

BRIEF REPORT

Hypogonadism in a Patient with a Mutation in the Luteinizing Hormone Beta-Subunit Gene

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SUMMARY

A 30-year-old man who presented with delayed puberty and infertility was found to have hypogonadism associated with an absence of circulating luteinizing hormone. The patient had a homozygous missense mutation in the gene that encodes the beta subunit of luteinizing hormone (Gly36Asp), a mutation that disrupted a vital cystine knot motif and abrogated the heterodimerization and secretion of luteinizing hormone. Treatment with human chorionic gonadotropin increased circulating testosterone, promoted virilization, and was associated with the appearance of normal spermatozoa in low concentrations. This case illustrates the important physiological role that luteinizing hormone plays in male sexual maturation and fertility.

SEXUAL MATURATION AND FERTILITY IN MEN REQUIRES NORMAL TESTICULAR development, which is governed by chorionic gonadotropin in utero and thereafter by luteinizing hormone and follicle-stimulating hormone. The most frequent causes of hypogonadotropic hypogonadism are abnormalities affecting the secretion of hypothalamic gonadotropin-releasing hormone or pituitary gonadotropic hormones; these disorders result in delayed puberty and infertility. Genetic mutations that interfere with the signaling of gonadotropic hormones or their interactions with their receptors can also impair sexual maturation and fertility.^{1,2}

The glycoprotein hormones luteinizing hormone, follicle-stimulating hormone, chorionic gonadotropin, and thyrotropin share a common alpha subunit but have unique beta subunits; alpha-beta heterodimerization is required for normal receptor binding and biologic activity.³ Naturally occurring inactivating mutations of the gene encoding the alpha subunit of glycoprotein hormone have not been described, but rare mutations in the beta-subunit sequence that produce truncated or abnormally folded proteins have been reported. Mutations in the beta subunit of follicle-stimulating hormone cause hypogonadism and azoospermia in affected men,^{4,5} whereas delayed puberty or infertility occurs in women with either homozygous⁶ or compound heterozygous⁷ mutations in the beta subunit of follicle-stimulating hormone. There has been only one report of a patient with an inactivating mutation in the luteinizing hormone beta subunit that caused low serum testosterone levels, delayed puberty, and arrested spermatogenesis.^{8,9} That patient had a missense mutation that prevented the binding of heterodimeric luteinizing hormone to its receptor.

We describe a man with delayed puberty and infertility due to an isolated deficiency in luteinizing hormone. The patient had a novel homozygous missense mutation in the gene encoding the luteinizing hormone beta subunit, which prevented the heterodimer-

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ization and secretion of luteinizing hormone and abolished its biologic activity.

CASE REPORT

A 30-year-old man from Cameroon was referred for investigation of sexual infantilism. He was 191 cm tall, weighed 100 kg, and had an arm span of 205 cm. He had a eunuchoid habitus, gynecomastia, and a juvenile voice. Penile length was 4 cm, and testicular volume was 8 ml. Scant, normally distributed pubic hair had been present since his late teens. No family members were available for genetic testing, but no case of infertility was reported among the patient's immediate and second-degree relatives. Consanguinity could not be definitively ruled out.

The results of initial laboratory tests were as follows: an undetectable luteinizing hormone level (less than 0.2 mIU per milliliter; normal range, 2.0 to 10.0), an elevated follicle-stimulating hormone level (23 mIU per milliliter; normal range, 1.0 to 8.0), a low testosterone level (0.3 ng per milliliter [1.0 nmol per liter]; normal range, 2.5 to 10.0 [8.7 to 34.7]); a low serum dihydrotestosterone level (73 ng per liter; normal range, 200 to 1000), and a low dehydroepiandrosterone sulfate level (851 μ g per liter; normal range, 900 to 3700). The patient had normal or low-normal levels of inhibin B (156 ng per liter; normal range, less than 400), progesterone (0.1 μ g per liter; normal range, 0.1 to 0.7), estradiol (26 ng per liter [95.4 pmol per liter]; normal range, 10 to 70 [36.7 to 257.0]), and chorionic gonadotropin beta subunit (less than 2.0 IU per liter; normal range, 0 to 5.0). Ninety minutes after the intravenous administration of gonadotropin-releasing hormone (100 μ g), the patient's level of follicle-stimulating hormone rose from 23 to 48 mIU per liter; however, no luteinizing hormone was detected. Magnetic resonance imaging of the brain and pituitary gland showed no abnormalities.

