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A scarce case: Co-occurrence of neurofibromatosis type 1 and Klinefelter syndrome

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ABSTRACT

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder with a heterogeneous group of symptoms, including characteristic cafe-au-lait macules, axillary or inguinal freckling, Lisch nodules, as well as skeletal deformation, scoliosis, mental retardation, and tumors of the nervous system. Klinefelter syndrome (KS) is a gonadal dysgenesis, with symptoms in males, including an extra X chromosome, leading to tall stature, hypogonadism, and infertility. Although the co-occurrence of NF1 and KS is a rare finding, this report describes this unique entity detected in an eight-year-old boy with numerous hyperpigmentation spots, a multitude of skin and subcutaneous nodules, seizures, arterial stenosis, and mild gynecomastia. Whole-exome sequencing (WES) was conducted along with copy number analysis for the proband and his parents. Multiplex Ligation-dependent Probe Amplification (MLPA) is used to validate the copy number variations detected by next-generation sequencing (NGS). The results showed a pathogenic heterozygous mutation (c.246_247del, p.Gln83Valfs*23) in a human neurofibromin 1 gene (*NF1*), detected in the proband and his father, whilst the genetic analysis performed by the karyotype revealed a copy gain of the X chromosome (47, XXY) leading to KS. This rare occurrence of NF1 with co-occurrence of KS may raise some concerns and difficulties in the clinical management of this case, particularly Testosterone hormone replacement therapy and the potential risks of malignancies. Therefore, clinicians may ask for KS genetic tests in male patients with NF1 who have symptoms of gynaecomasia or infertility, and closely monitor for potential malignancies and other complications. Compellingly, this case emphasizes the importance of advanced genetic analysis in providing genetic tools for diagnosing and managing individuals with rare and complex syndromes with overlapping clinical features. Early detection and comprehensive clinical interventions are the key cornerstones to improving patient outcomes.

Introduction

Neurofibromatosis type 1 (NF1) (OMIM®: 162200) is a common autosomal dominant disorder, occurring in about one in 2500–3000 people worldwide [1]. NF1 presents as a neurogenetic condition with diverse clinical manifestations, affecting multiple organ systems such as the skin, bone, and nervous system [2]. Clinical features range from café -au-lait macules and skin-fold

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freckling to neurofibromas, Lisch nodules, glaucomas, learning disabilities, and skeletal abnormalities [3]. Neurofibromatosis type 1 results from the *NF1* gene located on chromosome 17q11.2, spanning over 300 kb of genomic DNA with approximately 60 exons that encode a 220–250 kDa protein named neurofibromin [4]. Neurofibromin is a tumor suppressor, which acts as a GTPase activating protein (GAP) and regulates RAS activity by converting active RAS-GTP to inactive RAS-GDP. Its interaction with Ras proto-oncogenes suggests a role as a negative cell growth regulator that controls cell proliferation and differentiation [5]. Diverse mutations in the *NF1* gene reduce neurofibromin expression, contributing to different phenotypes such as various malignancies [6]. While NF1 typically results from inherited mutations in this gene, approximately half of NF1 cases occur sporadically [7]. Therefore, mutational analysis has become vital for diagnosing NF1 and aiding prenatal screenings [8]. NF1 represents a common diagnosis in dermatology, underscoring its broad impact on healthcare [9]. Presently, there is no treatment except to relieve symptoms, by focusing on spotting signs early and using specific therapies to enhance the life quality of NF1 patients. However, the complexity of symptoms makes finding effective treatments challenging [10].

Klinefelter syndrome (KS), discovered in 1942, is defined by the presence of an extra X chromosome (XXY) in males, resulting in a range of clinical manifestations such as tall stature with long limbs, hypergonadotropic hypogonadism, less or no facial hair, gynecomastia, indications of low androgen levels, testicular failure, and infertility, particularly azoospermia [11]. KS is a multifaceted condition that spans various medical disciplines and has garnered increased attention over time, with an approximate occurrence rate of 0.1–0.2 % in the general population [12]. KS typically does not present with major congenital abnormalities. That is why only certain instances might be detected prenatally; others may not show symptoms until later due to behavioral differences or infertility [13]. Symptoms of KS can appear at various stages of life, leading to delays in diagnosis. Despite advancements, diagnosing KS remains challenging and there are no standardized guidelines for diagnosing KS [14]. The genetic basis of KS involves chromosomal non-disjunction, which can occur either during parental meiosis or during mitosis in the early post-zygotic divisions, leading to aneuploidy in sex chromosomes [15]. Although the classic form (47,XXY) comprises the majority of cases (80–90 %), other variations like mosaicism (47,iXq,Y or 47,XXY/46,XY) and aneuploidies of greater severity (like 48,XXXY or 48,XXYY) make up the remainder [16]. Mosaic cases typically exhibit less severe symptoms leading to many cases going undetected [17]. Moreover, the actual occurrence of mosaic variants might be undervalued due to the possibility that chromosomal mosaicism could solely detected by testes, while the chromosomal makeup of peripheral white blood cells remains normal [18]. The main treatment for KS patients with hypogonadism is testosterone therapy, which has beneficial effects on the morbidity and mortality of adult patients [19].

