



Hypogonadotropic hypogonadism associated with another small supernumerary marker chromosome (sSMC) derived from chromosome 22, a case report

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Abstract: The idiopathic hypogonadotropic hypogonadism (IHH) is portrayed as missing or fragmented pubescence, cryptorchidism, small penis, and infertility. Clinically it is characterized by the low level of sex steroids and gonadotropins, normal radiographic findings of the hypothalamic-pituitary areas, and normal baseline and reserve testing of the rest of the hypothalamic-pituitary axes. Delay puberty and infertility result from an abnormal pattern of episodic GnRH secretion. Mutation in a wide range of genes can clarify ~40% of the reasons for IHH, with the majority remaining hereditarily uncharacterized. New and innovative molecular tools enhance our understanding of the molecular controls underlying pubertal development. In this report, we aim to present a 26-year-old male of IHH associated with a small supernumerary marker chromosome (sSMC) that originated from chromosome 22. The G-banding analysis revealed a karyotype of 47,XY,+mar. High-throughput DNA sequencing identified an 8.54 Mb duplication of 22q11.1-q11.23 encompassing all the region of 22q11 duplication syndrome. Pedigree analysis showed that his mother has carried a balanced reciprocal translocation between Chromosomes 22 and X[t(X;22)]. To the best of our knowledge, this is the second confirmed case of IHH with an sSMC deriving from chromosome 22. Based on our study, the duplicated chromosome fragment 22q11.1-q11.23 might be the reason for the phenotype of our case. Meanwhile, High-throughput DNA sequencing combined with cytogenetic analysis can provide a more accurate clinical diagnosis for patients carrying sSMCs.

Keywords: Small supernumerary marker chromosome (sSMC); 22q11.1-q11.23; 22q11 duplication syndrome; high-throughput DNA sequencing; hypogonadotropic hypogonadism (HH)

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Introduction

Idiopathic hypogonadotropic hypogonadism (IHH) is a rare genetic disease, which is described by missing or inadequate puberty, cryptorchidism, infertility, and small penis in males. It is mainly because of deficiency in the secretion or function of gonadotropin-releasing hormone (GnRH) (1,2). Until now, around 50 genes have been reported to be associated with IHH, which account for only 50% of IHH cases (2). Small supernumerary marker chromosomes (sSMC) are

little, extra, and abnormal chromosomes, which are present along with the other 46 normal chromosomes. It is usually equivalent in size to or a little smaller than chromosome 20 of a similar metaphase spread, and can't be portrayed by regular banding cytogenetics (3). The frequency of sSMC is 0.044% in newborn, 0.075% in prenatal cases, 0.288% in mentally retarded patients and 0.125% in subfertile subjects (4). Some studies believed that 6–19% of sSMCs are originated from chromosome 22 (5,6). About 80% of sSMCs

originated from chromosome 22 are presented as non-mosaic dicentric duplications of 22q11.2, and congenital abnormalities like malignant tumors, and the cat-eye syndrome were associated with clinical phenotypes (7).

However, marker chromosomes are very rare in IHH cases. Up to now, it has been reported that only 1 infertile male case of hypogonadotropic hypogonadism (HH) carried chromosome aberrations of a supernumerary inv dup22q11.1 (8). In this report, we present the first case of a supernumerary dup22q11.1-q11.23 with IHH. The current case had a karyotype of 47,XY,+mar, and was assessed for delayed puberty. We present the following article in accordance with the CARE reporting checklist (available at <http://dx.doi.org/10.21037/tau-20-1087>).

Case presentation

A 26-year-old male patient presented in our department was examined properly and then referred for chromosome analysis because of genital retardation with cryptorchidism. He was born as a second child of a healthy Chinese couple. He also suffered from congenital heart disease, cataract, and retinal detachment, but no smell disorders. The medical history of the patient was unremarkable, with no significant history of hazard factors, drugs, toxins, or radiation. Physical examination: height 165 cm, body proportion is normal. No development of bilateral breasts. The penis is juvenile with sparse pubic hair. No testes are touched in bilateral dysplastic scrotum. While testes can be touched in the bilateral inguinal region, and the volume of testes was 3 ml, respectively. Repeated hormone analysis (chemiluminescence method) indicated HH, with a lower level of serum testosterone (0.214–1.302 nmol/L, normal range is 8.64–29.0 nmol/L), relatively low follicle-stimulating hormone level (2.263–3.2 mIU/mL, normal range is 1.5–12.4 mIU/mL) and normal luteinizing hormone level (1.484–1.68 mIU/mL, normal range is 1.7–8.6 mIU/mL).

