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ORIGINAL RESEARCH

The Ser434Phe *Androgen Receptor* Gene Mutation Does Not Affect Fertility but is Associated with Increased Prolactin

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Introduction: Prolactin is a hormone secreted by the anterior pituitary gland essential for lactation. Non-physiological hyperprolactinemia characterized by serum prolactin levels exceeding 20 ng/mL in men and 25 ng/mL in women, often results from medication use or pituitary gland tumors. In a minority of cases, the cause of hyperprolactinemia remains unknown despite clinical investigations. Familial idiopathic hyperprolactinemia may stem from mutations in genes encoding prolactin (*PRL*) and its receptor (*PRLR*).

Methods: This study investigated genetic polymorphisms in *PRL* and *PRLR* genes using polymerase chain reaction (PCR) and Sanger sequencing in three sisters affected by familial idiopathic hyperprolactinemia. No mutations were found in these genes, prompting whole exome sequencing (WES) of the proband to identify other potentially involved genes.

Results: WES revealed a heterozygous missense substitution c.1301C>T (p.Ser434Phe) in the *androgen receptor* (*AR*) gene. Next-generation sequencing (NGS) for the *AR* gene confirmed that the proband and her two affected sisters, along with three asymptomatic sisters, were all heterozygous carriers of the mutation. Their father was hemizygous, while their mother had a normal genotype.

Conclusion: The heterozygous missense mutation in the *AR* gene found in this family with familial idiopathic hyperprolactinemia is not yet explained. Hence, further research is warranted to elucidate the functional implications of this mutation on AR and its role in the pathogenesis of hyperprolactinemia.

Keywords: familial idiopathic hyperprolactinemia, androgen receptor gene, mutation

Introduction

Pathological hyperprolactinemia (ie >20 ng/mL in men and >25 ng/mL in women) may lead to infertility, hypogonadism, and galactorrhea.[1] Such hyperprolactinemia usually occurs due to the use of certain drugs (eg antipsychotic) and pituitary gland tumors; half of the non-physiological hyperprolactinemia cases are a result of prolactinomas, while the others are caused by systemic disorders or Hypothalamic/pituitary stalk disorders.[2] However, few patients with hyperprolactinemia who undergo investigations have normal findings on pituitary gland MRI. These patients with idiopathic hyperprolactinemia may have a microadenoma below the limit of MRI detection or a different cause.[3,4]

The existence of idiopathic hyperprolactinemia in families has been proposed to occur due to a genetic cause. Reviewing previous studies suggests that prolactin gene (*PRL)* and prolactin receptor *(PRLR)* gene are the candidate genes related to familial hyperprolactinemia.[5] Prolactin is a peptide hormone, encoded by the *PRL* gene and secreted by the lactotroph cells in the anterior pituitary gland; it is essential for the induction and maintenance of lactation in the peripartum and postpartum periods.[1]

In this study, we investigated *PRL* and *PRLR* genes in three sisters affected by idiopathic Hyperprolactinemia. However, our findings revealed normal sequences for both *PRL* and *PRLR*, prompting WES analysis for the proband to identify genetic components potentially associated with idiopathic hyperprolactinemia. WES confirmed the absence of genetic abnormalities in *PRL* and *PRLR* but unraveled a heterozygous missense substitution (Ser434Phe) in the *AR* gene,

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which was further validated by next-generation sequencing (NGS) of *AR* in the proband, her affected sisters, and family. This study aims to enhance our understanding of the disorder and facilitate genetic counseling for the family in the future. Additionally, identifying uncommon forms of familial hyperprolactinemia through this research could contribute valuable insights to broader community health.

Case Presentation

The proband is a product of a non-consanguineous marriage with two affected sisters and three asymptomatic sisters and parents. The proband sought advice in our clinic regarding hyperprolactinemia. She is a 23-year-old female with an unremarkable other medical history, except for a similar condition in 2 other sisters.

