

SNP Microarray Characterization and Genotype-Phenotype Analysis in a Patient with a Ring Chromosome 22

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ABSTRACT Ring chromosome 22 is a rare cytogenetic anomaly. The aim of this study was to present a case carrying ring chromosome 22 in a 9-year-old Chinese girl with long face, thick eyebrows, large and low-set ears, mental retardation, severe speech delay, autistic disorders and talipes equinovarus (TEV). A chromosome analysis of the proband revealed a de novo 46,XX,r(22)(p13;q13) karyotype and the deleted region was confirmed by means of SNP microarray analysis showing deletion range from 22q13.31 to 22q13.33 (3.8Mb). The present report describes the case of a patient with a ring chromosome 22 abnormality completely characterized by SNP microarray which provided additional information for genotype-phenotype studies.

INTRODUCTION

Ring chromosome 22, firstly described by Weleber et al. (1968), is a rare cytogenetic anomaly. Its most consistent findings are overall developmental delay with severe language impairment, growth and mental retardation. It's frequently associated hypotonia and craniofacial anomalies such as microcephaly, normally placed but large and dysplastic ears, long face, thick eyebrows, epicanthus, long eyelashes with full eyebrows and so on. Here the researchers report a case of de novo ring chromosome 22 in a 9-year-old girl presented with mental retardation, severe speech delay, minor dysmorphic features, hypotonia, autistic disorders and talipes equinovarus (TEV). The abnormal karyotype was identified by conventional cytogenetics, while chromosome rearrangements were characterized by SNP microarray. The researchers tried to establish the size of the associated deletion in ring chromosome 22 by means of SNP microarray and to obtain more precise details for genotype-phenotype correlations.

CASE REPORT

The proband, a 9-year-old girl, normal spontaneous full term neonate with the birth weight

of 3900g, was the first child born to Chinese healthy non-consanguineous parents, 34-year-old father and 33-year-old mother. Her congenital TEV of left foot failed to respond to some conservative treatment. She didn't like hugs, could sit supported at 8 months old and took her first independent steps at 26 months, however, she couldn't talk, no recognizable speech, occasional babbling words like "ma ma" and "da da". She was referred to the Child Disease Department because of the complaints of mental retardation and speech delay and diagnosed with mental retardation at 4 years of age. Her height, weight, head circumference and nutritional status were still normal. However, her psychomotor milestones were always behind her peers and she was diagnosed with autism based on DSM-IV diagnostic criteria. She also had long face, thick eyebrows, long eyelashes with full eyebrows, epicanthic folds, large and low-set ears and TEV. There were no abnormal results from magnetic resonance imaging of the brain and analysis of acylcarnitines from dry blood spots. Karyotyping from cultured lymphocytes revealed 46,XX, r(22)(p13;q13) (Fig. 1). The SNP microarray study was performed using the Affymetrix Genome-Wide Human SNP Array 6.0. The breakpoint was located on 22q13.31 and the deletion was estimated to be 3.8 Mb on the long arm (Fig. 2). After cytogenetic analysis of the parents, both mother and father showed normal female karyotype (46,XX) and male karyotype (46,XY), respectively. Therefore, the proband's chromosome alteration was considered as 'de novo'.

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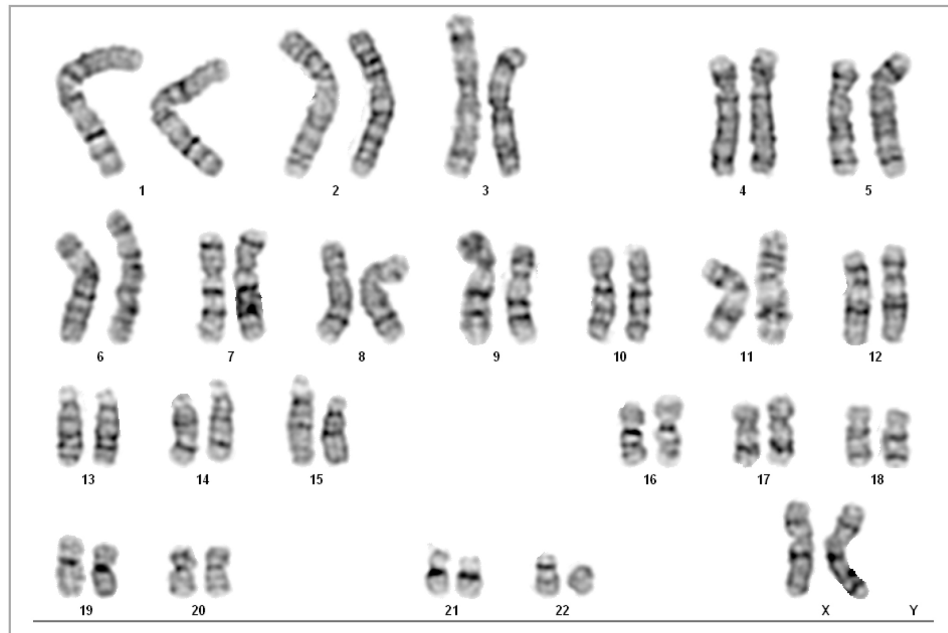