The other sex hormones were normal, estradiol (12.029–40.1 pmol/L, normal range is 28–156 pmol/L), progesterone (0.314–0.75 nmol/L, normal range is 0.159–0.5 nmol/L), prolactin (9.4–9.62 ng/mL, normal range is 4.04–15.2 ng/mL), dehydroepiandrosterone sulfate (5.59 μ mol/L, normal range is 4.34–12.2 μ mol/L). Thyroid function tests (chemiluminescence assay) showed normal with serum triiodothyronine [T3 6.54 μ g/dL, normal range is 4.4–13.5 μ g/dL], thyroxine [T4 1.61 ng/mL, normal range is

0.78–2.20 ng/mL] and thyroid-stimulating hormone [TSH 0.98 uIU/mL, normal range is 0.25–5 uIU/mL]. Bone age assessment based on hand X-ray Image showed as boys aged 15–16. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

Cytogenetics

After obtaining written informed consent, approved by the Human Research Ethics board of the First Affiliated Hospital, School of medicines, Xi'an Jiaotong University, chromosomal analysis was carried out on peripheral blood lymphocytes (PBL) cultures using GTG banding technique based on 300–400 band level according to the standard protocol. The parents' karyotypes of the proposita(proband) with 47,XY,+mar was further examined to analyze the source and presence of additional small marker chromosomes.

Molecular cytogenetics (detection of chromosome aberration)

Chromosome aberration, i.e., Chromosomal aneuploidy or a known pathogenic genomic copy number variation (CNVs) above 100 Kb of PBL were tested by High-throughput DNA sequencing, i.e., Next-generation sequencing technology.

Results

Chromosome G-banding analysis of patients

The chromosomal analysis confirmed sSMCs in blood lymphocytes, in all metaphases (n=200), each containing an additional marker chromosome, i.e., G-banding karyotype of chromosome 47,XY,+mar (*Figure 1*).

Detection results of chromosome aberration

High-throughput DNA sequencing of the proband revealed a result of: seq[hg19]dup22q11.1-q11.23, chr22:g.16840001_25380000dup, which is an 8.54 Mb region of the chromosome 22 q11.1-q11.23 repeats (*Figure 2*), including all of the 22q11 duplication syndrome (*Appendix 1*).