A specimen from a testicular biopsy showed hypoplastic seminiferous tubules with a predominance of Sertoli cells (Fig. 1A). Spermatogenesis was evident, though greatly reduced. A scant number of spermatozoa were noted (Fig. 1B). Leydig cells were visible on staining with hematoxylin and eosin (Fig. 1C). Interstitial microcalcifications were present.

A diagnosis of hypogonadotropic hypogonadism due to an isolated luteinizing hormone deficiency was made. The patient was treated initially with

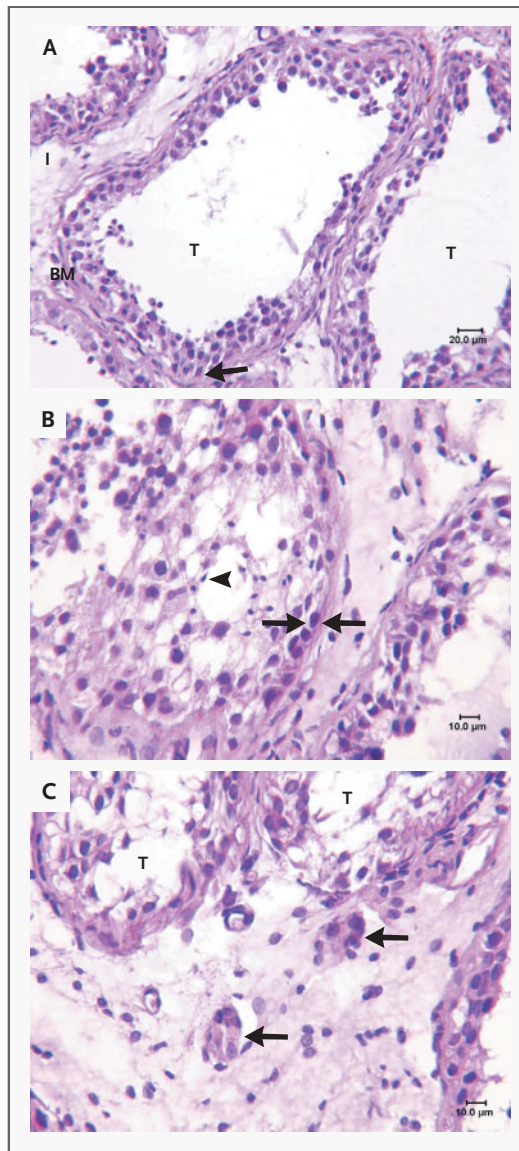


Figure 1. Testicular-Biopsy Specimen from the Patient with Hypogonadism and a Mutation in the Luteinizing Hormone Beta-Subunit Gene (Hematoxylin and Eosin).

Panel A shows representative hypoplastic seminiferous tubules (T) with predominant Sertoli cells (arrow), a thickened basement membrane (BM), and a fibroedematous interstitium (I). Multiple stages of spermatogenesis are evident in the specimen, although at a greatly reduced level. Panel B shows the section with the greatest differentiation. The thickness of the germinal layer is reduced (arrows), and only scattered spermatozoa are present (arrowhead). Panel C shows two clusters of Leydig cells (arrows) below two seminiferous tubules (T).

intramuscular testosterone (Sustanon 250, Organon) at a dose of 1 ml every three weeks. After two weeks, the level of serum follicle-stimulating hormone normalized (3.5 mIU per milliliter), and serum testosterone was 3.5 ng per milliliter (12.1 nmol per liter). During the next 12 weeks, testosterone induced penile growth to 8 cm and masculinization, but testicular volume remained unchanged, and ejaculate was azoospermic. At the end of three months, testosterone treatment was discontinued, and treatment with chorionic gonadotropin (1500 IU administered intramuscularly three times a week for one month, then 5000 IU given weekly) was instituted, which maintained testosterone secretion and increased testicular volume to 14 ml. After 12 months of therapy with human chorionic gonadotropin, the patient remained oligospermic (1000 spermatozoa per milliliter), though the spermatozoa predominantly had normal shape and motility.

