Clinical Case Report

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Atypical microdeletion in 22q11 deletion syndrome reveals new candidate causative genes

A case report and literature review

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Abstract

Rationale: 22q11 deletion syndrome, the most common chromosomal microdeletion disease, is caused by megabase-sized deletions on chromosome 22q11.2. It is characterized by a wide spectrum of congenital anomalies in velopharyngeal and facial, cardiac, genitourinary, vertebroskeletal, respiratory, digestive, and central nervous systems. Phenotype–genotype studies have revealed several causative genes that regulate the development of the third and fourth pharyngeal arches in human. However, the exact pathogenesis of this syndrome remains unknown. Herein, we report a case of 22q11 deletion syndrome with an atypical microdeletion of 125 kb.

Patient concerns: A 15-year-old Chinese girl presented with symptoms of facial dysmorphia, cardiac defects, velopharyngeal insufficiency, splenomegaly, immunodeficiency, and thrombocytopenia.

Diagnoses: Microarray analysis revealed a 22q11.23 deletion of 125 kb (chromosome 22: 24276973–24402263), suggesting the diagnosis of 22q11 deletion syndrome. The haploinsufficient genes included *GSTT2B*, *GSTT2*, *DDTL*, *DDT*, *GSTTP1*, *LOC391322*, *GSTT1*, and *GSTTP2*.

Interventions: The patient was administrated glucocorticoids and calcium supplements.

Outcomes: No epistaxis or petechiae episode occurred during the follow-up; her platelet count ranged between 60×10^9 and 80×10^9/L.

Lessons: Although none of the previous reported causative genes were affected in the patient, her clinical manifestations were typical of 22q11 deletion syndrome, apart from her progressive splenomegaly. This case indicated 8 new candidate pathogenic genes for 22q11 deletion syndrome. Given that the loss of these genes was sufficient to induce 22q11DS defects, whether these genes directly influence the pathogenesis of 22q11DS or through interactions with known hotspot mutations is worthy of research.

Abbreviations: 22q11DS = 22q11 deletion syndrome, DGCR = Digeorge syndrome chromosome region, Mb = megabase, MIF = migration inhibitory factor.

Keywords: 22q11 deletion syndrome, atypical microdeletion, causative gene, splenomegaly

1. Introduction

22q11 deletion syndrome (22q11DS), also known as DiGeorge syndrome or velocardiofacial syndrome, is the most common chromosomal microdeletion disease, with an incidence of 1/4000 to 1/6000 live births.[1] This disease is attributed to genomic microdeletions located to chromosome 22q11.21 to q11.23, which disrupt the development of the third and fourth pharyngeal arches in human embryogenesis.

Patients with 22q11DS exhibit great genetic and clinical heterogeneity. A 3-megabase (Mb) fragment containing >35 genes, also called Digeorge syndrome chromosome region (DGCR), is lost in about 85% to 90% of these patients. A smaller fragment of about 1.5 Mb near the centromere end of the DGCR is lost in 8% to 10% of the patients. The remaining 2% to 3% of patients harbor atypical deletions, genetic mutations, or chromosomal translocations. A variety of phenotypes have been described, such as velopharyngeal insufficiency, facial anomalies, cardiac defects, immunodeficiency, mental retardation, parathyroid dysfunction with hypocalcaemia, and genitourinary anomalies. However, the type or size of deletion and phenotype are not directly related.[2,3]

Herein, we report a case of 22q11 deletion syndrome with atypical microdeletion; 8 new candidate causative genes could help address correlations between genotype and phenotype of this disease.

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2. Case report

The 15-year-old Chinese girl was referred to our clinic in June 2017 with a chief complaint of recurrent epistaxis and petechiae for 1 month. A complete blood picture revealed the following: hemoglobin, 101 g/L; leukocyte, 6.62×10^9/L; and platelets, 7×10^9/L. Assessments of the coagulation profile and platelet aggregation were unremarkable. Bone marrow analysis revealed increased number of megakaryocytes, reduced proportion of thromocytogenic megakaryocytes, and decrease in platelet count. Thrombocytopenia was first detected in 2013; the lowest platelet count was 1×10^9/L. Epistaxis and petechiae recurrently attacked when her platelet level dropped. Platelet concentrate, glucocorticoids, and gamma globulin were administrated, which were partially effective; her platelet count fluctuated between 60×10^9 and 80×10^9/L. Childhood splenomegaly was detected and her spleen enlarged progressively to a maximum of 20 cm ×6 cm ×12 cm in July 2017.