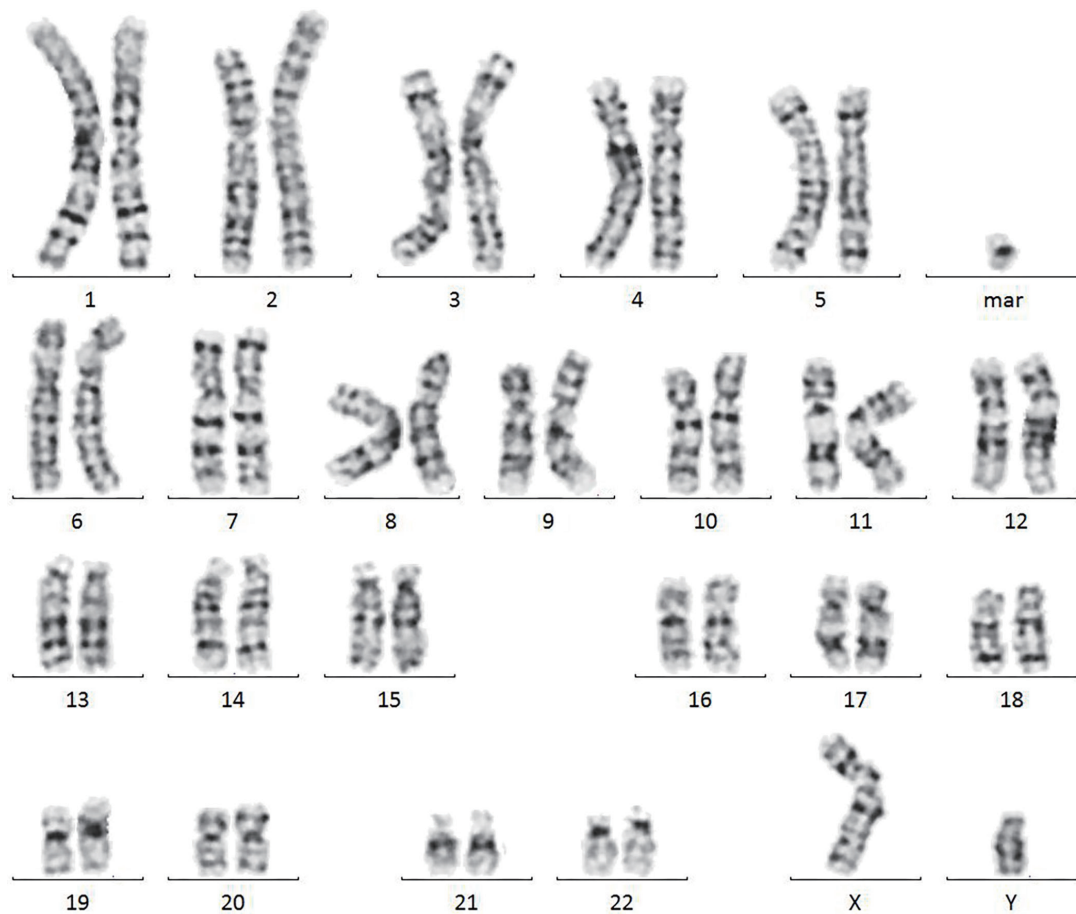


Figure 1 Metaphase karyotype of the patient in GTG banding displaying the detected small supernumerary marker chromosomes: 47,XY,+mar.

Pedigree investigation and genetic study of the proband

The paternal karyotypes were normal, and the maternal chromosome banding revealed a balanced reciprocal translocation between chromosome 22 and X chromosome, which is 46, X, t(X;22) (p22.3; q11.2) (*Figure 3*). Therefore, it is suggested that the genetic abnormality in the patient with supernumerary dup22q11.1-q11.23 was inherited from his mother.

Discussion

The small supernumerary chromosome markers (sSMC) are defined by Liehr *et al.*, whereas abnormal chromosome structure cannot be identified just by using conventional cytogenetic techniques. They have the same size or are smaller than the metaphase chromosome 20 in the

same preparation. A larger event on Ssmc found in some databases showed that they may be present in a karyotype with an abnormal number (e.g., down's syndrome), or with abnormal structure (e.g., balanced translocation, and ring chromosomes). It is believed that most of the sSMC found in normal healthy people come from the short arm of the acrocentric chromosomes. Euchromatin-free sSMCs are usually not harmful. However, duplications near 22q centromere are clinically insignificant (4). The published data presented sSMCs, a supernumerary inv dup22q11.1 in infertile men with HH (9). However, in various studies on sterile males, sSMCs were found more often than expected. An incidence of 0.3% was found in men from the oligozoospermic group and 0.2%, in men of the IVF and ICSI groups (9).

In 2011, Mikelsaar *et al.* (8) introduced the first case of HH with a marker chromosome. The patient was 32 years

