CASE REPORT

Many Term infants with Persistent Patency of the Ductus Arteriosus could be Trisomy 21 Mosaics

Akhil Maheshwari[1,2], Srijan Singh[2,3], Varun Sharma[4], Papagudi G Subramanian[5], Amita S Garg[6,7,8]

Received on: 24 February 2024; *Accepted on*: 18 March 2024; *Published on*: 26 March 2024

Abstract

We report findings from a term infant with persistent patency of the ductus arteriosus (PDA). His fetal tests had shown some ambiguity for trisomy 21. However, he did not show any of the frequently-seen phenotypic features associated with trisomy 21 *in utero* or after birth, and the postnatal karyotype was reported as normal. One of our team members decided to request for a repeat karyotype and he was then identified as a mosaic for this aneuploidy. These observations are potentially important because the proportion of affected cells could very well be a determinant of the phenotypic variability seen in infants with Down syndrome. Hence, mosaicism might need to be meticulously excluded in patients who are presented with only one or more phenotypic features associated with trisomy 21. In this report, we have briefly reviewed the need for evaluation in such infants; the diagnosis requires specific evaluation of *in-vitro* cultured blood lymphocytes from the patients, siblings, and parents for somatic and germinal trisomy 21 mosaicism. The mechanisms underlying the origin of trisomy 21 mosaicism are still unclear; embryonic meiotic errors such as nondisjunction and anaphase lag, and subsequent mitotic malsegregation may be responsible. Uniparental disomy needs investigation. In the absence of somatic recombination, postzygotic malsegregation in an originally unaffected, disomy 21 zygote could also be a cause. The incidence of this condition in the community might be higher than hitherto believed.

Keywords: Anaphase lag, Case report, Copy-number alteration, Fluorescence *in situ* hybridization, Germinal trisomy 21 mosaicism, High-grade mosaics, Infant, Meiotic errors, Mitotic malsegregation, Newborn, Neonate, Nondisjunction, Postzygotic malsegregation, Somatic trisomy 21 mosaicism.

Newborn (2024): 10.5005/jp-journals-11002-0090

Highlights

- Infants with trisomy 21 frequently have persistent patency of ductus arteriosus (PDA) and/or other cardiac defects.
- We present a term male infant who had a persistent PDA. He did not show the phenotypic features that are usually seen in infants with trisomy 21 and initial tests showed a normal karyotype. Repeat tests identified him as a mosaic.
- The diagnosis was confirmed using examination of *in vitro* cultured blood lymphocytes for somatic and germinal trisomy 21 mosaicism.
- This disorder might be more common in the general population than previously believed, and hence, appropriate investigations might have to be considered in more patients.

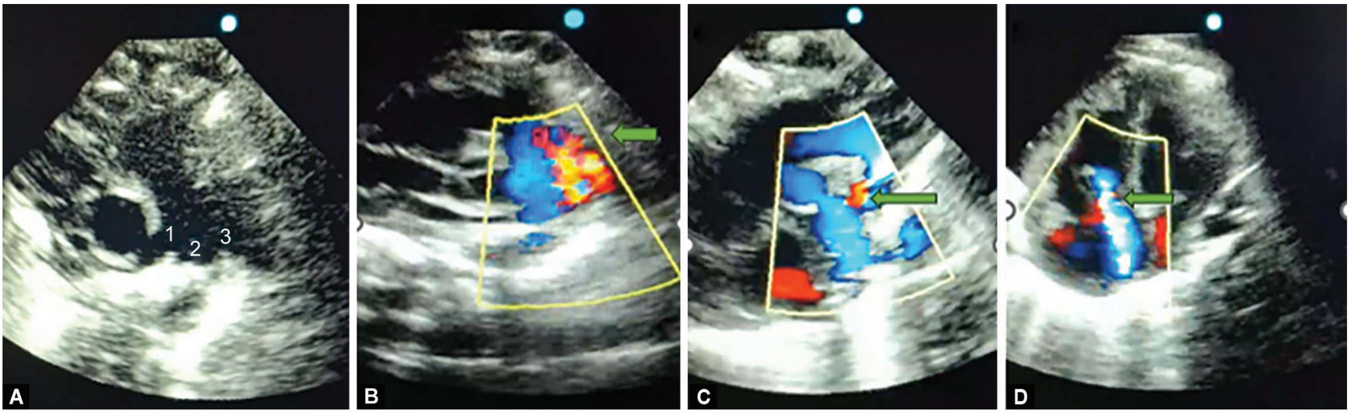
In this brief report, we present findings from a term infant with persistent PDA. He did not show the characteristic phenotypic features of trisomy 21 but turned out to have mosaicism for this karyotypic aneuploidy. The incidence of mosaicism could be higher than previously believed, and could very well be an important mechanism of the phenotypic variability seen in this condition.[1–5] Hence, mosaicism might need to be meticulously excluded in patients with a limited or an overall less-severe phenotype.[5,6] Other than specific mutations in key genes, mosaicism could also be an important reason for the geographical variation in the cardiac manifestations of trisomy 21.[7–13] The severity of somatic manifestations, the incidence of complications, and the overall prognosis may also be related to mosaicism.[14–21]

