JIG Journal of Interdisciplinary Genomics

https://doi.org/10.22742/JIG.2024.6.1.1
Journal of Interdisciplinary Genomics 2024;6(1):1-5
eISSN 2671-6771

Deletion or Duplication Syndromes of Chromosome 22: Review

Kyung Ran Jun

Department of Laboratory Medicine, Haeundae Paik Hospital, Inje University College of Medicine, Busan, Korea

Chromosome 22 is an acrocentric chromosome containing 500–600 genes, representing 1.5%–2% of the total DNA in cells. It was the first human chromosome to be fully sequenced by the Human Genome Project. Several syndromes involving the partial deletion or duplication of chromosome 22 are well descibed, including 22q11.2 deletion syndrome, 22q11.2 duplication syndrome, 22q11.2 distal deletion syndrome, Phelan-McDermid syndrome caused by a 22q13 deletion or pathogenic variant in *SHANK3*, and cat-eye syndrome caused by a 22 pter–q11 duplication. This review aims to provide concise information on the clinical characteristics of these syndromes. In particular, the similarities in features among these syndromes, genetic basis, and standard detection techniques are described, providing guidance for diagnosis and genetic counselling.

Key words: Chromosome 22, 22q11.2 deletion, 22q11.2 duplication, 22q11.2 distal deletion, Phelan-McDermid syndrome, Cat-eye syndrome

REVIEW ARTICLE

Received: April 21, 2024
Revised: April 23, 2024
Accepted: April 24, 2024

Correspondence to: Kyung Ran Jun, MD, PhD
Department of Laboratory Medicine, Haeundae Paik Hospital, Inje University College of Medicine, 875 Haeun-daero, Haeundae-gu, Busan 48108, Korea
Tel: +82-51-797-3191
Fax: +82-51-797-3194
E-mail: jun@paik.ac.kr

ORCID
https://orcid.org/0000-0001-8904-2327

INTRODUCTION

Chromosome 22, one of 23 pairs of chromosomes in human cells, was the first human chromosome to be fully sequenced by the Human Genome Project [1,2]. Human chromosomes are numbered by their apparent size in the karyotype, with chromosome 1 being the largest. Chromosome 22 was originally identified as the smallest; however, genome sequencing has revealed that chromosome 21 is smaller. Chromosome 22 is an acrocentric chromosome containing ribosomal RNA genes on the short p-arm; it contains 500–600 genes, representing 1.5%–2% of the total DNA in cells. Fig. 1 revealed ideogram and G-banding patterns generated for normal human chromosome 22 observed under a microscope at resolutions of 400–550 bands [3] (Fig. 1A, B).

Various conditions caused by copy number changes in partial chromosome 22 are previously reported [4]. Among them, well-described syndromic disorders of chromosome 22 are focused and their clinical features are summarized in this review: 22q11.2 deletion syndrome, 22q11.2 duplication syndrome, 22q11.2 distal deletion syndrome, Phelan-McDermid syndrome, and cat-eye syndrome (22 pter-q11 duplication syndrome) (Fig. 1C). Furthermore, considerations related to testing and genetic counseling are discussed.

22q11.2 DELETION SYNDROME

22q11.2 deletion syndrome is an autosomal dominant syndrome involving a set of contiguous genes [5]. It includes phenotypes previously described as DiGeorge syndrome (MIM #188400), velocardiofacial syndrome (MIM #192430), conotruncal anomaly face syndrome [6], autosomal dominant Opitz G/BBB syn-

