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Deletion or Duplication Syndromes of Chromosome 22: Review

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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 described, 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

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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 Di-George syndrome (MIM #188400), velocardiofacial syndrome (MIM #192430), conotruncal anomaly face syndrome [6], autosomal dominant Opitz G/BBB syn-

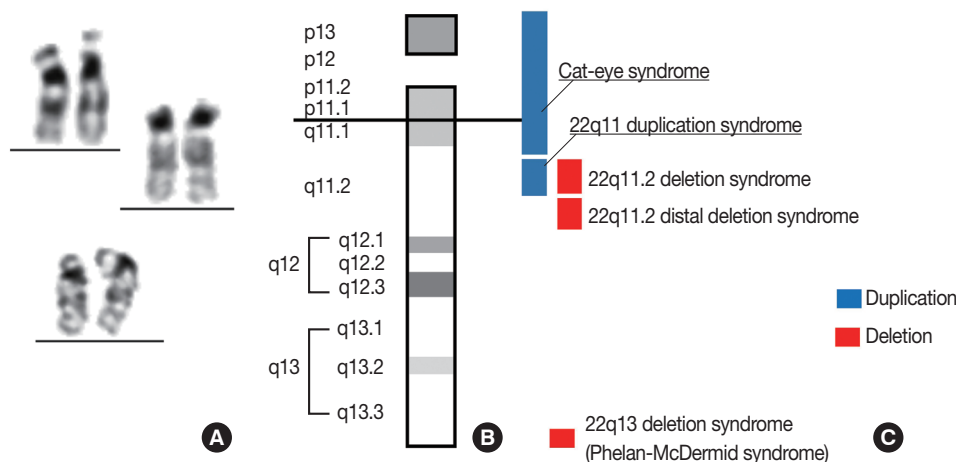


Fig. 1. (A) Cases of G-banded karyogram for normal chromosome 22 captured from constitutional chromosome study using human peripheral blood lymphocytes. (B) 550-band level ideogram of G-banding patterns for normal human chromosome 22 based on the ISCN 2020. The location and width of bands are not based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

volves 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, inguinal 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 mid-face, 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 parents with its mosaicism was possible [25,26].

Other conditions associated with deletion or duplication of chromosome 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.

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Clinical Application of ABO Genotyping: 10 Years' Experience in the Southeastern Korea

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Background: ABO typing is crucial for ensuring safe blood transfusion and is commonly performed by examining antigen-antibody interactions. Determining ABO blood group can be difficult when dealing with ABO discrepancy and ABO subgroups. ABO genotyping may be necessary to resolve ABO discrepancy. ABO genotyping primarily involves direct sequencing, with the possibility of using other molecular methods.

Methods: PCR and direct sequencing of exons 6 and 7 were performed for total 108 samples from June 2010 to December 2019. Also, other molecular methods including cloning sequencing and short tandem repeat analysis were carried out just in case. Sequencing data were compared with allele information of blood group antigen mutation databases.

Results: The predominant causal allele among 108 ABO discrepant cases was *cis-AB01*, with 28 cases. This was followed by rare ABO alleles (*B309*, *B306*, *A204*, *Bw29*, and *Ax01*) with 14 cases, and blood chimera with 5 cases. Five new alleles were identified during the investigation.

Conclusion: This study reaffirms that *cis-AB* is the most common cause of inherited ABO discrepancies, and *cis-AB01* is the most prevalent *cis-AB* allele in the Korean population, also in the southeastern region. In addition, we discovered five new alleles and five blood chimeras by adopting sequencing analysis and additional molecular techniques to resolve ABO discrepancies, which provide regional data on rare alleles. This study presents rare and new ABO alleles and blood chimeras identified over a ten-year period at two major university hospitals in Southeastern Korea.