This report describes a rare co-occurrence of neurofibromatosis and Klinefelter syndrome in a case. The patient has given informed consent for the publication of this case.

Material and methods

Clinical manifestations

An eight-year-old boy with a dizygotic female twin was brought to Near East Hospital due to the presence of numerous hyperpigmentation in various parts of his body. During his physical examination, his height was determined as 125.5 cm (−0.26 sds) and his weight was 22.5 kg (−0.4 sds). The patient exhibited extensive café -au-lait macules and subcutaneous nodules throughout the body. There were no indications of speech or behavioral disorders observed as early manifestations of Klinefelter syndrome. Phenotypically, no structural anomalies suggestive of Klinefelter syndrome such as eunuchoid body habitus were detected. The neurological examination yielded normal findings, and upon examination of the genital system, the testicles were palpated as 2 ml bilaterally within the scrotum, with the patient being classified as prepubertal. Micropenis was not identified. All other systemic examinations were within normal limits, and both auditory and ocular assessments were normal. Following a comprehensive clinical examination, the patient has been identified as a potential case of neurofibromatosis. Further evaluation and genetic analysis were recommended to confirm the diagnosis and assess the extent of the condition. During the genetic consultation and analysis of the family pedigree (see Fig. 1), it was determined that the patient is the offspring of nonconsanguineous parents. Notably, symptoms indicative of neurofibromatosis type 1 (NF1) were observed in both the patient's father and one of his siblings. The patient's father, a 49-year-old male, presents with arterial stenosis, multiple café -au-lait spots, seizures, as well as skin and subcutaneous nodules. Nevertheless, no suspicious symptoms were observed in the proband's mother during the physical examination.

The patient's most recent clinical evaluation, conducted at 9 years and 3 months of age, recorded a weight of 25.5 kg (0.41 sds) and a height of 130.5 cm (0.68 sds). During the puberty assessment, bilateral testicular volumes were noted to be 2 ml. The patient was classified as Tanner Stage 1, indicative of a prepubertal status, and was thus placed under clinical observation. Further clinical examination will guide the decision regarding the initiation of pubertal induction. The patient, who is neurologically stable and free of seizures, is being monitored without any specific treatment.

Methods

Since the patient's father has a history of NF1, a trio whole exome sequence analysis was conducted for the proband and his parents as a screening measure, after obtaining informed consent. Blood samples were gathered, and genomic DNA was isolated using the EZ1 Advanced XL Blood kit (QIAGEN, Germany). Additionally, copy number analysis was conducted using the QIAamp DNA Blood Mini QIAcube Kit from Qiagen (Valencia, CA, USA). Before sequencing analysis, the extracted DNA samples were preserved at −20 °C, and their quality and concentration were evaluated utilizing a qubit fluorometer.

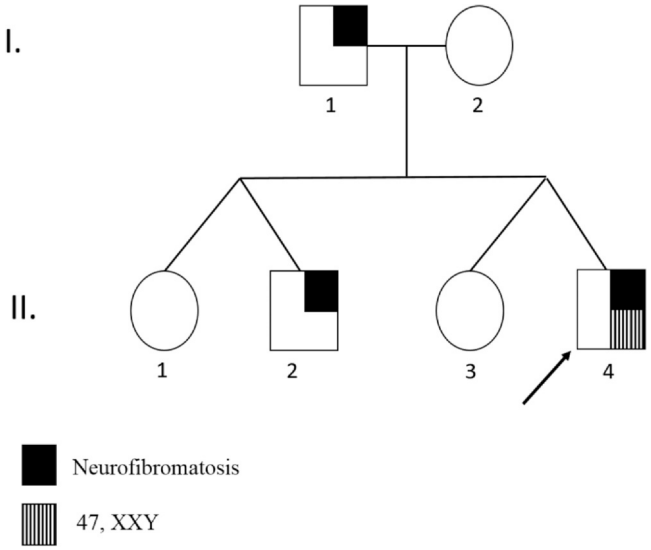

Fig. 1. Proband's family Pedigree. The filled black symbols show Neurofibromatosis (I1, II2, II4). The Stripes symbol (II4) indicates 47, XXY. All of the white symbols are healthy.

