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Human Gm, Km, and Am Allotypes: WHO/IMGT Nomenclature and IMGT Unique Numbering for Immunoinformatics and Therapeutical Antibodies

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Abstract: Human immunoglobulin allotypes are allelic antigenic determinants (or "markers") determined serologically, classically by hemagglutination inhibition, on the human immunoglobulin (IG) or antibody heavy and light chains. The allotypes have been identified on the gamma1, gamma2, gamma3, and alpha2 heavy chains (designated as G1m, G2m, G3m, and A2m allotypes, respectively) and on the kappa light chain (Km allotypes). Gm and Am allotypes have been one of the most powerful tools in population genetics, as they are inherited in fixed combinations, or Gm–Am haplotypes, owing to the linkage of the human IGHC genes in the IGH locus on chromosome 14. They have been very instrumental in molecular characterization of the human IGHC genes (gene polymorphisms or alleles, and IG heavy-chain structure in domains) and of the IGH locus (IGHC gene order, gene conversion, and copy number variation (CNV)). They represent a major system for understanding immunogenicity of the polymorphic IG chains in relation to amino acid and conformational changes. The WHO/IMGT allotype nomenclature and the IMGT unique numbering for constant (C) domain bridge Gm–Am and Km alleles to IGHC and IGKC gene alleles and structures and, by definition, to IG chain immunogenicity, opening the way for immunoinformatics of personalized therapeutic antibodies and engineered variants.

Keywords: ImMunoGeneTics (IMGT); immunogenetics; immunoinformatics; immunoglobulin (IG); antibody; allotype; Gm–Am haplotype; IMGT Collier de Perles; allelic polymorphism; IMGT variants

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1. Introduction

Allotypes are allelic antigenic determinants identified serologically in humans on the immunoglobulin (IG) gamma1, gamma2, gamma3, and alpha2 heavy chains (designated as G1m, G2m, G3m, and A2m allotypes, respectively) and on the IG kappa light chain (Km allotypes) [1,2]. The first allotype was identified by Grubb in 1956 [3,4], and for a period of twenty years, Gm, Am, and Km allotypes were discovered and characterized [3–29]. Currently, 26 allotypes (20 Gm, 3 Am, and 3 Km) are known. Gm and Am allotypes are inherited in fixed combinations, i.e., Gm–Am haplotypes [30–36], owing to the linkage of the corresponding encoding human IG heavy constant (IGHC) genes (IGHG3, IGHG1, IGHG2, and IGHA2, respectively, from 5′ to 3′ in the IGH locus on chromosome 14) [1,2,37]. This system is unique in its ability to characterize human populations by specific sets of haplotypes, and for years, the Gm haplotypes have been the most powerful tools for the characterization of different populations [30–36,38–71]. The Gm system is very instrumental for population genetics research, as it is highly polymorphic and unbalanced with respect to linkage. Interestingly, it is also one of the cheapest and one of the most informative systems. Vast screenings of human populations worldwide have uncovered considerable variability both in the contents of Gm haplotypes and in their frequencies, which has enabled the investigators to examine valuable data with regard to gene admixture, genogeography,

ethno-anthropology, and evolutionary and population genetics [1,2]. It is one of the most powerful tools to characterize the polymorphism between individuals [1,2]. Prior to the development of DNA fingerprinting techniques, Gm haplotypes were used for follow-up of bone marrow transplants [72], forensic medicine, and paternity testing [1,2].

Gm analysis has thrown light on the molecular characterization and evolution of the human IGHC genes [1,2,30–36,73–97], including evidence for "silent" IGHG3 on three exceptional haplotypes in seven homozygous individuals in two related Lebanese and Syrian families [31], gene conversion [84,86,87,90], gene duplications and deletions, and gene copy number variations (CNV) [81–83,86,89,91,92,94,95]. It is worthwhile to note that it is the absence of the G1m allotypes in a healthy, consanguineous Tunisian woman that led to the first description of a large deletion of 150 kilobases encompassing several IGHC genes on both chromosomes 14 and of the simultaneous and complete absence of the IgG1, IgG2, IgG4, and IgA1 subclasses in a healthy individual [81–83]. This multigene deletion contributed to the identification of the order of the human IGHC genes [81,98,99] and was the first demonstration of a CNV of the IGHC genes in humans [81–83]. Correlations between Gm and restriction fragment length polymorphism (RFLP) have been carried out for haplotypes from diverse populations [1,2,100–106].

Although allotypes are defined serologically and experimentally, they have been characterized over the years at the molecular level and most of the time by the same groups that identified them. Nowadays, Gm, Am, and Km allotypes have been correlated to amino acid changes and therefore represent a major system for understanding immunogenicity of the polymorphic IG chains. Moreover, the first complete molecular characterization of the G3m alleles, illustrated by the "IMGT G3m allele butterfly" [2] representation, has confirmed the importance of conformational configuration in the expression of allotypes. Recently, allotypes regained a lot of attention owing to the development of therapeutical monoclonal antibodies [107] and their potential immunogenicity [108,109] and to the usefulness of understanding immune responses against therapeutical antibodies of various isotypes and allotypes in different populations. In this paper, we use the standardized World Health Organization (WHO)/ImMunoGeneTics (IMGT) allotype nomenclature, based experimentally on characterized reagents, and the IMGT unique numbering for IG constant (C) domains for bridging epitope specificities of the Gm, Am, and Km allotypes to amino acid changes of the IGHC and IGKC gene alleles and structures. The information, which is already provided in the definitions of the antibodies of the WHO/International Nonproprietary Names (INN) to characterize the allotypic IG chain immunogenicity, opens the way for immunoinformatics of personalized therapeutic antibodies and engineered variants.

2. Allotype and Isoallotype

2.1. Human IG Allotype Discovery

Allotypy within IgG was first described by Grubb, who showed that certain human sera would agglutinate erythrocytes sensitized with human "incomplete" anti-Rh antibody (an "incomplete" antibody binds to erythrocytes or bacteria but does not produce agglutination) [3,4]. Polymorphism of the C region of human IG heavy gamma and alpha and of human IG light kappa chains was subsequently recognized by serological typing using the classical reaction of inhibition of hemagglutination [3–29]. Thus, by definition, an allotype is immunogenic, and the discovery of this polymorphism demonstrated that exposure of an individual to IgG or IgA of a non-self allotype can induce an anti-allotype response.

2.2. Gm, Am, and Km Allotype Definition

Allotypes of IG are unique allelic antigenic determinants (or IG "markers") recognized by specific antibodies. (In terms of immunogenicity, they represent B-cell epitopes.) Allotypes correspond to serologically detected amino acid changes that characterize the polymorphism of an IG chain within a given isotype. By definition, allotypes are shared amongst individuals within populations. Allotypes have been identified on the C region

of the human IG heavy gamma1, gamma2, gamma3, and alpha2 chains of the IgG1, IgG2, IgG3, and IgA2 subclasses, respectively, and on the C region of the human IG light kappa chains. They are designated as Gm (gamma marker), Am (alpha marker), and Km (kappa marker), with a number for the subclass: G1m, G2m, and G3m for allotypes of the gamma1, gamma2, and gamma3 chains and A2m for allotypes of the alpha2 chains [1,2].

2.3. Allotype Nomenclature

At present, 26 human allotypes are known: 20 Gm, 3 A2m, and 3 Km allotypes (Table 1) [2]. The 20 Gm allotypes comprise 18 "classical" ones found initially on the IG heavy-chain gamma1, gamma2, or gamma3 of a single subclass and 2 "surnumerary" ones, G1m27 and G1m28, so-called because they were found initially on the gamma3 chain (as classical G3m27 and G3m28) but later also found on the gamma1 chain.

Table 1. WHO/IMGT nomenclature of the Gm and Km allotypes and correspondence with previous designations [2] and this paper.

Localization [a]		**Nomenclature**		
IG Heavy Chain	**Domain**	**WHO/IMGT Nomenclature** [b]	**Previous Designation**	
H-GAMMA1	CH3	G1m1	G1m(a)	Grubb 1956 [3]; Grubb and Laurell 1956 [4]
	CH3	G1m2	G1m(x)	Harboe and Lundevall 1959 [5]
	CH1	G1m3	G1m(f)	Steinberg and Wilson 1963 [6]; Gold et al., 1965 [7,8]
	CH1	G1m17	G1m(z)	Litwin and Kunkel 1966 [9]
	CH3	G1m27 [c]		van Loghem et al., 1982 [80]
	CH3	G1m28 [c]		van Loghem et al., 1982 [80]
H-GAMMA2	CH2	G2m23	G2m(n)	Kunkel et al., 1966 [10]
H-GAMMA3	CH3	G3m5	G3m(b1)	Harboe 1959 [11]
	CH3	G3m6	G3m(c3)	Steinberg et al., 1960 [12]
	CH3	G3m10	G3m(b5)	Ropartz et al.,1963 [13]
	CH3	G3m11	G3m(b0)	Ropartz et al., 1963 [13]
	CH3	G3m13	G3m(b3)	Steinberg and Goldblum 1965 [14]
	CH3	G3m14	G3m(b4)	Steinberg and Goldblum 1965 [14]
	CH3	G3m15	G3m(s)	Martensson et al., 1966 [15]
	CH2	G3m16	G3m(t)	Martensson et al., 1966 [15]
	CH2	G3m21	G3m(g1)	Natvig 1966 [16]
	CH3	G3m24	G3m(c5)	van Loghem and Martensson 1967 [17]
	CH3	G3m26	G3m(u)	van Loghem and Grobbelaar 1971 [18]
	CH3	G3m27 [d]	G3m(v) [d]	Schanfield and Fudenberg 1974 [19]
	CH3	G3m28 [d]	G3m(g5) [d]	Blanc et al., 1976 [20]
H-ALPHA2	CH1	A2m1	A2m1	Vyas and Fudenberg 1969 [22]; Kunkel et al., 1969 [23]
	CH1	A2m2	A2m2	van Loghem et al., 1973 [24]
	CH3	A2m3 [e]		
IG light chain	Domain	WHO/IMGT nomenclature [b]	Previous designation	
L-KAPPA	C-KAPPA	Km1	Km1	Ropartz et al., 1962 [26]
	C-KAPPA	Km2	Km2	Ropartz et al., 1961 [25]
	C-KAPPA	Km3	Km3	Steinberg et al., 1962 [27]

[a] IMGT labels for chains and domains are written in capital letters (IMGT-ONTOLOGY concepts of description) [110,111]. [b] The World Health Organization (WHO) allotype nomenclature [28,29] was established in 1976 and adopted by the ImMunoGeneTics (IMGT) Lefranc's Laboratory at USJ Beirut, Lebanon [30,31]. It has been integrated in the IMGT nomenclature (IMGT-NC) [112,113] and in the IMGT Repertoire, https://www.imgt.org/IMGTrepertoire/ (accessed on 23 June 2023) > Allotypes [114] of IMGT®, the international ImMunoGeneTics information system® [115]. For the G3m, the number is based on the chronological order of their discovery. Specificities for which there are no more antisera include Gm (7, 9, 18, 19, 20, and 22), whereas Gm (8) is a marker of uncertain status. Correspondence with older designations are available in reference [33]. [c] Observed in Negroid populations and in rare, unusual haplotypes with "surnumerary" G1m27 and G1m28 in other populations [35,36,78,79,86]. G1m27 and G1m28 are detected with the same reagents as G3m27 and G3m28. [d] In Caucasoid and Mongoloid populations, Gm27 and Gm28 are on gamma3 (G3m27 and G3m28); however, in rare, unusual haplotypes, "surnumerary" Gm27 and Gm28 may be explained by the presence of G1m27 and G1m28 [35,36,78,79,86]. In Negroid populations, Gm27 can be on the gamma3 chains (G3m27), but also on the gamma1 chains (G1m27), Gm28 is always "surnumerary" and on the gamma1 chains (G1m28) [80]. [e] Identified with TOU II-5 sera (IGHA2*02 allele) [82,84,85] (van Loghem E., GL, and MPL).