Key words: ABO genotype, Rare allele, Novel allele, Chimerism, Sequencing

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INTRODUCTION

ABO blood group typing is a crucial test for ensuring safe transfusion and transplantation. Currently, most laboratories are conducting phenotypic tests utilizing antigen-antibody reactions. ABO phenotyping, in use for over a century, is recognized as a very accurate test with an error probability of less than 1 in 500,000 [1]. ABO phenotypic testing assesses both cell and serum typing to identify blood type, with variations in results commonly arising from many sources. ABO discrepancies between cell and serum typing in ABO phenotyping can be caused by technical reasons, alterations in antigenicity, and decreased antibody titers due to the patient's underlying disease or immune status, inappropriate transfusions, bone marrow transplantation, auto and allogeneic antibodies, acquired B, ABO variants, and other issues. Therefore, we should conduct different supplementary tests depending on the specific circumstances to address this inconsistency. Even with additional tests, there are situations where conclusive proof of the blood type is not possible. Consequently, there has been a rise in cases where ABO genotyping is used to accurately determine the blood type for safe transfusion recommendations [2-5].

ABO genotyping is more expensive than phenotype testing; the testing proce-

ture is complicated, and it requires special equipment and specialized personnel to perform, so it has been difficult to use as a routine test in general laboratories so far. However, recently there have been reports of cases where various cases of blood type and serum type discrepancies have been resolved through analysis of the ABO gene [2,6], and it is also being used effectively in the discovery of chimerism [6-10]. The ABO gene located at 9q34 of the long arm of chromosome 9 is known to express A, B type glycosyltransferase, and exons 6 and 7 account for 77.5% of the total base [11], so this area is mainly used for genotyping analysis. Methods of ABO genotyping include direct sequencing, polymerase chain reaction (PCR)-restriction fragment length polymorphism, allele-specific PCR, single-strand conformation polymorphism analysis, DNA microarray hybridization, and next-generation sequencing [12,13]. There were reviews about ABO genotyping for the Korean population, but these data were mainly from the Seoul capital area and the southwestern part of Korea [2,14-16]. We need to analyze the genotyping results from Southeastern Korea and gather information on the uncommon alleles that cause ABO discrepancies.

This study aims to present the present state of ABO genotyping by retrospectively examining the outcomes of direct sequencing and supplementary genotyping techniques conducted for cases referred for ABO genotype testing due to ABO discrepancies in the last decade.

METHODS

We conducted a retrospective analysis of ABO genotyping results on 108 samples that were requested to resolve discrep-

ancies between cell and serum type in ABO typing at two major university hospitals in Busan from June 2010 to December 2019. The study was conducted with the approval of the Institutional Bioethics Committee at Haeundae Paik Hospital under the IRB number 2020-09-008-001.

Routine phenotypic ABO blood grouping test was performed by standard methods and automated analysis using blood bank system IH-500 (Bio-rad, Cressier FR, Switzerland). DNA was extracted using the QIAamp DNA Blood Mini kit (Qiagen GmbH, Hilden, Germany), and direct sequencing was performed by amplifying exons 6 and 7 by PCR, and additional analysis was conducted using previously published primers [17] when the exact genotype was not confirmed. After PCR amplification, sequencing was conducted using the ABI3130 or 3500 genetic analyzer (Applied Biosystems, Foster City, CA, USA), and the results were interpreted by comparing the information of ABO alleles in the blood group antigen gene mutation database (dbRBC) of the National Center for Biotechnology Information (NCBI) [18], ISBT nomenclature (v.1.1), and ErythroGene (<https://www.erythroGene.com/>) [19].

If a definitive genotype was not identified by direct sequencing in existing databases, TA cloning was performed to isolate and redefine the alleles. The new alleles discovered in this study were submitted to the public nucleotide sequence repository NCBI/GenBank. When chimerism was suspected, it was decided to confirm it by short tandem repeat (STR) analysis.