Whole-exome sequencing analysis service was obtained from CENTOGENE® (Rostock, Germany), which encompasses several steps. Initially, genomic DNA undergoes enzymatic fragmentation, and DNA capture probes are employed to enrich target regions, covering roughly 41 megabases of the genome. Sequencing is conducted on an Illumina platform with the aim of achieving a minimum coverage depth of 20x for over 98 % of the targeted bases. Following sequencing, an in-house bioinformatics pipeline is applied, involving read alignment, variant calling, annotation, and variant filtering. Variants occurring with a minor allele frequency (MAF) below 1 % in the gnomAD database and known disease-causing variants are scrutinized, with a focus on coding exons and adjacent intronic nucleotides of genes. The variant classification was done by following ACMG guidelines [20], and all variants associated with the patient's phenotype and family history are documented.

In this investigation, Multiplex Ligation-dependent Probe Amplification (MLPA) serves as a supplementary technique to verify any possible disparities in copy number analysis performed by NGS. MLPA assesses the copy number of particular genomic regions. Therefore, if NGS detects any differences or discrepancies in copy numbers, MLPA can validate the precision of the results or detect any potential inaccuracies or deviations in the NGS analysis. Essentially, MLPA functions as a quality control measure to guarantee the dependability and precision of the copy number analysis outcomes derived from NGS.

Results

Detection of a pathogenic NF1 mutation

Following whole-exome sequencing analysis, a harmful heterozygous mutation was found in both the proband and his father in the *NF1* gene at codon 83 (NM_001042492.2: c.246_247del, p.Gln83Valfs*23). This mutation causes a frameshift, resulting in a premature stop codon 22 positions downstream (rs771115661). This specific mutation has formerly been documented as disease-causing for neurofibromatosis type 1 [21–23]. ClinVar reported this mutation as pathogenic (ID: 527470) and according to ACMG guidelines, it is categorized as pathogenic (class 1). Due to the autosomal dominant inheritance pattern of NF1, the obtained heterozygous pathogenic variant is consistent with a genetic diagnosis of neurofibromatosis type 1 and based on the National Institute of Health (NIH) criteria, it confirms a final diagnosis of NF1 for both the proband and his father.

Incidental finding: X chromosome copy gain

In addition to the NF1 mutation, an incidental finding of a copy gain on the X chromosome was identified. Though not the primary focus of the investigation, this discovery became important in the context of the broader analysis. To ensure the accuracy of this finding, Multiplex Ligation-dependent Probe Amplification (MLPA) analyses were performed, using SALSA MLPA probemix P095-A4 provided by MRCHolland, as an internal control. MLPA outcomes were consistent with those obtained from NGS, validating the reliability and consistency of the copy number analysis conducted via NGS. Consequently, the identification of the copy gain on the X chromosome led to the genetic diagnosis of Klinefelter syndrome (47,XXY). This diagnosis was not solely dependent on NGS data; it was also independently confirmed through karyotype analysis (Fig. 2). Through the confirmation of an extra X chromosome via both molecular (NGS and MLPA) and cytogenetic (karyotype analysis) approaches, the diagnosis of Klinefelter syndrome was thoroughly confirmed, enhancing confidence in the diagnostic result.