Fig. 1. G-banding karyotype from a peripheral blood metaphase of the patient: 46,XX, r(22)(p13;q13)

DISCUSSION

Ring chromosomes, which are derivative chromosomes formed by breakage in both arms of a chromosome with fusion of the points of fracture and loss of the distal fragments. Ring chromosome 22 is a rare human cytogenetic anomaly, in which one chromosome 22 forms a circular structure. Because of its rare cytogenetic finding, the exact incidence remains unknown.

The most consistent clinical features of ring chromosome 22 are overall developmental delay with growth retardation, severe speech delay and associated hypotonia. Besides, craniofacial anomalies such as microcephaly, epicanthus, normally placed but large and dysplastic ears, long face and thick eyebrows long eyelashes with full eyebrows are frequently observed. Occasionally, high arched palate, dental malocclusion (Weleber et al. 1968), mild hypertelorism (Ishmael et al. 2003) 2-3 toe syndactyly, unsteady gait, autistic disorders (Maclean et al. 2000), azoospermia (Zuccarello et al. 2010; Rajesh et al. 2011), hyperactivity and aggressive behavior (Demirhan et al. 2010) have also been reported. However, TEV associated with ring chromosome

22 were rare in previous literature. TEV is a structural abnormality of the lower leg in which both the forefoot and the heel are inverted, giving the foot a club-like appearance (Barry 2005), which is presented frequently isolated foot deformity, occasionally associated chromosomal anomaly such as trisomy 21, trisomy 18 and so on. Approximately half of those cases achieve correction with conservative management, but it is not effective in this case due to hypotonia and severity of foot deformity. The patient in this study had many of those findings previously described in the literature except that growth retardation, mild hypertelorism, high arched palate, dental malocclusion, syndactyly between toes 2 and 3, hyperactivity and aggressive behavior have not been found in this patient.

Different clinical features might be due to different deletion sizes. In this report, the breakpoint was located on 22q13.31 and the deletion was estimated to be 3.8 Mb on the long arm. This region is very large and contains a great number of genes such as ALG12, MLC1, SCO2, TYMP, ARSA and SHANK3. ALG12 on 22q13.33, encodes a member of the glycosyltransferase 22 family. A multisystem disorder