She had galactorrhea as the main symptom, starting around the age of 12 years. Prolactin level was checked accordingly by her primary care physician and was found to be 86 ng/mL, so she was started on low-dose cabergoline (~0.5 mg weekly) to treat hyperprolactinemia. Menarche and regular menstrual cycles ensued after around one year of treatment. She has unremarkable physical exam. Other laboratory tests ruled out secondary causes of hyperprolactinemia including hypothyroidism, abnormal kidney or liver function, and hyperandrogenemia. No evidence of any adenoma was found on pituitary magnetic resonance imaging.

Her prolactin level was normal. A trial to stop her medication for 3 months resulted in a rise of prolactin level to 69 ng/mL, and symptoms of an irregular menstrual cycle were reported. Later, she was restarted on cabergoline 0.5 mg weekly, and her prolactin quickly came down to 6 ng/mL.

Upon questioning, we found that she has two younger sisters (ages 22 and 16 years) with the same medical problem. Their histories are similar to their older sister too. They had galactorrhea as well around the age of 12 years which prompted their mother to seek medical attention again and to get them tested. They were diagnosed similarly with hyperprolactinemia and started on cabergoline. They both reported regular menstrual cycles on treatment.

They never had MRI of the pituitary prior to visiting our clinic. At the initial visit, all causes of secondary hyperprolactinemia were ruled out. Furthermore, no evidence of microadenoma was found on pituitary imaging later.

They were counselled about the possibility of a familial form of hyperprolactinemia. They gave consent to draw samples for genetic testing.

Our proband got married and stopped cabergoline when she became pregnant. She gave birth to a full-term healthy baby one year ago, and she is still lactating her baby. Our patient is 2nd in birth order of her siblings. The oldest sister is 24 years old. She had menarche at age 13 years, with regular menses, and she never checked her prolactin level. The youngest 2 sisters are 13 and 12 years old. They reportedly have not menstruated yet, and they did not check their prolactin level.

Subjects and Methods

Sample Collection

EDTA blood samples were collected from three sisters diagnosed with idiopathic hyperprolactinemia who were attending the endocrinology outpatient clinic at King Abdullah University Hospital. Blood samples were also collected from the parents and 10 family relatives [the remaining 3 sisters, 2 aunts from father's side and their 5 daughters (cousins)].

The study was approved by the IRB committees at Jordan university of science and technology and King Abdullah II hospital (#134/136/2020). Written informed consents to participate in the study were obtained from study participants before sample collection. The parents of the family members under 18 years of age provided informed consent for participation and publication of the case details.

DNA Extraction and PRL and PRLR Genotyping

DNA was extracted from peripheral blood mononuclear cells (PBMC) using Zymo Research quick DNA miniprep kit® (ZYMO RESEARCH, USA), according to manufacturer's instructions, and evaluated by NanoDrop spectrophotometer (Thermo Fisher Scientific NanoDrop, USA). The exons for *PRL* and *PRLR* genes were amplified by PCR using GoTaq® Green Master Mix (Promega, USA) and previously reported exon-specific primers (Table 1).[5] The obtained PCR