Physical examinations revealed a small chin and splenomegaly. The patient was born to a nonconsanguineous couple with no family history of hereditary or systemic diseases. Three most significant manifestations of her medical history were cardiac defects, velopharyngeal insufficiency, and compromised immunity (Table 1), which made her vulnerable to upper and lower respiratory tract infections, otitis media, and sinusitis. She had congenital atrial septal defect and received surgical repair at age 3. She underwent a series of corrective surgeries to alleviate her velopharyngeal malformation. Apart from recurrent infections, her respiratory tract obstruction resulted in obstructive sleep apnea–hypopnea syndrome, for which reason she received surgical repair at age 12. She is still on long-term nasal oxygen inhalation and continuous positive airway pressure treatment during the night. She was immunocompromised with a decreased B-cell count of 69.56 cells/μL (200–1600 cells/μL) and reduced level of IgG (5.12 g/L, 7.51–15.6 g/L). The complement system was also impaired with low levels of C3 (0.29 g/L, 0.79–1.52 g/L) and C4 (0.03 g/L, 0.16–0.38 g/L).

Her T-cell count was within normal range. Serum levels of luteinizing hormone, follicle-stimulating hormone, estradiol, adrenocorticotrophic hormone, progesterone, testosterone, and growth hormone were also normal. Tests of thyroid hormones and thyroid autoantibodies were unremarkable. No hypocalcemia episode in neonatal stage was recorded. Apart from splenomegaly, a positron emission tomography scan suggested no kidney and urinary tract anomaly or skeletal abnormality. Hearing and vision were not affected. Her growth and development were similar to those of her peers, and she had no learning disabilities. Autoantibodies and antistreptolysin-O were also negative.

Microarray analysis revealed a 22q11.23 deletion of 125 kb (chromosome 22: 24276973–24402263), confirming her diagnosis of 22q11DS (Fig. 1). The haploinsufficient genes included *GSTT2B*, *GSTT2*, *DDTL*, *DDT*, *GSTTP1*, *LOC391322*, *GSTT1*, and *GSTTP2*. The patient was administrated methylprednisolone (28 mg, qd) and Caltrate D (600 mg, qd) for half a month; her platelet count increased to 67×10^9/L. During the follow-up, the dosage of methylprednisolone was gradually reduced by 8 mg every month. Her platelet count stabilized at around 70×10^9/L. She remains on monthly follow-up for the evaluation of platelet count and spleen size.

3. Discussion

22q11DS, one of the most frequent chromosomal abnormalities, is caused by microdeletions located to 22q11. The pathogenic mutation occurs *de novo* during embryogenesis in most cases, but may also be inherited in an autosomal-dominant manner for 10% to 20% of all cases. 22q11DS is characterized by a variety of phenotypes such as velopharyngeal and facial anomalies, congenital cardiac defects, T-cell deficiency, mental retardation, hypoparathyroidism, and urinary tract dysmorphisms. Over 35 genes are mapped to DGCR, which is important for the early morphogenesis of the head and neck, heart, kidney, skeleton, and brain. These genes exhibit different functions, such as transcription regulation, cell cycle regulation, and cell adhesion. However, the exact correlation between genotype and phenotype remains to be elucidated.

Table 1

Timeline of the patient's medical history.

Dates	Summaries of visits	Diagnostic testing	Interventions
2005	Recurrent respiratory tract infections; diagnosis: congenital atrial septal defect	Echocardiography: atrial septal defect	Surgical repair
2006	Cervical submaxillary lymph node enlargement	Endoscope: tonsillar hypertrophy	Tonsillectomy
2013	Recurrent respiratory tract infections	Fiberoptic bronchoscope: tracheostenosis	Tracheal lymph node extirpation
July 2014	Snoring and buccal respiration; diagnosis: obstructive sleep apnea–hypopnea syndrome	Polysomnography: apnea–hypopnea index 22.2, SaO_2 87%	Lymph node ablation, occipital lipoma partial excision, bilateral tympanic membrane catheterization, long-term nasal oxygen inhalation, and continuous positive airway pressure treatment
January 2016	Progressive hearing loss and tinnitus for 2 months; diagnosis: chronic bilateral catarrhal otitis media and sinusitis	Computed tomography: otomastoiditis and sinusitis	Bilateral tympanic membrane catheterization
June 2017	Recurrent epistaxis or petechiae for 1 month	Platelet count: 7×10^9/L bone marrow: increased number of megakaryocytes, reduced proportion of thromocytogenic megakaryocytes, and decrease in platelet count	Administration of intravenous dexamethasone; upon discharge: methylprednisolone (28 mg, qd) and Caltrate D (600 mg, qd)
July–November 2017	No epistaxis or petechiae episode during the treatment; diagnosis: 22q11 deletion syndrome	Platelet count: between 60 and 80×10^9 /L (September– November 2017); microarray analysis: 22q11.23 deletion of 125 kb (chromosome 22: 24276973–24402263)	A gradual decrease to methylprednisolone (8 mg, qd) and Caltrate D (600 mg, qd)