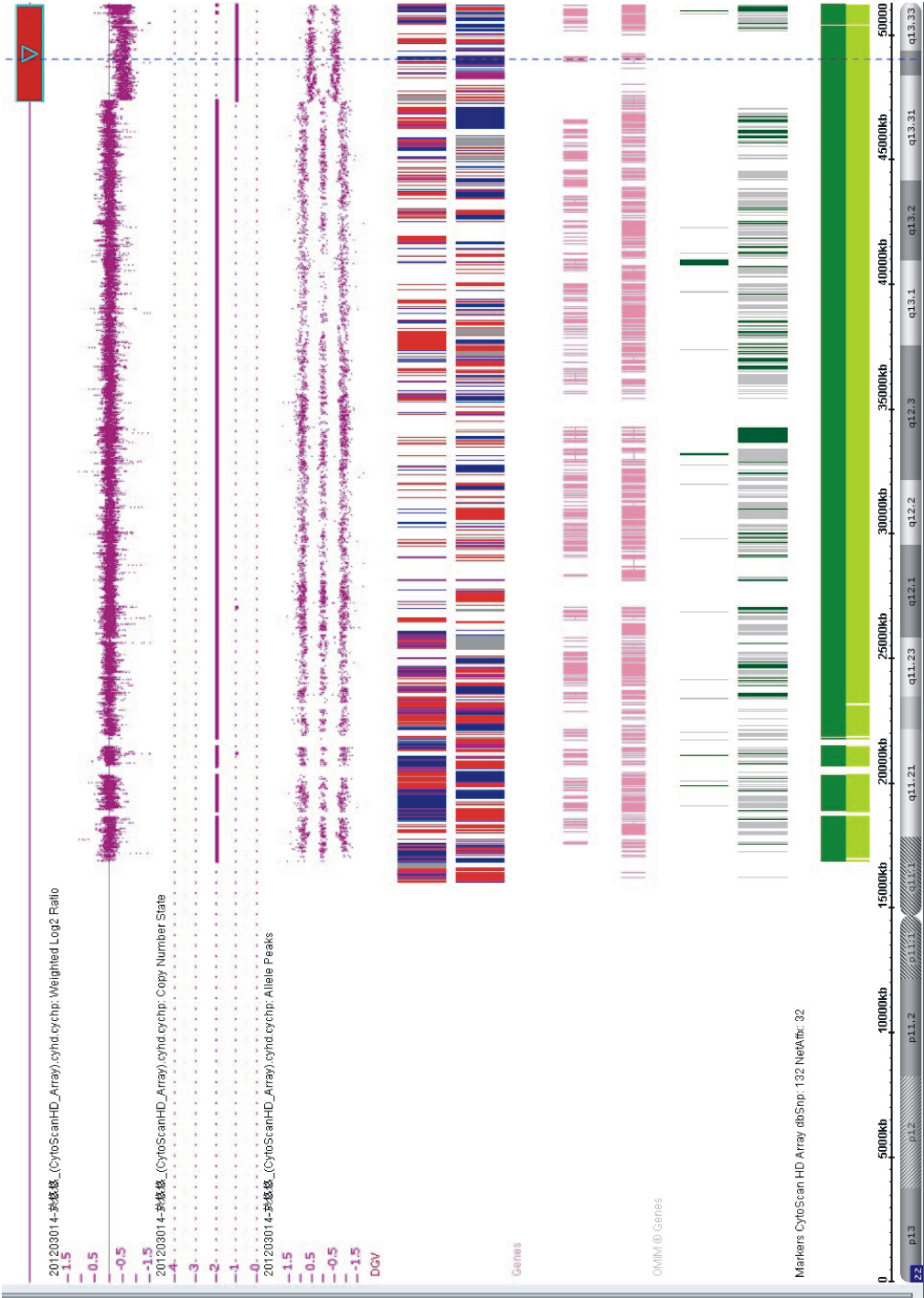


Fig. 2. SNP microarray showed the magnification of the 22q (3.8Mb) deletion

caused by a defect in glycoprotein biosynthesis and characterized by under-glycosylated serum glycoproteins. Congenital disorders of glycosylation result in a wide variety of clinical features, such as defects in the nervous system development, psychomotor retardation, dysmorphic features, hypotonia, coagulation disorders, and immunodeficiency. The clinical signs reported in this patient are mental retardation, psychomotor retardation, dysmorphic features and hypotonia. MLC1, megalencephalic leukoencephalopathy with subcortical cysts 1 (Xie et al. 2012), on 22q13.33, provides instructions for making a protein that is found in the brain, spleen, and leukocytes. Mental retardation was found in this patient, but there was no abnormal result from magnetic resonance imaging of the brain. It is unknown how a lack of MLC1 protein impairs brain development and function, causing the signs and symptoms of megalencephalic leukoencephalopathy with subcortical cysts. SHANK3 maps at chromosome 22q13.3, encoding a structural protein of the post-synaptic density. Many researches show that deletion of the SHANK3 gene contributes to the developmental delay, intellectual disability, and absent or severely delayed speech characteristic of people with 22q13.3 deletion syndrome (Hannachi et al. 2013), also autism spectrum disorders is reported.

In summary, the researchers reviewed the reports of patients with ring chromosome 22 in the previous medical literature and compared them with the patient in the present study. This report describes more accurate and complete characterization of a ring chromosome 22. Moreover, it provides additional information to study genotype-phenotype and improve the understanding of the clinical features associated with the ring chromosome 22. This is a female patient, whether the ring chromosome 22 influences her

secondary sex characteristics develop or subsequent fertility still needs to be followed up.

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