Case Description

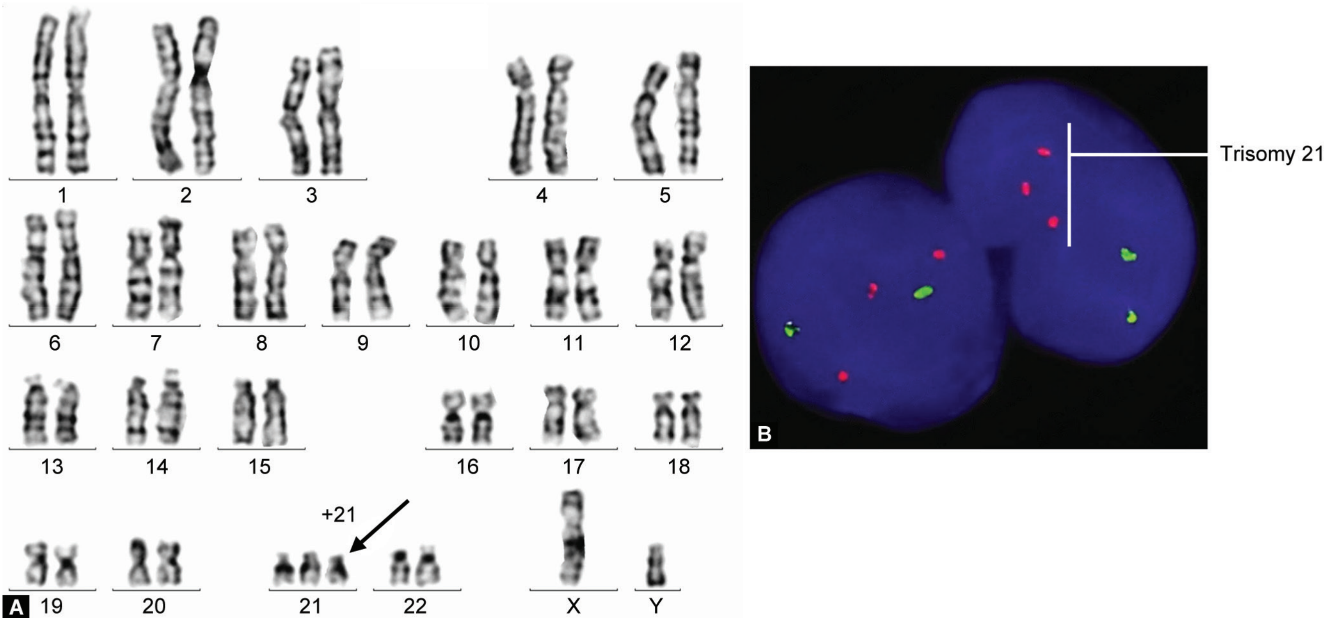
We evaluated plasma samples from a mother at 18 weeks' gestation for cell-free fetal DNA; there was a possibility of fetal aneuploidy in some samples but overall, the results were ambiguous. After delivery, the full-term male infant was noted to have a systolic murmur that was audible even on postnatal day 3. He did not show any of the frequently-seen phenotypic features associated with trisomy 21 on a detailed, careful physical examination performed by multiple care-providers, and the postnatal karyotype was reported