Table 1 Primers for genomic amplification of *PRLR* and *PRL* exons

Gene	Exon	Primers
PRLR	3	F: CCCAGAATAAAGTGGTGGATG R: TCCACCCTGTTGACAAACAC
PRLR	4	F: AAGGGTCAAATGGTTAAATGGA R: GGCCTGGAGAATGGGAGTA
PRLR	5	F: CCAAAGGCCAGTGGTATTGA R: TCCATCCAAAACCCAAGAAG
PRLR	6	F: AAGCCAAAGAAAAGGTGCAA R: TATCCTTGCCAAAGGCCATA
PRLR	7	F: AGGGGAAAACTCTCTTTCTTCA R: ACCATTTAAAACATATTTAGGGACA
PRLR	8	F: GAATGGAGGAAAACACTCTTGG R: TGACTATCATGATTGGGAGGAA
PRLR	9	F: AGCTGCCAAACCAAGTCCTA R: AAGGCTGGCTGAAACTACCA
PRLR	10	F: GGGATGCTGATTTGGAATGT R: GGTAAGAGGATCTGGGGTTG
PRLR	10	F: CCCTTTTGTCTGAAAAGTGTGA R: GGCGTATCCTGGTCAGTCTC
PRL	1	F: GGAAATTTAATGACAGTGTAACAGG R: GCCCTCTTGTAAACCTGCAA
PRL	2	F: TTCCTCGGCAGGATTACTTC R: GCTCGGGAGGTTTTCTAGGT
PRL	3	F: TCTGCTAATGGATTCATTTATTCAA R: CCCATATACTGCCTTGGTTG
PRL	4	F: TCACAAGTAACTAACCCCATTGT R: GAGGTCACCGCTTATATTAATGAG
PRL	5	F: TCAACAGTTAGAAAGAACAAGGACA R: TGGGAGTGATAGATTTTCTTTTGA

products were visualized on 2% agarose gel and then subjected to sanger sequencing. The acquired sequences were analyzed by ChromasPro software and Mutation Surveyor (Pennsylvania, USA).

Whole Exome Sequencing (WES)

Library preparation and exome enrichment was carried out using Agilent's SureSelect Human All Exon V6 kit following the manufacturer's instructions. The enriched library was sequenced on an Illumina platform. More than 20,000 genes were sequenced, and ~98.75% of these genes were covered at least >10x. GRCh37/hg19 genome assembly was used for reads alignment. All variants with minor allele frequency (MAF) <1% in the gnomAD database (version: 4.1) as well as pathogenic, likely pathogenic variants, and variants of uncertain significance reported in HGMD and ClinVar databases were considered. We analyzed nonsense and nonsynonymous, splice site variants (±10 intronic bases), as well as insertions and deletions (indels). Various in-silico prediction tools such as SIFT,[6] Polyphen2,[7] Mutation Taster,[8] and others were also used to predict the functional impact of identified variants. The classification of variants was based on

ACMG guidelines[9] in which the variants were classified into pathogenic, likely pathogenic, uncertain significance, likely benign, and benign. Both benign and likely benign variants were excluded from the analysis.

Next-Generation Sequencing of AR Gene

Next-generation sequencing (NGS) for the *AR* gene (NM_000044.4) was performed following the manufacturer's instructions. Specific primers for exon 1 (AR_1-F4-Forword: 5'- CGACTACTACAACTTTCCACTGGCTCTG-3' and AR_1-R4-Reverse: 5'- TTTACCCTGCTGAGCTCTCCCAG-3' were designed using (https://primer3.ut.ee/).

Specific 30 nucleotides were added to the 5' ends of the two primers for indexing. The PCR amplicons were purified using the NucleoFast® 96 PCR kit (MACHEREY-NAGEL GmbH). The purified products were quantified by a spectrophotometer and diluted according to recommendations by Illumina Inc. before sequencing on the Miseq platform (Illumina Inc).

This BioProject accession number is PRJNA1138788. Our Sequence Read Archive (SRA) records will be accessible with the following link: https://www.ncbi.nlm.nih.gov/sra/PRJNA1138788

Results

Normal PRL and PRLR Genotypes of Proband

Sanger sequencing results of *PRL* and *PRLR* exons listed in Table 1 did not demonstrate any genetic abnormalities. This was further validated by the WES results of the proband below.

