Balanced Reciprocal Translocation t(17;22)(p11.2;q11.2) and 10q23.31 Microduplication in a Infertility Male Suffering from Teratospermia

Shan Huang

Guangxi Medical University First Affiliated Hospital <https://orcid.org/0000-0003-1340-9158>

Huiling Wu

Guangxi Medical University First Affiliated Hospital

Yunwei Qi

Guangxi Medical University First Affiliated Hospital

Liqiang Wei

Guangxi Medical University First Affiliated Hospital

Xiaodan Lv

Guangxi Medical University First Affiliated Hospital

Yu He (✉ heyu31@163.com)

Guangxi Medical University First Affiliated Hospital

Research

Keywords: Male infertility, Balanced reciprocal translocation, Microduplication, Copy number variations(CNVs)

Posted Date: November 1st, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-962774/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

We describe the first case of two chromosomal abnormalities, balanced reciprocal translocation t(17;22)(p11.2;q11.2) and a microduplication in the region 10q23.31, in an infertility man suffering from teratospermia. Several genes located on the translocation breakpoints or the region of duplication show rich expression in the tissue of testis. They have been reported to be associated with developmental disorder and retardation, which might also be the risk factors affecting in spermatogonial differentiation and spermatogenesis. More studies should be carried out for identification of new genes associated with semen quality. Our case might support the opinion that haploinsufficiency of the testis-expressed gene could be the cause of sperm immotility and abnormal sperm morphology. The two chromosomal abnormalities that carry additional reproductive risks, is apparently harmful with regard to the male infertility, and could contribute to the genomic instability resulting in disease.

Introduction

It has been observed that declining fertility rates is among the most salient features of global demography over the last decade. Male infertility, affecting approximately 50% of the couples with problems to have children, is getting more and more concern(1). It is highly vary for the causes of male infertility, which can be related to the acquired, congenital or idiopathic factors that impair spermatogenesis. Despite many health conditions and lifestyle factors can affect fertility, the diagnosis in around 40% of infertility men remain to be elucidated, which might be underlying genetic causes(2). So far, recognized genetic causes of spermatogenic failure include karyotype abnormalities, Y-chromosome microdeletions, systemic syndromes, and gene mutations. The formation of normal bivalents during the meiosis is disrupted in these patients resulting in an inefficient spermatogenesis. To investigate, one of the routinely genetic tests to be performed in infertility patients is karyotype analysis. Besides numerical abnormalities, chromosome structural defects are detected 5–10 times more frequently in infertile men(3)(4). There are some potential pathogenic mechanisms related to effects on the expression of genes, when they are targets of chromosomal rearrangements (such as deletions, duplications and breakpoints). The presence of structural chromosomal abnormalities in the sperm increases the risk of aneuploidy and unbalanced chromosomal complements in the fetus. The most frequent structural abnormalities are translocations, especially reciprocal translocations (1.3–1.4%), being more common in oligozoospermic males than in azoospermics(2)(5)(6). In carriers of an apparently balanced reciprocal translocation, it could be an increased risk of reproductive issues. Reciprocal translocations t(17;22) with different breakpoints have been published in two cases with infertility male in the literature(7)(8). The existence of multiple independent structural abnormalities and resulting phenotypes are often more complex than expected. We report clinical, cytogenetic and copy number variations(CNVs) findings for the first male who suffers from teratospermia, and has both a balanced reciprocal translocation t(17;22)(p11.2;q11.2) and a microduplication in the region 10q23.31. In view of assisted reproductive techniques, it is especially important to gain information about the genetic causes of male infertility, as these defects can be transmitted across generation(s).

Materials And Methods

Study samples

The patient came to the hospital for infertility and genetic counseling. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University, and written informed consent was

obtained from the patient.

Semen analysis

Briefly, semen analysis was performed according to the method recommended by the fifth edition of the World Health Organization guidelines(9). Semen samples were collected twice for patient with an interval of 2-7 days after abstinence. Sperm motility was calculated by counting more than 200 spermatozoa.

Karyotypes analysis

The peripheral blood cells were treated with colchicine for 1.5 hour, incubated in hypotonic solution and fixed with methanol-acetic acid solution, according to the laboratory standard program. The karyotype analysis were carried out with 400-550 bands in G-banding of metaphase chromosomes. Twenty metaphase counts and eight karyotypes were analyzed. The karyotypes were described according to the International Human Cytogenetic Nomenclature System (ISCN 2020)(10).

Molecular analysis

Y-microdeletion studies were performed using a multiplex PCR amplification based method(11). In brief, DNA was extracted using standard techniques followed by two separate multiplexed PCR reactions. The patient was considered to have Y-microdeletion, if a deletion was detected in at least one marker within the verification marker set.

Microarray analysis

CNVs analysis was performed in the illumina NovaSeq 6000 (Illumina Inc, USA). Experiments were carried out with the NovaSeq 6000 S4 Reagent Kit and the S4 flowcell, according to the manufacturer's protocol. The NovaSeq 6000 PE150 was used for genotype calling, quality control and CNVs identification. For annotation of genes in the deleted or duplicated genomic segments, the public databases including Database of DGV, ClinGen, OMIM, gnomAD, GeneReview and DECIPHER were used for interpretation and classification of the clinical significance of candidate CNVs.

Bioinformatics analysis

The data on expression levels in different normal tissues of candidate genes, which located on the breakpoints of translocation and duplication, were extracted from NCBI gene database(<https://www.ncbi.nlm.nih.gov/gene/>) and the projects of human protein atlas (HPA)(12)(<http://www.proteinatlas.org>). The functions of these genes were obtained from the published literature and the neXtProt knowledgebase(13)(<https://www.nextprot.org>). The interaction network of genes was performed in GeneMANIA(14)(<https://www.genemania.org>).

