Tetrasomy 9p Syndrome

Contents

Tetrasomy 9p syndrome, a clinically diagnosable condition, is a rare cytogenetic disorder characterized by tetrasomy 9p associated with a distinctive patterns of multiple congenital anomalies. In *1973*, Ghymers et al. (1973) first described the syndrome.

Synonyms and Related Disorders

Supernumerary isochromosome 9p syndrome

Genetics/Basic Defects

1. Caused by de novo supernumerary isodicentric chromosome 9p (presence of four copies of the short arm of the chromosome 9) (9pter to 9q2101) (Abe et al. 1977)
    1. Pure tetrasomy 9p
    2. Tetrasomy involving the varying segment of the short arm of chromosome 9
2. Cytogenetic types of tetrasomy 9p
    1. Presence of an extra dicentric chromosome 9 consisting entirely of 9p
    2. Presence of an extra dicentric chromosome 9 consisting of 9p and the proximal part of 9q
    3. Mosaicism involving tetrasomy 9p: mosaic of i(9p) cells
    4. Nonmosaic partial tetrasomy involving all of the short arms and asymmetrical segments of the long arms (Shapiro et al. 1985)
3. Hypotheses proposed to explain tetrasomy 9p
    1. A meiosis I disturbance with nondisjunction and rearrangement in two of the four chromatids of a bivalent 9, resulting in the formation of an isochromosome 9p
    2. Meiosis II nondisjunction followed by rearrangements (isochromosome formation) with duplication of the short arm and loss of the acentric long arm at the subsequent mitosis
    3. Dicentric versus monocentric (de Azevedo Moreira et al. 2003)
        1. Using conventional cytogenetics and banding techniques revealed an additional dicentric 9p chromosome in most cases.
        2. Using molecular studies using a chromosome 9 classic satellite probe shows an error in the division of centromere 9 by a double-break event, resulting in the formation of a monocentric isochromosome 9p.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_226

Clinical Features

1. Tetrasomy 9p: a unique, clinically recognizable syndrome (Jalal et al. 1991; Fryns 1998)
2. Craniofacial abnormalities (El Khattabi et al. 2015)
    1. Delayed closure of the anterior fontanel
    2. Ocular hypertelorism
    3. Telecanthus
    4. Strabismus
    5. Enophthalmos/microphthalmia
    6. Epicanthal folds
    7. Prominent beaked or bulbous nose
    8. Down-turned corners of the mouth
    9. Microretrognathia
    10. Low-set, malformed ears
    11. Cleft lip/palate
    12. High-arched palate
3. Cardiac anomalies
    1. Ventricular septal defect
    2. Atrial septal defect
    3. Patent ductus arteriosus
    4. Persistent left superior vena cava
    5. Double outlet of the right ventricle
    6. Hypoplastic right ventricle
    7. Hypoplastic left heart ventricle
4. Lung anomalies
    1. Lung hypoplasia
    2. Abnormal lobulation of the lung
5. Renal anomalies
    1. Renal hypoplasia
    2. Multicystic dysplasia
    3. Hydroureter
    4. Hydronephrosis
6. Genital anomalies
    1. Cryptorchidism
    2. Genital hypoplasia
    3. Micropenis
    4. Hypoplastic shawl-like scrotum
    5. Ambiguous genitalia
    6. Duplications 9p may result in impairment of ovarian function (Cuoco et al. 1982)
7. Gastrointestinal anomalies
    1. Intestinal malrotation
    2. Hirschsprung disease (Melaragno et al. 1992)
8. CNS anomalies
    1. Psychomotor retardation
    2. Hypotonia
    3. Microcephaly
    4. Brachycephaly
    5. Hydrocephalus
    6. Cerebral hypoplasia
    7. Dandy-Walker cyst
    8. Absence of olfactory bulbs
    9. Hypoplastic cerebellum
9. Skeletal anomalies
    1. Growth retardation
    2. Short stature
    3. Short neck
    4. Dysplastic fingernails
    5. Limb anomalies
    6. Clinodactyly of the fifth fingers
    7. Club feet
    8. Articular dislocations
    9. Shortened hands and feet
10. Other features
    1. Single umbilical artery
    2. Failure to thrive
    3. Redundant skin
    4. Widely spaced nipples
    5. Single palmar crease
    6. Sacral dimple
    7. Mosaic tetrasomy 9p predisposes to pediatric-onset inflammatory myositis and lupus-like features (Frémond et al. 2015)
11. The severity of the phenotype correlates with size of the tetrasomic region and the degree of tissue mosaicism for the tetrasomy 9p.
12. A case of nonmosaic tetrasomy 9p with long-term survival reported (Tonk 1997)
13. Cases of isochromosome tetrasomy 9p mosaicism associated with a normal phenotype reported (Papoulidis et al. 2012)