The 18 "classical" Gm allotypes comprise four G1m, G1m (1, 2, 3, and 17); one G2m, G2m (23); and thirteen G3m, G3m (5, 6, 10, 11, 13, 14, 15, 16, 21, 24, 26, 27, and 28). The two "surnumerary" allotypes, G1m27 and G1m28, correspond to allotypes demonstrated to be on gamma1 chains in Negroid populations instead of being on gamma3, as expected [80]. The A2m and Km allotypes comprise A2m (1, 2, and 3) and Km (1, 2, and 3), respectively.

No allotypes have been found on the gamma4 and alpha1 chains of the IgG4 and IgA1 subclasses, respectively. Only one allotype, Em1, has been discovered on the epsilon chain of the IgE [116]. As the concentration of IgE is very low, Em1 cannot be typed using the hemagglutination inhibition method, as with the other allotypes, but instead using a radioimmunoassay with a monoclonal antibody [117]. Em1 is very common in all populations and therefore not very informative. It has not been characterized at the amino acid level and currently is not determined. Allotypic markers have not been reported for IG lambda (IGL) chains; however, there are multiple lambda chain isotypes, and the number of IGLC genes vary between individuals [37,118–121].

2.4. Allotype Determination

2.4.1. Hemagglutination Inhibition Methodology

Allotypes are determined by serological typing using a classical reaction of inhibition of hemagglutination. The methodology uses human O Rh+ erythrocytes (red blood cells) sensitized (coated) with "incomplete" anti-Rh IgG antibodies of known allotypes (e.g., G1m1) and human reagents (polyclonal IgG specific for a given allotype, e.g., anti-G1m1). The polyclonal IgG reagents are obtained from multiparous women, multiple transfused individuals, and normal blood donors. If the tested serum is G1m1-negative, the anti-G1m1 reagent binds the G1m1-positive antibodies coating the erythrocytes, and hemagglutination occurs. In contrast, if the tested serum is G1m1-positive, the anti-G1m1 reagent binds the G1m1-positive antibodies contained in the serum, and hemagglutination is inhibited. The reactions are performed with different dilutions of the reagents and of the tested sera [30,31,35,36]. The determination of some allotypes (G2m23, A2m1, and A2m2) is more delicate owing to the rarity of the reagents and, in particular, the absence of available anti-Rh antibodies for the coating. In those cases, myeloma proteins are coupled using chromic chloride [122]. It is highly recommended to provide the list and source of the anti-Rh, myeloma proteins, polyclonal IgG and eventually their dilutions, the list of tested allotypes, and the number of individuals tested for each allotype for allowing standardized result comparison.

2.4.2. Other Methodologies

To compensate for the rarity of some reagents, attempts were made to obtain monoclonal antibodies; however, the main difficulty resides in the characterization of their specificity [117,123]. Molecular biology was first used for the determination of A2m2 by RFLP [85], and this method is particularly interesting given the rarity of the reagents and was the first protocol to determine allotypes in the absence of serum (e.g., from cell lines). Polymerase chain reaction (PCR) amplification methods, using allele-specific oligonucleotides (ASO) or specific restriction sites, were subsequently developed for the determination of the Km allotypes [124] and of some Gm allotypes [109,125–128], but their application remains limited. Indeed, whereas these molecular biology methods are useful to confirm known allotypes in small samples and familial studies, they are not easily applicable in large-scale population genetics. Moreover, and by contrast to the hemagglutination inhibition methodology, they do not allow the discovery of new allotypes that by definition are characterized by their immunogenicity.

2.5. Gm (or Gm–Am) Phenotype and Genotype Deduction

Positive results (corresponding to an hemagglutination inhibition) and negative results (corresponding to an hemagglutination) obtained for the tested allotypes allow assignment of the "Gm phenotype" (or "Gm–Am phenotype" if the A2m allotypes are tested) of an

individual. In populations where the main Gm (or Gm–Am) haplotypes are already known, it is usually possible to deduce, from the phenotype, the Gm (or Gm–Am) genotype, that is, the two haplotypes that contribute to it [30–36]. However, it is not always possible to deduce the genotype. In those cases, familial studies with allotype typing of several members are needed.

2.6. Allotype Localization on Domains and Correlation with Amino Acid Changes

The localization of the allotypes has been determined by inhibition studies with Fab and Fc fragments (obtained by papain digestion) and with pF'c fragments (obtained by pepsin digestion) of Gm-positive or Gm-negative myeloma proteins [129–134]. Amino acid sequence analysis of peptides obtained from Fd (part of the heavy chain from a Fab) and from pF'c have revealed amino acid changes, allowing establishment of correlations between serologically defined allotypes and amino acid sequences. Except for G1m3 and G1m17 located on the CH1 of gamma1, all other Gm allotypes are localized on the Fc (on CH2 or on CH3) (Table 1). Thus, for example, the G3m21 allotype was detectable on the Fc fragment of gamma3 chains but not on isolated CH3 domains and therefore was localized on the CH2 [132]. G3m10, G3m11, and G3m13 were localized on the CH3 domain of the gamma3 chain [132]. G3m28 was localized on the CH3 domain of a G3m28 myeloma protein [21]. However, the first detailed correlation between G3m allotypes and amino acid changes has only been possible following the complete nucleotide sequencing of many IGHG3 alleles from individuals homozygous for well-characterized G3m alleles [88,90,97]. G3m allotypes and their localization and correspondence with G3m alleles are illustrated by the "IMGT G3m allele butterfly" representation [2].

2.7. Isoallotypes

By definition, allotypes are found on chains within one IG isotype (encoded by one given IG gene). However, the same amino acids may be found in chains of other isotypes (encoded by other IG genes) but without being polymorphic in these isotypes. If these amino acids are detected in vitro by antibody reagents, they are referred as "isoallotypes" (designated with the letter "n" preceding the allotype name, e.g., nG1m1). Seven isoallotypes have been identified for the gamma chains [135–139] and one for the alpha chains identified on the CH3 domain [140] (Table 2).

Table 2. Nomenclature and distribution of the isoallotypes [2] and this paper.

Isoallotype Nomenclature		**Distribution on IG Heavy Chains**					
WHO/IMGT	**Previous Designation**	**Gamma1**	**Gamma2**	**Gamma3**	**Gamma4**	**Alpha1**	**Alpha2**
nG1m1	nG1m(a)	allo	iso	iso	iso [a]	-	-
nG1m17	nG1m(z)	allo	-	iso	iso	-	-
nG3m5	nG3m(b1)	iso [b]	iso	allo	-	-	-
nG3m11	nG3m(b0)	iso	iso	allo	-	-	-
nG3m21	nG3m(g)	-	iso	allo	-	-	-
nG4m(a)	nG4m(a)	iso	-	iso	allo	-	-
nG4m(b)	nG4m(b)	-	iso	-	allo	-	-
nA2m3 [c]	nA2m(2)	-	-	-	-	iso	allo

"allo" indicates that the isoallotype is antithetical to the corresponding allotype (or for gamma4 to the other isoallotype). [a] Isoallotype nG1m1 only detected by some antisera on gamma4. [b] In Negroid populations, the G1m28 allotype can be expressed instead of nG3m5. [c] nA2m3 has been renamed in the WHO/IMGT nomenclature, as this isoallotype is located on the CH3 domain, and is antithetical to the A2m3 allele. (It is not antithetical to A2m2 located on the CH1.) (With permission from M-P. Lefranc and G. Lefranc, LIGM, Founders and Authors of IMGT®, the international ImMunoGeneTics information system®, https://www.imgt.org (accessed on 29 May 2023).)

As isoallotypes are present in several subclasses, typing of isoallotypes can only be performed on isolated proteins. This is the case for example of the nG4m(a) and nG4m(b) isoallotypes.

2.8. Protein Displays and IMGT Colliers de Perles

Protein displays are standardized IMGT representations of the amino acid sequences of the coding regions of the genes [37,114]. Protein displays of C domains show the sequences per domain, using the IMGT unique numbering for C domain [141]. They allow a standardized localization of the amino acids involved in the allotypes in relation to the strands and loops of the domains. Figure 1 provides the protein displays of the C domains (CH1, CH2, and CH3) of the IGHG and IGHA genes [114]. Only the first allele is shown. Other alleles are available in IMGT/DomainDisplay [114,115] and from IMGT/GENE-DB [142], IMGT/2Dstructure-DB, and IMGT/3Dstructure-DB [143,144]. IMGT/DomainGapAlign [144] allows gaps to be inserted in C domains of the IGHG, IGHA, and IGKC genes according to the IMGT unique numbering [141].

Correspondences with the exon numbering and the Eu and Kabat numberings are available in the IMGT Scientific chart for *Homo sapiens* IGHC (https://www.imgt.org/IMGTScientificChart/Numbering/Hu_IGHGnber.html (accessed on 23 June 2023)) (Supplementary Table S1) and IGKC (https://www.imgt.org/IMGTScientificChart/Numbering/Hu_IGKCnber.html (accessed on 23 June 2023)) (Supplementary Table S2). Standardized representations or IMGT Colliers de Perles of the C domains can be obtained using the IMGT/Collier-de-Perles tool [114,145,146]. Amino acid properties of the allotype amino acids displayed in IMGT Collier de Perles are according to the IMGT 'Physicochemical' classes of the 20 common amino acids properties [147] (https://www.imgt.org/IMGTeducation/Aide-memoire/_UK/aminoacids/IMGTclasses.html (accessed on 23 June 2023)) (Supplementary Table S3). Protein displays for *Homo sapiens* IGHC are available in IMGT Repertoire (Supplementary Tables S4 and S5).

2.9. IMGT Correspondence between "Gm, Am, or Km Allele" and "Gene Allele"

G3m, A2m, and Km alleles are defined by the amino acid changes that characterize an allotype or the combination of allotypes identified serologically on a given chain ([2] and in this paper, in the sections below). As the amino acid sequences of the constant region of the IG gamma1, gamma2, gamma3, alpha2, and kappa chains are encoded, respectively, by the IGHG1, IGHG2, IGHG3, IGHA2, and IGKC genes, a correspondence can be established between Gm, Am, or Km alleles and the alleles of a gene (or "gene alleles" or "alleles"). Gene alleles are part of the concepts of classification of IMGT-ONTOLOGY [110,111]. They correspond to polymorphic variants of a gene that differ by at least one nucleotide in their coding region [37]. They include the IMGT gene symbol with an asterisk, followed by a number starting from *01, e.g., IGHG1*01, IGHG1*02, etc. Gene alleles are available from IMGT/GENE-DB [142] and in IMGT Repertoire (https://www.imgt.org/IMGTrepertoire/ (accessed on 23 June 2023) > Alignments of alleles [114]). As gene alleles are identified at the nucleotide level, the same amino acid sequence may be encoded by different alleles.