Results

A 35-year-old male who came to the department of prenatal and genetic diseases in our hospital for consultation during to miscarriage of his wife, was referred for karyotype analyses. Physical examinations were practically normal in the couples. The medical history was unremarkable regarding some risk factors of infertility: no exposure to roentgen radiation or toxins, and no trauma of the tests were known. Two different semen analyses of the patient showed asthenospermia and teratospermia. The results of the normal sperm count of 20.1×10^6 /ml ($\geq 15 \times 10^6$ /ml), lower progressive motility sperms 27.7% ($A+B \geq 32\%$), and abnormal sperm morphology 100% ($>96\%$) were observed, according to the guidelines for semen analysis from the fifth edition of World Health Organization (9). Normal spermatozoa from fertile men have elongated shape with a 2.4/1 length to transversal diameter ratio. The acrosome covers approximately 2/3 of the head surface, which closely attaches to the head. In contrast, spermatozoa from the cases possessed conspicuous head-shaped and acrosomal anomalies (Fig. 1AB). Sperm heads were close to the ratio of 1/1 spherical with absent or minute acrosomes. Others were pyriform or irregularly ovoid and had small acrosomes, not well attached to the nuclear surface or completely disengaged from it (acrosome hypoplasia). Unfortunately, we didn't get medical information from their family members.

The cytogenetic analysis (G-banding) showed that patient's karyotype was 46,XY,t(17;22)(p11.2;q11.2) (Fig. 2) and his wife's karyotype was 46, XX. No microdeletion was found in AZF regions (sy84, sy86, sy127, sy134, sy254 and sy255) in the Y chromosome analysis. CNVs showed a microduplication approximately 224.98-kb in size, and the result described as seq[GRCh37]dup(10)(q23.31q23.31) chr10:g.91371499_91596485dup. However, this microduplication was not mentioned in any public database before (Fig. 3).

Discussion

Previously, reciprocal translocation between chromosome 17 and chromosome 22 had been described in two male patients with reproductive problems of repeated spontaneous abortions in his wife (Table 1). Interestingly, the two involving chromosomes are characterized by the presence of chromosome-specific low copy repeats (LCR) (15)(16). The enrichment of LCR precipitated a high frequency of nonallelic homologous misalignments and unequal recombination during the meiosis, leading to the instabilities in the region of the chromosome 17 and chromosome 22. It is well known that, duplication of chromosome 17p11.2 results in Potocki-Lupski syndrome (PTLS), while its reciprocal deletion leads to Smith-Magenis syndrome (SMS) (17). In addition, alteration of gene dosage on part of 22q is responsible for the aetiology of a number of human congenital anomaly disorders including cat eye syndrome (CES) and DiGeorge syndrome/velocardiofacial (DGS/VCFS) (18)(19). The dosage change of significant genes could play an important role in several distinct processes such as transcription, cell differentiation, and DNA repair. When translocation occurs, although the genome may change in balance, it will also have a serious impact, such as t(15;17) occurring in acute myeloid leukemia, and t(9;22) occurring in chronic myeloid leukemia (20)(21). Recent epidemiological studies have identified an association between male infertility and cancer, and some 'male infertility-cancer genes' have been established as risk factors in cancer progression (22). Some shared biological processes could explain the shared etiology of cancer and male infertility, such as cell survival, cell fate, and genome maintenance (Fig. 4). Disruption in any of these pathways would be expected to lead to loss or damage of germ cells and the associated expression of male infertility.

Translocations involving chromosome 17 have been thought to be harmful for the fertility of the carrier (7). The breakpoint of chromosome 17p11.2, also the critical region of SMS, was contained genes involved in several pathogenesis of cancers and reproductive physiology processes. ALKBH5 (alkB homolog 5) was an ubiquitously expressed protein in testis and brain, and was described as a cancer/testis gene (Table 2) (23). In the animal study,

ALKBH5 resulted in impaired fertility by affecting meiotic metaphase-stage spermatocytes apoptosis(24). Stained testis and epididymis sections of ALKBH5 knockout male mice, observed to contain no mature sperm, but germ cells of degeneration resembling round, elongating, or elongated spermatids(25). In our patient, sperm morphology supported this result as well. Besides, DRC3 (Dynein regulatory complex subunit 3) was a critical hub for the control of flagellar motility, which was also key component of the N-DRC (nexin-dynein regulatory complex). DRC3 regulated to the waveform of flagella together with dynein g, and its mutant caused decreasing the movement speed(26). In addition, COPS3 (COP9 signalosome subunit 3), known as CSN3, is a component of the COP9 signalosome complex (CSN), which involved in various cellular and developmental processes(27). CNS3 knockout mice could not finish meiosis phase I. Meanwhile, PLD6 (phospholipase D family member 6), also known as MitoPLD, is the endonuclease that plays a critical role in PIWI-interacting RNA (piRNA) biogenesis during the spermatogenesis(28). The destruction of UBB (Ubiquitin B) gene was related to the low expression of many proteins involving in spermatogenesis and the reducing of germ cell number(29). UBB gene knockout mice were infertility, because of the structure destruction in gonad and reproductive organ, resulting in unformed gametes(30). Some other genes, such as CCDC144NL-AS1, LLGL1, FLII, TOP3A and ULK2, were involved in important functions like cell proliferation(31), embryonic development(32)(33)(34) and autophagy(35). Genes exhibit multiple physiological and pathological functions depending on the tissue and/or cell type where they are expressed(36). Thus, genes that highly expressed in testis might probably play roles in the process of sperm function and male fertility. There are still several genes, including GID4, SPECC1 and PRPSAP2, expressed highly in testis. Resulting haploinsufficiency of these genes from translocation could produce an increased risk of male infertility. Since the role of some genes remain unexplored in the development of male reproductive, studies in this direction would be very interesting in the future.