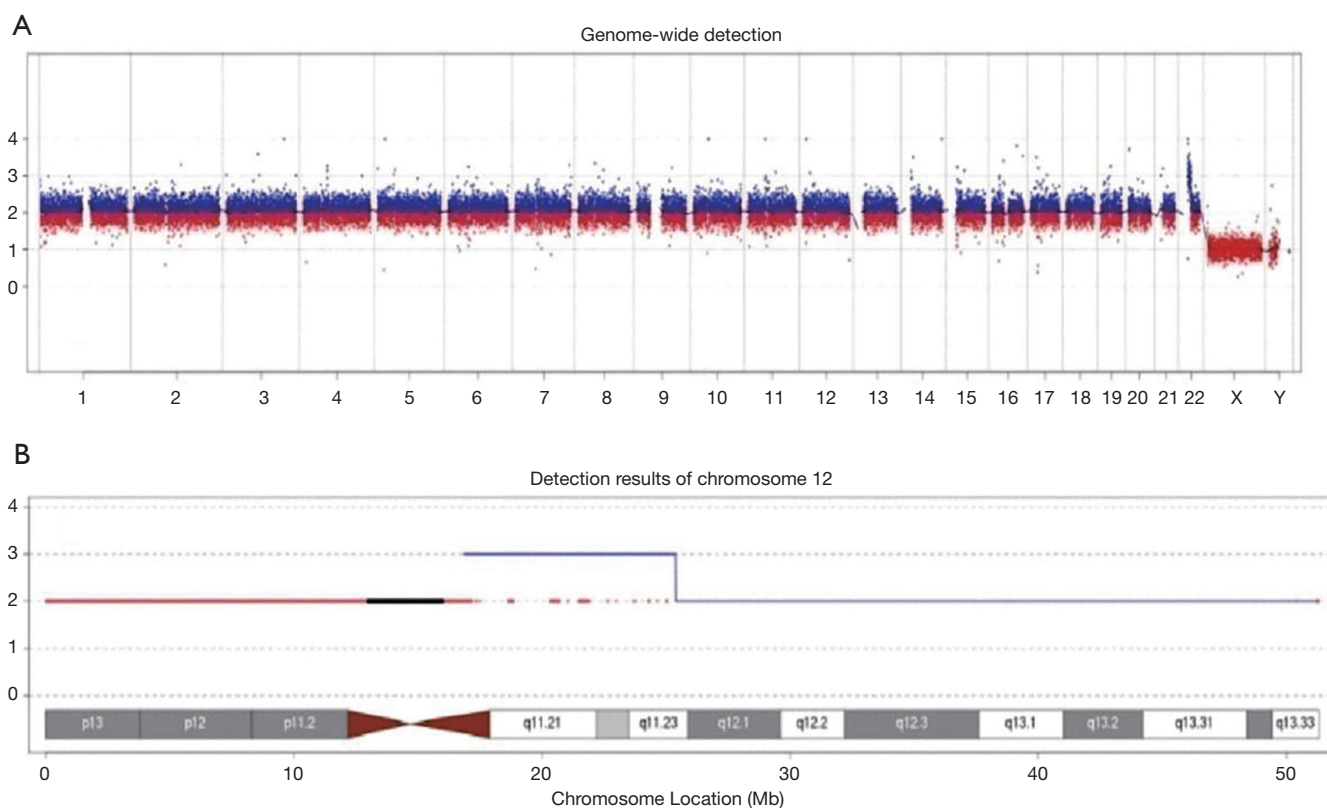


Figure 2 Result of chromosomal aneuploidy or a known pathogenic genomic copy number variation (CNVs) above 100 Kb: (A) genome-wide detection showed Genome copy number variation (CNVs) increased, originating from chromosome 22; (B) detection of chromosome 22 showed a 8.54 Mb Trisomy duplication in the 22q11.1–q11.23 region.

of age with a 47,XY,+mar karyotype, presented with growth and developmental delay, microphallus, and bilateral cryptorchidism. The marker originating from chromosome 22 was determined (distance ~9.6–14.4 Mb from 22pter to 22q11.1) utilizing the fluorescent *in situ* hybridization (FISH) technique.

In our case, the karyotype of the G-band chromosome analysis revealed sSMCs in blood lymphocytes i.e., 47,XY,+mar. Detection of Genome-wide by next-generation sequencing technology showed an 8.54 Mb duplication in the chromosome 22 q11.1–q11.23 region, including all of the 22q11 duplication syndrome. Pedigree investigation and genetic study of the proband suggested the genetic abnormality in the patient with supernumerary dup22q11.1–q11.23 was inherited from the mother, who has a balanced reciprocal translocation between Chromosome 22 and X Chromosome, 46,X,t(X;22)(p22.3;q11.2). 22q11 duplication syndrome has an incomplete appearance, and the patient's phenotype varied from normal, almost

normal to multiple defects, mild learning difficulties, and shared features with DiGeorge/velocardiofacial syndromes (DGS/VCFS), including heart defects, velopharyngeal insufficiency with or without cleft palate, or hypernasal speech, and urogenital abnormalities (10,11). Our patient who carried a sSMC also had retarded puberty, bilateral cryptorchidism, and microphallus as a primary symptom, which coincides with the literature data that the acrocentric sSMC has a causative role in male HH, and its presence is more frequently associated with oligozoospermia (7%) and less with azoospermia (<1%) (12).

The mechanism by which sSMC causes problems with HH in men is still unclear. As with other chromosomal abnormalities, supernumerary dup22q11.1–q11.23 can cause hypothalamic or pituitary dysfunction (13), which may induce impaired secretion of GnRH. Molecular bases of HH are only recognized in 25–30% of patients, and mutations mainly occur in *KAL1* (Xp22.32), *FGFR1* (8p11.2–p11.1), and *GnRHR* (4q21.2) genes. These mutations adversely



Figure 3 Metaphase karyotype of the patient's mother in GTG banding displaying balanced reciprocal translocation between Chromosome 22 and X Chromosome (arrow), i.e., 46,X,t(X;22)(p22.3;q11.2).

regulate neuroendocrine function and thus affect pubertal development, infertility, and spermatogenesis. Even though there are a large number of HH genes, none are located on chromosome 22. In our sample, it was found that no relevant molecular alterations had a possible connection with the phenotype by High-throughput DNA sequencing.