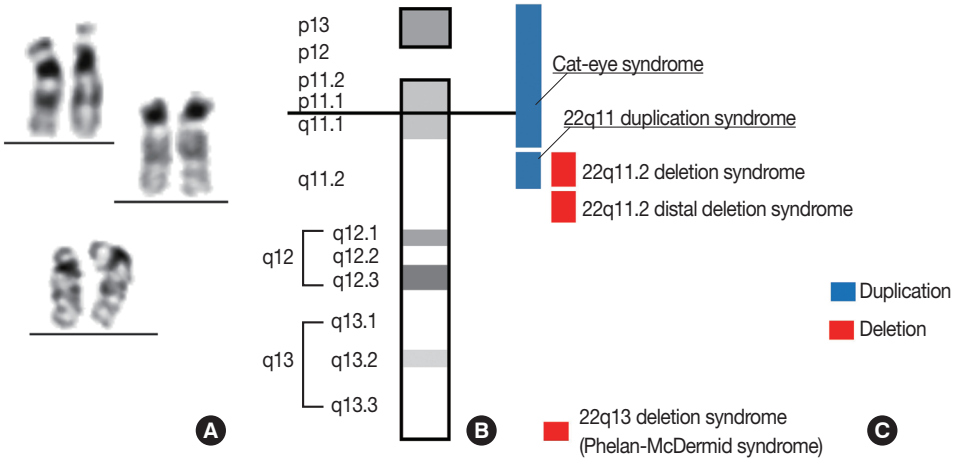

Fig. 1. (A) Cases of G-banded karyogram for normal chromosome 22 captured from constitutional chromosome study using human peripheral blood lymphocytes. (B) 550-band level ideogram of G-banding patterns for normal human chromosome 22 based on the ISCN 2020. The location and width of bands are not based on any measurements. (C) Schematic representation of altered regions in chromosome 22 deletion or duplication syndromes.

drome (MIM #145420), Sedlackova syndrome [7], and Cayler cardiofacial syndrome (MIM #125520) (https://rarediseases.info.nih.gov/diseases/10299/22q112-deletion-syndrome).

The 22q11.2 region spans 6.6 million base pairs (Mb: Genome GRCh/38/hg38 Assembly; chr22:18,125,038-24,727,631), including 101 protein-coding genes, 11 miRNA genes, and low-copy repeats (LCR22s). Most individuals with 22q11.2 deletion syndrome are lacking approximately 3 million base pairs on one copy of chromosome 22. The deletion is near the middle of the chromosome at q11.2, in a region containing approximately 30 genes, many of which are not well-characterized. Among the genes of interest in this region, *TBX1* (MIM* 602054), a member of the T-box gene family, is thought to be responsible for many of the physical characteristics of 22q11.2 deletion syndrome, except learning disabilities [8,9].

The features of 22q11.2 deletion syndrome are highly variable, even within families. The major clinical manifestations include heart defects, feeding difficulties, gastrointestinal problems, developmental delay, cleft palate, distinctive facial features, low calcium levels, increased risk of behavioral problems, psychiatric illnesses, and autoimmune disorders [5].

The detection of this alteration is not by karyotyping due to detection limits, and most cases are identified by chromosomal microarray analyses, which are useful tools for detection of genome-wide copy number changes on chromosomes.

22q11.2 DUPLICATION SYNDROME

22q11.2 duplication syndrome (MIM#608363) typically involves approximately 3 Mb of additional genetic material in the region that is missing in 22q11.2 deletion syndrome (described above) [10,11] (https://rarediseases.info.nih.gov/diseases/10557/22q112-duplication-syndrome).

The features of this condition vary widely, even among members of the same family. Affected individuals may have hypotonia, intellectual or learning disabilities, global developmental delay, short stature, pharyngeal anomalies, a cleft palate, anxiety, and autism. Duplication as same as deletion is not identified by karyotyping but by chromosomal microarray analyses.

22q11.2 DISTAL DELETION SYNDROME

The 22q11.2 distal deletion is a rarer deletion located far from the centromere of chromosome 22q11, which does not overlap with the common cases with 22q11.2 deletion syndrome. The information guide for this disorder was separated from that for the 22q11.2 deletion syndrome by Unique (https://rarechromo.org/disorder-guides/).

The clinical features associated with the 22q11.2 distal deletion syndrome include developmental delay, learning difficulties, heart problems, behavioral difficulties, and subtly unusual facial features. Several adults have been reported in the literature [12]. Apparently they had no health or developmental problems, apart from recurrent infections, inqunal hernia, short stature, or mild to moderate learning difficulties.

The genes responsible for the clinical features associated with 22q11.2 distal deletion syndrome have not been clearly

defined. However, *CRKL* (MIM*602007) and *MAPK1* (MIM*176948) are candidate genes for heart anomalies [13,14]. *SMARCB1* (MIM*601607) on very distal region are associated with an increased risk of malignant rhabdoid tumours. So case of a deletion including *SMARCB1* gene should require prolonged monitoring for this tumor [15,16].

The molecular techniques, such as chromosomal microarray, are needed to detect this microdeletion.