RESULTS

ABO genotypes according to serologic phenotypes

The total number of specimens submitted for ABO genotyp-

Table 1. ABO genotypes according to serologic phenotypes

Phenotype	Genotype (No. of cases)	Total No. (% , N = 108)
A1Bw	<u>A102/B101</u> (9), <u>cis-AB01/O01</u> (4), <u>A102/B306</u> (3), <u>A102/B309</u> (3), <u>A102/B316</u> (3), <u>A102/Bw29</u> (2), <u>cis-AB01/O02</u> (2), <u>cis-AB01/A102</u> (1), <u>A102/B102</u> (1), <u>A102/B^{new1}</u> (1)	29 (26.85)
A2Bw	<u>cis-AB01/O02</u> (10), <u>cis-AB01/O01</u> (9), <u>A102/B101</u> (4), <u>cis-AB01/O04</u> (1), <u>cis-AB01/B101</u> (1), <u>cis-AB^{new}/O02</u> (1)	26 (24.07)
Aw	<u>A102/O01</u> (7), <u>A101/O01</u> (3), <u>A101/O02</u> (2), <u>Ax01/O01</u> (1), <u>A^{new}/O01</u> (1), <u>A^{new}/O02</u> (1), <u>A101/O01/O02</u> (1), <u>A102/O01/O02</u> (1)	17 (15.74)
Bw	<u>B101/O01</u> (7), <u>B101/O02</u> (4), <u>B309/O01</u> (2), <u>B309/B101</u> (1), <u>B^{new2}/O02</u> (1)	15 (13.89)
AwB	<u>A^{new}/B101</u> (5), <u>B101/B101</u> (2), <u>A102/B101</u> (1), <u>A102/B101/O02</u> (1)	9 (8.33)
AwBw	<u>A101/B101</u> (1), <u>A102/A102</u> (1), <u>A102/B101</u> (1), <u>A102/B101/O01</u> (2)	5 (4.63)
A2B	<u>A204/B101</u> (2), <u>A102/B101</u> (1)	3 (2.78)
A2	<u>A101/O01</u> (1), <u>A102/O01</u> (1)	2 (1.85)
A1	<u>A101/O02</u> (1)	1 (0.93)
B	<u>B101/O02</u> (1)	1 (0.93)

Underlined, causative uncommon alleles and chimerism.

ing was 108. The most prevalent ABO discrepant phenotype was A1Bw, with 29 cases (26.9%), followed by A2Bw with 26 cases (24.1%), Aw with 17 cases (15.9%), Bw with 15 cases (13.9%), AwB with 9 cases (8.3%), AwBw with 5 cases (4.6%), A2B with 3 cases (2.8%), and A2 with 2 cases (1.9%) in descending order (Table 1). Two cases, one with A1 (cell type A, serum type AB) and another with B (cell type B, serum type O), were part of the investigation, but their genotypes (*A101/O02*, *B101/O02*) were not distinct.

The two most frequently encountered phenotypes, A1Bw and A2Bw, were attributed to the presence of cis-AB alleles (*cis-AB01*, *cis-AB^{new}*) with frequencies of 24.1% (7/29) and 84.6%

(22/26), respectively. Twelve A1Bw phenotypes (41.4%, 12/29) and four Bw phenotypes were induced by rare and novel B alleles (*B306*, *B309*, *B316*, *Bw29*, *B^{new1}*, and *B^{new2}*). 17.6% of Aw and 55.5% of AwB phenotypes were attributed to rare and novel A alleles (*Ax01* and *A^{new}*) in the case of weak A. One *A204* allele was found among three A2B phenotypes and two A2 phenotypes. Blood chimerism were confirmed in 2 cases of Aw, 1 case of AwB, and 2 cases of AwBw phenotype.

Uncommon alleles leading to ABO discrepancy

The most common causative allele among 108 ABO discrepant instances was *cis-AB01*, found in 28 cases (Table 2). In this

