome 1 sequence	Anosmin 1
Symbol aliases	KAL1, KAL-1, ADMLX, KAL, KALIG-1, KALIG1, HHA, KALM_HUMAN, KMS, WFDC19,	ANOS1
Gene name aliases	Adhesion molecule-like X-linked anosmin-1, Kallmann syndrome interval gene 1, WAP four-disulfide core domain 19, Kallmann syndrome 1 protein, Kallmann syndrome protein	–

chromosome' [11]. As neither symbol fitted with HGNC guidelines, the symbol *KAL1* was retained for the cloned gene.

The first study on the protein encoded by *KAL1* named this protein 'anosmin-1' to reflect the loss of smell, or anosmia, in patients with KS [24]. The name anosmin-1 grew in popularity over the years, and it became the convention to refer to the gene as *KAL1* and the protein as anosmin-1. The protein name has been used for different species such as zebrafish [35], tamar wallaby [31] and Asian musk shrew [57].

In early 2015, the HGNC proposed updating the gene nomenclature to be in line with the protein name because this is more transferrable across species and avoids any confusion between 'KAL1' and other genes that cause forms of KS. Additionally, the name 'anosmin' is indicative of function since the lack of sense of smell in KS is because of the role of the protein in axonal outgrowth in the olfactory system. This nomenclature scheme may also be readily adapted to incorporate additional genes encoding other anosmins that would be eventually identified in the future. The symbol *Anos1* [35] had already been published as an abbreviation for 'anosmin-1', and as this symbol is unique, the HGNC proposed the symbol *ANOS1* and named *anosmin1* for the gene. Hyphens were omitted to follow the conventions of gene nomenclature. The HGNC contacted researchers who had previously published on *KAL1*, and there was community support for the change.

The change in nomenclature of *KAL1* resulted in a concordant change for the inactive homolog, which is present on the Y chromosome. This gene was first reported as a pseudogene because of frameshift and premature stop codons and named *KALP* [15]. Surrounding gene order and theories on Y chromosome evolution [58, 59] suggest that *KALP* has degraded *in situ* rather than being a duplication of *ANOS1*. According to annotation by the HAVANA group [60], this pseudogene is still transcribed. Therefore, *KALP* has been renamed as *ANOS2P* for 'anosmin2, pseudogene' to reflect its status as a degraded homolog of *ANOS1* and not as a duplicated pseudogene of *ANOS1* (which would have been given the symbol format *ANOS1P1*).

We hope that interested researchers and the scientific community, overall, will use the new nomenclature *ANOS1* for the gene encoding for anosmin-1 and responsible for the X-linked form of KS, and *ANOS2P* for the pseudogene on the Y chromosome. The symbol *ANOS1* will be propagated to orthologs in vertebrate species, and we request that researchers working on other species will also use the updated symbols.

Key Points

- A different nomenclature is used to define Kallmann syndrome 1 gene (*KAL1*) and its proteic product (anosmin-1).
- The most recent knowledge on the *KAL1* gene and anosmin-1 confirms their involvement in the pathophysiology of Kallmann's disease but also in other diseases.
- The HUGO Gene Nomenclature Committee (HGNC) with a panel of consultants propose an update of the nomenclature of the *KAL1* gene in *anosmin1* (*ANOS1*) and *ANOS2P* for the pseudogene present on the Y chromosome.
- This nomenclature scheme may also be readily adapted to incorporate additional genes encoding other anosmins that would be eventually identified in the future.

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The new nomenclature was also considered and unanimously approved by the European consortium on GnRH deficiency (COST Action BM1105, www.gnrhnetwork.eu).

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