Among the individuals associated with translocation of chromosome17, the rate of unbalanced gametes was up to 81% in the case of t(17;22)(q11;q12), most of others were around 50%(37). This suggested that together with chromosome 17 and chromosome 22 might be a risk factor for abnormal meiotic segregation. Genes mapped within or just adjacent to the breakpoint region of 22q11.2 had been identified to be involved in hematological malignancies such as chronic myeloid leukemia and other disorders in development(19)(21). Among them, there was a gene, SPECC1L(sperm antigen with calponin homology and coiled-coil domains 1 like), expressed highest in testis compare to other tissues(table2). This gene was first identified to be disrupted by a balanced translocation t(1;22)(21.3;q11.23) in a female patient with bilateral oromedial-canthal (Tessier IV) clefts(38). It encoded a 'cross-linking' protein that functionally interacts with both microtubules and the actin cytoskeleton, which was necessary for cell adhesion and migration(39). It was also found in the cases of Opitz G/BBB syndrome, SPECC1L mutations could cause syndromic forms of facial clefting which support the original correlation to chromosome 22q11.2(40). Another gene CDC45 (cell division cycle 45) was a member of the pre-initiation complex in DNA replication, which was important for early steps of DNA replication in eukaryotes. Biallelic mutations of CDC45 caused a spectrum of phenotypes including isolated short stature and craniosynostosis(41)(42). Meanwhile, it might promote hepatocellular carcinoma (HCC) or non-small cell lung cancer (NSCLC) and correlated with worse prognosis in patients(43)(44). Another well-studied gene, T-box transcription factor 1(TBX1), had been reported that its haploinsufficiency caused abnormal growth and remodeling in the pharyngeal apparatus and related structures(45). Same as, haploid 22q11 gene insufficiency in the patients disrupt orofacial and cranial nerve development by modifying retinoic acid-modulated anterior-posterior hindbrain differentiation(46)(47). These disruptions likely contributed to dysphagia in infants and young children with 22q11DS. Several other genes in the 22q11 region had been implicated in the pathogenesis of developmental disorders. It had been reported that gene PI4KA was implicated in the pathogenesis of cerebellar hypoplasia and arthrogryposis(48). Ess2 (also termed

Dgcr14) was a nuclear protein that bridged transcriptional regulators and spliceosomal complexes via distinct interacting domains, which might impact in the pathogenesis of DiGeorge syndrome(49). Gene SNAP29 has been shown to be involved in formation of primary cilia, epidermal differentiation, membrane fusion and autophagy, which implicated in a number of pathological conditions such as recessive neurocutaneous cerebral dysgenesis, neuropathy, ichthyosis, and keratoderma(50). Gene DGCR8 encodes a subunit of the microprocessor complex which mediates the biogenesis of microRNAs from the primary microRNA transcript. It could enhance Tri-negative breast cancer cell migration and invasion via targeting TGF- β (51). Taken these together, genes mentioned above were associated with developmental disorder and retardation, which also the shared biological processes of cancer and infertility, might also affect in spermatogonial differentiation and spermatogenesis.

It was known that the chromosomal rearrangement associated with other chromosomal changes, particularly those involving segmental duplications, might contribute to a very genomic instability(5)(52). Many implicated risk genes in CNVs were responsible for different cellular processes, including cell signaling, sensing and repair(53). Impairment of these genes was expected to disrupt the functions specifically involved with cellular development and lead to cause diseases. In addition to the reciprocal translocation, the array analysis also revealed a novel 224.98-kb microduplication in chromosome 10q23.31. Reports of 10q duplication with other chromosomal abnormality are uncommon, and two cases with breakpoints in 10q23.31(chr10:91371499-91596485) had been reported so far. DECIPHER Patient 341717 documented with growth delay, intellectual disability and emotional lability, detected an overlapped CNVs of 8.52Mb(chr10:90100579-98618234). Similarly, DECIPHER Patient 252137 documented with phenotypes including: delayed puberty obesity, autism, cognitive impairment, intellectual disability, and abnormality of limbs, head and neck, detected an overlapped CNV of 2.63Mb(chr10:89584411-92213522).

In current study, we identified a previously unreported copy number variation at 10q23.31(chr10:91371499-91596485). This microduplication encompassed approximately four genes, FLJ37201, KIF20B, LINC00865 and PANK1(table2). None of these genes were identified in OMIM as disease causing. By now, it is unknown whether one of these genes could be dosage sensitive and responsible for the male infertility. FLJ37201 was described as tigger transposable element derived 2 pseudogene. Although pseudogenes were considered to be evolutionally conserved, they were found to act as a gene reservoir that might allowed the genome to carry out novel functions effectively(54). It was reported that pseudogenes might be present in reproductive cells more than in somatic cells(55). Moreover, transposable elements could create chromosomal insults or rearrangements and impacted gene expression, which were recognized as contributors to genomic innovations as well as genome instability(56). In this view, with a higher expression in testis, FLJ37201 could be regarded as a new candidate gene for recognizing mechanisms in male infertility. LINC00865 was a member of long noncoding RNAs (lncRNAs). lncRNAs with sequence lengths over 200 nucleotides, were considered to be regulators of many cellular processes, particularly in tumorigenesis and cancer progression(57). It had been revealed that lncRNAs could be regulated in both gene level and transcription level, and induce both cell-cycle arrest and apoptosis(58). Difference with other lncRNAs, LINC00865 was indicated highly expression in the tissue of testis, which could be recognized as a cancer/testis gene. Since its role remain unexplored in male reproductive, studies in this direction would be very interesting.