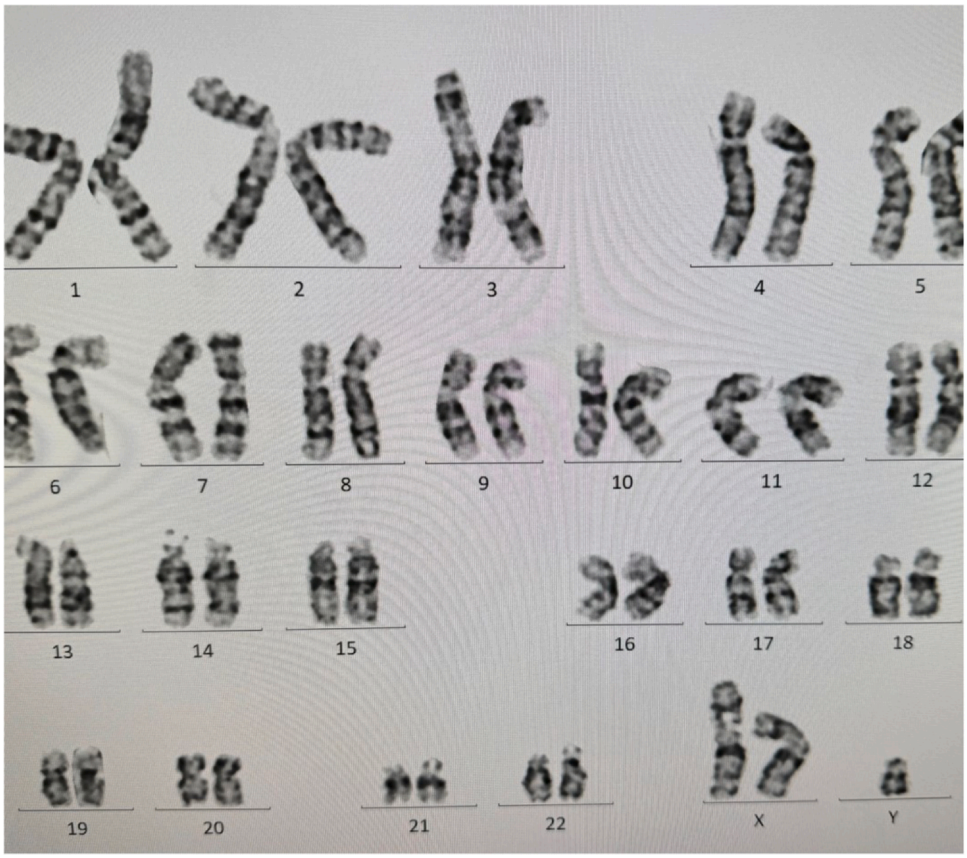

Fig. 2. Karyogram of the proband in which the existence of two X chromosomes along with one Y chromosome led to the genetic diagnosis of Klinefelter syndrome (47,XXY).

Discussion

In this report, we present an 8-year-old boy diagnosed with both Neurofibromatosis type I (NF1) and Klinefelter syndrome (KS), a rare co-occurrence that adds complexity to the clinical picture. Neurofibromatosis type I (NF1), characterized by an autosomal dominant inheritance pattern, is a multifaceted condition distinguished by various symptoms such as café -au-lait spots, Lisch nodules, and skin fibromatous tumors [3]. Ocular issues like optic pathway gliomas and Lisch nodules often appear early in life and skeletal abnormalities and intellectual challenges may also occur [4]. Café -au-lait macules typically emerge before age two, while cutaneous and subcutaneous neurofibromas commonly manifest in late childhood or early adolescence, proliferating progressively over time [1]. While cutaneous neurofibromas are usually benign, plexiform neurofibromas can cause complications and may become cancerous later [9]. Individuals affected by this condition confront an increased susceptibility to both benign and malignant tumors, with clinical presentations exhibiting considerable variation, even within families [10].

While, NF1 patients face a heightened cancer risk, particularly for malignant peripheral nerve sheath tumors (MPNST), leukemia, and breast cancer [7], On the other hand, although KS typically manifests with symptoms like gynecomastia, infertility, and hypogonadism, germinal cell tumors are a common malignancy associated with the condition [11,24]. These tumors have the potential to transform into some other cancer types too [11]. In addition, individuals with KS are at a heightened risk of developing several cancers, particularly male breast cancer. While the overall cancer incidence in men with KS appears to resemble that of the general population, certain types of cancer are more prevalent in this population such as leukemia [24,25]. According to this information, the concurrent presence of NF1 and KS in an individual might heighten the risk of certain malignancies in the affected case, though further research is needed to confirm this claim. Given the young age of our patient, a thorough investigation of this association is impractical.