Diagnostic Investigations

1. Cytogenetic studies to identify supernumerary marker chromosomes (Tan et al. 2007)
    1. Conventional and high-resolution analyses
    2. A whole-chromosome paint probe for chromosome 9 to identify the supernumerary chromosome, using the fluorescence in situ

hybridization (FISH) technique (Callen et al. 1992; Crolla et al. 1998; Eggermann et al. 1998)
3. Microdissection and reverse FISH (micro-FISH) (Mahjoubi et al. 2005; de Pater et al. 2006)
4. Multiplex-FISH (M-FISH) technique (Uhrig et al. 1999)
5. Centromere-specific multicolor-FISH assays (Nietzel et al. 2001)
6. AcroM-FISH technique (Langer et al. 2001): involves a newly generated probe mix, which consists of painting probes for all acrocentric chromosomes, centromere probes for chromosomes 13/21, 14/22, 15, and a probe specific for rDNA, each labeled with a specific combination of fluorochromes. This probe mix is sufficient to characterize approximately 80% of all SMCs (supernumerary marker chromosomes). For the other 20% of SMCs, chromosomes can be analyzed in a second hybridization by multicolor karyotyping, for example, multiplex FISH (M-FISH), to check for the presence of euchromatin of other chromosomes.
7. Tissue-limited mosaicism (Lloveras et al. 2004): Isochromosome 9p shows a strong propensity to tissue-limited mosaicism. It occurs predominantly in peripheral blood cultures, often at a lower frequency or even absent in skin, amniotic fluid, or chorionic villous cell cultures. Tissue-limited nature of mosaicism may render prenatal detection of this condition very difficult. This cytogenetic interpretation was substantiated by quantitative measurement of erythrocyte galactose-1-P-uridyltransferase (GALT) activity, which is consistent with the expression of four normal GALT genes (Papenhausen et al. 1990)
8. Array CGH is able to detect mosaicism, establish the euchromatic content of supernumerary marker chromosomes, and identify imbalances elsewhere in the genome allowing more accurate counselling and prognosis for patients (Shehab et al. 2011)

2. Echocardiography for cardiovascular malformations
3. Radiography
    1. Microcephaly
    2. Hypertelorism
    3. Hypoplastic first and 12th ribs
    4. Kyphoscoliosis
    5. Clinodactyly and brachymesophalangy of the fifth fingers
    6. Delayed ossification of pubic bones and ischiopubic synchondrosis
    7. Delayed ossification of femoral heads
    8. Spina bifida occulta
    9. Generalized osteoporosis
4. Ultrasonography of renal abnormalities

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: not increased
    2. Patient's offspring: patient not surviving to reproductive age
2. Prenatal diagnosis
    1. Ultrasonography (Dhandha et al. 2002; Tan et al. 2007; Nakamura-Pereira et al. 2009)
        1. Increased nuchal translucency in the first trimester
        2. Intrauterine growth retardation
        3. Genitourinary/renal anomalies
        4. Cleft lip/palate
        5. CNS anomalies
            1. Dandy-Walker malformation
            2. Ventriculomegaly
            3. Hypoplastic/absent vermis
            4. Agenesis of corpus callosum
        6. Limb malformations: bilateral club feet
        7. Vertebral anomalies
        8. Cardiac anomalies
        9. Genitourinary anomalies
        10. Polyhydramnios/oligohydramnios
        11. Absent nasal bone as a marker of tetrasomy 9p (Podolsky et al. 2011)
    2. 3D ultrasonography at 16 weeks' gestation (Lazebnik and Cohen 2015)
        1. Widely open metopic suture and anterior fontanel