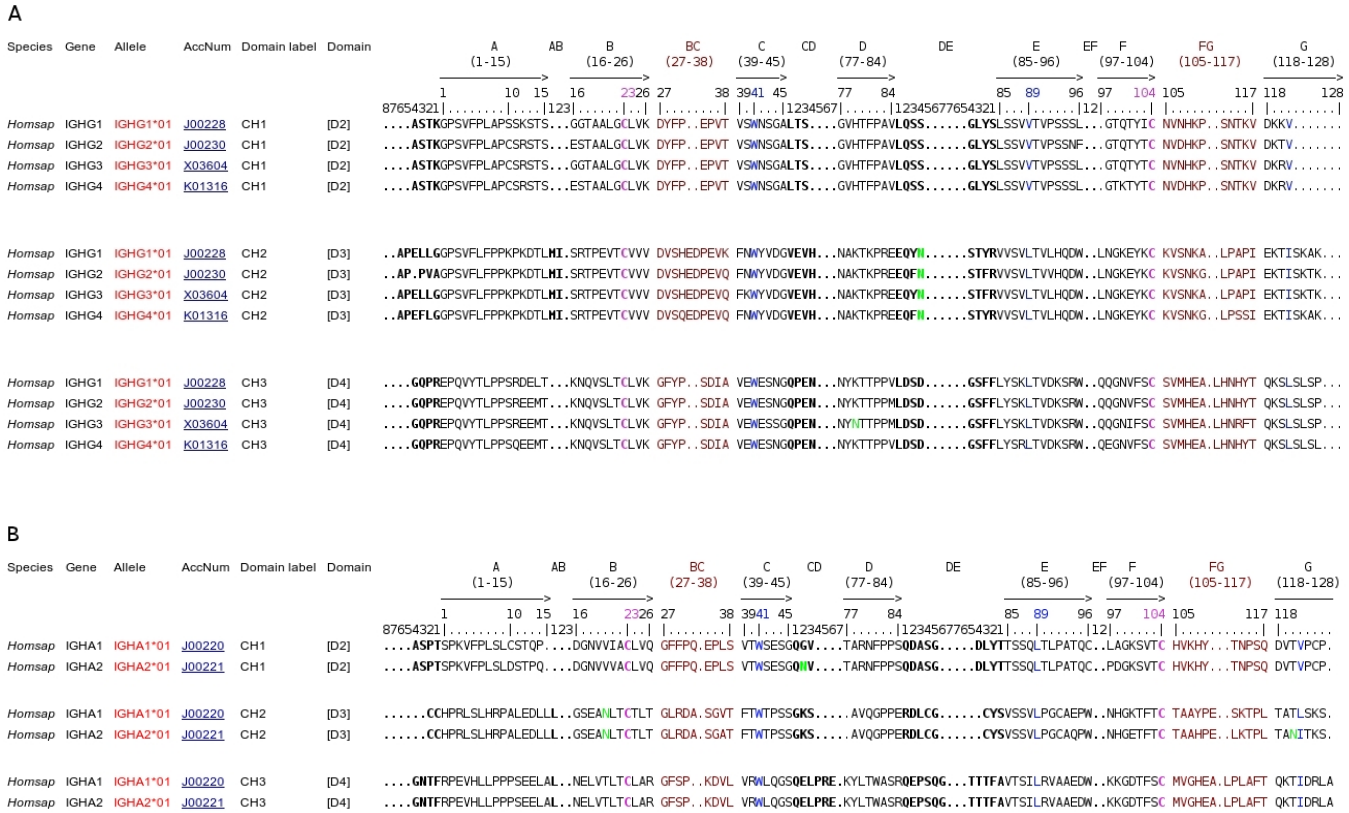

Figure 1. Protein display of the human IGHG and IGHA constant (C) domains [2] and this paper. (**A**) Human IGHG CH domains. (**B**) Human IGHA CH domains. Only allele *01 is shown. Other alleles are available in IMGT Repertoire, https://www.imgt.org/IMGTrepertoire/ (accessed on 23 June 2023) > Alignments of alleles [114]. The alignments are based on the IMGT unique numbering for C domain [141]. Hinge and CHS regions are not shown. Domains are numbered with [D1] being the variable domain (not shown). The four conserved amino acid positions of the C domain are colored: C23 (1st-CYS) and C104 (2nd-CYS) of the disulfide bridge are in pink; CONSERVED-TRP W41 and hydrophobic L89 are in blue [141]. Asparagine (N) of the N-glycosylation site of the motif N-X-S/T (where X is any amino acid except proline, S is serine, and T is threonine) are in green. There is a unique site in each of the four IGHG: CH2 N84.4 (**A**); one site in IGHA1: CH2 N20; and three sites in IGHA2: CH1 N45.2, CH2 N20, and N120) (**B**). BC and FG loops colored in brown correspond to the CDR1-IMGT and CDR3-IMGT, respectively, of a V-domain. The CD transversal strand of the C-domain replaces the C′ strand, C′C″ loop, or CDR2-IMGT and C″ strand of a V-domain [141]. Single-letter code amino acids in bold indicate additional positions in the C-domain compared to the V-domain. Dots indicate positions occupied in other C-domain sequences according to the IMGT unique numbering for C-domain [141]. (With permission from M-P. Lefranc and G. Lefranc, LIGM, Founders and Authors of IMGT®, the international ImMunoGeneTics information system®, https://www.imgt.org (accessed on 29 May 2023)).

3. G1m Allotypes and nG1m Isoallotypes

G1m allotypes and nG1m isoallotypes are shown in Table 3 and are described in the following subsections.

Table 3. G1m allotypes and nG1m1 isoallotypes [2] and this paper.

G1m Allotypes and Isoallotypes	Amino Acid Positions [a]							
	Domain	**CH1**	**CH3** [b]					
	IMGT	**120**	**12**	**14**	**101**	**110**	**115**	**116**
	Eu	***214***	***356***	***358***		***431***		
G1m1			Asp D12	Leu L14				
nG1m1			Glu E12	Met M14				
G1m2						Gly G110		
G1m3		Arg R120 + Ileu I103						
G1m17		Lys K120						
nG1m17		Arg R120						
G1m27 [b]					Ileu 101			
G1m28 [b]							Arg R115	Tyr Y116

[a] Positions in bold are according to the IMGT unique numbering for C domain [141] and in italics Eu numbering. [b] G1m27 and G1m28 have been found in Negroid populations [80]. G1m27 most probably corresponds to IGHG1 CH3 Ileu I101 and G1m28 to IGHG1 CH3 Arg R115, Tyr Y116. (With permission from M-P. Lefranc and G. Lefranc, LIGM, Founders and Authors of IMGT®, the international ImMunoGeneTics information system®, https://www.imgt.org (accessed on 29 May 2023)).

3.1. G1m1 Allotype and nG1m1 Isoallotype

G1m1 (previously G1m(a)) was the first discovered allotype [3]. In 1956, Grubb noticed that 60% of normal human sera could inhibit the agglutination of human O Rh+ erythrocytes sensitized by means of certain "incomplete" anti-Rh sera, and the factor responsible for the inhibition was called Gm(a) (now G1m1 allotype). Grubb and Laurel demonstrated that Gm(a) was transmitted as a dominant autosomal Mendelian trait [4].

By inhibition studies with IgG1 fragments, it was established that G1m1 is located on the CH3 domain and was associated with aspartate (D) 356 and leucine (L) 358 (Eu numbering) [129]. According to the IMGT unique numbering for C domain [141], the G1m1 allotype corresponds to IGHG1 CH3 Asp D12 and Leu L14 (Table 3) (Figures 2 and 3).

In the G1m1-negative gamma1 chains and in the gamma chains of the other IgG subclasses, glutamate (E) and methionine (M) are found, respectively, at positions 12 and 14 of the CH3 domain [134]. These amino acid changes can be determined, by specific antisera, on the G1m1-negative gamma1, gamma2, and gamma3 chains (Table 2). This epitope corresponds to the isoallotype nG1m1. The gamma4 chains also express CH3 E12 and M14, but the corresponding epitope is only detected by certain antisera [148]. This restricted accessibility of the nG1m1 epitope of the gamma4 chains has been correlated with the presence, at position 11 of CH3, of a glutamine (Q) instead of an arginine (R), as found in the other subclasses [37] (Figure 1A). In old world monkeys (OWM) [149], the IGHG1 CH3 sequence contains E12 and L14, and it has therefore be postulated that two independent single amino acid changes may have led to the G1m1 allotype (CH3 E12 > D) and to the nG1m1 isoallotype (CH3 L14 > M).

3.2. G1m2 Allotype

The G1m2 allotype was discovered in 1959 by Harboe and Lundevall [5]. The G1m2 allotype was detected on the CH3 domain [132]. It corresponds to a glycine at position 110 (IGHG1 CH3 Gly G110), whereas the absence of the allotype correlates to alanine at that position [150]. Alanine is present at position 110 of CH3 in G1m2-negative gamma1 chains and in the gamma chains of the other IgG subclasses (Figure 1A); however, CH3 Ala A110 is not an isoallotype, as no antibody reagent has been characterized (Table 3) (Figures 2 and 3).

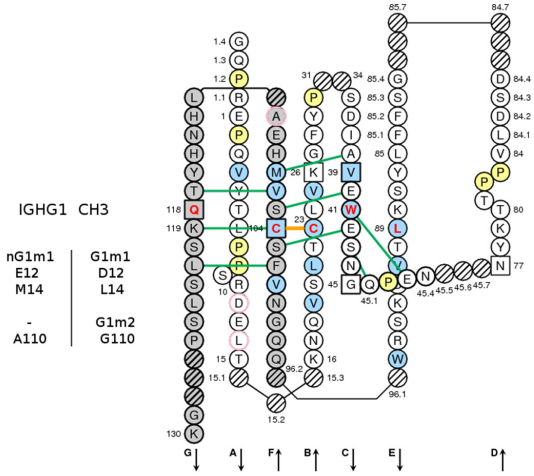

Figure 2. IMGT Collier de Perles of the IGHG1 CH3 domain [2] and this paper. The CH3 domain is from the b12 antibody (IMGT/3Dstructure-DB [143,144], code PDB:1hz). The IMGT Collier de Perles [114,145,146] is shown on two layers, with hydrogen bonds shown as green lines. Hatched positions correspond to gaps according to the IMGT unique numbering for C domain [141]. The disulfide bridge between C23 (1st-CYS) and C104 (2nd-CYS) is indicated by an orange line. The aspartate D12 and leucine L14 (strand A) correspond to G1m1, whereas glutamate E12 and methionine M14 (not shown) correspond to nG1m1. In G1m2-negative chain, as that of b12, there is an alanine at position 110. A glycine at position 110 would correspond to G1m2. The amino acids glycine (G) and lysine (K) at positions 129 and 130 represent the CHS in secreted IG. (With permission from M-P. Lefranc and G. Lefranc, LIGM, Founders and Authors of IMGT®, the international ImMunoGeneTics information system®, https://www.imgt.org (accessed on 29 May 2023).)

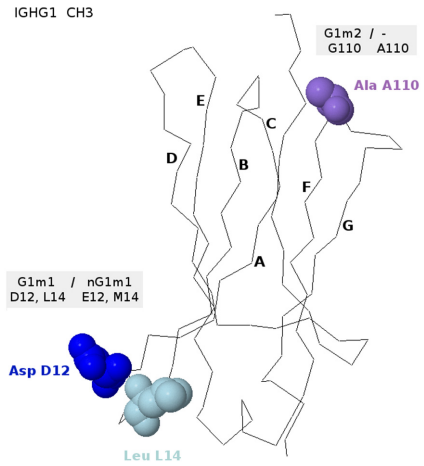

Figure 3. Three-dimensional structure of the IGHG1 CH3 domain [2] and this paper. The CH3 domain is from the b12 antibody (IMGT/3Dstructure-DB [143,144], code PDB:1hzh). The seven anti-parallel strands of the CH3 (C-domain) are indicated by the letters A to G. Positions 12 and 14 of the G1m1/nG1m1 allotype, and position 110 of the G1m2/− allotype in the IGHG1 CH3 domain are shown. The aspartate D12 and leucine L14 correspond to G1m1, whereas alanine A110 corresponds to nG1m2. Glutamate E12 and methionine M14 correspond to nG1m1, whereas a glycine G110 corresponds to G1m2. (With permission from M-P. Lefranc and G. Lefranc, LIGM, Founders and Authors of IMGT®, the international ImMunoGeneTics information system®, https://www.imgt.org (accessed on 29 May 2023).)

3.3. G1m3 and G1m17 Allotypes and nG1m17 Isoallotype

G1m3 was first identified by Steinberg and Wilson in 1963 [6] and then further characterized by Gold et al. [7,8]. G1m3, located on the CH1 domain, corresponds to an arginine at position 120 (IGHG1 CH1 Arg R120) [130] (Figures 4 and 5).