KIF20B (previously called MPHOSPH1 or MPP1) was a member of the Kinesin-6 family, which had been involved in cerebral cortex growth and midbody organization of neural stem cells in mouse(59). It could accelerate or coordinate midbody maturation, and regulate late steps of maturation in a human cell line. Meanwhile, KIF20B was found to serve important roles in multiple types of cancer, which could function as cancer-testis antigen specific to

human bladder cancer (60). It also regulated cell proliferation, apoptosis and tumor growth in hepatocellular carcinoma associating with the tumor suppressor p53 (61)(62). Similarly, gene PANK1 (pantothenate kinase 1) worked as a p53 transcriptional target, played an importance role in metabolic regulation, as well as modulates energy balance in the adaptive(63). Taking these into account, this 10q23.31 duplications most likely represents a risk factor for sperm immotility and abnormal sperm morphology. Increasing dosage of the four duplicate genes might disrupt diverse cellular processes, and implicated in the pathogenesis of male infertility. Since there was no evidence of a phenotypically well-defined syndrome resulting from 10q23.31 duplication so far, and its clinical significance remains unclear. Combined with the balanced reciprocal translocation t(17;22), 10q23.31 duplication could have more severe consequences for gametogenesis, and could be treated as a risk factor in our infertility patient.

Conclusion

In this study, we have identified two chromosomal abnormalities, a balanced reciprocal translocation t(17;22) (p11.2;q11.2) and a microduplication in the region 10q23.31, in our patient suffering from teratospermia. Genes located in the translocation breakpoints or the region of duplication show the highly expression in the tissue of testis, which are associated with developmental disorder and retardation. They might be risk factors in spermatogonial differentiation and spermatogenesis. The haploinsufficiency of these genes in our case could be the cause of sperm immotility and abnormal sperm morphology. The two chromosomal abnormalities is apparently harmful with regard to infertility, could contribute to the genetic instability resulting in disease. In the long run, it is important to accumulate more cases and investigate the genes affect by structural chromosomal abnormalities, regardless of the severity or the absence of manifestations. It could be better to understand about the mechanisms which lead to varied phenotypes, and provide improved genetic counseling.

Abbreviations

CNVs: Copy Number Variations

PCR: Polymerase Chain Reaction

DGV: Database of Genomic Variants

ClinGen: Clinical Genome Resource

OMIM: Online Mendelian Inheritance in Man

gnomAD: genome aggregation database

DECIPHER: Database of Chromosomal Imbalance and Phenotype in Humans Using Ensembl Resources

LCR: Low Copy Repeats

PTLS: Potocki-Lupski Syndrome

SMS: Smith-Magenis Syndrome

CES: Cat Eye Syndrome

DGS: DiGeorge Syndrome

VCFS: Velocardiofacial

ALKBH5: AlkB homolog 5

DRC3: Dynein regulatory complex subunit 3

COPS3: COP9 signalosome subunit 3

PLD6: Phospholipase D family member 6

UBB: Ubiquitin B

LLGL1: LLGL scribble cell polarity complex component 1

CCDC144NL-AS1: Coiled-coil domain containing 144NL antisense RNA 1

FLII : FLII actin remodeling protein

TOP3A: DNA topoisomerase III alpha

ULK2: Unc-51 like autophagy activating kinase 2

GID4: GID complex subunit 4 homolog

SPECC1: Sperm antigen with calponin homology and coiled-coil domains 1

PRPSAP2: Phosphoribosyl pyrophosphate synthetase associated protein 2

SPECC1L: Sperm antigen with calponin homology and coiled-coil domains 1 like

TBX1: T-box transcription factor 1

CDC45: Cell division cycle 45

PI4KA: Phosphatidylinositol 4-kinase alpha

Ess2 : Ess-2 splicing factor homolog

SNAP29: Synaptosome associated protein 29

DGCR8: DGCR8 microprocessor complex subunit

FLJ37201: Tigger transposable element derived 2 pseudogene

KIF20B: Kinesin family member 20B

LINC00865: Long intergenic non-protein coding RNA 865

PANK1: Pantothenate kinase 1

Declarations

Ethical Approval and Consent to participate: This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University. Informed consent was obtained from all participants before the start of this study.

Consent for publication: The patient signed informed consent regarding publishing their data and photographs.

Availability of supporting data: The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors report no conflict of interest.

Funding: None.

Authors' Contributions: SH participated in the project development and manuscript writing, HW,YQ analyzed and interpreted the data, LW, XL performed the experiments, YH reviewed and edited the manuscript. All authors read and approved the final manuscript.

Acknowledgments: The authors are thankful for the cooperation of the patient and their family.