KS is the most common sex chromosome aneuploidy in live male births, but less than 10 % of cases are identified before puberty. Indeed, early diagnosis is essential to address age-specific challenges with timely treatment and rehabilitation to minimize the problems that patients with XXY face with and to mitigate some of the complications seen in late diagnosed cases [26]. Having an extra X chromosome in our patient was approving to have Klinefelter syndrome (KS) while being evaluated genetically for NF1. KF can present with wide range of clinical features in males, including speech impediments, accelerated growth during childhood resulting in taller adult height, gynecomastia in adolescence, infertility, metabolic disorders, and psychosocial issues [16]. The absence of phenotypic features suggestive of Klinefelter syndrome during the prepubertal period in our case was noteworthy. Growth

velocity is known to be accelerated by the age of three years with a modest increase in adolescence [26]. In our patient diagnosed with prepubertal Klinefelter syndrome, a minimal increase in height SDS was observed during the one-year follow-up period.

Typically the extra chromosome in KF undergoes inactivation, though some genes escape this process and contribute to symptoms. Interestingly, many deregulated genes in KS are not on the X chromosome, implying that the extra chromosome can influence gene expression across the genome, leading to differential methylation at various sites [15]. This includes dysregulation of genes related to androgen synthesis, resulting in reduced androgen levels [18]. Since, reduced levels of androgens account for hypogonadism, androgen insufficiency, and gynecomastia, which are common in adult males with KS, testosterone therapy is usually a vital option to manage these symptoms, as testosterone also plays a crucial role in mood, cognition, and libido [13,27]. Although studies conducted thus far have not detected any significant adverse effects linked to well-controlled testosterone therapy in adult KS individuals which indicates it as a safe treatment for men with Klinefelter syndrome [19], its effect on our proband may be challenging due to the presence of NF1. In a recent study, there is no link between sex hormone fluctuations and the proliferation of plexiform neurofibromas, and none of the patients who are taking estrogen-progesterone contraceptives or receiving hormonal treatments reported tumor burden during puberty [27]. Another research revealed no significant correlation between puberty-related hormonal markers and changes in plexiform neurofibromas, which suggests the probable influence of additional factors on tumor growth in NF1 patients [28]. On the other hand, a comparison of Schwann cells of neurofibromas with one wildtype NF1 allele ($NF1^{+}/^{-}$) to Schwann cells without any normal NF1 allele ($NF1^{-}/^{-}$) in another study demonstrated heightened sensitivity of Schwann cells harboring mutated NF1 alleles to sex hormones, particularly estradiol, testosterone, and human chorionic gonadotropin (hCG). This study highlighted the hormone-dependent nature of cutaneous neurofibromas, owing to their growth during puberty and pregnancy [29]. In addition to the contribution of hormonal fluctuations during pregnancy to size expansion and quantity growth of cutaneous and plexiform neurofibromas in NF1 patients, particularly those lacking neurofibromin, there is also conjecture regarding hormone involvement in the progression from non-cancerous neurofibromas to malignant peripheral nerve sheath tumors (MPNSTs) [30]. Increased expression of steroid hormone receptors in tumor cells lacking both copies of the *NF1* gene in comparison to cells that have normal levels of neurofibromin expression was reported. However, the role of these receptors varies significantly across different tumor types and genders, indicating a complex interplay of hormonal pathways in NF1 progression which may influenced by factors within the tumor microenvironment [30].

Conclusion

In our case, if there had been no clinical findings suggestive of neurofibromatosis and no genetic analysis had been performed, a diagnosis of Klinefelter syndrome might not have been made prior to puberty. This case underscores the importance of recognizing that Klinefelter syndrome, although relatively common, can be overlooked. It is also emphasized that other conditions may be found coincidentally with Klinefelter syndrome. Close monitoring and detailed information about the risk of malignancies are essential for managing Klinefelter syndrome, with early diagnosis being crucial for addressing potential side effects from coexisting conditions.

CRediT authorship contribution statement

Haniyeh Rahbar Kafshboran: Formal analysis, Writing – review & editing. **Neşe Akcan:** Resources, Visualization, Writing – review & editing. **Doğa Ceren Polat:** Resources, Writing – review & editing. **Ergoren Mahmut Çerkez Ergören:** Conceptualization, Visualization, Supervision, Project administration, Funding acquisition, Resources, Investigation, Formal analysis, Writing – original draft, Writing – review & editing. All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: MAHMUT CERKEZ ERGOREN reports equipment, drugs, or supplies was provided by Near East University. Mahmut cerkez ergoren reports a relationship with Near East University that includes: employment. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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