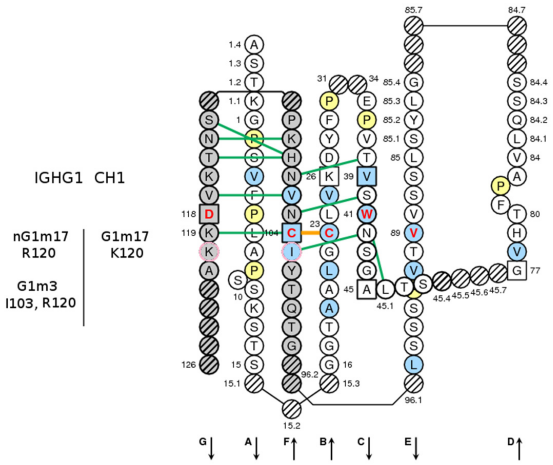

Figure 4. IMGT Collier de Perles of the IGHG1 CH1 domain [2] and this paper. The CH1 domain is from the b12 antibody (IMGT/3Dstructure-DB [143,144], code PDB:1hzh). The IMGT Collier de Perles [114,145,146] is shown on two layers, with hydrogen bonds shown as green lines. Hatched positions correspond to gaps according to the IMGT unique numbering for C domain [141]. The disulfide bridge between C23 (1st-CYS) and C104 (2nd-CYS) is indicated by an orange line. The lysine at position 120 (K120) corresponds to the G1m17 allotype. The isoleucine I103 is specific for the gamma1 chain isotype. If an arginine is expressed at position 120 (R120), the simultaneous presence of R120 and I103 corresponds to the expression of the G1m3 allotype. (With permission from M-P. Lefranc and G. Lefranc, LIGM, Founders and Authors of IMGT®, the international ImMunoGeneTics information system®, https://www.imgt.org (accessed on 29 May 2023).)

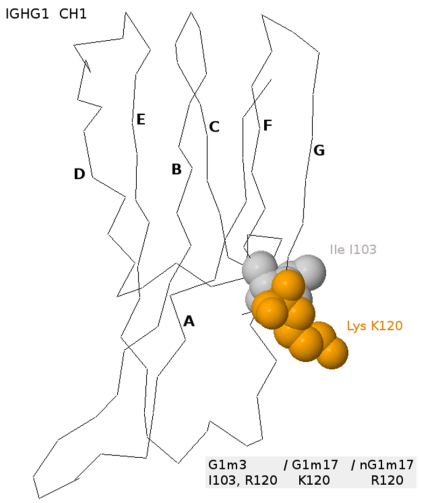

Figure 5. Three-dimensional structure of the IGHG1 CH1 domain [2] and this paper. The CH1 domain is from the b12 antibody (IMGT/3Dstructure-DB [143,144], code PDB:1hzh). The seven anti-parallel strands of the CH1 (C-domain) are indicated by the letters A to G. The lysine K120 (strand G) and the isoleucine I103 (strand F) are shown. The K120 corresponds to the G1m17 allotype. The simultaneous presence of I103 (specific of the gamma1 isotype) and of arginine R120 corresponds to the G1m3 allotype. The R120 corresponds to the nG1m17 isoallotype. (With permission from M-P. Lefranc and G. Lefranc, LIGM, Founders and Authors of IMGT®, the international ImMunoGeneTics information system®, https://www.imgt.org (accessed on 29 May 2023).)

The expression of G1m3 requires the presence of an amino acid specific for gamma1 because the CH1 Arg R120 is also present on the gamma3 and gamma4 chains (Figure 1A). It seems likely from the analysis of 3D structures of Fab and of the b12 antibody, which is the only complete human IG thus far crystallized (IMGT/3Dstructure-DB, code PDB:1hzh) [143,144], that the isoleucine at position 103 (IGHG1 CH1 Ile I103) is the amino acid involved in the expression of the G1m3 allotype (Figures 4 and 5). The presence of CH1 Ala A121 (IMGT numbering) in the 3D structure is a file error in PDB. It should be a valine (V), as in the b12 Fab (IMGT/3Dstructure-DB code PDB:1n0x_H. The sequence of the C region of the b12 heavy gamma1 chain (1hzh_H) should be IGHG1*01 100% in its entirety (IMGT/3Dstructure-DB entry card for 1hzh) [143,144].

G1m17 [9], located in the CH1 domain, corresponds to lysine at position 120 (IGHG1 CH1 Lys K120) [130]. G1m17 is mutually exclusive with ("antithetical to") G1m3 and is present on gamma1 chains that are G1m3-negative.

The isoallotype nG1m17 corresponds to arginine at position 120 in the CH1 (IGHG1 CH1 Arg R120). It is detectable on isolated gamma3 and gamma4 chains where R120 is present but without the gamma1-specific determinant CH1 Ileu I103. (Threonine T103 is found instead in the other subclasses; Figure 1A.)

3.4. G1m27 and G1m28 Allotypes

G1m27 and G1m28 have only been demonstrated to be present on the gamma1 chains in Negroid populations [80]; however, it is not excluded that these "surnumerary" allotypes may explain some uncommon haplotypes found in other populations [35,36,78,79,86]. G1m27 most probably corresponds to IGHG1 CH3 Ileu I101 (resulting from an amino acid change V101 > I) and G1m28 to IGHG1 CH3 Arg R115, Tyr Y116 (with an amino acid change H115 > R compared to the usual IGHG1 nG3m5).

3.5. IMGT Correspondence between G1m Alleles and IGHG1 Alleles

The heavy gamma1 chains of IgG1 may express four typical G1m alleles (combinations of G1m allotypes): G1m3; G1m3,1; G1m17,1; and G1m17,1,2 (and three additional G1m alleles: Gm17,1,27; Gm17,1,28; and Gm17,1,27,28, with the last two identified in Negroid populations [80]). The C region of the G1m3,1; G1m17,1; and G1m17,1,2 chains differs from that of the G1m3 chains by two, three, and four amino acids, respectively. The structural correlations with amino acids are illustrated in Figure 6.

The correspondence between the G1m alleles and IGHG1 alleles is shown in Table 4. IGHG1*07 and IGHG1*08, which were previously expected based on allotype determination (GL and MPL) [2], have been confirmed by nucleotide sequencing and added in IMGT Repertoire Alignments of alleles.

Thus, IGHG1*01 and IGHG1*02 are G1m17,1; IGHG1*03 is G1m3; IGHG1*04, IGHG1*05, and IGHG1*06 are G1m17,1,27, G1m17,1,28, and G1m17,1,27,28, respectively; IGHG1*07 is G1m17,1,2; and IGHG1*08 is G1m3,1. In Table 4, amino acids corresponding to G1m allotypes are shown in bold. The nG1m1 and nG1m17 isoallotypes present on the Gm1-negative and Gm-17 negative gamma-1 chains (and on other gamma chains, Table 2) are shown in italics. Correspondence between C numberings is available in IMGT Scientific chart [114] (Supplementary Table S1). "Alignments of alleles of *Homo sapiens* IGHG1" is available in IMGT Repertoire [114] (Supplementary Table S6).

In the G1m1-negative gamma1 chains and in the gamma chains of the other IgG subclasses, glutamate (E) and methionine (M) are found, respectively, at positions 12 and 14 of the CH3 domain [129]. These amino acid changes can be determined, by specific antisera, on the G1m1-negative gamma1, gamma2, and gamma3 chains (Table 2). This epitope corresponds to the isoallotype nG1m1. The gamma4 chains also express CH3 E12 and M14, but the corresponding epitope is only detected by certain antisera [148]. This restricted accessibility of the nG1m1 epitope of the gamma4 chains has been correlated with the presence, at position 11 of CH3, of a glutamine (Q) instead of an arginine (R), as found in the other subclasses [37] (Figure 1A). In old world monkeys (OWM) [149], the

IGHG1 CH3 sequence contains E12 and L14, and it has therefore be postulated that two independent single amino acid changes may have led to the G1m1 allotype (CH3 E12 > D) and to the nG1m1 isoallotype (CH3 L14 > M).

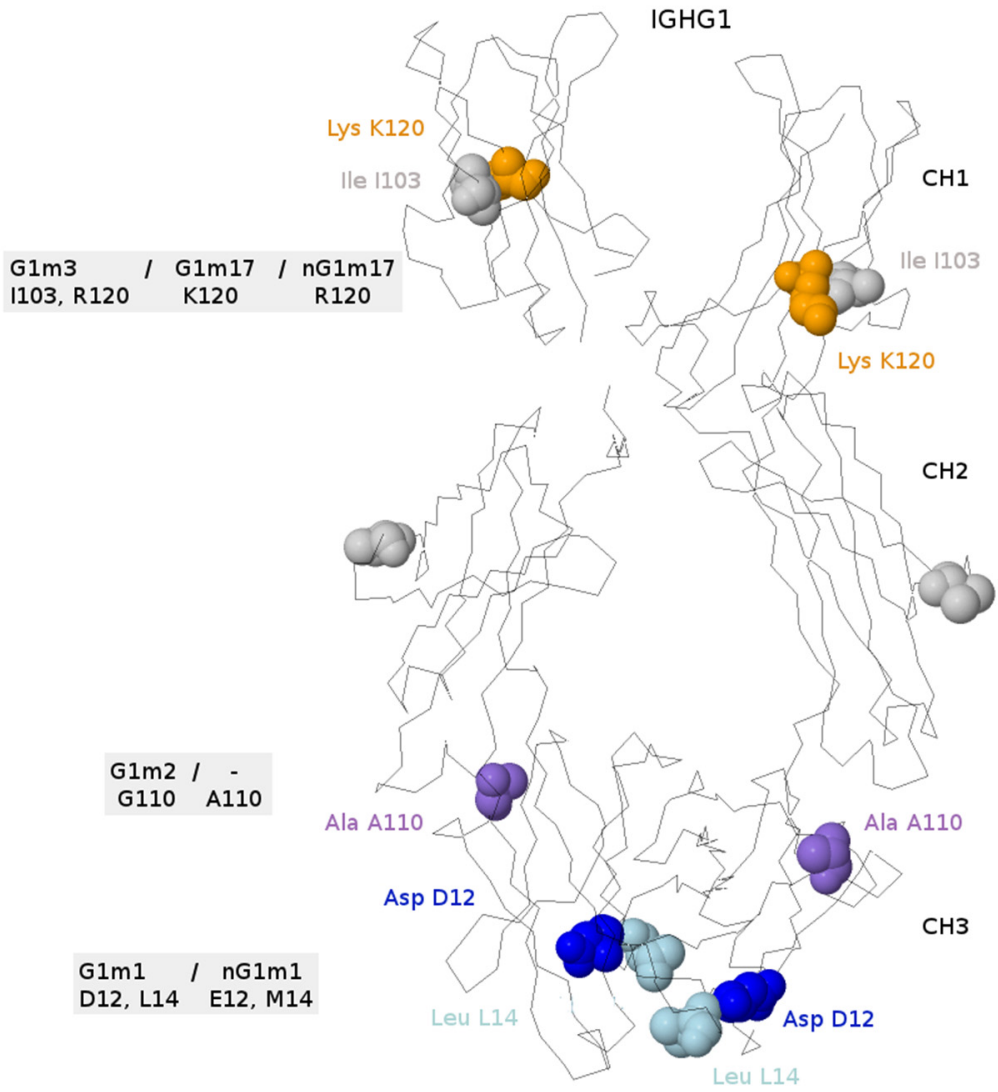

Figure 6. G1m allotypes localizations on gamma1 chains [2] and this paper. The CH1, CH2, and CH3 domains of the b12 gamma1 chains are shown (IMGT/3Dstructure-DB [143,144], code PDB:1hzh) with the positions involved in the G1m allotypes. The CH2 position 45.1 is not related to the G1m allotypes but indicates the amino acid position that should be responsible for the G2m23 allotype, or for its absence (G2m..), on a gamma2 chain. (With permission from M-P. Lefranc and G. Lefranc, LIGM, Founders and Authors of IMGT®, the international ImMunoGeneTics information system®, https://www.imgt.org (accessed on 29 May 2023).)