Authors' information:

Affiliations

Department of Clinical Laboratory, The First Affiliated Hospital of Guangxi Medical University, Nanning 530021, China

Shan Huang, Huiling Wu, Yunwei Qi, Liqiang Wei, Xiaodan Lv, Yu He

References

1. Agarwal A, Baskaran S, Parekh N, Cho CL, Henkel R, Vij S, et al. Male infertility. *Lancet*. 2021;397(10271):319-33.
2. Krausz C, Riera-Escamilla A. Genetics of male infertility. *Nat Rev Urol*. 2018;15(6):369-84.
3. Ferlin A, Raicu F, Gatta V, Zuccarello D, Palka G, Foresta C. Male infertility: role of genetic background. *Reprod Biomed Online*. 2007;14(6):734-45.
4. Chantot-Bastaraud S, Ravel C, Siffroi JP. Underlying karyotype abnormalities in IVF/ICSI patients. *Reprod Biomed Online*. 2008;16(4):514-22.
5. Hofherr SE, Wiktor AE, Kipp BR, Dawson DB, Van Dyke DL. Clinical diagnostic testing for the cytogenetic and molecular causes of male infertility: the Mayo Clinic experience. *J Assist Reprod Genet*. 2011;28(11):1091-8.
6. Elghezal H, Hidar S, Braham R, Denguezli W, Ajina M, Saad A. Chromosome abnormalities in one thousand infertile males with nonobstructive sperm disorders. *Fertil Steril*. 2006;86(6):1792-5.

7. Geneix A, Schubert B, Force A, Rodet K, Briancon G, Boucher D. Sperm analysis by FISH in a case of t(17; 22) (q11; q12) balanced translocation: case report. *Hum Reprod.* 2002;17(2):325-31.
8. Kim JW, Chang EM, Song SH, Park SH, Yoon TK, Shim SH. Complex chromosomal rearrangements in infertile males: complexity of rearrangement affects spermatogenesis. *Fertil Steril.* 2011;95(1):349-52, 52 e1-5.
9. WHO laboratory manual for the examination and processing of human semen - 5th ed. World Health Organization. 2010.
10. Simoni M, Bakker E, Eurlings MC, Matthijs G, Moro E, Muller CR, et al. Laboratory guidelines for molecular diagnosis of Y-chromosomal microdeletions. *Int J Androl.* 1999;22(5):292-9.
11. Uhlen M, Fagerberg L, Hallstrom BM, Lindskog C, Oksvold P, Mardinoglu A, et al. Proteomics. Tissue-based map of the human proteome. *Science.* 2015;347(6220):1260419.
12. Zahn-Zabal M, Michel PA, Gateau A, Nikitin F, Schaeffer M, Audot E, et al. The neXtProt knowledgebase in 2020: data, tools and usability improvements. *Nucleic Acids Res.* 2020;48(D1):D328-D34.
13. Franz M, Rodriguez H, Lopes C, Zuberi K, Montojo J, Bader GD, et al. GeneMANIA update 2018. *Nucleic Acids Res.* 2018;46(W1):W60-W4.
14. Babcock M, Yatsenko S, Hopkins J, Brenton M, Cao Q, de Jong P, et al. Hominoid lineage specific amplification of low-copy repeats on 22q11.2 (LCR22s) associated with velo-cardio-facial/digeorge syndrome. *Hum Mol Genet.* 2007;16(21):2560-71.
15. Shaw CJ, Withers MA, Lupski JR. Uncommon deletions of the Smith-Magenis syndrome region can be recurrent when alternate low-copy repeats act as homologous recombination substrates. *Am J Hum Genet.* 2004;75(1):75-81.
16. Neira-Fresneda J, Potocki L. Neurodevelopmental Disorders Associated with Abnormal Gene Dosage: Smith-Magenis and Potocki-Lupski Syndromes. *J Pediatr Genet.* 2015;4(3):159-67.
17. Knoll JH, Asamoah A, Pletcher BA, Wagstaff J. Interstitial duplication of proximal 22q: phenotypic overlap with cat eye syndrome. *Am J Med Genet.* 1995;55(2):221-4.
18. Jawad AF, McDonald-Mcginn DM, Zackai E, Sullivan KE. Immunologic features of chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). *J Pediatr.* 2001;139(5):715-23.
19. Kakizuka A, Miller WH, Jr., Umesono K, Warrell RP, Jr., Frankel SR, Murty VV, et al. Chromosomal translocation t(15;17) in human acute promyelocytic leukemia fuses RAR alpha with a novel putative transcription factor, PML. *Cell.* 1991;66(4):663-74.
20. Tarkkanen M, Wiklund T, Virolainen M, Elomaa I, Knuutila S. Dedifferentiated chondrosarcoma with t(9;22) (q34;q11-12). *Genes Chromosomes Cancer.* 1994;9(2):136-40.
21. Nagirnaja L, Aston KI, Conrad DF. Genetic intersection of male infertility and cancer. *Fertil Steril.* 2018;109(1):20-6.
22. Wang J, Wang J, Gu Q, Ma Y, Yang Y, Zhu J, et al. The biological function of m6A demethylase ALKBH5 and its role in human disease. *Cancer Cell Int.* 2020;20:347.
23. Zheng G, Dahl JA, Niu Y, Fedorcsak P, Huang CM, Li CJ, et al. ALKBH5 is a mammalian RNA demethylase that impacts RNA metabolism and mouse fertility. *Mol Cell.* 2013;49(1):18-29.
24. Tang C, Klukovich R, Peng H, Wang Z, Yu T, Zhang Y, et al. ALKBH5-dependent m6A demethylation controls splicing and stability of long 3'-UTR mRNAs in male germ cells. *Proc Natl Acad Sci U S A.* 2018;115(2):E325-E33.