[1]Department of Pediatrics, Louisiana State University, Shreveport, Louisiana, United States of America
[2]Global Newborn Society, Clarksville, Maryland, United States of America
[3]Department of Neonatology, Kailash Hospital, Noida, Uttar Pradesh, India
[4]Scientist, NMC Genetics, NMC Healthcare, Gurugram, Haryana, India
[5]Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Tata Memorial Center, Homi Bhabha National Institute-University, Mumbai, Maharashtra, India
[6]Department of Non-invasive Cardiology, Fortis Hospital, New Delhi, India
[7]Down Syndrome Parents Society, New Delhi, India
[8]Down Syndrome Federation of India, Chennai, Tamil Nadu, India
Corresponding Author: Amita S Garg, Department of Non-invasive Cardiology, Fortis Hospital, New Delhi, India; Down Syndrome Parents Society, New Delhi, India; Down Syndrome Federation of India, Chennai, Tamil Nadu, India, Phone: +91 9312239463, e-mail: singhal.amita@gmail.com
How to cite this article: Maheshwari A, Singh S, Sharma S, *et al*. Many Term infants with Persistent Patency of the Ductus Arteriosus could be Trisomy 21 Mosaics. Newborn 2024;3(1):61–64.
Source of support: Nil.
Conflict of interest: Dr Akhil Maheshwari is associated as Editor-in-Chief of this journal and this manuscript was subjected to this journal's standard review procedures, with this peer review handled independently of the Editor-in-Chief and his research group.

© The Author(s). 2024 Open Access. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by-nc/4.0/), which permits unrestricted use, distribution, and non-commercial reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.



Figs 1A to D: Patent ductus arteriosus (PDA) in a full-term infant. (A) A ductal view showing the classical "three-legged stool appearance" of the PDA. The numerical labels in this photograph indicate (1) the right pulmonary artery, (2) the left pulmonary artery, and (3) the PDA; (B and C) PDA (red) at its junction with the aorta, in subcostal (B) and suprasternal (C) views; (D) A 4-chamber view showing a tricuspid regurgitation jet (blue) indicating pulmonary hypertension related to ductal patency



Figs 2A and B: (A): Noninvasive prenatal testing was performed to detect fetal aneuploidy in cell-free DNA in maternal plasma. Samples were analyzed on an Affymetrix microarray platform by parallel shotgun sequencing. Sequencing libraries were prepared from plasma DNA and sequenced to generate millions of short-sequence reads. These were mapped to the reference human genome, allowing determination of the chromosome of origin for each sequence. The number of mapped sequences originating from each chromosome was calculated and normalized. Aneuploidy was noted by comparing test samples to known normal reference samples, using a z-score approach; This figure shows a karyotype showing trisomy 21 due to nondisjunction of chromosome 21 in affected cells. This extra copy of chromosome 21 gives a total chromosome count of 47. Most mosaics show an abnormal karyotype in only 1–2 of the usual 10–15 tested cells. In India, we are also seeing a larger number of infants with Robertsonian translocation t(14q;21q); not shown; (B) Fluorescence *in-situ* hybridization (FISH) can detect trisomy 21. Lymphocytes isolated from a peripheral blood (or bone marrow) sample and were cultured *ex-vivo*, and then smeared on glass slides. The slides were aged and then treated with pepsin to expose the nuclear chromatin in metaphase chromosomes. Fluorescent-labeled locus-specific DNA probes were used to target the long arm of chromosome 21 (21q22.13-q22.2 and 21q22.2-q22.3 regions). Before hybridization, the probes were heat-denatured to allow access to complementary chromosomal DNA. The denatured probes were applied to the slide and hybridization carried out at specific binding sites by overnight incubation at 37°C. Unbound probes were removed by washing and the nuclei were counterstained with DAPI. Fluorescence microscopy was used to visualize the labeled chromosomes 21. Unlike normal cells that show two homologs of chromosome 21, those with trisomy 21 show 3. A minimum of 10 metaphase spreads were examined and trisomy 21 was reported if ≥3 signals were seen in ≥10% cells; This figure shows trisomy 21 in FISH analysis of interphase cells. The cells were hybridized with an orange chromosome 21-specific probe and a control green probe for chromosome 12. Cells with trisomy 21 showed 3 orange signals instead of the normal 2. Infants who are mosaics for trisomy 21 have some cells with 2 and others 3 due to postzygotic nondisjunction. Magnification: 400x