Table 2. Uncommon alleles and combination causing ABO discrepancies

Allelic designation (dbRBC)	ISBT v.1.1	No. of cases	Nucleotide changes	Protein changes	References	Genbank Accession No.
Rare alleles						
<i>cis-AB01</i>	<i>cisAB.01</i>	28	<u>c.467C>T</u> ; <u>c.803G>C</u>	p.Pro156Leu; p.Gly268Ala		
<i>B309</i>	NA	6	<u>c.255C>T</u> ; c.297A>G; c.526C>G; c.657C>T; c.703G>A; c.796C>A; c.803G>C; c.930G>A	p.Arg176Gly; p.Gly235Ser; p.Leu266Met; p.Gly268Ala		
<i>B306</i>	<i>B3.06</i>	3	297A>G; 526C>G; 547G>A; 657C>T; 703G>A; 796C>A; 803G>C; 930G>A	p.Arg176Gly; p.Asp183Asn; p.Gly235Ser; p.Leu266Met; p.Gly268Ala		
<i>A204</i>	<i>A2.04</i>	2	c.297A>G; c.526C>G; c.657C>T; c.703G>A; c.771C>T; c.829G>A	p.Arg176Gly; p.Gly235Ser; p.Val277Met		
<i>Bw29</i>	NA	2	c.297A>G; <u>c.503G>A*</u> ; c.526C>G; c.657C>T; c.703G>A; c.796C>A; c.803G>C; c.930G>A	p.Arg168Gln*; p.Arg176Gly; p.Gly235Ser; p.Leu266Met; p.Gly268Ala		
<i>Ax01</i>	<i>AW.30.01</i>	1	<u>c.646T>A</u>	p.Phe216Ile		
New alleles						
<i>A^{new}</i>	NA*	7	<u>c.467C>T</u> ; <u>c.784G>A</u>	p.Pro156Leu; p.Asp262Asn	[20]	KU961549.2
<i>B316</i>	NA	3	c.297A>G; c.526C>G; c.657C>T; c.703G>A; <u>c.721C>G</u> ; c.796C>A; c.803G>C; c.930G>A	p.Arg176Gly; p.Gly235Ser; p.Arg241Gly; p.Leu266Met; p.Gly268Ala	[25]	KR057958.1
<i>B^{new1}</i>	NA	1	c.297A>G; c.526C>G; <u>c.538C>T</u> ; c.657C>T; c.703G>A; c.796C>A; c.803G>C; c.930G>A	p.Arg176Gly; p.Arg180Cys; p.Gly235Ser; p.Leu266Met; p.Gly268Ala	This study	KX018509.1
<i>B^{new2}</i>	<i>B3.02</i>	1	c.297A>G; c.526C>G; <u>c.646T>A</u> ; c.657C>T#; c.703G>A; c.796C>A; c.803G>C; c.930G>A	p.Arg176Gly; p.Phe216Ile; p.Gly235Ser; p.Leu266Met; p.Gly268Ala	This study	NA
<i>cis-AB^{new}</i>	NA	1	<u>c.467C>T</u> ; <u>c.803G>C</u> ; <u>c.930G>A</u> ; <u>c.1096G>A</u>	p.Pro156Leu; p.Gly268Ala	This study	KR870035.1
Blood chimerism						
<i>A102/B101/O01</i>	<i>A1.02/B.01/O.01.1</i>	2				
<i>A102/B101/O02</i>	<i>A1.02/B.01/O.01.02</i>	1				
<i>A101/O01/O02</i>	<i>A1.01/O.01.1/O.01.02</i>	1				
<i>A102/O01/O02</i>	<i>A1.02/O.01.1/O.01.02</i>	1			[6]	

NA, not applicable; Underlined, differences from common alleles (*A101*, *B101*, and *O01*); *, erroneously designated Aw.10; #, absent in ABO*B302 (dbRBC).

investigation, the unusual ABO alleles that caused ABO differences were *B309*, *B306*, *A204*, *Bw29*, and *Ax01*, listed in descending order.

Investigations of novel alleles

A novel Aw allele (*A^{new}*)

We discovered a new Aw allele in seven people. The group consists of four related family members and three unrelated people who exhibited weak A antigens with variable antigenic reactions based on antibody clones. This novel Aw allele differs from the *Aw10* (ISBT designation, *Aw.10*) allele by a single nucleotide at position 467. This A novel allele was published in an official new allele report section of Transfusion journal [20]. After publication, submitters of *Aw10* acknowledged their error of omitting the c.467C>T nucleotide alterations during registration [21–24]. Thus, this new variant is identical to the *Aw10* alleles previously identified in Korea.