METHODS

HORMONAL ASSAYS

An immunoassay system (Elecsys, Roche Diagnostics) was used to measure luteinizing hormone, follicle-stimulating hormone, testosterone, dehydroepiandrosterone sulfate, progesterone, and estradiol. The beta subunit of human chorionic gonadotropin, inhibin B, and dihydrotestosterone were measured with the use of immunoassays (CIS Bio International, Serotec, and Intertech, respectively). The interassay coefficient of variation for dihydrotestosterone was 18.6 percent or less. All other interassay and intrassay coefficients of variation were 7 percent or less. The absence of luteinizing hormone was confirmed with the use of two separate immunoassays, one that is specific for epitopes on both the assembled alpha-beta luteinizing hormone heterodimer and on the luteinizing hormone beta subunit alone (Roche Diagnostics) and one that is specific for the luteinizing hormone beta subunit alone (Biocode-Hyclon). The lower limit of detection for both assays was 0.1 mIU per milliliter; neither assay cross-reacted with other glycoprotein hormones.

DNA SEQUENCING AND ANALYSIS

Genomic DNA was extracted from leukocytes with the use of commercially available reagents (Nucleon BACC2, Amersham Biosciences). DNA obtained from one normal volunteer was used as a wild-type

control. A 1082-bp amplicon containing the complete luteinizing hormone beta-subunit gene was recovered by polymerase-chain-reaction (PCR) assay and sequenced in sense and antisense directions with the use of an automated sequencer. To avoid coamplification of the homologous chorionic gonadotropin beta-subunit gene or pseudogenes, the primers contained at least one last nucleotide that was mismatched at the 3' end. Alignments and comparisons between sequences were made with the use of two software programs (BestFit and PileUp from the GCG Wisconsin Package, Accelrys). To test whether any mutation that was discovered represented a polymorphism, chromosomes from 162 ethnically matched people from Cameroon were analyzed. DNA was extracted with the QIAamp DNA Blood Mini Kit (Qiagen) and was then subjected to PCR amplification and restriction-enzyme digestion with the *NaeI* enzyme.

FUNCTIONAL ANALYSIS OF MUTANT BETA SUBUNIT

All expression vectors for this study were constructed with the use of the backbone of pcDNA3 (Stratagene), into which the coding sequences of the proband and wild-type beta subunits and the common alpha subunit of human glycoprotein hormone were cloned. Since the insertion of polypeptides at the C-terminals of human glycoprotein hormone beta subunits does not affect alpha-beta heterodimerization,¹⁰ a tag (a 6 histidine residue [6xHis] for beta subunits and the V protein of simian virus 5 [V5] for the alpha subunit) was inserted in-frame into the C-terminal coding sequence just before the natural stop codon.

Plasmid constructs were verified by sequencing. Human embryonic kidney 293T cells were transfected with expression vectors (15 µg per plasmid) in 10-cm dishes, with the use of the calcium phosphate technique. Cell lysates were prepared 48 hours after transfection, and Western blotting or immunoprecipitation studies were performed. For immunoprecipitation studies, cell lysates (500 µg) were incubated with either 5 µg of an anti-V5 monoclonal antibody (Invitrogen) or 5 µg of an anti-6xHis monoclonal antibody (PharMingen) and then treated with protein G Sepharose (Amersham Biosciences). Immunoprecipitates were separated by 15 percent sodium dodecyl sulfate-polyacrylamide-gel electrophoresis (SDS-PAGE) under reducing conditions, electroblotted onto a polyvinylidene difluoride mem-