2. Abnormal profile due to micrognathia and low-set posteriorly rotated ears
3. Abnormal connection between the posterior fossa and the fourth ventricle, suggesting Dandy-Walker malformation of the cerebellum
4. Echogenic focus in the fetal heart
5. Single umbilical artery
6. Cervical spine abnormality as well as 11 bilateral ribs
7. Bilateral rocker bottom clubfoot

3. Chromosome analysis to demonstrate tetrasomy of the short arm of chromosome 9 (+i(9)(p10)) of amniocytes (Tang et al. 2004), CVS, or fetal blood from cordocentesis (Schaefer et al. 1991): Microdissection and pre-G-banded FISH is important in determining the origin of supernumerary marker chromosome in prenatal diagnosis
4. Prenatal diagnosis of mosaic tetrasomy 9p (Wang et al. 2015)
   1. Karyotype: 47,XX,+idic(9)(q12)/47,XX,+idic(9)(q12)
   2. Partial G-banded and C-banded karyotype showed two normal chromosomes 9 and the i psu dic(9)(pter → q12::q12 → pter)
   3. FISH with subtelomere probe: A chromosome 9p specific subtelomeric probe (TelVysion 9p, green signal) (Vysis, Downers Grove, IL, USA) demonstrates green signals on both ends of the supernumerary idic(9)
5. Mosaic tetrasomy 9p at amniocentesis (Chen et al. 2014)
   1. Array comparative genomic hybridization analysis of uncultured amniocytes detected a genomic gain at 9p24.3-9q21.11.
   2. Interphase fluorescence in situ hybridization analysis of uncultured amniocytes using a 9p24.3-specific probe RP11-31 F19 (spectrum red) showed four red signals in 47.1% (49/104 cells) in uncultured amniocytes.
   3. Cytogenetic analysis of cultured amniocytes revealed a karyotype of 47, XX, +idic(9)(pter → q21.11::q21.11 → pter)[4]/46,XX[20] and 16.7% (4/24 colonies) mosaicism for tetrasomy 9p.
   4. Quantitative fluorescent polymerase chain reaction confirmed a maternal origin of tetrasomy 9p.
   6. Tissue specific mosaicism in tetrasomy 9p which rendered the anomaly undetectable by CVS. It also demonstrates the mild end of the clinical spectrum associated with tetrasomy 9p (Grass et al. 1993)
3. Management
   1. Early intervention programs for mild developmental delay with minor anomalies
   2. Supporting care for severe cases with early death

References

Abe, T., Morita, M., Kawai, K., et al. (1977). Partial tetrasomy 9 (9qter 9q2101) due to extra iso-dicentric chromosome. *Annales de Génétique, 20*, 111–114.

Callen, D. F., Eyre, H. J., Yip, M. Y., et al. (1992). Molecular cytogenetic and clinical studies of 42 patients with marker chromosomes. *American Journal of Medical Genetics, 43*, 709–715.

Chen, C.-P., Wang, L.-K., Chern, S.-R., et al. (2014). Mosaic tetrasomy 9p at amniocentesis: Prenatal diagnosis, molecular cytogenetic characterization, and literature review. *Taiwanese Journal of Obstetrics & Gynecology, 53*, 79–85.

Crolla, J. A., Long, F. L., Rivera, H., et al. (1998). FISH and molecular study of autosomal supernumerary marker chromosomes excluding those derived from chromosomes 15 and 22. *American Journal of Medical Genetics, 75*, 355–366.

Cuoco, C., Gimelli, G., Pasquali, F., et al. (1982). Duplication of the short arm of chromosome 9. Analysis of five cases. *Human Genetics, 61*, 3–7.

de Azevedo Moreira, L. M., Freitas, L. M., Gusmao, F. A., et al. (2003). New case of non-mosaic tetrasomy 9p in a severely polymalformed newborn girl. *Birth Defects Research. Part A, Clinical and Molecular Teratology, 67*, 985–988.

de Pater, J., Van der Sijs-Bos, C., Prins, M., et al. (2006). Prenatal identification of a marker chromosome 16 by chromosome microdissection and reverse FISH. *European Journal of Medical Genetics, 49*, 306–312.

Dhandha, S., Hogge, W. A., Surti, U., et al. (2002). Three cases of tetrasomy 9p. *American Journal of Medical Genetics, 113*, 375–380.