PHELAN-MCDERMID SYNDROME

Phelan-McDermid syndrome (MIM#606232), previously referred to as 22q13 deletion syndrome, is caused by a heterozygous deletion at 22q13.3 near the end of the long arm of chromosome 22 or by a pathogenic variant in the *SHANK3* gene (MIM*606230) [17-22].

Most terminal or interstitial deletions of 22q13.3 arise *de novo* in the proband; however, the deletion may be the result of a chromosomal rearrangement or mosaicism in a parent. Pathogenic variants in *SHANK3* are mostly *de novo* [19].

The typical clinical findings of 22q13.3 deletion syndrome are neonatal hypotonia, severe developmental delay, delayed speech, intellectual disability, autistic-like behavior, and minor dysmorphic facial features, such as dolichocephaly, flat midface, deep-set eyes, long eyelashes, wide nasal bridge, full cheeks, and prominent ears. Other features include large, fleshy hands, dysplastic toenails, and hypohidrosis. The features distinguishing 22q13.3 deletion syndrome from other autosomal chromosomal disorders are a normal stature and head size [18].

Diagnosis is based on laboratory genetic testing: chromosomal study, chromosomal microarray, and molecular test for *SHANK3*.

CAT-EYE SYNDROME

Cat-eye syndrome (MIM#115470), also known as Schmid-Fraccaro syndrome, partial tetrasomy 22, partial trisomy 22, and inverted duplication of 22 pter-q11, is a rare disorder most often caused by duplicated genetic material on chromosome 22 [23,24]. It is thought to be underdiagnosis due to variable phenotypic variability, variable severity, and sometimes mosaicism.

The characteristic signs and symptoms of cat-eye syndrome are an eye abnormality called ocular iris coloboma. About half of patients with cat-eye syndrome have a colored iris that can make the pupil appear elongated (hence, the name "cat-eye"). Vision is not affected if only the iris is affected; however, colobomas in other layers of the eye may affect vision and cause blindness. Other features include small skin tags or pits in front of the ear, heart defects, kidney problems, anal atresia with a fistula, cleft palate, downslanting palpebral fissures, hypertelorism, skeletal abnormalities, and delayed development. Most of patients diagnosed with cat-eye syndrome have normal intellect or mild to moderate intellectual disability.

In cat-eye syndrome, the duplicated DNA exists as an additional chromosome material: ring form of small supernumerary marker chromosome (sSMC), dicentric sSMC, or interstitial duplication. These abnormalities are usually shown in germline chromosomal study or FISH for chromosome 22. For the precise diagnosis, molecular genetic test called chromosomal microarray may be needed.

The additional chromosome 22 material generally arises *de novo* during development, but direct transmission from asymptomatic patents with its mosaicism was possible [25,26].

Other conditions associated with deletion or duplication of chropmosome 22 are also reported but not described in this review: 22q11.2 distal duplication [27,28], Emanuel syndrome [29].

MANAGEMENT AND GENETIC COUNSELING

Patients with chromosomal deletion or duplication syndromes often have a wide range of health issues, and many of these symptoms mimic those of other conditions. Currently, no specific therapies are available. Therefore, the treatment of these syndromes is symptomatic.

Genomic testing identifying the deletion or duplication identified in the proband is recommended for apparently asymptomatic parents and siblings to reliably determine the recurrence risk and identify any other complications. Pregnant women must be monitored medically, accounting for preexisting conditions. Fetuses at high risk for genetic disorders should undergo prenatal evaluation. The optimal time for determining the genetic risk and discussing the availability of prenatal/preimplantation genetic testing is before pregnancy.

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance patterns, and implications of genetic disorders to help them make informed medical and personal decisions. If a deletion or duplication cannot be detected in the leukocyte DNA of either

parent, possible explanations include *de novo* change in the proband or germline mosaicism in the parent [30].

Because of clinical variability and/or reduced penetrance, a negative family history cannot be confirmed unless parents have been tested for the 22q11.2 alteration identified in the proband. If the 22q11.2 deletion/duplication identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk in siblings is slightly greater than that of the general population because of the possibility of parental germline mosaicism.