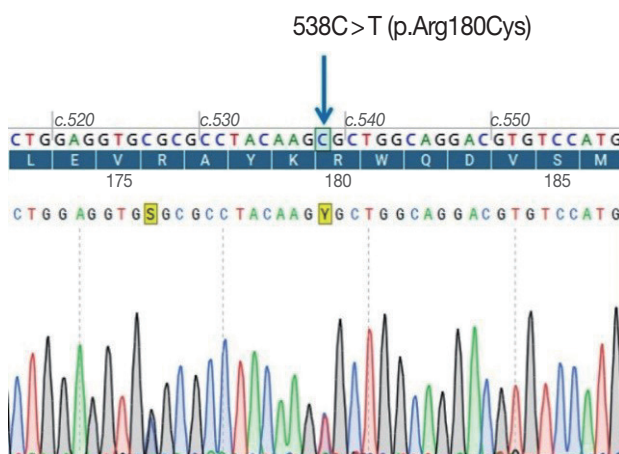


Fig. 1. Sequence analysis of a novel Bw allele (*B^{new1}*). Chromatogram of ABO gene exon 7 in an A1Bw individual with a new B allele (c.297A>G; c.526C>G; c.538C>T; c.657C>T; c.703G>A; c.796C>A; c.803G>C; c.930G>A). Blue arrows denote a different nucleotide from the common allele (*B101*).

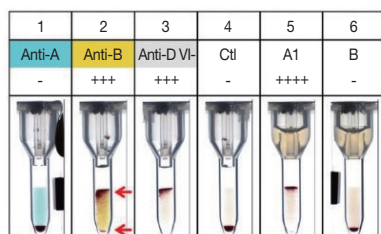


Fig. 2. Phenotype and genotype of a new B allele (*B^{new2}*). (A) Serologic ABO typing result showing Bw phenotype using micro-column agglutination (Red arrows, double cell populations with anti-B antisera). (B) Sequencing analysis of an individual with a new B allele (*B^{new2}*). Blue arrows denote sequence variations at the nucleotide 526, 646, and 657 positions.

A novel Bw allele (*B316*)

We found the novel Bw allele in a family of individuals showing mixed-field (B3 phenotype) or weak hemagglutination with anti-B reagent. Serologic tests on the proband, his wife, and two sons showed A1Bw, O, and Bw phenotypes, respectively. After separating the allele through TA cloning, this new allele that differs from the *B101* allele by a single c.721C>G missense mutation, was officially named *B316* and documented in Transfusion journal [25].

A novel Bw allele (*B^{new1}*)

A case with A1Bw demonstrating a weakened hemagglutination with anti-B reagents, was referred for further evaluation. Direct sequencing of ABO exons 6 and 7 revealed a *A102/B^{new}* genotype. This novel B allele has the mutation at position 538, where C was substituted with T, resulting in an amino acid change from arginine to cysteine. This novel B allele differs from the *B101* allele by a single nucleotide at position 538 (Fig. 1).

A novel Bw allele (*B^{new2}*)

A case was identified with Bw phenotype demonstrating mixed field agglutinations with anti-B reagents and double populations on a typing gel column (Fig. 2A). Direct sequencing of ABO exons 6 and 7 revealed an *O02/B^{new2}* genotype. This novel B allele has the mutation at position 646, where T was substituted with A, resulting in an amino acid change from phenylalanine to isoleucine in the background of *B101* allele. This new B allele differs from the *ABO*B302* registered in Genbank/dbRBC by a single nucleotide at position 657 (c.657C>T) (Fig. 2B). This new allele can be categorized into *ABO*B3.02* in ISBT designation because 657C>T is a synonymous variation.