Eggermann, T., Rossier, E., Theurer-Mainka, U., et al. (1998). New case of mosaic tetrasomy 9p with additional neurometabolic findings. *American Journal of Medical Genetics, 75*, 530–533.

El Khattabi, L., Jaillard, S., Andrieux, J., et al. (2015). Clinical and molecular delineation of tetrasomy 9p syndrome: Report of 12 new cases and literature review. *American Journal of Medical Genetics Part A, 167A*, 1252–1261.

Frémond, M.-L., Gitiaux, C., Bonnet, D., et al. (2015). Mosaic tetrasomy 9p: A Mendelian condition associated with pediatric-onset overlap myositis. *Pediatrics, 136*, e544–e547.

Fryns, J. P. (1998). Trisomy 9p and tetrasomy 9p. A unique, clinically recognisable syndrome. *Genetic Counseling, 9*, 229–230.

Ghymers, D., Hermann, B., Disteche, C., et al. (1973). Partial tetrasomy of number 9 chromosome, and mosaicism in a child with multiple malformations (author's translation). *Humangenetik, 20*(3), 273–282.

Grass, F. S., Parke, J. C., Kirkman, H. N., et al. (1993). Tetrasomy 9p: Tissue-limited idic(9p) in a child with mild manifestations and a normal CVS result. Report and review. *American Journal of Medical Genetics, 47*, 812–816.

Jalal, S. M., Kukolich, M. K., Garcia, M., et al. (1991). Tetrasomy 9p: An emerging syndrome. *Clinical Genetics, 39*, 60–64.

Langer, S., Fauth, C., Murken, M. R. J., et al. (2001). AcroM fluorescent in situ hybridization analyses of marker chromosomes. *Human Genetics, 109*, 152–158.

Lazebnik, N., & Cohen, L. (2015). Prenatal diagnosis and findings of tetrasomy 9p. *Journal of Obstetrics and Gynaecology Research, 41*, 997–1002.

Lloveras, E., Perez, C., Sole, F., et al. (2004). Two cases of tetrasomy 9p syndrome with tissue limited mosaicism. *American Journal of Medical Genetics, 124A*, 402–406.

Mahjoubi, F., Peters, G. B., Malafiej, P., et al. (2005). An analphoid marker chromosome inv dup(15)(q26.1qter), detected during prenatal diagnosis and characterized via chromosome microdissection. *Cytogenetic and Genome Research, 109*, 485–490.

Melaragno, M. I., Brunoni, D., da Silva Patricio, F. R., et al. (1992). A patient with tetrasomy 9p, Dandy-Walker cyst and Hirschsprung disease. *Annales de Génétique, 35*, 79–84.

Nakamura-Pereira, M., do Cima, L. C., Llerena, J. C., Jr., et al. (2009). Sonographic findings in a case of tetrasomy 9p associated with increased nuchal translucency and Dandy-Walker malformation. *Journal of Clinical Ultrasound, 37*, 471–474.

Nietzel, A., Rocchi, M., Starke, H., et al. (2001). A new multicolor-FISH approach for the characterization of marker chromosomes: Centromere-specific multicolor-FISH (cenM-FISH). *Human Genetics, 108*, 199–204.

Papenhausen, P., Riscile, G., Miller, K., et al. (1990). Tissue limited mosaicism in a patient with tetrasomy 9p. *American Journal of Medical Genetics, 37*, 388–391.

Papoulidis, I., Kontodiou, M., Tzimina, M., et al. (2012). Tetrasomy 9p mosaicism associated with a normal phenotype in two cases. *Cytogenetic and Genome Research, 136*, 237–241.

Podolsky, R., Saltzman, D., Auerbach, M., et al. (2011). Absent nasal bone as a marker of tetrasomy 9p. *Prenatal Diagnosis, 31*, 1313.

Schaefer, G. B., Domek, D. B., Morgan, M. A., et al. (1991). Tetrasomy of the short arm of chromosome 9: Prenatal diagnosis and further delineation of the phenotype. *American Journal of Medical Genetics, 38*, 612–615.

Shapiro, S., Hansen, K., & Littlefield, C. (1985). Brief clinical report: Non-mosaic partial tetrasomy and partial trisomy 9. *American Journal of Medical Genetics, 20*, 271–276.