Table 4. IMGT correspondence between the G1m alleles and IGHG1 alleles [2] and this paper.

G1m Alleles [b]	IGHG1 Alleles	Amino Acid Positions [a]					
		Domain	**CH1**			**CH3**	
		IMGT 103	**120**	**12**	**14**	**101**	**110**
		Exon (82)	**(97)**	**(16)**	**(18)**		**(91)**
		Eu *199*	***214***	***356***	***358***		***431***
			G1m17/ nG1m17 [c]	**G1m1/nG1m1**		**G1m27/-**	**G1m2/-**
			G1m3 [c]				
G1m17,1	IGHG1*01, IGHG1*02	Ile I103 atc	**Lys K120 aaa**	**Asp D12 gat**	**Leu L14 ctg**	Val 101 gtc	Ala A110 gct
G1m3 *nG1m1, nG1m17*	IGHG1*03	**Ile I103** atc	**Arg R120** aga	Glu E gag	Met M atg	Val 101 gtc	Ala A110 gct
G1m17,1,27	IGHG1*04	Ile I103 atc	**Lys K120** aaa	**Asp D12** gat	**Leu L14** ctg	**Ile I101** atc	Ala A110 gct
G1m17,1,2	IGHG1*07	Ile I103 atc	**Lys K120** aaa	**Asp D12** gat	**Leu L14** ctg	Val 101 gtc	**Gly G110** ggt
G1m3,1 *nG1m17*	IGHG1*08	**Ile I103** atc	**Arg R120** aga	**Asp D2** gat	**Leu L14** ctg	Val 101 gtc	Ala A110 gct
G1m17,1,28 [b]	IGHG1*05p [c]	Ile I103 (atc)	**Lys K120** (aaa)	**Asp D12** (gat)	**Leu L14** (ctg)	Val 101 (gtc)	Ala A110 (gct)
G1m17,1,27,28 [b]	IGHG1*06p [c]	Ile I103 (atc)	**Lys K120** (aaa)	**Asp D12** (gat)	**Leu L14** (ctg)	**Ileu I101** (atc)	Ala A110 (gct)
G1m17 *nG1m1*	IGHG1*09p [c]	Ile I103 (atc)	**Lys K120** (aaa)	Glu E (gag)	Met M (atg)	Val 101 (gtc)	Ala A110 (gct)

[a] Positions in bold are according to the IMGT unique numbering for C domain [141]; between parentheses, exon numbering [37]; in italics, Eu numbering. [b] In Negroid populations, the G1m17,1 allele frequently includes G1m27 and G1m28, leading to new G1m alleles, G1m17,1,28 and G1m17,1,27,28, as demonstrated serologically [80]. They were assigned to IGHG1*05p and IGHG1*06p, respectively, following the sequencing of IGHG1*04. IGHG1*05p and IGHG1*06p amino acids and codons between parentheses are expected (GL and MPL) [37]. Amino acid changes and codons for G1m28 (most probably CH3 Arg R115, Tyr Y116) are not shown in the table. [c] The letter "p" indicates that these alleles have not yet been sequenced at the nucleotide level and therefore are not shown in IMGT Repertoire. (IG and TR) > Alignments of alleles. [c] The presence of R120 is detected by anti-nG1m17 antibodies, whereas the simultaneous presence of I103 and R120 in the gamma1 chains is detected by anti-Gm3 antibodies. Mutated nucleotides between codons are undelined. Colors highlight the amino acids involved in the allotype or isoallotype: pale blue (G1m17), dark blue (G1m3), yellow (G1m1), pale yellow (nG1m1), green (G1m27), and violet (G1m2). (With permission from M-P. Lefranc and G. Lefranc, LIGM, Founders and Authors of IMGT®, the international ImMunoGeneTics information system®, https://www.imgt.org (accessed on 29 May 2023).)

4. G2m Allotype

4.1. G2m23 Allotype

G2m23 [10] is the only allotype shown on the IgG2 heavy chains, and the gamma2 chains are either G2m23 or G2m.. (Two dots indicate that a specimen was tested and found to be negative for G2m23 [31,35,36]). G2m23 [10] was detected by using an antiserum produced in a nonhuman primate. Since then, no polyclonal human anti-G2m23 has been found [117].

G2m23 is localized on the CH2 domain (detectable on the Fc of G2m23 myeloma proteins but not on isolated CH3 domains) [132]. Amino acid sequence and 3D structure comparisons show that the G2m23 allotype is correlated with methionine 45.1 (".1" for first position in the transverse CD strand [141]) in the CH2 (IGHG2 CH2 Met M45.1), whereas the absence of the allotype (G2m..) is correlated with valine 45.1 (IGHG2 CH2 Val V45.1) [37] (Figure 7).

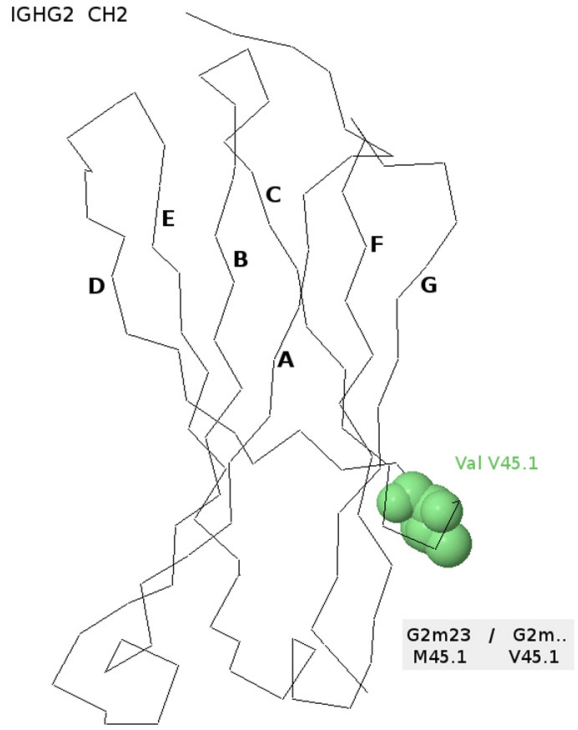

Figure 7. Three-dimensional structure of the IGHG2 CH2 domain [2] and this paper. The CH2 domain was superimposed with the CH2 of the b12 gamma1 chains (IMGT/3Dstructure-DB [143,144], code PDB:1hzh) for this schematic representation and an easier comparison. The seven anti-parallel strands of the CH2 (C-domain) are indicated by the letters A to G. Position 45.1 (first position of the transversal CD strand) corresponds to the G2m23/G2m.. allotype. Valine V45.1 corresponds to G2m.., whereas a methionine corresponds to G2m23. (With permission from M-P. Lefranc and G. Lefranc, LIGM, Founders and Authors of IMGT®, the international ImMunoGeneTics information system®, https://www.imgt.org (accessed on 29 May 2023).)

The G2m23-positive gamma2 chains are also characterized by the presence of threonine 92 in the CH1 domain (IGHG2 CH1 Thr T92) [37]. In contrast, the G2m23-negative chains and the gamma chains of other IgG subclasses have proline 92 in the CH1 domain (IGHG2 CH1 Pro P92) [37] (Figure 1A). Being located on the CH1 domain, this amino acid change is not involved in the expression of the G2m23 allotype, but owing to the strong linkage on the same chain, the CH1 Thr T92 codon has been used for the molecular characterization of the G2m23 chains [128].

4.2. IMGT Correspondence between the G2m Alleles and IGHG2 Alleles

The G2m alleles are characterized by the presence or absence of the G2m23 allotype. Only the IGHG2*02 allele is G2m23. The other alleles, namely IGHG1*01, IGHG2*03, IGHG2*04, IGHG2*05, and IGHG2*06, are G2m23-negative (or G2m..) (Table 5).

Table 5. IMGT correspondence between the G2m alleles and IGHG2 alleles [2] and this paper.

G2m Alleles	IGHG2 Alleles	Amino Acid Position [a]	
		Domain	**CH2**
		IMGT	**45.1**
		Exon	**(52)**
		Eu	***282***
			G2m23/G2m..
G2m23	IGHG2*02		**Met M45.1** atg
G2m..	IGHG2*01, IGHG2*03, IGHG2*04, IGHG2*05, IGHG2*06		Val V45.1 gtg

[a] Positions in bold are according to the IMGT unique numbering for C domain [141]; between parentheses, exon numbering [37]; in italics, Eu numbering. Mutated nucleotides between codons are underlined. (With permission from M-P. Lefranc and G. Lefranc, LIGM, Founders and Authors of IMGT®, the international ImMunoGeneTics information system®, https://www.imgt.org (accessed on 29 May 2023).)

A G2m23-positive serum can be from a homozygous individual G2m23/G2m23 or from a heterozygous individual G2m23/G2m.. Because there is no antiserum to detect G2m.., the hemagglutination inhibition method cannot distinguish between sera from homozygotes or from heterozygotes. Correspondence between C numberings is available in IMGT Scientific chart [114] (Supplementary Table S1). "Alignments of alleles of *Homo sapiens* IGHG2" is available in IMGT Repertoire [114] (Supplementary Table S7).

5. G3m Allotypes and nG3m

5.1. G3m Allotypes and IGHG3 Sequences

The G3m allotypes make the gamma3 chain the most polymorphic IG chains in humans. Thirteen G3m allotypes are characterized: G3m5, G3m6, G3m10, G3m11, G3m13, G3m14, G3m15, G3m16, G3m21, G3m24, G3m26, G3m27, and G3m28 (Table 1). Three isoallotypes (nG3m5, nG3m11, and nG3m21) have also been characterized (Table 2).

Amino acids that could give rise to subclass-specific epitopes and to G3m allotypes were identified following the first complete nucleotide sequence of the IGHG3 gene by Huck et al. in 1986 [88]. The IGHG3 gene was from an healthy Tunisian individual (EZZ, TOU II-4) homozygous for a multigene IGHC deletion (encompassing IGHG1 to IGHG4) and homozygous for the G3m5* allele (G3m5,10,11,13,14,26,27 or G3mb0,b1,b3,b4,b5,u,v) [88]. The IGHG3 EZZ translation was compared with amino acid sequences of heavy-chain disease (HCD) gamma3 proteins (ZUC [151], Wis [152], and OMM [153]), of myeloma gamma3 chains (Goe [154] and JIR [155]), and of gamma chains of other subclasses [88]. Although only G3m5*, G3m21*, and G3m16* could be compared, the analysis confirmed that the number of amino acid changes was lower than the number of allotypes and suggested that the conformational structure of a combination of amino acids was required to explain several allotypes.

In 1989, Huck et al., published the sequence of a new allele from an healthy Tunisian individual (LAT) homozygous for the G3m24* allele (G3m5,6,11,24,26 or G3mb0,b1,c3,c5,u) and demonstrated that this allele results from a gene-conversion event [90]. In 2001, Dard et al. sequenced 51 full-length genomic IGHG3 alleles from healthy individuals from African, Siberian, West Asian, and European population samples whose sera were typed for the Gm allotypes [97]. Different levels of molecular diversity were observed for the G3m alleles. (EZZ [88] and LAT [90] were included in the analysis.) Analysis of 19 DNA sequences of the G3m5* allele yielded 11 different IGHG3 alleles; similar analysis of 10 DNA sequences of the G3m21* allele yielded 4 distinct IGHG3 alleles; in contrast, the 9 DNA sequences of the G3m24* allele were monomorphic [97]. These data allowed the first identification of the amino acids involved in the G3m allotypes; however, detailed correlations remained to be defined. In 2012, we reported, for the first time, the

full elucidation of the G3m allotypes and amino acid correlations, taking into account conformational structures that may involve two or even three amino acids [2] (Figure 8). Two mosaics of G3m allotypes were identified in which the number of allotypes is greater than the number of amino acid changes [2].