A novel cis-AB allele (*cis-AB^{new}*)

We found a novel *cis-AB* variant allele characterized by addi-

tional 930G>A and 1096G>A polymorphisms at exon 7 on the background of *cis-AB01*. Following allele separation by TA cloning, one of the two alleles displayed a point deletion at position 261 in exon 6 and point mutations at position 297 (A>G) in exon 6 and at position 646 (T>A), 681 (G>A), 771 (C>T) and 829 (G>A) in exon 7, defining *O02* allele. The second allele displayed a distinct point mutation at positions 467, 803, 930, and 1096 in exon 7, indicating a gene fusion between A102 (467C>T) and B101 (803G>C, 930G>A, and 1096G>A) at locations 796 and 803 (Fig. 3A). The 5' sequence of the new allele starting from nucleotide 796 in exon 7 matched the A102 allele, whereas the sequence after nucleo-

tide 803 in exon 7 corresponded to the B101 allele, indicating the formation of a hybrid gene (Fig. 3B). The patient exhibited an AwBw phenotype.

Blood chimerism

A total of five cases of blood chimeras were discovered. Blood chimerism and a tri-allelic ABO genotype (*A102/O01/O02*) were identified in a subject with the Aw phenotype using TA cloning sequencing and STR analysis. This case was documented in publication [6].

Two of them were dizygotic brothers in triplets. The proband is one of the triplets and has two dizygotic twins. He did

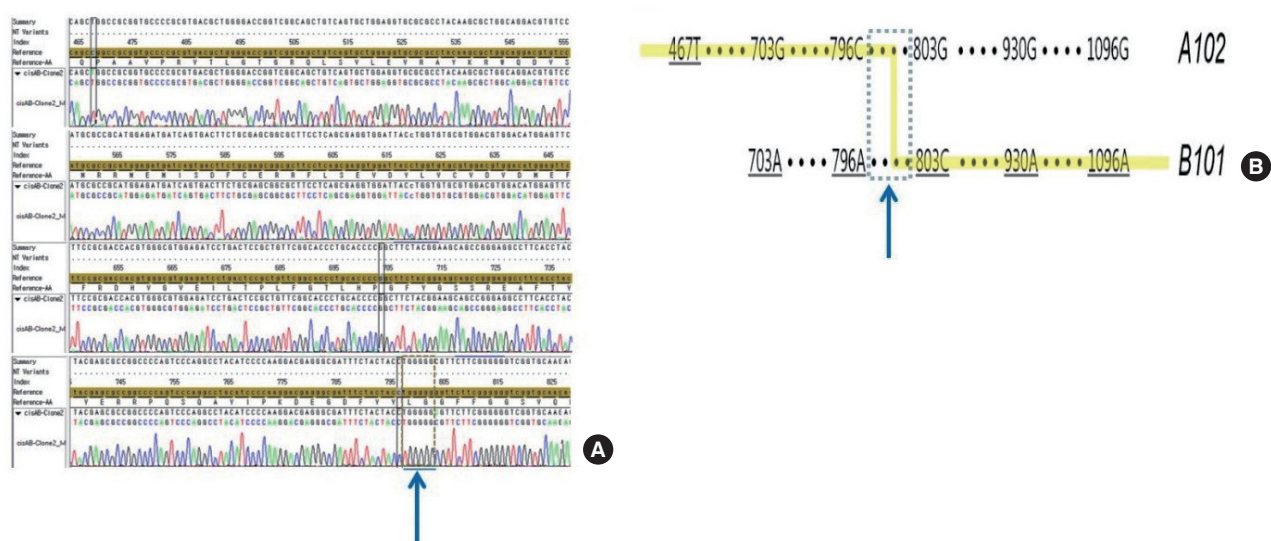


Fig. 3. A novel *cis-AB* allele (*cis-AB^{new}*). (A) Sequence analysis of a novel *cis-AB* allele (*c.467C>T*; *c.803G>C*; *c.930G>A*; *c.1096G>A*). A novel *cis-AB* allele was isolated by TA cloning. The arrow indicates the probable site of the fusion breakpoint. (B) Putative structure of the hybrid gene sequence between A102 and B101 on exon 7. The probable fusion breakpoint (arrow) is between the nucleotide positions 796 and 803. The underlined position denotes different nucleotides from the reference allele (A101).