Shehab, M. I., Mazen, I., & Bint, S. (2011). Tissue-specific mosaicism for tetrasomy 9p uncovered by array CGH. *American Journal of Medical Genetics Part A, 155A*, 2496–2500.

Tan, Y.-Q., Chen, X. M., Hu, L., et al. (2007). Prenatal diagnosis of nonmosaic tetrasomy 9p by microdissection and FISH: Case report. *Chinese Medical Journal, 120*, 1281–1283.

Tang, W., Wenger, S. L., Boyd, B. K., et al. (2004). Prenatal diagnosis of tetrasomy 9p. *American Journal of Medical Genetics, 126A*, 328.

Tonk, V. S. (1997). Moving towards a syndrome: A review of 20 cases and a new case of non-mosaic tetrasomy 9p with long-term survival. *Clinical Genetics, 52*, 23–29.

Uhrig, S., Schuffenhauer, S., Fauth, C., et al. (1999). Multiplex-FISH (M-FISH) for pre- and postnatal diagnostic applications. *American Journal of Human Genetics, 65*, 448–462.

Wang, H., Xie, L.-S., Wang, Y., et al. (2015). Prenatal diagnosis of mosaic tetrasomy 9p in a fetus with isolated persistent left superior vena cava. *Taiwanese Journal of Obstetrics & Gynecology, 54*, 204–205.

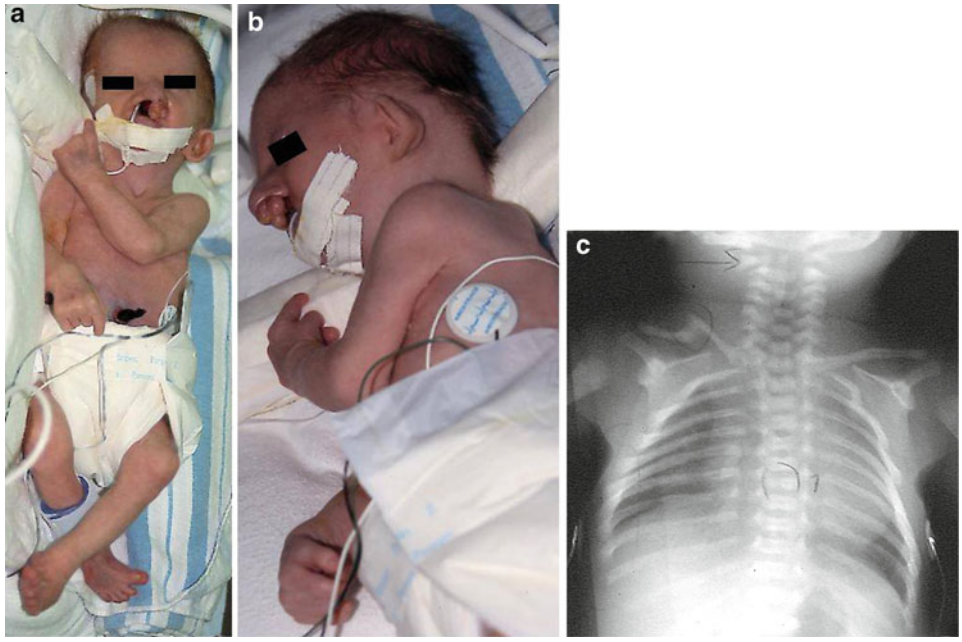

Fig. 1 (**a**–**c**) An infant (**a**, **b**) with tetrasomy 9p syndrome presenting with widened anterior fontanel, microbrachycephaly, a broad nasal root, telecanthus, bilateral cleft lip and palate, retromicrognathia, small eyes, low-set lop ears, and a skin tag on the antihelix of the right ears. In addition, the infant had short neck with excess nuchal fold, bilateral webbing of the anterior axillary folds, pectus excavatum, congenital heart defects, right hydronephrosis, diastasis recti with an umbilical hernia, a right inguinal hernia, sacral dimple with a tag, micropenis, bilateral metatarsus adductus, bilateral transverse palmar creases, clinodactyly of the fifth fingers, short thumbs, and hypoplastic nails. Chest X-ray (**c**) showed hemivertebrae in the thoracic spine and fractured right clavicle with callus formation. A rectal biopsy confirmed the diagnosis of Hirschsprung disease