A Missense Mutation in AR

In this proband, a total of 22,161 genes were covered by WES. Out of 200,925 variants, 32,106 variants (11,173 genes) were missense, nonsense, frameshift and splice sites variants. After removing common variants (MAF >1%), 1,164 variants in 979 genes were detected. Subsequent filtering by phenotype, pattern of inheritance and in silico pathogenic prediction tools, the missense variant c.1301C>T in exon 1 of *AR* was prioritized. This variant results in a substitution of Serine 434 to phenylalanine (p.Ser434Phe) in the N-terminal domain of AR. Table 2 displays the genotypes of the

Table 2 The Variant Genotypes and the Clinical Phenotypes of the Study Subjects

Sample	Sex	Relation to Proband	c.1301C>T Genotype	Clinical Phenotype
1	Female	Proband	Heterozygous	Hyperprolactinemia
2	Female	Sister	Heterozygous	Hyperprolactinemia
3	Female	Sister	Heterozygous	Hyperprolactinemia
4	Female	Sister	Heterozygous	Reportedly none
5	Female	Sister	Heterozygous	Not known (no menarche yet)
6	Female	Sister	Heterozygous	Not known (no menarche yet)
7	Female	Mother	Not determined	None
8	Male	Father	Hemizygous	Reportedly none
9	Female	Paternal Aunt	Heterozygous	Irregular menstrual cycles (not investigated)
10	Female	Cousin	Not determined	None
11	Female	Cousin	Heterozygous	Irregular menstrual cycles (not investigated)
12	Female	Paternal Aunt	Heterozygous	Irregular menstrual cycles (not investigated)
13	Female	Cousin	Heterozygous	Irregular menstrual cycles (not investigated)
14	Female	Cousin	Heterozygous	Irregular menstrual cycles (not investigated)
15	Female	Cousin	Heterozygous	Irregular menstrual cycles (not investigated)

subjects for the *AR* variant. Both affected sisters, unaffected sisters, aunts, and four cousins exhibit heterozygosity for c.1301C>T, whereas the proband's father is hemizygous. Conversely, the proband's mother and one cousin do not carry the variant.

Discussion

The trigger to investigate a genetic cause of hyperprolactinemia in this patient was the striking history of symptomatic hyperprolactinemia in 2 other sisters. Reviewing the literature to explore a possible genetic explanation, we found studies exploring the prolactin gene (*PRL)* and the prolactin receptor gene *(PRLR)* as the candidate genes related to familial hyperprolactinemia.[5] Therefore, we initially investigated genetic polymorphisms in *PRL* and *PRLR* genes in three sisters affected by idiopathic Hyperprolactinemia. Results turned normal for *PRL* and *PRLR* genotypes, which prompted us to employ whole exome sequencing to search for alternative genetic variants. As a result, we identified a missense mutation (c.1301C>T) in *AR* gene. The hormone prolactin is mostly connected to the lactation process. Nonetheless, it has been discovered that it is implicated in more than 300 distinct physiological processes in both males and females.[10] The anterior pituitary's lactotroph cells generate prolactin. A balance between stimulation and inhibition allows for control of lactotroph prolactin synthesis and release appropriate for the organism's physiological state. Oxytocin, thyrotropin-releasing hormone, vasoactive intestinal peptide (VIP), and estrogen are examples of prolactin-releasing factors.[11,12] On the other hand, androgens inhibit prolactin release.[13] It has been shown that male mice with conditional pituitary AR knockout (PARKO) exhibit an increase in the pituitary *PRL* transcript and circulating prolactin levels[13] develop a female-specific lactotroph ultrastructure that likely contributes to the increase in circulating prolactin.[14] This suggests that precise regulation of AR activity is required to maintain a balanced level of prolactin expression and release. AR is a member of the family of nuclear receptors that is ubiquitously expressed throughout organisms and organs and affects many biological processes beyond its fundamental function in male reproductive development and regulation.[15] After binding to androgen, AR elicits its various functions in several cell compartments: it regulates gene transcription in the nucleus, it triggers cell signaling in the plasma membrane, and it controls energy production in the mitochondria.[16] A lot of point mutations in *AR* have been reported,[17,18] which can have profound effects on protein function and clinical outcomes. In the ligand-binding domain (LBD), mutations can disrupt the receptor's ability to bind testosterone or dihydrotestosterone (DHT), leading to altered hormone binding affinity.[19] This can impair downstream signaling pathways crucial for male sexual development and maintenance. Mutations affecting coactivator or corepressor binding sites can dysregulate gene transcription,[20,21] impacting cellular functions governed by androgen signaling. Furthermore, mutations may hinder proper nuclear translocation of the AR protein upon ligand binding, thereby compromising its transcriptional activity.[22] Conformational changes induced by mutations can alter the AR protein's structure, affecting its interactions with DNA and other regulatory proteins involved in transcriptional regulation.[18,23] Clinically, most of these mutations underlie a spectrum of conditions known as androgen insensitivity syndromes (AIS),[24] where varying degrees of androgen resistance manifest, ranging from mild undervirilization to complete androgen insensitivity, which presents with a female phenotype despite a male genetic background (46,XY). These consequences highlight the critical role of the *AR* gene mutations in both molecular dysfunction and clinical phenotypic variability.

