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Unilateral Renal Agenesis as an early marker for genetic screening in Kallmann Syndrome.

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Abstract

Isolated GnRH Deficiency (IGD) that is either displayed as Kallmann Syndrome (KS) or normosmic idiopathic hypogonadotropic hypogonadism (nIHH) is a rare Mendelian disorder with wide clinical and genetic variability. Apart from the arrest of pubertal development, IGD is also characterized by a variety of non- reproductive features including unilateral renal agenesis (URA), midline defects, dental & ocular defects and many more. In this analysis we explored the role of unilateral renal agenesis, as a screening tool for detection of genetic changes associated with IGD. We performed detailed genetic screening with Sanger sequencing in 14 genes associated with Isolated GnRH Deficiency as well as screening of intragenic deletions in the gene of anosmin 1-ANOS1 with MLPA. No genetic variation was detected, suggestive of an alternative genetic cause for URA in these normosmic patients, highlighting the necessity of further genetic screening.

Keywords

GnRH; Unilateral renal agenesis; genetic screening

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Author's contributions: MIS conceived part of the study, participated in its design and coordination, participated in the molecular genetics studies and drafted the manuscript; PL participated in coordination of the project, carried out the molecular genetic studies and participated in the sequence alignment; AGT examined the patients, performed all hormonal and imaging tests and made the final diagnosis, referred the patient for genetic testing and obtained informed consents; DS examined the patients, performed all hormonal and imaging tests and made the final diagnosis, referred the patient for genetic testing and obtained informed consents; KV participated in coordination of the project and carried out part of the molecular genetic studies; GAN conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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Dear Editor,

Isolated Gonadotropin-releasing hormone (GnRH) Deficiency (IGD), is a rare Mendelian disorder, characterized by genetic and phenotypic heterogeneity. Apart from the failure of sexual maturation and pubertal development (i.e. the normosmic form of idiopathic hypogonadotropic hypogonadism (nIHH) or the anosmic form of Kalmann Syndrome (KS)), the disorder is also characterized by various **non-reproductive features** including unilateral renal agenesis (URA). Interestingly, family members of the affected patients usually display milder forms of IGD or its non-reproductive features, such as isolated anosmia and URA highlighting the variable expressivity of the disorder[1,2]

We have previously reported the prepubertal diagnosis of KS in a male patient with URA, who carried a mutation in the gene of anosmin 1- *ANOS1*, previously known as kallmann-1 (*KAL1*) [3], whereas other non-reproductive IGD features have been utilized for an early KS diagnosis [4]. With this letter we would like to share our experience in examining the role of URA as an early prepubertal marker for IGD.

Nine prepubertal normosmic male patients were clinically evaluated and screened for mutations in 14 IGD genes. Genomic DNA was obtained from peripheral blood samples by standard phenol-chloroform extraction. Exonic and proximal intronic (≤15 bp from splice sites) DNA sequences of the following genes was amplified by PCR and determined by direct sequencing: *ANOS1* (OMIM 308700), *GNRH1*(OMIM 152760), *GNRHR* (OMIM 138850), *KISSlR*(OMIM 604161), *KISS1*(OMIM 603286), *CHD7*(OMIM 608892), *NMSF*(OMIM 608137), *FGF8*(OMIM 600483), *FGFR1*(OMIM 136350), *PROK2*(OMIM 607002), *PROKR2* (OMIM 607212), *HS6ST1* (OMIM 604846), *TAC3*(OMIM 162330), and *TACR3*(OMIM 162332). To detect exonic deletions/duplications across the entire coding region of *ANOS1*, gene dosage analysis was performed using the SALSA MLPA kit P132 Kallmann-1 (MRC Holland). Informed consents were obtained.

A summary of the clinical characteristics is shown in Table 1. Importantly, none of the children evaluated was anosmic, whereas signs of GnRH development disruption, such as cryptorchidism, as well as other non-reproductive features were seen in family members. A rare sequence variant (RSV) was defined as a) a variant affecting splice junctions within lObp of coding sequence; or a protein-altering/protein-truncating non-synonymous variant; and b) present in <1% minor allele frequency (MAF) in Exome Variant Server, NHLBI GO Exome Sequencing Project (ESP), Seattle, WA (URL: http://evs.gs.washington.edu/EVS./), [February 2016], 1000Genome project [http://www.1000genomes.org/home] [5] and the non – Finish European population of the Exome Aggregation Consortium (ExAC), Cambridge, MA (URL: http://exac.broadinstitute.org) [February 2016].