JAYPEE

as normal. An echocardiogram on postnatal day 4 showed a patent "ductus arteriosus" with a significant left-to-right shunt (Fig. 1). Signs of congestive heart failure became evident at 4–5 weeks, and so the duct was surgically ligated at 6 weeks of postnatal age. The recovery was uneventful; the infant was discharged from the hospital 1 week later. As is evident in the above description, this clinical course was typical of an infant with a hemodynamically-significant PDA. However, in view of the prenatal ambiguity in the karyotype, one of our team members decided to request another evaluation of the karyotype at 2 weeks after birth; he was identified as a mosaic for trisomy 21 (Fig. 2).[22]

Brief Review

Current information suggests that 2–4% of all infants with trisomy 21 are karyotypic mosaics.[7,23] We know that nearly 95% of all cases of Down syndrome result from chromosomal nondisjunction of chromosome 21 (47, XX, +21 or 47, XY, +21) at conception.[2,24,25] The process of oogenesis is lengthy and involves meiotic arrest, which makes the ova more vulnerable to malsegregation of chromosomes than spermatogenesis.[26,27] Increasing age of the ova can also promote the degradation of cellular proteins involved in spindle formation,[28,29] sister chromatid cohesion,[30] and anaphase separation of sister chromatids in oocytes, which increases the risk of nondisjunction during meiosis.[31] Such translocations are often familial, most frequently involving chromosomes 14 and 21.[7] In 1% of all cases of Down syndrome, the extra chromosome 21 material originates from other rearrangements.[32]

The etiopathogenesis of mosaicism is still unclear. Unlike infants with "complete" trisomy 21 who show the extra chromosome 21 in all cells, most mosaics show an abnormal karyotype in only 1–2 of the usual 10–15 tested cells (Fig. 1). In these "possibly positive" patients, the analysis is usually extended to 50 or more cells. The diagnosis of mosaicism may require examination of *in vitro* cultured blood lymphocytes from the patients, siblings, and parents for somatic and germinal trisomy 21 mosaicism.[33,34] Currently, most mosaics who are being identified are possibly the ones with the "high-grade"condition[35,36] but the sensitivity is likely to improve with advancement in methods of testing and as our threshold for requesting these tests improves.[36,37]

The chromosomal abnormalities in mosaics do not appear to be unique.[38] Embryonic meiotic errors such as nondisjunction and anaphase lag, and subsequent mitotic malsegregation may be responsible just as in the majority of infants with Down syndrome.[39] Uniparental disomy needs investigation.[40] In the absence of somatic recombination, mosaicism could originate from postzygotic malsegregation in an originally unaffected, disomy 21 zygote.[36] Postfertilization formation of a Robertsonian translocation t(14q;21q) and an isochromosome is also now being recognized with increasing frequency.[41–43]

Currently, the methodology of choice for detecting the number of chromosomes 21 is fluorescence *in situ* hybridization (FISH; Fig. 2).[44–46] The sensitivity of these tests in conventional cytogenetic analysis can be enhanced by testing cultured blood lymphocytes; these tests may show trisomy 21 in 1 in 60 metaphase cells.[36] When combined with FISH analyses of interphase nuclei from uncultured blood cells, trisomy 21 may be seen in up to 10% cells.[36,47] Similarly, trisomy 21 can also be identified in cells obtained in chorionic villus sampling/amniocentesis.[48]

We also need efforts to identify trisomy 21 mosaics who might have alterations in systems other than the hematopoietic system.[49] Evaluation of mucosal cells obtained from buccal swabs, cultured skin fibroblasts, or even DNA from whole-skin biopsies can be helpful.[50] Copy-number alteration can be identified with sensitivity rates as high as 20% using next-generation sequencing (NGS) of whole-skin biopsy DNA.[51–54]

Authors' Contributions

Authors AM, SS, PGS, and ASG provided data and wrote the manuscript; VS reviewed and made important and critical revisions.