25. Awata J, Song K, Lin J, King SM, Sanderson MJ, Nicastro D, et al. DRC3 connects the N-DRC to dynein g to regulate flagellar waveform. *Mol Biol Cell*. 2015;26(15):2788-800.
26. Kim E, Yoon SJ, Kim EY, Kim Y, Lee HS, Kim KH, et al. Function of COP9 signalosome in regulation of mouse oocytes meiosis by regulating MPF activity and securing degradation. *PLoS One*. 2011;6(10):e25870.
27. Watanabe T, Chuma S, Yamamoto Y, Kuramochi-Miyagawa S, Totoki Y, Toyoda A, et al. MITOPLD is a mitochondrial protein essential for nuage formation and piRNA biogenesis in the mouse germline. *Dev Cell*. 2011;20(3):364-75.
28. Han B, Jung BK, Park SH, Song KJ, Anwar MA, Ryu KY, et al. Polyubiquitin gene Ubb is required for upregulation of Piwi protein level during mouse testis development. *Cell Death Discov*. 2021;7(1):194.
29. Ryu KY, Sinnar SA, Reinholdt LG, Vaccari S, Hall S, Garcia MA, et al. The mouse polyubiquitin gene Ubb is essential for meiotic progression. *Mol Cell Biol*. 2008;28(3):1136-46.
30. Wang Y, Guo B, Xiao Z, Lin H, Zhang X, Song Y, et al. Long noncoding RNA CCDC144NL-AS1 knockdown induces naive-like state conversion of human pluripotent stem cells. *Stem Cell Res Ther*. 2019;10(1):220.
31. Jossin Y, Lee M, Klezovitch O, Kon E, Cossard A, Lien WH, et al. Llg1 Connects Cell Polarity with Cell-Cell Adhesion in Embryonic Neural Stem Cells. *Dev Cell*. 2017;41(5):481-95 e5.
32. Yang GN, Ahangar P, Strudwick XL, Kopecki Z, Cowin AJ. Overexpression of Flii during Murine Embryonic Development Increases Symmetrical Division of Epidermal Progenitor Cells. *Int J Mol Sci*. 2021;22(15).
33. Li W, Wang JC. Mammalian DNA topoisomerase IIIalpha is essential in early embryogenesis. *Proc Natl Acad Sci U S A*. 1998;95(3):1010-3.
34. Chan EY, Longatti A, McKnight NC, Tooze SA. Kinase-inactivated ULK proteins inhibit autophagy via their conserved C-terminal domains using an Atg13-independent mechanism. *Mol Cell Biol*. 2009;29(1):157-71.
35. Benet J, Oliver-Bonet M, Cifuentes P, Templado C, Navarro J. Segregation of chromosomes in sperm of reciprocal translocation carriers: a review. *Cytogenet Genome Res*. 2005;111(3-4):281-90.
36. Dasouki M, Barr M, Jr., Erickson RP, Cox B. Translocation (1;22) in a child with bilateral oblique facial clefts. *J Med Genet*. 1988;25(6):427-9.
37. Saadi I, Alkuraya FS, Gisselbrecht SS, Goessling W, Cavallero R, Turbe-Doan A, et al. Deficiency of the cytoskeletal protein SPECC1L leads to oblique facial clefting. *Am J Hum Genet*. 2011;89(1):44-55.
38. Kruszka P, Li D, Harr MH, Wilson NR, Swarr D, McCormick EM, et al. Mutations in SPECC1L, encoding sperm antigen with calponin homology and coiled-coil domains 1-like, are found in some cases of autosomal dominant Opitz G/BBB syndrome. *J Med Genet*. 2015;52(2):104-10.
39. Knapp KM, Fellows B, Aggarwal S, Dalal A, Bicknell LS. A synonymous variant in a non-canonical exon of CDC45 disrupts splicing in two affected sibs with Meier-Gorlin syndrome with craniosynostosis. *Eur J Med Genet*. 2021;64(4):104182.
40. Unolt M, Kammoun M, Nowakowska B, Graham GE, Crowley TB, Hestand MS, et al. Pathogenic variants in CDC45 on the remaining allele in patients with a chromosome 22q11.2 deletion result in a novel autosomal recessive condition. *Genet Med*. 2020;22(2):326-35.
41. Lu HP, Du XF, Li JD, Huang SN, He RQ, Wu HY, et al. Expression of Cell Division Cycle Protein 45 in Tissue Microarrays and the CDC45 Gene by Bioinformatics Analysis in Human Hepatocellular Carcinoma and Patient Outcomes. *Med Sci Monit*. 2021;27:e928800.
42. Huang J, Li Y, Lu Z, Che Y, Sun S, Mao S, et al. Analysis of functional hub genes identifies CDC45 as an oncogene in non-small cell lung cancer - a short report. *Cell Oncol (Dordr)*. 2019;42(4):571-8.