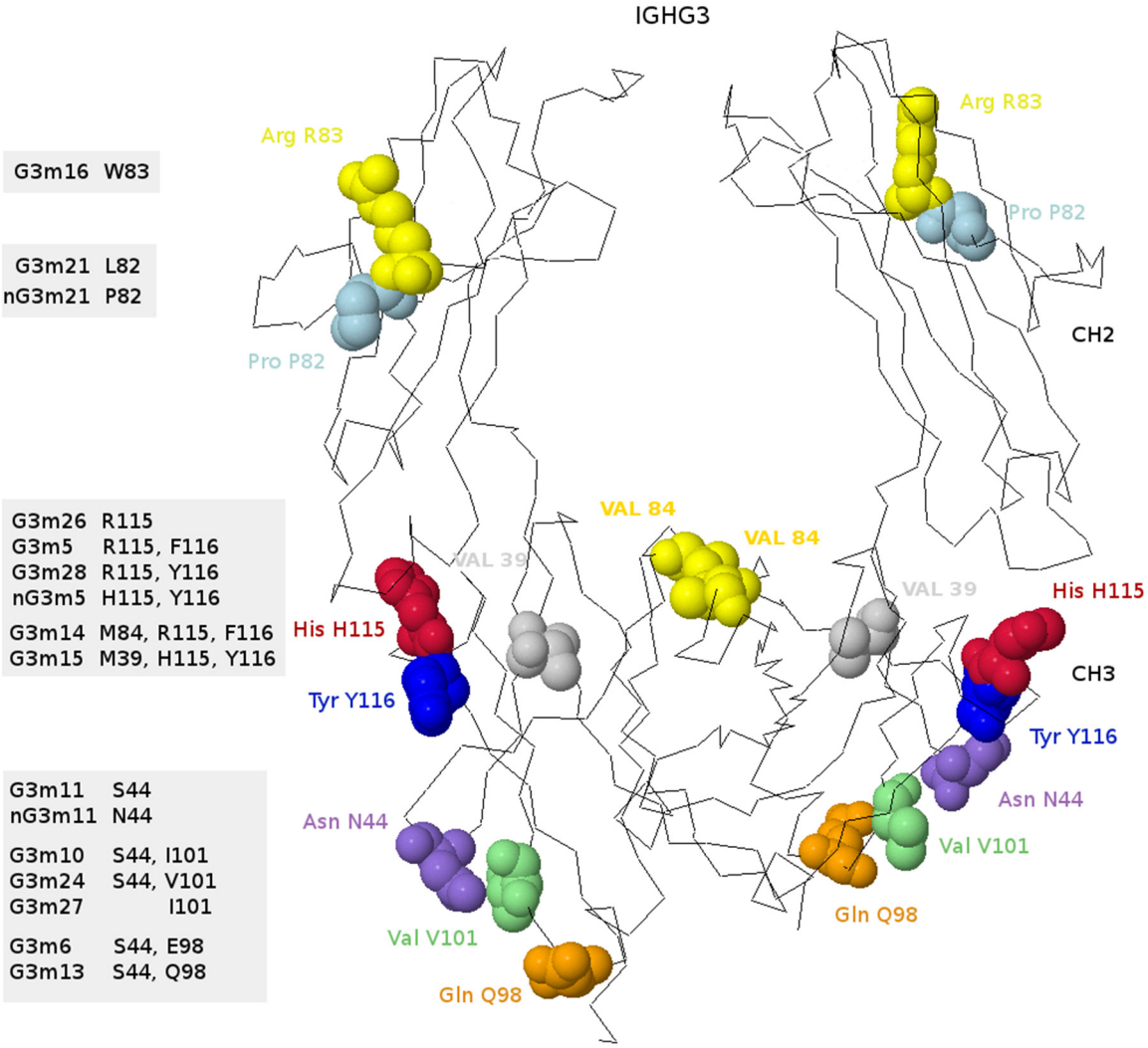

Figure 8. G3m allotypes localizations on gamma3 chains [2] and this paper. The CH2 and CH3 domains were superimposed with the CH2 and CH3 domains of the b12 gamma1 chains (IMGT/3Dstructure-DB [143,144], code PDB:1hzh) for this schematic representation and an easier comparison. G3m16 (tryptophan Trp W83), G3m21 (leucine Leu L82), and nG3m21 (proline Pro P82) are located on the CH2, whereas G3m14 (M84, R115, F116) and G3m15 (M39, H115, Y116) are located on the CH3, as discussed in the text. The other G3m allotypes form two mosaics on the CH3. The first mosaic comprises G3m6 (S44, E98), G3m10 (S44, I101), G3m11 (S44), G3m13 (S44, Q98), G3m24 (S44, V101), G3m27 (I101), and antithetical isoallotype nG3m11 (N44). The second mosaic comprises G3m5 (R115, F116), G3m28 (R115, Y116), G3m26 (R115), and the antithetical isoallotype nG3m5 (H115 and Y116). (With permission from M-P. Lefranc and G. Lefranc, LIGM, Founders and Authors of IMGT®, the international ImMunoGeneTics information system®, https://www.imgt.org (accessed on 29 May 2023).)

5.2. First Mosaic: G3m6, G3m10, G3m11, G3m13, G3m24, G3m27, and Antithetical Isoallotype nG3m11

A first mosaic of G3m allotypes on the CH3 was defined around G3m11 with a total of six allotypes (G3m6, G3m10, G3m11, G3m13, G3m24, and G3m27) and one antithetical isoallotype (nG3m11) [2]. G3m11 is characterized by a serine at position 44 of the CH3

(IGHG3 CH3 Ser S44), whereas nG3m11 depends on an asparagine at the same position (IGHG3 CH3 Asn N44) [97].

Haplotype analysis shows that four allotypes, namely G3m6, G3m10, G3m13, and G3m24, depend on the presence of G3m11 [32–36]. Extensive analysis of the sequence [88,90,97] and genetic data demonstrate the following:

- G3m10 corresponds to the simultaneous expression of S44 (G3m11) with an isoleucine at position 101 (IGHG3 CH3 Ile I101) [2];
- G3m24 corresponds to the simultaneous expression of S44 (G3m11) with a valine at position 101 (IGHG3 CH3 Val V101) [2];
- G3m6 corresponds to the simultaneous expression of S44 (G3m11) with a glutamate at position 98 (IGHG3 CH3 Glu E98) [2].;
- G3m13 corresponds to the simultaneous expression of S44 (G3m11) with a glutamine at position 98 (IGHG3 CH3 Gln Q98) [2].

These data confirm that G3m27 corresponds to isoleucine at position 101 in the CH3 domain (IGHG3 CH3 Ileu I101) [2]. G3m27 is expressed with G3m10 but not G3m24, which is in agreement with the observation that G3m24 and G3m27 are antithetical in genetic analysis [2].

These data are also in agreement with the genetic data that show that the allotypes G3m6 and G3m13 are antithetical (owing to an amino acid change at the same position: E98 for G3m6 and Q98 for G3m13) [2].

5.3. Second Mosaic: G3m5, G3m28, G3m26, and Antithetical Isoallotype nG3m5

The second mosaic, also observed on the CH3 domain of IGHG3, is defined around G3m5 with a total of three G3m allotypes (G3m5, G3m28, and G3m26) and one antithetical isoallotype (nG3m5) [2]. Extensive analysis of sequences [88,90,97] and genetic data [32–36,73–80,86] demonstrate that -G3m5 corresponds to the simultaneous expression of arginine at position 115 (IGHG3 CH3 Arg R115) and phenylalanine at position 116 (IGHG3 CH3 Phe F116) [2], whereas nG3m5 isoallotype corresponds to the simultaneous expression of histidine at position 115 (IGHG3 CH3 His H115) and tyrosine at position 116 (IGHG3 CH3 Tyr Y116) [2].

- G3m28 corresponds to the simultaneous expression of arginine at position 115 (IGHG3 CH3 Arg R115) and tyrosine at position 116 (IGHG3 CH3 Tyr Y116). This observation is in agreement with the genetic data that show that G3m5 and G3m28 are antithetical and mutually exclusive on the gamma3 chains [2].

These data confirm that G3m26 corresponds to arginine at position 115 (IGHG3 CH3 Arg R115). This explains the high frequency of G3m26 present on all Gm5-positive (R115, F116) and G3m28-positive (R115, Y116) gamma3 chains and its absence, with the arginine being replaced by an histidine, on G3m15-positive gamma3 chains that are nG3m5 (H115,Y116) [2].

5.4. G3m14 and G3m15

G3m14 has been the subject of discussion concerning its localization on either the CH2 or CH3 domain with contradictory serological data (discussed in [33]). Extensive analysis of previously published data of usual and uncommon haplotypes, supported by familial studies [30–36,73–79,86], led us to postulate that G3m14 corresponds to the simultaneous presence on CH3 of a methionine at position 84 (IGHG3 CH3 Met M84) with G3m5 (CH3 Arg R115, Phe F116) [2].

Gm15 was reported to be located first on the CH2 domain. In 1983, Matsumoto et al. postulated that G3m15 correlates with histidine at position Eu 435 (IGHG3 CH3 H115) and G3m16 with methione at position Eu 379 (IGHG3 CH3 M39) on JIR, a G3m15,16-positive myeloma gamma3 protein [155]. In 1986, Matsumoto et al. reported that the G3m15 is located on the CH3 domain of Kam, another G3m15,16-positive myeloma gamma3 protein [156]. Dard et al. [97] showed that His H115 alone cannot be respon-

sible of G3m15, as it is found in all the nG3m5 chains, and suggested a role for Met M39. Based on these observations, and in a similar way as for Gm14, we postulated that G3m15 corresponds to the simultaneous presence on CH3 of Met M39 (IGHG3 Met M39) with nG3m5 (CH3 His H115, Tyr Y116) [2].

Interestingly, G3m14 and G3m15, the localization of which has been controversial for a long time, are two allotypes that require an amino acid at a position that interferes with the binding site but is not directly located at the epitope site. This emphasizes the importance of the conformational configuration but at a degree that was not suspected.

5.5. G3m16 and G3m21 Allotypes

Two allotypes, G3m16 and G3m21, are localized on the CH2 domain. G3m16 correlates with a tryptophane at position 83 (IGHG3 CH2 Trp W83), whereas G3m16-negative chains have an arginine at that position [97]. G3m21 correlates with a leucine at position 82 (IGHG3 CH2 Leu L82), whereas nG3m21 correlates with Pro P82 [97] (IMGT Repertoire, https://www.imgt.org/IMGTrepertoire/ > Alignments of alleles, *Homo sapiens* IGHG3 [114] (accessed 23 June 2023)).

5.6. "Silent" G3m Allotypes

Among data obtained by Dard et al. [97], one sequence was noted as unusual, as it presents an asparagine (N44) (IGHG3*08 in IMGT Repertoire, https://www.imgt.org/IMGTrepertoire/ > Alignments of alleles, *Homo sapiens* IGHG3 (accessed 23 June 2023)), whereas a serine (S44) was expected given the G3m5* phenotype. The individual, Mand114, is heterozygous for a normal G3m5* haplotype associated to the unusual haplotype (the one that was sequenced) [97]. We postulate that the unusual haplotype corresponds to G3m5,14,26, with an absence of G3m (10,11,13), as previously demonstrated in the Tunisian family 275 [79,86]. Two nucleotide substitutions in codon 44 (as a result of mutations or of a gene conversion) are the most probable explanation for these silent G3m (10,11,13) allotypes.

5.7. "Surnumerary" Gm27 and Gm28 Allotypes

In Caucasoid and Mongoloid populations, G3m28 is frequently associated with G3m21, although exceptions have been shown [21,35,36,78,79,86]. In contrast, Negroid populations are G3m21-negative, and interestingly, for individuals who are Gm28-positive, this allotype appears as "surnumerary". It has been demonstrated in Lat-IV-5 (homozygous for G3m24*) and Sno (homozygous for G3m6*) that the surnumerary allotype Gm28 is expressed on the gamma1 chains [80]. Thus, in Negroid populations, Gm28 represents a G1m28 allotype. The amino acid change on the gamma1 chain, nG3m5 (H115, Y116) to G1m28 (R115, Y116), most probably corresponds to a single nucleotide mutation (a344 > g, H115 > R) (Table 6).