Orcid

Akhil Maheshwari https://orcid.org/0000-0003-3613-4054

Srijan Singh https://orcid.org/0000-0002-2103-5232

Papagudi G Subramanian https://orcid.org/0000-0001-9107-5937

References

1. Hulten MA, Jonasson J, Iwarsson E, et al. Trisomy 21 mosaicism: We may all have a touch of Down syndrome. Cytogenet Genome Res 2013;139(3):189–192. DOI: 10.1159/000346028.
2. Patterson D, Costa AC. Down syndrome and genetics: A case of linked histories. Nat Rev Genet. 2005;6(2):137–147. DOI: 10.1038/nrg1525.
3. Zhang Y, Zhong M, Zheng D. Chromosomal mosaicism detected by karyotyping and chromosomal microarray analysis in prenatal diagnosis. J Cell Mol Med 2021;25(1):358–366. DOI: 10.1111/jcmm.16080.
4. Ko JM. Genetic syndromes associated with congenital heart disease. Korean Circ J 2015;45(5):357–361. DOI: 10.4070/kcj.2015.45.5.357.
5. Martinez–Glez V, Tenorio J, Nevado J, et al. A six-attribute classification of genetic mosaicism. Genet Med 2020;22(11):1743–1757. DOI: 10.1038/s41436-020-0877-3.
6. Leon E, Zou YS, Milunsky JM. Mosaic Down syndrome in a patient with low-level mosaicism detected by microarray. Am J Med Genet A 2010;152A(12):3154–3156. DOI: 10.1002/ajmg.a.33739.
7. Plaiasu V. Down syndrome: Genetics and cardiogenetics. Maedica (Bucur) 2017;12(3):208–213. PMID: 29218069.
8. Jacobs EG, Leung MP, Karlberg J. Distribution of symptomatic congenital heart disease in Hong Kong. Pediatr Cardiol 2000;21(2):148–157. DOI: 10.1007/s002469910025.
9. Lo NS, Leung PM, Lau KC, et al. Congenital cardiovascular malformations in Chinese children with Down's syndrome. Chin Med J (Engl) 1989;102(5):382–386. PMID: 2530065.
10. Kim MA, Lee YS, Yee NH, et al. Prevalence of congenital heart defects associated with Down syndrome in Korea. J Korean Med Sci 2014;29(11):1544–1549. DOI: 10.3346/jkms.2014.29.11.1544.
11. de Rubens Figueroa J, del Pozzo Magaña B, Hach JLP, et al. Rev Esp Cardiol 2003;56(9):894–899. DOI: 10.1016/s0300-8932(03)76978-4.
12. Vida VL, Barnoya J, Larrazabal LA, et al. Congenital cardiac disease in children with Down's syndrome in Guatemala. Cardiol Young 2005;15(3):286–290. DOI: 10.1017/S1047951105000582.
13. Elmagrpy Z, Rayani A, Shah A, et al. Down syndrome and congenital heart disease: Why the regional difference as observed in the Libyan experience? Cardiovasc J Afr 2011;22(6):306–309. DOI: 10.5830/CVJA-2010-072.
14. Baird PA, Sadovnick AD. Life expectancy in Down syndrome. J Pediatr 1987;110(6):849–854. DOI: 10.1016/s0022-3476(87)80395-5.
15. Baird PA, Sadovnick AD. Life tables for Down syndrome. Hum Genet 1989;82(3):291–292. DOI: 10.1007/BF00291175.
16. Esbensen AJ. Health conditions associated with aging and end of life of adults with Down syndrome. Int Rev Res Ment Retard 2010;39(C):107–126. DOI: 10.1016/S0074-7750(10)39004-5.