This patient had HH and carried supernumerary dup22q11.1–q11.23 causing trisomy of the centromeric and/or pericentromeric locale of chromosome 22. These regions are known to contain a series of highly repetitive DNA blocks, including genes that encode ribosomal structural RNA.

As far as we know, our case is the second case of HH with a sSMC originated from chromosome 22. By combining the information from the literature of Mikelsaar *et al.* (8), our results demonstrated that supernumerary dup22q11.1q11.23 might result in HH through disturbing GnRH secretion.

We suggest that the duplicated chromosome segment 22q11.1–q11.23 might be liable for the phenotype of our case and may likewise be an applicant locus of HH. Besides, he also suffered from congenital heart disease, cataracts, and retinal detachment. So, we suggest that each new case of IHH should simultaneously have some cytogenetics and molecular genetics tests, especially with multiple malformations. High-throughput DNA sequencing combined with cytogenetic analysis will give us more details about the accurate genotype-phenotype relationships for dysmorphic syndromes.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <http://dx.doi.org/10.21037/tau-20-1087>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tau-20-1087>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

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Appendix:

seq[hg19]dup(22)(q11.1q11.23)

chr22:g.16840001_25380000dup

RefSeqGenes:CRKL,THAP7,TPTEP1,ADORA2A,TUBA8,TUBA3FP,SNRPD3,TMEM191A,ANKRD62P1-

PARP4P3,MIR648,CES5AP1,TMEM191B,TBX1,GSTT2,SUSD2,GNB1L,FBXW4P1,ARVCF,USP18,MIR3198-

1,POM121L4P,COMT,TANGO2,DGCR6L,MICAL3,P2RX6P,MIR301B,POM121L10P,ADORA2A-

AS1,DGCR6,LINC00896,PI4KAP1,GAB4,IGLL1,DERL3,UFD1L,LOC101929374,ZNF280A,C22orf39,ZNF70,MIR130B,MIR5571,VPREB1,SNAP29,CLDN5,TXNRD2,PRODH,DGCR11,MED15,TMEM211,TSSK2,GSTT2B,C22orf29,MRPL40,LOC101928891,LOC100996342,SDF2L1,RTN4R,LOC388849,RSPH14,MIR185,FAM230B,MIR3618,RGL4,SLC25A18,PI4KAP2,GUCD1,UBE2L3,CCT8L2,C22orf15,TMEM191C,THAP7-

AS1, TOP3B,BCRP2,ZNF74,GNAZ,FLJ41941,POM121L9P,HIC2,MIF,SLC25A1,DDT,CDC45,PIWIL3,HSFY1P1,BCR,BCL2L13,CLTCL1,GSTT1,SLC2A11,DGCR5,ATP6V1E1,BID,DGCR2,DDTL,PEX26,HIRA,SPECC1L,CCDC116,DRICH1,RIMBP3B, TOP1P2,P2RX6,IGLL5,SGSM1,DGCR9,LOC391322,LRR75B,DGCR14,PRAME,PI4KA,GSTTP2,LL22NC03-

63E9.3,POM121L1P,MAPK1,VPREB3,GP1BB,RIMBP3,GSTTP1,GUSBP11,LOC101929372,TRMT2A,MIF-AS1,YDJC,GGTLC2,LOC388882,LOC284865,MIR649,CECR6,SEPT5-

GP1BB,LINC01311,XKR3,SERPIND1,CHCHD10,GGT1,SLC7A4,RANBP1,CECR1,KLHL22,SMARCB1,LINC00895,LRR74B,BMS1P20,BCRP3,MIR6816,SPECC1L-

ADORA2A,AIFM3,CECR3,ZDHHC8,RAB36,LZTR1,GGT3P,POM121L8P,RIMBP3C,MIR650,ZDHHC8P1,ZNF280B,SCARF2,YPEL1,CABIN1,PPIL2,SEPT5,DGCR8,CECR2,CECR7,CECR5,DGCR10,CECR5-

AS1,MIR1286,LINC00528,GGT5,MIR4761,PPM1F,GSC2,IL17RA,MIR1306,MMP11,UPB1.