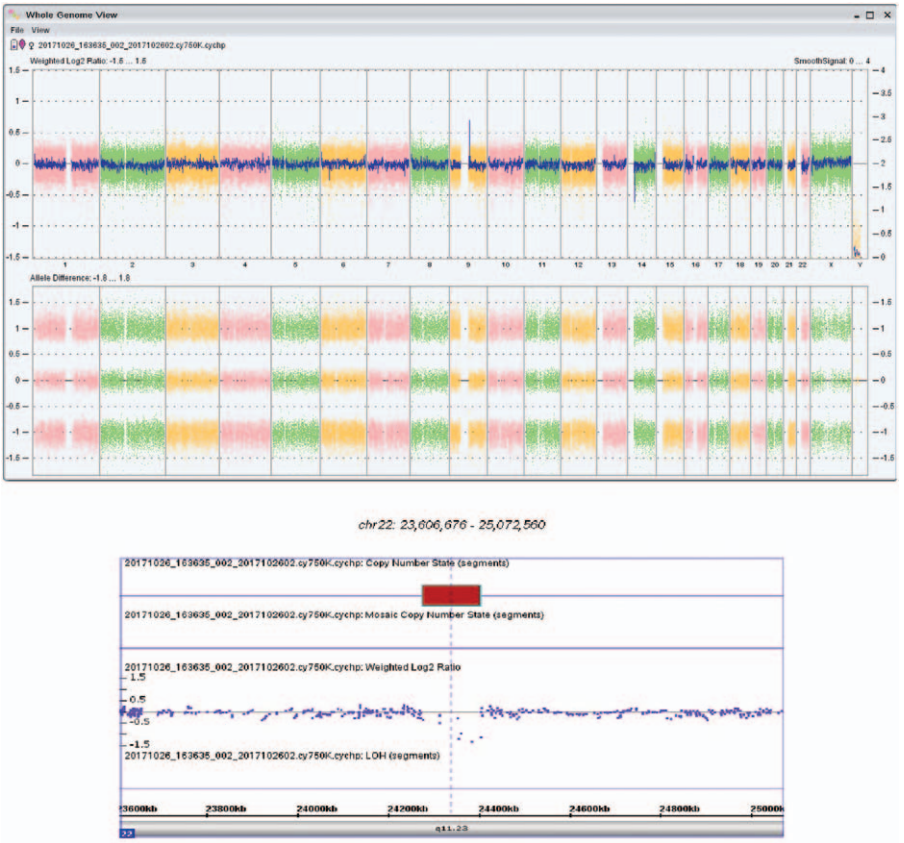

Figure 1. Microarray analysis revealing a deletion of 125 kb in length (chromosome 22: 24276973–24402263), involving 8 genes: *GSTT2B*, *GSTT2*, *DDTL*, *DDT*, *GSTTP1*, *LOC391322*, *GSTT1*, and *GSTTP2*.