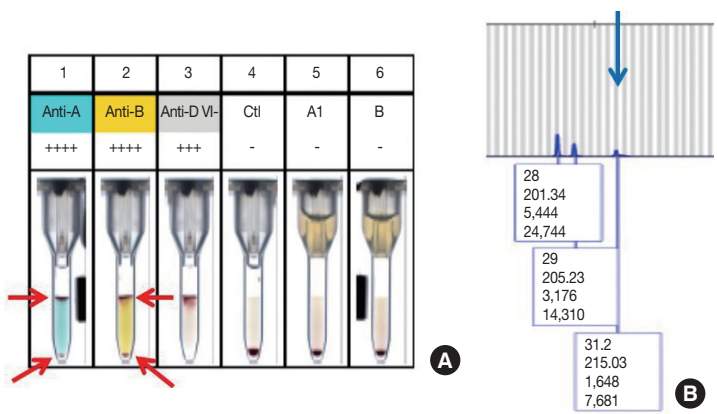


Fig. 4. Blood chimerism causing an ABO discrepancy (AwBw). (A) Serologic test using micro-column agglutination showing double cell population (red arrows). (B) STR analysis of the proband showing triple peaks (two major alleles and one minor allele (blue arrow) on D21S11).

Table 3. ABO phenotype and genotype in triplets with blood chimerism

Subject	ABO phenotype	ABO genotype		STR marker (D21S11)	
		Blood	Buccal swab	Blood	Buccal swab
Proband	AwBw	<i>A102/B101/O01</i>	<i>A102/O01</i>	28 29 31.2 chimeric	28 maternal 29 paternal
Dizygotic brother	AwBw	<i>A102/B101/O01</i>	<i>B101/O01</i>	28 29 chimeric 31.2	28 maternal 31.2 paternal
Dizygotic sister	A1	<i>A102/O01</i>	<i>A102/O01</i>	29 29	29 maternal 29 paternal

not have any history of transfusions or transplantations. The red blood cells showed double cell populations in a gel column with anti-A and anti-B, suggesting AwBw phenotype in the serologic test (Fig. 4A). In sequencing analysis, small consecutive phase-shifted peaks were shown before and after the site of the deletion (c.261delG) and we found that two major allele and one minor allele were present with polymorphisms c.467C>T, c.297A>G, c.526C>G, c.703G>A, c.796C>A, c.803G>C, c.930G>A, c.261delG. Further evaluation of chimerism, short tandem repeat (STR) analysis, cloning and sequencing analysis including blood, buccal swab samples were performed. We isolated the *A102*, *B101* and *O01* alleles, respectively, in blood sample verifying tri-allelic ABO genotype. Additionally, eleven loci (D8S1179, D21S11, D7S820, CSF1PO, TH01, D13S317, D16S539, D19S433, D18S51, D5S818, and FGA) revealed more than one additional allele in the blood sample, apart from those in the buccal swabs in STR analysis (Fig. 4B). We also carried out ABO serologic testing, ABO genotyping, and STR marker analysis in his family members. Among the triplet, identical blood chimerism was demonstrated in the patient and his dizygotic brother (Table 3). They both showed AwBw phenotype and tri-allelic ABO genotypes in the blood, *A102/B101/O01*. However, in buccal swabs analysis, the proband showed *A102/O01* and his brother showed *B101/O01*. Other members of the family (father, mother, and dizygotic sister) had regular ABO blood types in serological test, normal peaks in the STR analysis.

DISCUSSION

The implementation of ABO genotype has resolved inconsistencies in ABO phenotypic testing, leading to the identification of rare and new alleles and the verification of uncommon occurrences like chimerism. Recently, cases have been reported where the all coding sequence of the ABO gene is analyzed

through next-generation sequencing to discover new alleles and microchimerism [12], or to understand the frequency of ABO alleles [13].

In this study, the frequently referring phenotypes for ABO genotyping were A1Bw (26.9%) and A2Bw (24.1%). These two most frequently encountered phenotypes were caused by the presence of cis-AB alleles with frequencies of 24.1% and 84.6%. The cis-AB allele is the primary cause of ABO differences in Southeastern Korea, as in other regions of Korea [14,16,21,26-29].