Table 6. IMGT correlation between G3m allotypes and isoallotypes and amino acids [2] and this paper.

G3m Allotypes and Isoallotypes	Amino Acid Position [a]									
	Domain	**CH2**					**CH3**			
	IMGT	**82**	**83**	**39**	**44**	**84**	**98**	**101**	**115**	**116**
	Exon	**(61)**	**(62)**	**(39)**	**(44)**	**(57)**	**(79)**	**(82)**	**(95)**	**(96)**
	Eu	***291***	***292***	***379***	***384***	***397***	***419***	***422***	***435***	***436***
G3m5									Arg R cgc	Phe F ttc
nG3m5									His H cac	Tyr Y tac
G3m6					Ser S agc		Glu E gag			
G3m10					Ser S agc			Ileu I atc		
G3m11					Ser S agc					
nG3m11					Asn N aat					
G3m13					Ser S agc		Gln Q cag			
G3m14						Met M atg			Arg R cgc	Phe F ttc
G3m15				Met M atg					His H cac	Tyr Y tac
G3m16			Trp W tgg							
G3m21		Leu L ctg								
nG3m21		Pro P ccg								
G3m24					Ser S agc			Val V gtc		
G3m26									Arg R cgc	
G3m27								Ileu I atc		
G3m28									Arg R cgc	Tyr Y tac

[a] Positions in bold are according to the IMGT unique numbering for C domain [141]; between parentheses, exon numbering [37]; in italics, Eu numbering. Mutated nucleotides between codons are undelined. (With permission from M-P. Lefranc and G. Lefranc, LIGM, Founders and Authors of IMGT®, the international ImMunoGeneTics information system®, https://www.imgt.org (accessed on 29 May 2023)).

5.8. Correlation between G3m Allotypes and Isoallotypes and Amino Acids

The IMGT correlation between G3m allotypes and isoallotypes and the amino acids is shown in Table 6 [2] and this paper.

The presence of surnumerary Gm27 has also been demonstrated on the gamma1 chain of Lat IV-5 and Sno, representing a G1m27 allotype [80]. The amino acid change on the gamma1 chain most probably corresponds to a single nucleotide mutation (g301 > a, V101 > I).

Both Gm27 and Gm28 are qualified as "alloallotype", i.e., being an allotype for two different gamma chains, namely gamma1 (G1m27, G1m28) and gamma3 (G3m27, G3m28), depending on the populations.

5.9. IGHG3 Hinge CNV Exon Polymorphism

For the gamma3 chains, an additional polymorphism results from differing numbers (CNV) of hinge exons. The hinge is encoded by 2–5 exons depending on the alleles [88,90,96,97]. Thus, the hinge region can vary from 27 to 83 amino acids and can influence structural conformations.

5.10. G3m Alleles and the "IMGT G3m Allele Butterfly" Representation

The thirteen G3m allotypes are inherited in different combinations or G3m alleles. The six most prevalent G3m alleles are shown in Table 7 and illustrated in Figure 9 as "IMGT G3m alleles butterfly" representation. For convenience, these most common G3m alleles can be written in a simplified form indicated with an asterisk (Table 7), provided that all the corresponding allotypes of the WHO/IMGT Nomenclature have been confirmed.

Table 7. The six most prevalent G3m alleles ([2] and this paper). The asterisk of the simplified form indicates that all the allotypes characteristic of the allele in the WHO/IMGT Nomenclature are present.

Most Prevalent G3m Alleles (WHO/IMGT Nomenclature)	Simplified Form
G3m5,10,11,13,14,26,27	G3m5*
G3m5,6,10,11,14,26,27	G3m6*
G3m5,6,11,24,26	G3m24*
G3m10,11,13,15,27	G3m15*
G3m10,11,13,15,16,27	G3m16*
G3m21,26,27,28	G3m21*

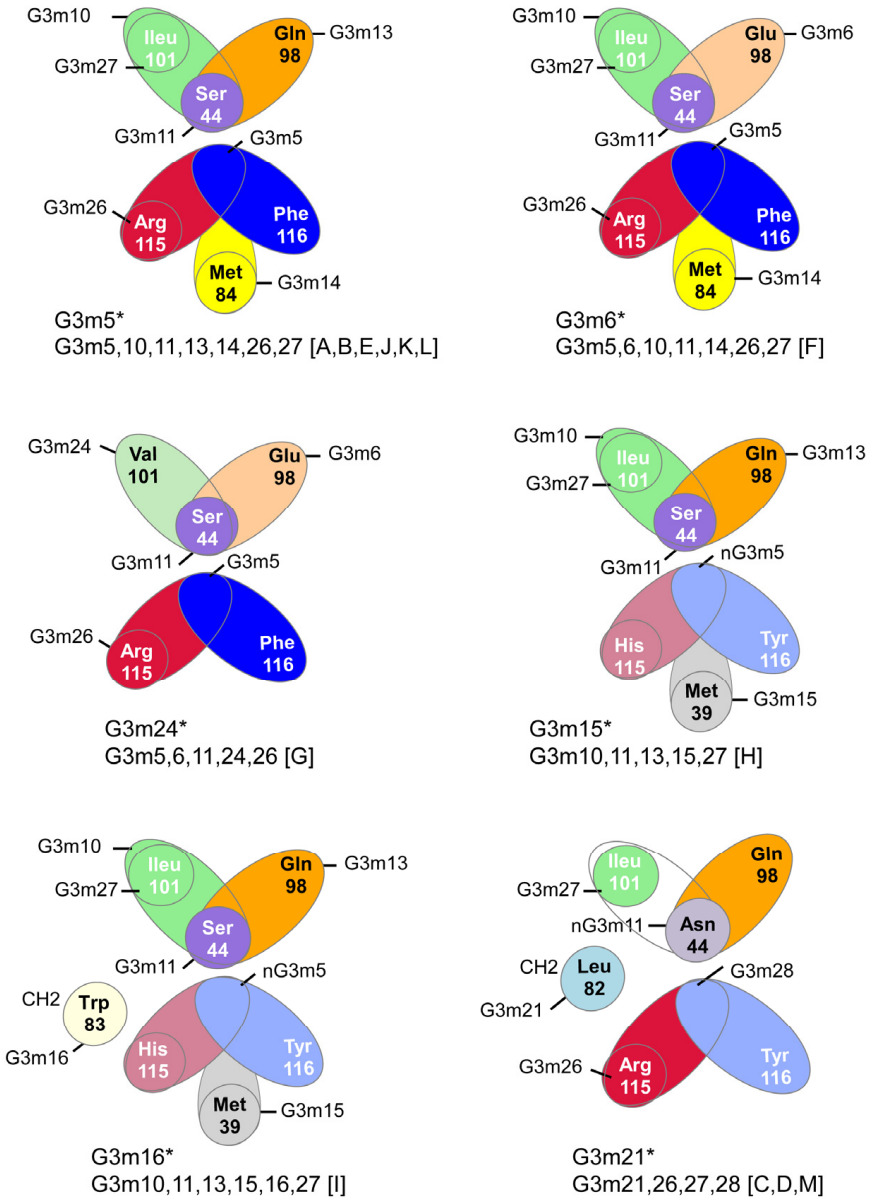

Figure 9. "IMGT G3m allele butterfly" representation [2]. The two mosaics on the CH3 domain are shown for each G3m allele. The first mosaic around G3m11 is on the top with G3m27, G3m10/G3m24, and G3m13/G3m6. The second mosaic is at the bottom with G3m26 and G3m5/nG3m5/G3m28. Amino acids involved in the allotype expression and their position according to the IMGT unique numbering for C domain [141] are indicated. Two allotypes are on the CH2 domain: G3m16 (Trp W83) and G3m21 (Leu L82). G3m allele names are indicated below each butterfly representation. The asterisk of the simplified form indicates that all corresponding allotypes of the WHO/IMGT Nomenclature are present (Table 7). Haplotypes to which the G3m alleles belong are indicated by a letter A to M between square brackets (Section 8). (With permission from M-P. Lefranc and G. Lefranc, LIGM, Founders and Authors of IMGT®, the international ImMunoGeneTics information system®, https://www.imgt.org (accessed on 29 May 2023).)

5.11. Correspondence between the G3m Alleles and IGHG3 Alleles

The correspondence between the G3m alleles and IGHG3 alleles is shown in Table 8.

Table 8. Correspondence between the G3m alleles and IGHG3 alleles [2] and this paper.

G3m Alleles and IGHG3 Alleles	Amino Acid Position [a,b]								
Domain	**CH2**					**CH3**			
IMGT	**82**	**83**	**39**	**44**	**84**	**98**	**101**	**115**	**116**
Exon	**(61)**	**(62)**	**(39)**	**(44)**	**(57)**	**(79)**	**(82)**	**(95)**	**(96)**
Eu	***291***	***292***	***379***	***384***	***397***	***419***	***422***	***435***	***436***
G3m5* (G3m5,10,11,13,14,26,27) *nG3m21* IGHG3*01, IGHG3*05, IGHG3*06, IGHG3*07, IGHG3*09, IGHG3*10, IGHG3*11, IGHG3*12	Pro P ccg	Arg R cgg	Val V gtg	**Ser S** agc	**Met M** atg	**Gln** Qcag	**Ileu** Iatc	**Arg R** cgc	**Phe F** ttc
G3m6* (G3m5,6,10,11,14,26,27) *nG3m21* IGHG3*13	Pro P ccg	Arg R cgg	Val V gtg	**Ser S** agc	**Met M** atg	**Glu** Egag	**Ileu** Iatc	**Arg R** cgc	**Phe F** ttc
G3m24* (G3m5,6,11,24,26) *nG3m21* IGHG3*03	Pro P ccg	Arg R cgg	Val V gtg	**Ser S** agc	Val V gtg	**Glu** Egag	**Val** Vgtc	**Arg R** cgc	**Phe F** ttc
G3m15* (G3m10,11,13,15,27) *nG3m5*, *nG3m21* IGHG3*17	Pro P ccg	Arg R cgg	**Met M** atg	**Ser S** agc	Val V gtg	**Gln** Qcag	**Ileu** Iatc	**His H** cac	**Tyr Y** tac
G3m16* (G3m10,11,13,15,16,27) *nG3m5*, *nG3m21* IGHG3*18, IGHG3*19	Pro P ccg	**Trp W** tgg	**Met M** atg	**Ser S** agc	Val V gtg	**Gln** Qcag	**Ileu** Iatc	**His H** cac	**Tyr Y** tac
G3m21* (G3m21,26,27,28) *nG3m11* IGHG3*14, IGHG3*15, IGHG3*16	**Leu L** ctg	Arg R cgg	Val V gtg	Asn N aat	Met M atg	Gln Q cag	**Ileu** Iatc	**Arg R** cgc	**Tyr Y** tac

[a] Positions in bold are according to the IMGT unique numbering for C domain [141]; between parentheses, exon numbering [37]; in italics, Eu numbering. Mutated nucleotides between codons are underlined. [b] The amino acid change asparagine/lysine at position 79 in the CH3 domain (IGHG3 CH3 Asn/Lys N79/K) (exon numbering (52), Eu numbering *392*), is not reported in the table, as no specific antibody (and therefore no allotype) has been characterized. It should be noted that the asparagine Asn N79, if present, belongs to a N-glycosylation site in alleles IGHG3*01 to *05, *08 to *12, *14, and *16). (With permission from M-P. Lefranc and G. Lefranc, LIGM, Founders and Authors of IMGT®, the international ImMunoGeneTics information system®, https://www.imgt.org (accessed on 29 May 2023)).