17. Ali FE, Al-Bustan MA, Al-Busairi WA, et al. Cervical spine abnormalities associated with Down syndrome. Int Orthop 2006;30(4):284–289. DOI: 10.1007/s00264-005-0070-y.
18. Xavier AC, Taub JW. Acute leukemia in children with Down syndrome. Haematologica 2010;95(7):1043–1045. DOI: 10.3324/haematol.2010.024968.
19. Kim GE, Sin DS, Kim SS, et al. End-stage renal disease in a Down syndrome patient caused by delayed diagnosis of nonneurogenic bladder: A case report. Medicine (Baltimore) 2019;98(15):e15145. DOI: 10.1097/MD.0000000000015145.
20. Danopoulos S, Deutsch GH, Dumortier C, et al. Lung disease manifestations in Down syndrome. Am J Physiol Lung Cell Mol Physiol 2021;321(5):L892–L899. DOI: 10.1152/ajplung.00434.2020.
21. Dierssen M. Down syndrome: The brain in trisomic mode. Nat Rev Neurosci 2012;13(12):844–858. DOI: 10.1038/nrn3314.
22. Truty R, Rojahn S, Ouyang K, et al. Patterns of mosaicism for sequence and copy-number variants discovered through clinical deep sequencing of disease-related genes in one million individuals. Am J Hum Genet 2023;110(4):551–564. DOI: 10.1016/j.ajhg.2023.02.013.
23. Thorpe J, Osei–Owusu IA, Avigdor BE, et al. Mosaicism in human health and disease. Annu Rev Genet 2020;54:487–510. DOI: 10.1146/annurev-genet-041720-093403.
24. Ghosh S, Feingold E, Dey SK. Etiology of Down syndrome: Evidence for consistent association among altered meiotic recombination, nondisjunction, and maternal age across populations. Am J Med Genet A 2009;149A(7):1415–1420. DOI: 10.1002/ajmg.a.32932.
25. Day T, Taylor PD. Chromosomal drive and the evolution of meiotic nondisjunction and trisomy in humans. Proc Natl Acad Sci USA 1998;95(5):2361–2365. DOI: 10.1073/pnas.95.5.2361.
26. Oliver TR, Feingold E, Yu K, et al. New insights into human nondisjunction of chromosome 21 in oocytes. PLoS Genet 2008;4(3):e1000033. DOI: 10.1371/journal.pgen.1000033.
27. DiLuigi A, Weitzman VN, Pace MC, et al. Meiotic arrest in human oocytes is maintained by a Gs signaling pathway. Biol Reprod 2008;78(4):667–672. DOI: 10.1095/biolreprod.107.066019.
28. Hawley RS, Frazier JA, Rasooly R. Separation anxiety: The etiology of nondisjunction in flies and people. Hum Mol Genet 1994;3(9):1521–1528. DOI: 10.1093/hmg/3.9.1521.
29. Goutas A, Outskouni Z, Papathanasiou I, et al. The establishment of mitotic errors-driven senescence depends on autophagy. Redox Biol 2023;62:102701. DOI: 10.1016/j.redox.2023.102701.
30. Wolstenholme J, Angell RR. Maternal age and trisomy: A unifying mechanism of formation. Chromosoma 2000;109(7):435–438. DOI: 10.1007/s004120000088.
31. MacLennan M, Crichton JH, Playfoot CJ, et al. Oocyte development, meiosis and aneuploidy. Semin Cell Dev Biol 2015;45:68–76. DOI: 10.1016/j.semcdb.2015.10.005.
32. Pelleri MC, Locatelli C, Mattina T, et al. Partial trisomy 21 with or without highly restricted Down syndrome critical region (HR-DSCR): Report of two new cases and reanalysis of the genotype-phenotype association. BMC Med Genomics 2022;15(1):266. DOI: 10.1186/s12920-022-01422-6.
33. Papavassiliou P, Charalsawadi C, Rafferty K, et al. Mosaicism for trisomy 21: A review. Am J Med Genet A 2015;167A(1):26–39. DOI: 10.1002/ajmg.a.36861.
34. Papavassiliou P, York TP, Gursoy N, et al. The phenotype of persons having mosaicism for trisomy 21/Down syndrome reflects the percentage of trisomic cells present in different tissues. Am J Med Genet A 2009;149A(4):573–583. DOI: 10.1002/ajmg.a.32729.
35. Sanchez–Pavon E, Mendoza H, Garcia–Ferreyra J. Trisomy 21 and assisted reproductive technologies: A review. JBRA Assist Reprod 2022;26(1):129–1241. DOI: 10.5935/1518-0557.20210047.
36. Hulten MA, Jonasson J, Nordgren A, et al. Germinal and somatic trisomy 21 mosaicism: How common is it, what are the implications for individual carriers and how does it come about? Curr Genomics 2010;11(6):409–419. DOI: 10.2174/138920210793176056.