Several genes have been identified to be responsible for the pathogenesis of 22q11DS (Table 2). *TBX1*, encoding a T-box transcription factor, plays a pivotal role in early vertebrate development. Haploinsufficiency or mutation of *TBX1* is associated with several major phenotypes of 22q11DS, including facial dysmorphia, cardiac abnormalities, velopharyngeal insufficiency, hypoplastic thymus, and hypoparathyroidism.[4,5] Given the essential function of *TBX1*, genes involved in its downstream pathways or its activity modifiers also contribute to the pathogenesis of 22q11DS.[6] For example, *WNT5A*, as a putative transcriptional target of *TBX1*, has been reported to be required for second heart field deployment to outflow tract myocardium, the disruption of which could result in cardiac defects.[7]

Interestingly, *TBX1* was not affected in this patient although she also displayed symptoms of facial dysmorphia, cardiac defects, and velopharyngeal insufficiency. This indicates that the 8 deleted genes might also contribute to the development of the third and fourth pharyngeal arches, or they could regulate or be regulated by known causative genes responsible for 22q11DS abnormality. To our knowledge, these 8 genes were not among the reported loci interactive with the main pathogenic genes including *TBX1*.

GSTT1, *GSTT2*, and *GSTT2B* constitute the theta class of human glutathione S-transferase genes, which are involved in glutathione metabolism. Recently, these genes have been reported to be associated with tumor pathogenesis.[8,9]*GSTTP1* and

Table 2

Genes and relevant phenotypes of 22q11 deletion syndrome.

Genes	Phenotype	References
TBX1	Conotruncal anomaly face, cardiac abnormalities, thymic hypoplasia, hypoparathyroidism, and velopharyngeal insufficiency with cleft palate	Yagi et al[4], Gao et al[5]
WNT5A	Cardiac defects	Sinha et al[7]
CRKL	Congenital anomalies of the kidney and urinary tract	Lopez-Rivera et al[17]
COMT, PRODH	Cognitive and psychiatric problems	Radoeva et al[18], Raux, 2007[19]
HIRA	Autism spectrum disorder	Ramelli et al[20]
GSCL	Sleep/wakefulness imbalance	Funato et al[21]
UFD1L, CDC45L	Cardiac and craniofacial defects	Kunte et al[22]
SMARCB1	Head-and-neck tumors	Marom et al[23]
GPIbβ	Thrombocytopenia	Kato et al[14]

GSTTP2 are 2 pseudogenes related to glutathione metabolism. *GSTT1* is naturally absent in some people, while *GSTT2* might be a pseudogene in certain populations. DDT, a homologue of macrophage migration inhibitory factor (MIF), is responsible for D-dopachrome metabolism. *DDT* and *MIF* were involved in different diseases such as multiple sclerosis[10] and human cervical cancer.[11]*DDTL*, an important paralog of *DDT*, has an effect in schizophrenia. *LOC391322*, a member of the *MIF* gene family, might play a role in immunology-related phenotypes.[12] To our knowledge, no relationship between these genes and 22q11DS has been reported. Given that the loss of these genes was sufficient to induce 22q11DS defects, whether these genes directly influence the pathogenesis of 22q11DS or through interactions with known hotspot mutations is worthy of research.

What differs this patient from previous reported 22q11DS cases is the prominent progressive splenomegaly complicated with immunodeficiency and thrombocytopenia. Approximately 35% patients with 22q11DS show clinical manifestations of thrombocytopenia, most of which were macrothrombocytopenia.[13] One possible explanation is haploinsufficiency of the deleted *GPIbβ* gene in some 22q11DS patients, which is one of the causative genes for Bernard–Soulier syndrome, an autosomal-recessive bleeding disorder characterized by macrothrombocytopenia.[14] However, no giant platelet was found in this patient's blood smear, and the *GPIbβ* gene was not involved in the microdeletion fragment. On the other hand, humoral immunity was involved in this patient, with a decrease in B-cell numbers and function, although for most cases, T-cell abnormalities are more frequent.[15] In previous reports, immune thrombocytopenia, severe infections, and autoimmune hemolytic anemia were recorded in patients with profound antibody deficiency.[16] It is likely that immunodeficiency or immune dysregulation caused thrombocytopenia in this patient. In addition, her hypersplenism could add to the destruction of platelets. The fact that glucocorticoids and gamma globulin were partially effective supported this supposition. However, the complete etiology remains unknown as the platelet level has not increased to normal. To our knowledge, splenomegaly has not been identified as a part of this syndrome previously. The relationship between splenomegaly, immunodeficiency, and thrombocytopenia in 22q11DS patients remains to be elucidated.

4. Conclusion

In summary, we report a case with not only typical syndromes of 22q11DS but also uncommon splenomegaly. Microarray analysis revealed haploinsufficiency of 8 new candidate causative genes for 22q11DS. Further investigation is warranted to address the pathogenic mechanisms of these genes in the development of 22q11DS.

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