CONCLUSION

Individuals with partial deletions or duplications of chromosome 22 exhibit variable features, and many symptoms are similar among these syndromes. Diagnosis based on clinical features and physical examination can be challenging. Moreover, most cases cannot be detected by routine karyotyping due to its detection limits. Especially chromosomal microarray analyses is useful tools for detecting genome-wide copy number changes on chromosomes. Nowadays, the rising number of chromosomal microarray testing has led to a greater possibility of identifying deletion or duplication syndromes related to chromosome 22. Useful detection methods, along with well-organized information, careful attention, and active inspection by medical doctors, could enable earlier identification and proactive care.

CONFLICTS OF INTEREST

Not applicable.

REFERENCES

1. Kaplan JC, Aurias A, Julier C, Prieur M, Szajnert MF. Human chromosome 22. J Med Genet 1987;24(2):65-78. doi: 10.1136/jmg.24.2.65.
2. Mayor S. First human chromosome is sequenced. BMJ 1999;319(7223):1453A. doi: 10.1136/bmj.319.7223.1453a.
3. McGowan-Jordan J, Hastings RJ, Moore S, editors. ISCN 2020: An International System for Human Cytogenomic Nomenclature. Basel: Karger. 2020.
4. Yu S, Graf WD, Ramalingam A, Brawner SJ, Joyce JM, Fiedler S, et al. Identification of copy number variants on human chromosome 22 in patients with a variety of clinical findings. Cytogenet Genome Res 2011;134(4):260-8. doi: 10.1159/000330123.
5. McDonald-McGinn DM, Sullivan KE, Marino B, Philip N, Swillen A, Vorstman JA, et al. 22q11.2 deletion syndrome. Nat Rev Dis Primers 2015;1:15071. doi: 10.1038/nrdp.2015.71.
6. Matsuoka R, Takao A, Kimura M, Imamura S, Kondo C, Joh-o K, et al. Confirmation that the conotruncal anomaly face syndrome is associated with a deletion within 22q11.2. Am J Med Genet 1994;53(3):285-9. doi: 10.1002/ajmg.1320530314.
7. Fokstuen S, Vrticka K, Riegel M, Da Silva V, Baumer A, Schinzel A. Velofacial hypoplasia (Sedlackova syndrome): a variant of velocardiofacial (Shprintzen) syndrome and part of the phenotypical spectrum of del 22q11.2. Eur J Pediatr 2001;160(1):54-7. doi: 10.1007/s004310000647.
8. 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. doi: 10.1016/s0140-6736(03)14632-6.
9. Gao S, Li X, Amendt BA. Understanding the role of Tbx1 as a candidate gene for 22q11.2 deletion syndrome. Curr Allergy Asthma Rep 2013;13(6):613-21. doi: 10.1007/s11882-013-0384-6.
10. Bartik LE, Hughes SS, Tracy M, Feldt MM, Zhang L, Arganbright J, et al. 22q11.2 duplications: Expanding the clinical presentation. Am J Med Genet A 2022;188(3):779-87. doi: 10.1002/ajmg.a.62577.
11. Yu A, Turbiville D, Xu F, Ray JW, Britt AD, Lupo PJ, et al. Genotypic and phenotypic variability of 22q11.2 microduplications: an institutional experience. Am J Med Genet A 2019;179(11):2178-89. doi: 10.1002/ajmg.a.61345.
12. 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. doi: 10.1002/ajmg.a.35517.
13. Breckpot J, Thienpont B, Bauters M, Tranchevent LC, Gewillig M, Allegaert K, et al. Congenital heart defects in a novel recurrent 22q11.2 deletion harboring the genes CRKL and MAPK1. Am J Med Genet A 2012;158A(3):574-80. doi: 10.1002/ajmg.a.35217.
14. Burnside RD. 22q11.21 Deletion syndromes: a review of proximal, central, and distal deletions and their associated features. Cytogenet Genome Res 2015;146(2):89-99. doi: 10.1159/000438708.
15. Beddow RA, Smith M, Kidd A, Corbett R, Hunter AG. Diagnosis of distal 22q11.2 deletion syndrome in a patient with a teratoid/rhabdoid tumour. Eur J Med Genet 2011;54(3):295-8. doi: 10.1016/j.ejmg.2010.12.007.
16. Fagerberg CR, Graakjaer J, Heinl UD, Ousager LB, Dreyer I, Kirchhoff M, et al. Heart defects and other features of the 22q11 distal deletion syndrome. Eur J Med Genet 2013;56(2):98-107. doi: 10.1016/j.ejmg.2012.09.009.
17. Anderlid BM, Schoumans J, Anneren G, Tapia-Paez I, Dumanski J, Blennow E, et al. FISH-mapping of a 100-kb terminal 22q13 deletion. Hum Genet 2002;110(5):439-43. doi: 10.1007/s00439-002-0713-7.
18. Jeffries AR, Curran S, Elmslie F, Sharma A, Wenger S, Hummel M, et al. Molecular and phenotypic characterization of ring chromosome 22. Am J Med Genet A 2005;137(2):139-47. doi: 10.1002/ajmg.a.30780.