43. Lindsay EA, Vitelli F, Su H, Morishima M, Huynh T, Pramparo T, et al. Tbx1 haploinsufficiency in the DiGeorge syndrome region causes aortic arch defects in mice. *Nature*. 2001;410(6824):97-101.
44. Yagi H, Furutani Y, Hamada H, Sasaki T, Asakawa S, Minoshima S, et al. Role of TBX1 in human del22q11.2 syndrome. *Lancet*. 2003;362(9393):1366-73.
45. Verhagen JM, Diderich KE, Oudesluijs G, Mancini GM, Eggink AJ, Verkleij-Hagoort AC, et al. Phenotypic variability of atypical 22q11.2 deletions not including TBX1. *Am J Med Genet A*. 2012;158A(10):2412-20.
46. Pagnamenta AT, Howard MF, Wisniewski E, Popitsch N, Knight SJ, Keays DA, et al. Germline recessive mutations in PI4KA are associated with perisylvian polymicrogyria, cerebellar hypoplasia and arthrogryposis. *Hum Mol Genet*. 2015;24(13):3732-41.
47. Takada I, Tsuchiya M, Yanaka K, Hidano S, Takahashi S, Kobayashi T, et al. Ess2 bridges transcriptional regulators and spliceosomal complexes via distinct interacting domains. *Biochem Biophys Res Commun*. 2018;497(2):597-604.
48. Martens MC, Edelkamp J, Seebode C, Schafer M, Stahlke S, Krohn S, et al. Generation and Characterization of a CRISPR/Cas9-Mediated SNAP29 Knockout in Human Fibroblasts. *Int J Mol Sci*. 2021;22(10).
49. Cui CY, Pan QW, Wang MH, Ai X, Yan YZ, Tian Y, et al. DGCR8 promotes the metastasis in triple-negative breast cancer by epigenetically regulating TGF-beta. *Eur Rev Med Pharmacol Sci*. 2020;24(5):2557-63.
50. Manvelyan M, Schreyer I, Hols-Herpertz I, Kohler S, Niemann R, Hehr U, et al. Forty-eight new cases with infertility due to balanced chromosomal rearrangements: detailed molecular cytogenetic analysis of the 90 involved breakpoints. *Int J Mol Med*. 2007;19(6):855-64.
51. Yoon J, Mao Y. Dissecting Molecular Genetic Mechanisms of 1q21.1 CNV in Neuropsychiatric Disorders. *Int J Mol Sci*. 2021;22(11).
52. Chen X, Wan L, Wang W, Xi WJ, Yang AG, Wang T. Re-recognition of pseudogenes: From molecular to clinical applications. *Theranostics*. 2020;10(4):1479-99.
53. Noll A, Raabe CA, Churakov G, Brosius J, Schmitz J. Ancient traces of tailless retropseudogenes in therian genomes. *Genome Biol Evol*. 2015;7(3):889-900.
54. Klein SJ, O'Neill RJ. Transposable elements: genome innovation, chromosome diversity, and centromere conflict. *Chromosome Res*. 2018;26(1-2):5-23.
55. Zhang M, Gao F, Yu X, Zhang Q, Sun Z, He Y, et al. LINC00261: a burgeoning long noncoding RNA related to cancer. *Cancer Cell Int*. 2021;21(1):274.
56. Zhai S, Xu Z, Xie J, Zhang J, Wang X, Peng C, et al. Epigenetic silencing of LncRNA LINC00261 promotes c-myc-mediated aerobic glycolysis by regulating miR-222-3p/HIPK2/ERK axis and sequestering IGF2BP1. *Oncogene*. 2021;40(2):277-91.
57. Janisch KM, McNeely KC, Dardick JM, Lim SH, Dwyer ND. Kinesin-6 KIF20B is required for efficient cytokinetic furrowing and timely abscission in human cells. *Mol Biol Cell*. 2018;29(2):166-79.
58. Kanehira M, Katagiri T, Shimo A, Takata R, Shuin T, Miki T, et al. Oncogenic role of MPHOSPH1, a cancer-testis antigen specific to human bladder cancer. *Cancer Res*. 2007;67(7):3276-85.
59. Liu X, Zhou Y, Liu X, Peng A, Gong H, Huang L, et al. MPHOSPH1: a potential therapeutic target for hepatocellular carcinoma. *Cancer Res*. 2014;74(22):6623-34.
60. Li ZY, Wang ZX, Li CC. Kinesin family member 20B regulates tongue cancer progression by promoting cell proliferation. *Mol Med Rep*. 2019;19(3):2202-10.

61. Wang SJ, Yu G, Jiang L, Li T, Lin Q, Tang Y, et al. p53-Dependent regulation of metabolic function through transcriptional activation of pantothenate kinase-1 gene. Cell Cycle. 2013;12(5):753-61.

Tables

Table 1. the carriers of the reciprocal translocation t(17;22)

Karyotype of the carrier	Clinical outcome of the translocation	Reference
46,XY,inv(1)(p13;q21),t(17;22)(p11:p11)	Recurrent abortion	(Kim et al. 2011)
46,XY,t(17;22)(q11;q12)	Miscarriage; Oligoteratozoospermia	(Geneix et al. 2002)

Table2 Genes located at the breakpoint(17p11.2 and 22q11.2) and the duplicated region(10q23.31)