ABO genotyping is a valuable tool in resolving ABO blood grouping discrepancies in the reference laboratory. However, it is essential to consider clinical information on individuals and regional allele data due to the complex genetic nature of the ABO gene and ambiguities related to cis/trans interactions. [11]. This study offers rare allele data for ABO genotyping on a regional level. The main causative allele responsible for ABO differences was cis-AB01, followed by rare ABO alleles including *B309*, *B306*, *A204*, *Bw29*, and *Ax01* in decreasing order of occurrence. When examining ABO genotypes, having data on rare alleles can aid in distinguishing common and rare alleles within clinical information.

Five new alleles (1 Aw variant, 3 Bw variants, and 1 cis-AB variant) were identified during the investigation. The sequence data of these new alleles were deposited in a publicly accessible database. Two of them were published in the Transfusion journal [20,25]. Before closing of NCBI/dbRBC, we designated one Bw allele as B316 from NCBI/dbRBC.

One novel cis-AB was cloned and sequenced in this study, revealing that its structure would originate from hybrid gene formation between *A102* and *B101*. The previous cis-AB alleles, including the most prevalent cis-AB01, did not originate from hybrid gene formation but from point mutations in the background of common A or B alleles. The structure of cis-AB01 (c.803G>C in the background of *A102*) is different from what

the researchers expected before the sequencing era [30].

The NCBI/dbRBC database was terminated several years ago. We believe it is crucial to provide an alternative allele database for ABO genotyping to precisely identify ABO alleles. Currently, the only database available is ISBT (v.1.1), which offers less detailed ABO allele information and is updated less frequently compared to the previous NCBI/dbRBC. ISBT designations seem to recognize nonsynonymous variations, however, it is important to also consider nucleotide alterations, such as synonymous or intronic variations, when analyzing sequencing data. For example, *B309* has one synonymous variant affecting antigenic responses, which cannot be categorized using the ISBT nomenclature system. If we do not update the database often, we will not be able to genotype recently discovered alleles. For example, *Bw29*, which were updated in the last stage of NCBI/dbRBC and the new alleles included in this study, cannot be named by ISBT nomenclature.

We require the authoritative database for ABO genotyping and the official naming organization such as IMGT/HLA for HLA polymorphisms. Meeting the criteria for official novel allele designations is advised to create a high-quality database for ABO genotyping. Initially, separate or create a clone of the novel allele from the second allele prior to sequencing to prevent confusion regarding cis/trans orientation. Secondly, thoroughly describe the sequences of a new allele, highlighting any differences from the reference allele, and then upload them to a publicly accessible database like NCBI/GenBank to offer crucial and detailed genotyping data.

During the investigation, we found five blood chimeras. Automatic blood typing analyzers have been introduced in recent years. It is commonly known to be more sensitive than the manual method, so it can be more useful to detect chimerism [31]. In our cases, we could suspect blood chimerism for the first time by the ABO discrepancy (double cell populations in cell typing), which is generated from an automated ABO phenotyping test. We could also find more than three alleles in STR analysis and confirmed blood chimerism by cloning-sequencing. Additionally, tissue chimerism can be excluded by sequencing using buccal swabs.

In conclusion, this study reaffirms that cis-AB is the most common cause of inherited ABO discrepancies, and *cis-AB01* is the most prevalent cis-AB allele in the Korean population, also in the southeastern region. In addition, we discovered five new alleles (two of them reported in the official new allele report) and five blood chimeras by adopting sequencing analysis and additional molecular techniques to resolve ABO dis-

crepancies, which provide regional rare allele data. This study presents rare and new ABO alleles and blood chimeras identified over a ten-year period at two major university hospitals in Southeastern Korea.

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CONFLICTS OF INTEREST

Not applicable.

AUTHOR CONTRIBUTIONS

Investigation: Song SA, Yu EK. Writing original draft preparation: Song SA, Oh SH. Writing review: Oh SH. Funding acquisition: Song SA. All authors have read and agreed to the published version of the manuscript.

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