37. Munne S, Wells D. Detection of mosaicism at blastocyst stage with the use of high-resolution next-generation sequencing. Fertil Steril 2017;107(5):1085–1091. DOI: 10.1016/j.fertnstert.2017.03.024.
38. Taylor TH, Gitlin SA, Patrick JL, et al. The origin, mechanisms, incidence and clinical consequences of chromosomal mosaicism in humans. Hum Reprod Update 2014;20(4):571–581. DOI: 10.1093/humupd/dmu016.
39. Pangalos C, Avramopoulos D, Blouin JL, et al. Understanding the mechanism(s) of mosaic trisomy 21 by using DNA polymorphism analysis. Am J Hum Genet 1994;54(3):473–4781. PMID: 8116616.
40. Chen CP, Liou JD, Chern SR, et al. Prenatal diagnosis of maternal uniparental disomy 21 in association with low-level mosaic trisomy 21 at amniocentesis in a pregnancy associated with intrauterine growth restriction and a favorable outcome. Taiwan J Obstet Gynecol 2022;61(1):146–149. DOI: 10.1016/j.tjog.2021.11.025.
41. Bandyopadhyay R, McCaskill C, Knox–Du Bois C, et al. Mosaicism in a patient with Down syndrome reveals post-fertilization formation of a Robertsonian translocation and isochromosome. Am J Med Genet A 2003;116A(2):159–163. DOI: 10.1002/ajmg.a.10113.
42. Petersen MB, Adelsberger PA, Schinzel AA, et al. Down syndrome due to de novo Robertsonian translocation t(14q;21q): DNA polymorphism analysis suggests that the origin of the extra 21q is maternal. Am J Hum Genet 1991;49(3):529–536. PMID: 1831959.
43. Shaffer LG, Agan N, Goldberg JD, et al. American College of Medical Genetics statement of diagnostic testing for uniparental disomy. Genet Med 2001;3(3):206–211. DOI: 10.1097/00125817-200105000-00011.
44. Iourov IY, Vorsanova SG, Yurov YB. Chromosomal mosaicism goes global. Mol Cytogenet 2008;1:26. DOI: 10.1186/1755-8166-1-26.
45. Namba A, Nishiyama M, Weiser JJ, et al. Prenatal diagnosis of complex rearrangement of chromosome 21: The significance of interphase and metaphase fluorescence in situ hybridization and comparative genomic hybridization. Clin Case Rep 2013;1(2):50–53. DOI: 10.1002/ccr3.22.
46. Witters I, Devriendt K, Legius E, et al. Rapid prenatal diagnosis of trisomy 21 in 5049 consecutive uncultured amniotic fluid samples by fluorescence in situ hybridisation (FISH). Prenat Diagn 2002;22(1):29–33. DOI: 10.1002/pd.225.
47. Davies AF, Barber L, Murer–Orlando M, et al. FISH detection of trisomy 21 in interphase by the simultaneous use of two differentially labelled cosmid contigs. J Med Genet 1994;31(9):679–685. DOI: 10.1136/jmg.31.9.679.
48. Beverstock GC, Hansson K, Helderman–van den Enden AT, et al. A near false-negative finding of mosaic trisomy 21: A cautionary tale. Prenat Diagn 1998;18(7):742–746. PMID: 9706658.
49. Li J, Kalev–Zylinska ML. Advances in molecular characterization of myeloid proliferations associated with Down syndrome. Front Genet 2022;13:891214. DOI: 10.3389/fgene.2022.891214.
50. Livy A, Lye S, Jagdish CK, et al. Evaluation of quality of DNA extracted from buccal swabs for microarray based genotyping. Indian J Clin Biochem 2012;27(1):28–33. DOI: 10.1007/s12291-011-0154-y.
51. Singh AK, Olsen MF, Lavik LAS et al. Detecting copy-number variation in next generation sequencing data from diagnostic gene panels. BMC Med Genomics 2021;14(1):214. DOI: 10.1186/s12920-021-01059-x.
52. Qin D. Next-generation sequencing and its clinical application. Cancer Biol Med 2019;16(1):4–10. DOI: 10.20892/j.issn.2095-3941.2018.0055.
53. Ramachandran D, Mulle JG, Locke AE, et al. Contribution of copy-number variation to Down syndrome-associated atrioventricular septal defects. Genet Med 2015;17(7):554–560. DOI: 10.1038/gim.2014.144.
54. Rambo–Martin BL, Mulle JG, Cutler DJ, et al. Analysis of copy-number variants on chromosome 21 in Down syndrome-associated congenital heart defects. G3 (Bethesda) 2018;8(1):105–111. DOI: 10.1534/g3.117.300366.