Number	Genes	Description	Location	Expression (the first / the second)	function
1	ALKBH5	alkB homolog 5	17p11.2	Testis / Brain	Spermatogenesis(GO:0007283); Cell differentiation(GO:0030154)
2	DRC3	dynein regulatory complex subunit 3		Testis / Thyroid	Protein binding (GO:0005515)
3	COPS3	COP9 signalosome subunit 3	17p11.2	Testis / Bone marrow	In utero embryonic development (GO:0001701); Protein binding (GO:0005515); Protein deneddylation (GO:0000338)
4	PLD6	phospholipase D family member 6	17p11.2	Testis / Prostate	DNA methylation involved in gamete generation (GO:0043046);Meiotic cell cycle (GO:0051321); Spermatid development (GO:0007286)
5	UBB	ubiquitin B	17p11.2	liver / Testis	Male meiosis I (GO:0007141), Seminiferous tubule development (GO:0072520); Positive regulation of intrinsic apoptotic signaling pathway by p53 class mediator (GO:1902255)
6	LLGL1	LLGL scribble cell polarity complex component 1	17p11.2	Brain / Testis	Regulation of establishment or maintenance of cell polarity (GO:0032878); Regulation of protein secretion (GO:0050708)
7	CCDC144NL- AS1	coiled-coil domain containing 144NL antisense RNA 1	17p11.2	Testis / Placenta	knockdown of CCDC144NL-AS1 was related to conversion of human pluripotent stem cells. Knockdown of CCDC144NL- AS1 dramatically altered the distribution of cytoskeletal filamentous actin (F-actin) stress fibers compared to the negative control group treatment.
8	FLII	FLII actin remodeling protein	17p11.2	Testis / Spleen	Multicellular organism development (GO:0007275); Actin binding (GO:0003779)
9	TOP3A	DNA topoisomerase III alpha	17p11.2	Testis / Bone marrow	Chromosome separation (GO:0051304); Meiotic cell cycle (GO:0051321); DNA topoisomerase activity (GO:0003916)
10	ULK2	unc-51 like autophagy activating kinase 2	17p11.2	Testis / Brain	Protein serine/threonine kinase activity (GO:0004674); Cellular response to DNA damage stimulus (GO:0006974);Neuron projection development (GO:0031175); Autophagy (GO:0006914)

11	GID4	GID complex subunit 4 homolog	17p11.2	Testis / Esophagus	Ubiquitin protein ligase activity (GO:0061630); Protein ubiquitination (GO:0016567)
12	SPECC1	sperm antigen with calponin homology and coiled-coil domains 1	17p11.2	Brain / Testis	Actin cytoskeleton organization (GO:0030036)
13	PRPSAP2	phosphoribosyl pyrophosphate synthetase associated protein 2	17p11.2	Lymph node / Testis	Protein binding (GO:0005515); Negative regulation of catalytic activity (GO:0043086); 5-phosphoribose 1-diphosphate biosynthetic process (GO:0006015)
14	SPECC1L	sperm antigen with calponin homology and coiled-coil domains 1 like	22q11.2	Testis / Thyroid	Protein binding (GO:0005515); Cell adhesion (GO:0007155); Cell cycle (GO:0007049) ; Cell division (GO:0051301)
15	TBX1	T-box transcription factor 1	22q11.2	Testis / Prostate	DNA-binding transcription factor activity, RNA polymerase II-specific (GO:0000981); Cell population proliferation (GO:0008283); Negative regulation of cell differentiation (GO:0045596); Positive regulation of transcription, DNA-templated (GO:0045893)
16	CDC45	cell division cycle 45	22q11.2	Testis / Bone marrow	Single-stranded DNA binding (GO:0003697); Mitotic DNA replication preinitiation complex assembly (GO:1902977); Double-strand break repair via break-induced replication (GO:0000727); Regulation of chromatin silencing at telomere (GO:0031938)
17	PI4KA	phosphatidylinositol 4-kinase alpha	22q11.2	Brain / Testis	Phosphatidylinositol kinase activity (GO:0052742); Signal transduction (GO:0007165); Phosphatidylinositol-mediated signaling (GO:0048015)
18	Ess2	ess-2 splicing factor homolog	22q11.2	Testis / Bone marrow	Protein binding (GO:0005515); mRNA splicing, via spliceosome (GO:0000398); Nervous system development (GO:0007399)
19	SNAP29	synaptosome associated protein 29	22q11.2	Testis / Brain	Protein binding (GO:0005515); Protein transport (GO:0015031); Synaptic vesicle fusion to presynaptic active zone membrane (GO:0031629)
20	DGCR8	DGCR8 microprocessor complex subunit	22q11.2	Testis / Placenta	Primary miRNA processing (GO:0031053); Protein homodimerization activity (GO:0042803); Protein-RNA adaptor activity (GO:0140517)
21	FLJ37201	tigger transposable	10q23.31	Testis /	More present in reproductive

		element derived 2 pseudogene		Thyroid	cells; Involving in genomic innovations and genome instability
22	KIF20B	kinesin family member 20B	10q23.31	Testis / Lymph node	Cell cycle arrest (GO:0007050); Cell division (GO:0051301)Positive regulation of cell population proliferation (GO:0008284); Positive regulation of cytokinesis (GO:0032467)
23	LINC00865	long intergenic non- protein coding RNA 865	10q23.31	Testis / Urinary bladder	Regulator of cellular processes
24	PANK1	pantothenate kinase 1	10q23.31	Liver / Kidney	Coenzyme A biosynthetic process (GO:0015937); Phosphorylation (GO:0016310); Protein homodimerization activity (GO:0042803); Pantothenate kinase activity (GO:0004594)

Figures

Figure 1

Morphology sperm images of our case. (A) Black arrow indicates a rounded acrosomeless head. White arrow indicates pyriform sperm head and midpiece comments are thick. (B) Black arrow indicates round without acrosome. White arrow indicates pyriform sperm head and less than 40% of the head is occupied by the acrosome.

Figure 2

Cytogenetic images of chromosome karyotype(from peripheral blood sample): 46, XY, t (17; 22) (p11.2; q11.2).

Figure 3

Copy number variations(CNVs) analysis was perform on the case. A microduplication 10q23.31(chr10:91371499-91596485) had been shown, affecting genes of FLJ37201, KIF20B, LINC00865 and PANK1.

Figure 4

The network of genes located on the breakpoints of translocation and duplication(available from GeneMANIA). We used GeneMANIA to perform an interactome analysis the set of candidate genes obtained from the breakpoints and investigate the relationships among these genes within the combined genetic functional network.