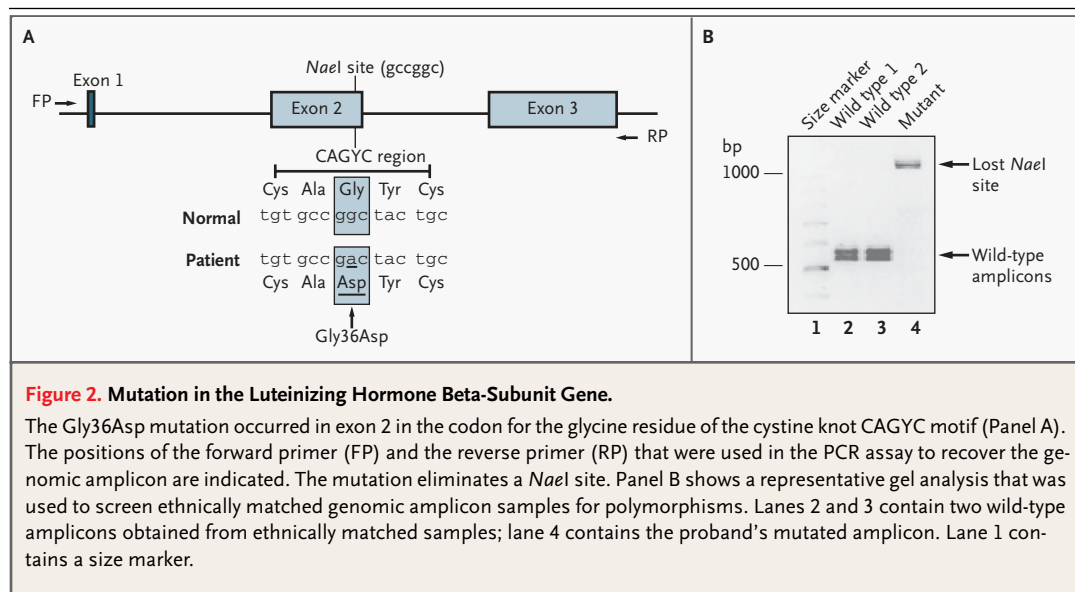
brane, and probed with either an anti-6xHis antibody or an anti-V5 antibody. Blots were visualized with the use of an enhanced chemiluminescence system (ECL, Amersham Biosciences). The same SDS-PAGE conditions and antibodies were used for Western blotting. Further details on standard plasmid cloning and conditions of the PCR assay are available on request.

The patient provided written informed consent for the study. Approval was obtained from the institutional review board of Lausanne University Hospital in Switzerland for all genetic and molecular investigations that were undertaken. The 162 ethnically matched subjects (324 chromosomes) and the normal male Swiss volunteer who provided DNA for use as the wild-type control all provided informed written consent as approved by the institutional review board.

RESULTS

The patient's karyotype was 46,XY. Analysis of his luteinizing hormone beta-subunit gene sequence revealed a single-nucleotide guanine-to-adenine substitution in the terminal part of exon 2 (Fig. 2A). This homozygous missense mutation induced a substitution of aspartic acid for glycine at position 36 of the luteinizing hormone beta-subunit sequence (Gly36Asp). All 324 ethnically matched control chromosomes had the normal, wild-type sequence, confirming that the mutation was not a polymorphism in this population (Fig. 2B).

Western blots of transiently transfected 293T cells showed that the mutated luteinizing hormone beta-subunit protein was synthesized correctly (Fig. 3A). The Gly36Asp substitution involved a highly conserved glycine residue located in the cystine knot motif of the luteinizing hormone beta subunit. We hypothesized that this mutation might produce the observed phenotype by interfering with alpha-beta heterodimerization of luteinizing hormone. Immunoprecipitates from 293T cells cotransfected with wild-type luteinizing hormone beta subunit showed coprecipitation of the alpha and beta subunits, indicating that heterodimerization had occurred (Fig. 3B). In contrast, immunoprecipitates from cells cotransfected with the proband's mutated luteinizing hormone beta subunit showed no beta-subunit band, confirming that the Gly36Asp mutation prevented alpha-beta heterodimerization. As expected, cells that were mock-transfected (transfected with a control construct) did not show any immunoprecipitation band (mock lane in Fig. 3B). Correct production of the V5-tagged alpha subunit in cotransfected cells was verified by Western blotting with an anti-V5 antibody (Fig. 3C). To confirm the results of the immunoprecipitation studies, we performed a reciprocal-format experiment, in which cell extracts were immunoprecipitated with anti-6xHis antibody followed by anti-V5 immunodetection. The alpha subunit could be detected only in extracts of cells that were cotransfected with the wild-type beta subunit (Fig. 3D).