Although the known mechanism of AR activation is direct androgen/ligand interaction, phosphorylation of AR has been shown to be involved in AR activities. A variety of kinases can control the AR by post-translationally altering serine (S), threonine (T), and tyrosine (Y) residues, resulting in modifications in its protein interactions. Most phosphosites, S16, S81, S94, S213, Y223, S256, Y267, T282, S293, S308, Y363, S424, S515, and Y534, are found in the N-terminal domain, which includes the AF1 region.[25,26] S578 is phosphorylated in the DNA binding domain, S650 is phosphorylated at the hinge region, and S791 and T850 are phosphorylated in the ligand-binding domain, which includes the AF2 domain.[25,26] Moreover, AR is phosphorylated on S405 and Y551/552 under specific circumstances.[25] Here, we report a missense mutation in the *AR* gene that results in a substitution of serine 434 with phenylalanine (p.Ser434Phe). This mutation was previously reported in a patient with partial AIS.[27] While the functional role of this phosphosite remains unreported, its location in the N-terminal domain suggests it may impact AR activity by abolishing phosphorylation at this site. Previous studies investigating serine phosphorylation near the WXXLF motif in the N-terminal domain, critical for AR transactivation, indicate mutations such as p.Ser405Arg disrupt transcriptional activation associated with co-

regulators like melanoma antigen-A11 (MAGE-11) and p300 histone acetyltransferase.[21,28] Given the proximity of S434 to the WXXLF motif, our findings suggest it may similarly affect AR transactivation, warranting further investigation. Upon searching the ClinVar database of NCBI, the following germline mutations were found in association with this mutation with different classifications of pathogenicity; Androgen resistance syndrome – Kennedy disease (Benign), non-obstructive azoospermia (likely pathogenic), malignant tumor of prostate (pathogenic), and male infertility (pathogenic).[29] However, the relationship between p.Ser434Phe and the reported hyperprolactinemia in the affected sisters remains unclear and needs further investigation. It seems that this mutation does not affect sexual function and fertility. Therefore, functional genetic studies in cells and animal models involving p.Ser434Phe mutation are highly recommended to address the molecular mechanism of prolactin regulation by AR. In conclusion, our study explored genetic factors underlying familial idiopathic hyperprolactinemia in a family presenting with three affected sisters. Initial investigation of *PRL* and *PRLR* genes revealed normal sequences, prompting WES analysis of the proband. This approach uncovered a heterozygous missense mutation (c.1301C>T; p.Ser434Phe) in the AR gene. Subsequent NGS confirmed the presence of this mutation in all affected and unaffected sisters, while the father was hemizygous, and the mother and one cousin lacked the variant. However, our study has several limitations. Firstly, the functional impact of the identified AR mutation on prolactin regulation remains speculative and requires further experimental validation. Secondly, the study's sample size is small, limiting generalizability to broader populations with familial hyperprolactinemia. Finally, as with all genetic studies, environmental or epigenetic factors may influence the clinical presentation and progression of hyperprolactinemia in affected individuals.

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Disclosure

There is no conflict of interest.

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