19. Tabet AC, Rolland T, Ducloy M, Levy J, Buratti J, Mathieu A, et al. A framework to identify contributing genes in patients with Phelan-McDermid syndrome. NPJ Genom Med 2017;2:32. doi: 10.1038/s41525-017-0035-2.
20. Terrone G, Vitiello G, Genesio R, D'Amico A, Imperati F, Ugga L, et al. A novel SHANK3 interstitial microdeletion in a family with intellectual disability and brain MRI abnormalities resembling Unidentified Bright Objects. Eur J Paediatr Neurol 2017;21(6): 902-6. doi: 10.1016/j.ejpn.2017.07.006.
21. Cammarata-Scalisi F, Callea M, Martinelli D, Willoughby CE, Tadich AC, Araya Castillo M, et al. Clinical and genetic aspects of Phelan-McDermid syndrome: an interdisciplinary approach to management. Genes (Basel) 2022;13(3). doi: 10.3390/genes13030504.
22. Phelan K. The impact of Phelan-McDermid syndrome on the child and family. Dev Med Child Neurol 2023;65(7):862-3. doi: 10.1111/dmcn.15500.
23. Meins M, Burfeind P, Motsch S, Trappe R, Bartmus D, Langer S, et al. Partial trisomy of chromosome 22 resulting from an interstitial duplication of 22q11.2 in a child with typical cat eye syndrome. J Med Genet 2003;40(5):e62. doi: 10.1136/jmg.40.5.e62.
24. Chen CP, Ko TM, Chen YY, Su JW, Wang W. Prenatal diagnosis and molecular cytogenetic characterization of mosaicism for a small supernumerary marker chromosome derived from chromosome 22 associated with cat eye syndrome. Gene 2013;527(1): 384-8. doi: 10.1016/j.gene.2013.05.061.
25. Luleci G, Bagci G, Kivran M, Luleci E, Bektas S, Basaran S. A hereditary bisatellite-dicentric supernumerary chromosome in a case of cat-eye syndrome. Hereditas 1989;111(1):7-10. doi: 10.1111/j.1601-5223.1989.tb00369.x.
26. Schinzel A, Schmid W, Fraccaro M, Tiepolo L, Zuffardi O, Opitz JM, et al. The "cat eye syndrome": dicentric small marker chromosome probably derived from a no.22 (tetrasomy 22pter to q11) associated with a characteristic phenotype. Report of 11 patients and delineation of the clinical picture. Hum Genet 1981; 57(2):148-58. doi: 10.1007/BF00282012.
27. Coppinger J, McDonald-McGinn D, Zackai E, Shane K, Atkin JF, Asamoah A, et al. Identification of familial and de novo microduplications of 22q11.21-q11.23 distal to the 22q11.21 microdeletion syndrome region. Hum Mol Genet 2009;18(8):1377-83. doi: 10.1093/hmg/ddp042.
28. Ou Z, Berg JS, Yonath H, Enciso VB, Miller DT, Picker J, et al. Microduplications of 22q11.2 are frequently inherited and are associated with variable phenotypes. Genet Med 2008;10(4):267-77. doi: 10.1097/GIM.0b013e31816b64c2.
29. Emanuel BS, Zackai EH, Medne L: Emanuel Syndrome. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, ed. GeneReviews((R)). Seattle (WA); 1993.
30. Koza SA, Tabet AC, Bonaglia MC, Andres S, Anderlid BM, Aten E, et al. Consensus recommendations on counselling in Phelan-McDermid syndrome, with special attention to recurrence risk and to ring chromosome 22. Eur J Med Genet 2023;66(7):104773. doi: 10.1016/j.ejmg.2023.104773.