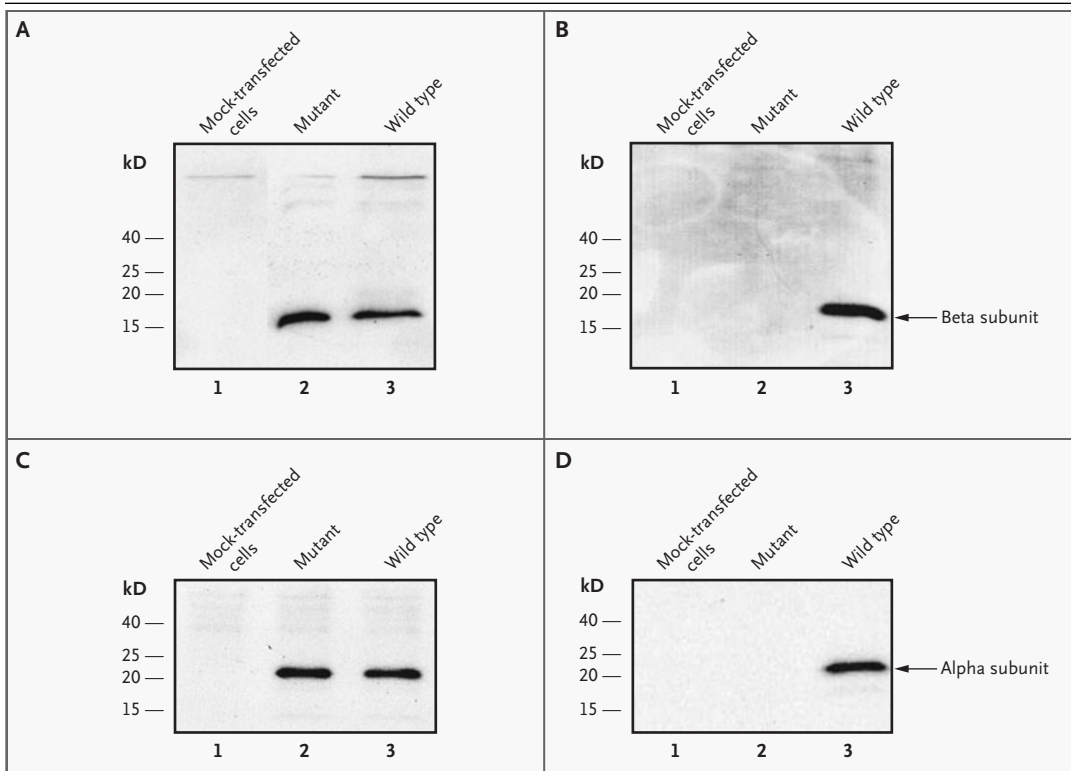


Figure 3. Lack of Alpha-Beta Heterodimerization in Cells Transfected with the Gly36Asp Mutation of the Luteinizing Hormone Beta Subunit.

The wild-type beta subunit and the Gly36Asp mutation are both correctly synthesized in 293T cells transiently transfected with 6xHis-tagged beta-subunit expression vectors (Panel A). Immunodetection with an anti-6xHis antibody reveals bands of the expected size (about 18 kD) for the glycosylated form of this subunit, and no band is detectable in the mock-transfected cells. Panel B shows alpha-beta heterodimer formation in 293T cells that were cotransfected with the V5-tagged alpha subunit and either the mutant or wild-type 6xHis-tagged beta-subunit expression vectors. Immunoprecipitation with an anti-V5 antibody recognizing the V5-tagged alpha subunit was followed by immunoblotting with an anti-histidine antibody recognizing the 6xHis-tagged beta subunit. Coprecipitation of the alpha and beta subunits occurred in cells cotransfected with the wild-type beta subunit but not in the mutant beta subunit or in the mock-transfected cells. Panel C shows the correct production of the alpha subunit (expected size, about 22 kD) in cotransfected 293T cells, as detected by Western blotting. Panel D shows the reciprocal format of the immunoprecipitation and immunoblotting experiment shown in Panel B; cell extracts were immunoprecipitated with the anti-6xHis antibody and then subjected to immunoblotting with the anti-V5 antibody. The alpha subunit was detected only in cells cotransfected with the wild-type beta subunit, further confirming the inability of the mutant beta subunit to heterodimerize with the alpha subunit.

