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Case Report

A Case of Koolen de vries Syndrome or 17q21.31 Microdeletion Syndrome Associated with Infertility: A Case Report

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Abstract

The chromosome 17q21.31 microdeletion syndrome (Koolen de vries Syndrome) is a genomic disorder in patients with unexplained mental retardation that has originally been identified using high resolution genome analyses such as array CGH. Here we report the clinical characterization of a man with the 17q21.31 microdeletion syndrome and infertility. Clinical examination reveals that mild developmental delay, poor speech development, stutter, facial dysmorphisms including a long face, high narrow palate, a tubular or pear-shaped nose and a bulbous nasal tip, a friendly behavior and the main characteristic features to refer was infertility. Other clinically important features include hypothyroidism, bilateral asymmetry in brain MRI, without any anomalies in urogenital examination and echocardiography. Using array CGH we found pathologic loss of 921 kb on 17q21.31compatible with Koolen de Vries syndrome. The chromosome 17q21.31 microdeletion syndrome or Koolen de Vries syndrome recognizable as a genomic disorder with broad features and infertility may be occur.

Introduction

New technologies such as array Comparative Genomic Hybridization (aCGH), have paved the way for identifying, a small but significant percentage of genomic disorders before their clinical description [1]. One of these cases is the chromosome 17q21.31 microdeletion syndrome (Mendelian Inheritance in Man (MIM) 610443) or Koolen de Vries Syndrome (KDVS) characterized by a recurrent 500-650 kb deletion [2]. Screening of large heterogeneous cohorts of individuals with Mental Retardation (MR) using a CGH led to identifying the recurrent microdeletion for first time [2]. The prevalence of this syndrome was estimated to be 1 in 16,000 individuals and most important features including developmental delay, a friendly/amiable behavior, hypotonia, and facial dysmorphisms such as a long face, a tubular or a 'pear-shaped' nose with a bulbous nasal tip, epilepsy, heart defects and urologic abnormalities [3]. The critical region that is missing in most individuals with KDVS is 424 kb encompasses at least six genes and *KANSL1* gene has been shown to make a major contribution to the phenotype [3]. Here, we report on an M.R patient referred to genetics clinic by an infertility& reproductive center.

Case Report

A 28 year old man with mental delay development referred to genetics clinic by the infertility & reproductive center. He was initially referred to an infertility & reproductive center as he was infertile. The proband was the last born boy to non consanguineous parents and without any history of MR and infertility in the family. He was born in good condition and did not require resuscitation without any prenatal/postnatal problems such as neonatal hypoxia and seizure. At the age of two years he was further referred to a pediatric clinic because of poor Verbal skills. It was noted that he still had poor speech development. Developmental delay was further confirmed some years later. The patient has a friendly behavior and mild intellectual disability. Clinical examination revealed sparse thick hair, a triangular face with a high flat forehead, ptosis, a bulbous nasal tip, high narrow palate, widely space nipple, scoliosis and ectodermal abnormalities such as multiple nevi, depigmentosa, hemangiomas. Her fingers are slender and long with hypoplastic muscles. In addition bilateral asymmetry was shown by brain MRI. Semen analysis or seminogram have been shown oligozoospermia (Very low sperm count), asthenozoospermia (poor sperm motility), teratozoospermia (sperm carry more morphological defects than usual). He has hypothyroidism, but levels of the prolactin and testosterone hormones are normal.

Cytogenetic and Molecular Studies

Cytogenetic karyotype of peripheral blood lymphocytes by GTG-banding, at the 450- 550 showed a normal 46, XY karyotype. However molecular analysis, array-CGH, showed the presence chromosomal alteration. Whole genome oligo array CGH was performed using CYTOCHIP ISCA 8X60K whole genome oligo array version 2 and was analyzed using BlueFuse Multi Software. The array consists of 60000 spots with average backbone resolution of 51 Kbs and close 500 targeted disease regions. The sample was hybridized twice against normal samples as references. Array-CGH analysis identified an interstitial deletion of a segment of ~921 kb on 17q21.31q21.31 from nucleotide 43,706,915 to 44,628,121 compatible with 17q21.31 microdeletion syndrome KDVS which is a contiguous gene syndrome caused by microdeletion (600-800kb) of chromosome 17q21.31 encompassing CRHR1(122561), MAPT(157140), STH (607067), IMP5 (608284) and KANSL1(612452).

Discussion

Mental retardation occurs in approximately 2-3% of the general population [4]. The 17q21.31 microdeletion syndrome is a new delay developmental syndrome [2,5]. Only a few cases can be detected based on the clinical features of the patient, so individuals with 17q21.31 microdeletion syndrome is currently highly under diagnosed and in majority of cases the microdeletion was identified after array-CGH [3]. Although microdeletion size can vary, most of them are between 500-650 kb [5]. A minimal chromosomal region has been refined to a segment of 424 kb at chr17:41046729-41470954 (hg 17) and includes the *MAPT, CRHR1, KANSL1, SPPL2C,* and *STH* genes [3]. A number of recent reports have shown that haplo insufficiency of *KANSL1* gene is sufficient to cause the full KdVS phenotype [6,7]. All of the signs and symptoms our patient presents have previously been seen in reported cases of the 17q21.31 microdeletion syndrome, with the exception infertility. There is no family history of infertility and ultrasounds indicate that the genitourinary system is healthy in our patient. Here, we reported a patient with one of the largest microdeletions ever described which consists of approximately 921 kb and contains the following genes: *MAPT, CRHR1, KANSL1, SPPL2C* and *STH,* the hypothetical ORF LOC644246 and the non-coding RNA MGC57346.

So far, for variety of reasons, there is no report that individual with KDVS is known to have had children of their own. For example because the lack of identification of affected people so remain undiagnosed or less likely to have children than normal people.

Haplo insufficiency of one or more other elements within the critical region or position effect resulting 17q21.31 with effect on gametogenesis perhaps representing the infertility seen in the KDVS syndrome. Because structural complexity of this genomic region and due to unknown the exact function of this region elements, infertility traits in individuals with KDVS can be challenging.

Here we reported a patient with KDVS associated infertility. No firm conclusions can be made about infertility because further clinical studies and more DNA testing in other patients with KDVS are needed.

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Author Contribution

Consulting and pedigree drawing and providing clinical case were done by Dr. Azra Moradalibeigi and she helped for writing the article. Dr Neda Asgharzadeh participate searching related articles and helped for writing the article. Hojatolah Rezaei wrote the article and final approval of the manuscript. All authors read and approved the final manuscript.

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