Neither RSVs in any of the 14 genes nor intergenic dosage alterations in *KAL1* were detected. The lack of a genetic association in this prepubertal normosmic cohort could be attributed to (i) the clinical presentation of our patients; even though nIHH cases with URA have been previously reported[6], the majority of studies have linked URA to KS and *ANOS1* genomic alterations, (ii) a missed genetic alternation in the rest of the 37 known IGD genes not screened here, or (iii) an independent genetic cause for URA; since nephrogenesis is

controlled by genes enhancing or inhibiting precursor cell growth[7], a different genetic cause for isolated URA cannot be excluded in these patients. In conclusion, the genetic screening for the 14 IGD genes in a small cohort of normosmic children with isolated URA has not revealed any genomic alterations. However, further genetic screening may reveal a genetic association, important for genetic counseling and clinical follow-up. Such genetic screening is especially recommended in patients with a strong family history and/or additional non-reproductive features of IGD.

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References

1. Pitteloud N, Quinton R, Pearce S, et al. Digenic mutations account for variable phenotypes in idiopathic hypogonadotropic hypogonadism. J Clin Invest 2007;117:457–63. [PubMed: 17235395]
2. Ml Stamou, Varnavas P, Kentrou M, et al. Isolated GNRH deficiency: genotypic and phenotypic characteristics of the genetically heterogeneous Greek population. EurJ Endocrinol 2017;176:L1–L5. [PubMed: 27884859]
3. Georgopoulos Neoklis A., Koika V, Varnavas P, et al. Can Kallmann syndrome be occasionally diagnosed during childhood? Genetic diagnosis in a child with associated renal agenesis and mirror movements. Asian Journal of Andrology 2009;11:521–3. [PubMed: 19234483]
4. Kaplan JD, Bernstein JA, Kwan A, Hudgins L. Clues to an early diagnosis of Kallmann syndrome. American journal of medical genetics Part A 2010;152A:2796–801. [PubMed: 20949504]
5. Abecasis GR, Auton A, Brooks LD, et al. An integrated map of genetic variation from 1,092 human genomes. Nature 2012;491:56–65. [PubMed: 23128226]
6. Quinton R, Duke VM, Robertson A, et al. Idiopathic gonadotrophin deficiency: genetic questions addressed through phenotypic characterization. Clinical endocrinology 2001;55:163–74. [PubMed: 11531922]
7. Sanna-Cherchi S, Caridi G, Weng PL, et al. Genetic approaches to human renal agenesis/hypoplasia and dysplasia. Pediatr Nephrol 2007;22:1675–84. [PubMed: 17437132]

Table 1:

Clinical Characteristics of 9 prepubertal male patients with URA.

Age	Age at Dx	cryptorchidism	anosmia	prematurity	Birth order	UT/ nephro defects	Ass. Abn	Fx of renal agenesis	Fx
6 yo	2.5 m	no	no	no	second	no	no	n/a	Anosmia in both grandfathers
15 yo	7 month of embryonic development	no	no	no	third	ureteropelvic junstion stenosis R, hydronephrosis R, chronic renal failure	no	n/a	Cleft lip and palate in maternal aunt, Psychiatric disorder in two grandparents
6 yo	2nd trimeter	no	no	no	first twin birth	no	no	nl	Depression paternal great uncle
8 yo	2nd trimester	no	no	no	second	no	verbal disorder, speech therapy	nl	T1D father, Nephrolithiasis paternal grandfather, Hypothyroidism paternal grandmother, Hyperthyroidism paternal great uncle, Epilepsy maternal uncle
5 yo	2nd trimester	no	no	no	third	no	no	n/a	Anosmia paternal great grandmother, Kidney malformation in maternal great uncle, Verterbal collum lipoma maternal aunt
6 yo	2nd trimester	cryptorchidiam R-orcheopexy at 18 m	no	no	third	no	no	n/a	T1D maternal aunt, Gastroschisis paternal grate grandfather
11 yo	at birth	no	no	no	third	no	hydrocele L, balanoposthetical adhensions	n/a	Hyposmia paternal great aunt, Skoliosis father, Skoliosis, osteoporosis and Parkinson's disease in paternal grandfather, Parkinson's diseasepaternal great uncle, Psoriasis paternal grandmother
6 yo	2nd trimester	no	no	no	second	no	no	brother with URA	Strabismus mother, Hypothyroidism-Thyroidectomy-T2D maternal grandmother
10 yo	9 m	no	no	no	first	hydroureter R, nephrocalycosis R	stravismus	brother with URA	Strabismus mother, Hypothyroidism-Thyroidectomy-T2D maternal grandmother

Table 1 shows the clinical characteristics of the 9 male prepubertal patients analyzed including their age, age at diagnosis, the presence of cryptorchidism, anosmia or prematurity, the birth order, the presence of urinary tract or renal defects, associated abnormalities, family history of unilateral renal agenesis or other diseases and disorders, including reproductive or non-reproductive features of IGD. Dx: Diagnosis, UT: Urinary tract, Ass. Abn: Associated Abnormalities, Fx: Family history. N/a: not available, nl: normal, T1D: type 1 diabetes, T2D: type 2 diabetes.