DISCUSSION

The development of Leydig cells and steroidogenesis are controlled by activation of luteinizing hormone receptors both before and after birth by placental chorionic gonadotropin and pituitary luteinizing hormone, respectively. The beta subunits of these hormones share more than 80 percent sequence homology and originate from a contiguous gene complex on chromosome 19q13.32.² During fetal life, chorionic gonadotropin stimulates the growth of primordial Leydig cells and the produc-

tion of testosterone, which in turn permits fetal masculinization.¹¹ Mutations in the luteinizing hormone receptor interfere with chorionic gonadotropin signaling in male fetuses, producing a spectrum of clinical disorders ranging from undervirilized genitalia to complete pseudohermaphroditism.¹² The assessment of the effect of an isolated loss of luteinizing hormone signaling on male sexual maturation has been a challenge, since inactivating mutations of the luteinizing hormone beta-subunit gene are exceptionally rare.

A previous report describes a 17-year-old boy

who presented with delayed puberty, elevated luteinizing hormone levels, and undetectable testosterone levels; a testicular biopsy showed no Leydig cells and arrested spermatogenesis.⁹ In that patient, a missense mutation encoding a substitution of arginine for glutamine at position 54 of the luteinizing hormone beta-subunit gene (Gln54Arg) rendered luteinizing hormone biologically inactive by impairing the binding of the heterodimeric hormone to its receptor.

In our patient, the Gly36Asp mutation of the luteinizing hormone beta subunit abolished both immunologic and biologic activities of luteinizing hormone through a failure of alpha-beta heterodimerization. This mutation disrupted a cystine knot, which is a key structural motif conserved in glycoprotein hormones.¹³ The cystine knot motif contains an eight-amino-acid ring with two disulfide bonds, which is penetrated by a third disulfide bond.¹⁴ The amino acid sequence CAGYC is crucial to the formation of this ring in human glycoprotein hormone beta subunits, since the conserved glycine residue allows the passage of the third, ring-penetrating disulfide bond.¹⁵ Amino acid substitution of this glycine impairs chorionic gonadotropin alpha-beta heterodimerization,^{15,16} whereas an analogous glycine-to-arginine substitution in the CAGYC region of the thyrotropin beta-subunit gene prevents heterodimerization of thyrotropin, resulting in central hypothyroidism.¹⁷

In vitro, free luteinizing hormone beta subunits are inefficiently secreted, and alpha-beta dimerization appears to be important for the secretion of luteinizing hormone.^{18,19} The absence of circulating intact luteinizing hormone or free luteinizing hormone beta subunits in our patient is consistent with these data.^{18,19} In contrast, luteinizing hormone beta subunits are more readily secreted from pituitary tumor cells.²⁰ Together, these findings suggest that in nonadenomatous tissue, the secretion of luteinizing hormone is dependent on adequate heterodimerization.

Both mutations in luteinizing hormone beta subunits that have been described to date abolished the bioactivity of luteinizing hormone, although by somewhat different mechanisms. Together, the phenotypes of these two patients provide important information on the role of luteinizing hormone in postnatal male sexual differentiation and maturation. Both patients were phenotypically male at birth, with descended testes, confirming that luteinizing hormone is not necessary for normal masculinization in utero and providing evidence of the role of chorionic gonadotropin in directing fetal testicular development and steroidogenesis.^{2,12} In response to the administration of chorionic gonadotropin, our patient had an increased testicular volume and an enhanced production of testosterone, suggesting that the persistent fetal Leydig cells observed in the testicular-biopsy specimen remained capable of steroidogenesis. These observations are generally consistent with recent data from studies of luteinizing hormone-receptor knockout mice (LuRKO), which are phenotypically normal at birth but fail to undergo substantial sexual maturation.²¹⁻²³ Caution is required when comparing data from mice with data from humans, however, since mice lack chorionic gonadotropin, indicating an alternative pathway for murine Leydig-cell development in utero. Both our patient and the one described by Weiss et al.⁹ had arrested spermatogenesis at diagnosis, suggesting that luteinizing hormone signaling and high levels of intratesticular testosterone are not absolutely essential for some degree of spermatogenesis to take place. This observation could account for the high rate of failure of male hormonal contraceptive therapy.²⁴

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