Correspondence between C numberings is available in IMGT Scientific chart [114] (Supplementary Table S1). "Alignments of alleles of *Homo sapiens* IGHG3" is available in IMGT Repertoire [114] (Supplementary Table S8).

6. nG4m Isoallotypes

6.1. nG4m(a) and nG4m(b) Isoallotypes

No allotype has been defined for the gamma4 chains of the IgG4 subclass. The only serologically defined polymorphism corresponds to the isoallotypes nG4m(a) and nG4m(b), described on the CH2 domain [136]. These antithetical determinants of the gamma4 chains behave as allotypes in the IgG4 subclass, but they are present on the other subclasses and therefore must be considered as isoallotypes.

It has been postulated that nG4m(a) was correlated to leucine 309 (IGHG4 CH2 Leu L92) and isoallotype nG4m(b) to a deletion at that position [157]. However, comparison with the translation of IGHG4 sequences did not confirm that deletion and instead showed that it was an amino acid change of leucine into valine (IGHG4 CH2 Val V92), which explained the "disappearance" of the leucine and was responsible for the expression of nG4m(b) chains [1,2,88]. The nG4m(a) epitope (IGHG4 CH2 Leu L92) is expressed on the gamma1 and gamma3 chains, whereas the nG4m(b) epitope (IGHG4 CH2 Val V92) is expressed on the gamma2 chains (Table 2).

6.2. IMGT Correspondence between G4m Alleles and IGHG4 Alleles

The G4m alleles comprise the nG4m(a) allele, which corresponds to IGHG4*01, IGHG4*03, and IGHG4*04, and the nG4m(b) allele, which corresponds to IGHG4*02 (Table 9).

Table 9. Correspondence between the G4m alleles and IGHG4 alleles [2] and this paper.

G4m Alleles	IGHG4 Alleles	Amino Acid Positions [a]	
		Domain	**CH2**
		IMGT	**92**
		Exon	**(79)**
		Eu	***309***
		nG4m(a)/nG4m(b)	
nG4m(a)	IGHG4*01, IGHG4*03, IGHG4*04	Leu L92 c̲tg	
nG4m(b)	IGHG4*02	Val V92 g̲tg	

[a] Positions in bold are according to the IMGT unique numbering for C domain [141]; between parentheses, exon numbering [37]; in italics, Eu numbering. Mutated nucleotides between codons are underlined. (With permission from M-P. Lefranc and G. Lefranc, LIGM, Founders and Authors of IMGT®, the international ImMunoGeneTics information system®, https://www.imgt.org (accessed on 29 May 2023)).

Correspondence between C numberings is available in IMGT Scientific chart [114] (Supplementary Table S1). "Alignments of alleles of *Homo sapiens* IGHG4" is available in IMGT Repertoire [114] (Supplementary Table S9).

7. A2m Allotypes and nA2m Isoallotype

7.1. A2m1 and A2m2 Allotypes

Two allotypes of the IGHA2 gene have been described: A2m1, identified by two groups independently [22,23], and A2m2 [24]. A2m1 and A2m2 are antithetical and located on the CH1 domain. A2m1 corresponds to a proline at position 115 (IGHA2 CH1 Pro P115) and is also correlated to a proline at position 124 (IGHA2 CH1 Pro P124) [158] (Figure 1B). A2m2 corresponds to a serine at position 115 (IGHA2 CH1 Ser S115) and is also correlated to an arginine at position 124 (IGHA2 CH1 Arg R124) [84,159] (Figure 10A).

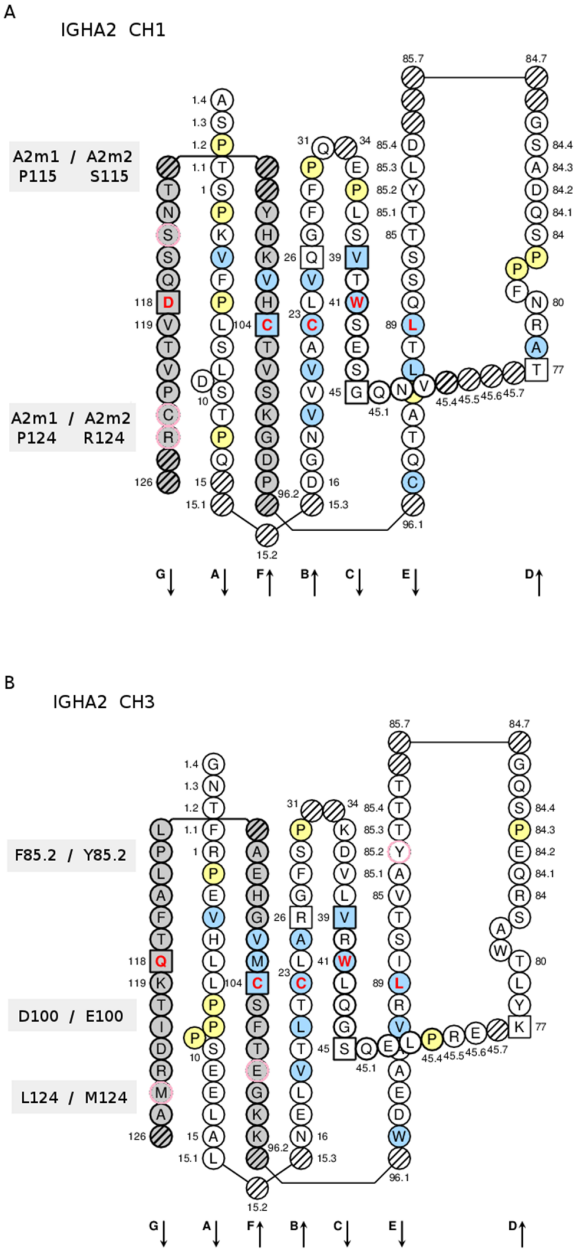

Figure 10. IMGT Colliers de Perles of the IGHA2*02 CH1 and CH3 domains [2] and this paper. The CH1 and CH3 domains are from IGHA2*02 [37] (IMGT/DomainDisplay, IMGT/GENE-DB [142] https://www.imgt.org/genedb (accessed 23 June 2023)). The IMGT Colliers de Perles [114,145,146] are shown on two layers. Hatched positions correspond to gaps according to the IMGT unique numbering [141]. (**A**) CH1 domain. The serine at position 115 (S115) corresponds to A2m2, with the arginine at position 124 (R124) also correlating to that allotype [37,84,85]. A proline at positions 115 (P115) and 124 (P124) would correspond to the A2m1 allotype [37,84,85]. (**B**) CH3 domain. One or several of the following amino acids in the CH3 domain, namely tyrosine Tyr at position 85.2 (Y85.2), glutamate Glu at position 100 (E100), or methionine Met at position 124 (M124), and/or in the CHS (not shown), namely isoleucine Ileu I134, or alanine Ala A143, may be involved in the A2m3 allotype [2,37,84]. One or several of the following amino acids in the CH3 domain, namely phenylalanine Phe F85.2, aspartate Asp D100, or leucine Leu L124, and/or in the CHS (not shown), namely valine Val V134 and valine Val V143, are involved in the antithetical nA2m3 allotype [2,37,84]. (With permission from M-P. Lefranc and G. Lefranc, LIGM, Founders and Authors of IMGT®, the international ImMunoGeneTics information system®, https://www.imgt.org (accessed on 29 May 2023).)

7.2. A2m1 and A2m2 Allotype Frequency

The frequency of the A2m1 and A2m2 allotypes varies a lot between and within most populations [36,61,66,74,78]. In Caucasoid populations, almost all individuals are homozygous for the A2m1 allotype. The A2m2 allotype, rare in Caucasoid populations, is present with a frequency of 0.40–0.75 in Mongoloid populations [62] and 0.60–0.85 in Negroid populations [63].

7.3. A2m1 and A2m2 Allotype Determination by RFLP

A2m1 and A2m2 allotypes can be determined at the DNA level by RFLP using appropriate restriction enzymes [85]. The amino acid responsible for the A2m2 allotype, serine 115, is encoded by nucleotides that are part of an *Eco*RI restriction site [85]. Due to a nucleotide substitution, this site is absent in the A2m1 allele. Thus, whereas the restriction enzyme *Pst*I yields two fragments containing the IGHA1 (1.2 kb) and IGHA2 (2 kb) genes [81,98], when DNA samples are probed with a Cα probe, the double digests *Eco*RI—*Pst*I show two different patterns: one similar to the *Pst*I one for the A2m1 allele and the other with a new 0.9 kb band for the A2m2 allele due to the existence of the *Eco*RI site [85]. The determination of A2m alleles by RFLP is particularly useful when reagents are not readily available for the serological determination of the allotypes. Moreover, it is the only way to identify A2m alleles when no serum is available (for instance cell lines).

7.4. Sequence Identity and Conformational Difference for A2m1 and the alpha1 Isotypic Epitope

The sequence of the A2m1 chain is identical to the sequence of the alpha 1 chain at positions 115 (CH1 Pro P115) and 124 (CH1 Pro P124) [93] (Figure 1B). However, the IGHA2 A2m1 allotype and the IGHA1 isotypic epitope are recognized by different antibodies (Erna van Loghem, GL, and MPL), due to a difference in the disulfide bridge. Indeed, in IgA1 (as in IgA2 A2m2), the cysteine (CH1 Cys C123) is normally involved in an heavy-light (H-L) disulfide bridge. In contrast, in IgA2 A2m1, there is no H-L disulfide bridge to the cysteine (CH1 Cys C123) due to a conformational hindrance of the Pro P124, and the two light chains are directly linked to each other [86].

7.5. A2m3 Allotype Antithetical to nA2m3

The C-terminal region (CH3 domain and/or CHS region) of the IGHA2*02 allele (TOU II-5) [37] (Figure 10B) was shown to be immunogenic and to correspond to a new allotype designated A2m3, as it was antithetical to the nA2m3 isoallotype (previously called nA2m(2)) (Erna van Loghem, GL, and MPL). One or several of the following IGHA2 amino acid changes may be involved in the A2m3 allotype/nA2m3 isoallotype expression: Tyr Y85.2/Phe F85.2, Glu E100/Asp D100, Met M124/Leu L124 (in the CH3), Ileu I134/Val V134, or Ala A143/Val V143 (in the CHS region) (IMGT Repertoire, https://www.imgt.org/IMGTrepertoire/ > Alignments of alleles, *Homo sapiens* IGHA2 [114] (accessed 23 June 2023)) (Figure 1B).

7.6. IMGT Correspondence between A2m Alleles and IGHA2 Alleles

The correspondence between A2m alleles and IGHA2 alleles is shown in Table 10. Three A2m alleles, namely A2m1, A2m2,3, and A2m2, are defined based on their allotypes. A2m1 corresponds to the IGHA2*01 allele, A2m2,3 to the IGHA2*02 (TOU II-5) allele, and A2m2 to the IGHA2*03 allele.

Table 10. IMGT correspondence between A2m alleles and IGHA2 alleles [2] and this paper.

A2m Alleles	IGHA2 Alleles	Amino Acid Positions [a]							
		Domain	**CH1**			**CH3**			**CH-S**	
		IMGT	**115**	**123**	**124**	**85.2**	**100**	**124**	**134**	**143**
		Exon	**(93)**	**(101)**	**(102)**	**(70)**	**(87)**	**(110)**	**(117)**	**(126)**
		Bur	***212***	***220***	***221***					
A2m1 *nA2m3* [b]	IGHA2*01		**Pro P** ccc	Cys C tgc	**Pro P** cca	Phe F ttc	Asp D gac	Leu L ttg	Val V gtc	Val V gtg
A2m2,3 [b]	IGHA2*02		**Ser S** tcc	Cys C tgc	**Arg R** cga	Tyr Y tac	Glu E gag	Met M atg	Ile I atc	Ala A gcg
A2m2 *nA2m3* [b]	IGHA2*03		**Ser S** tcc	Cys C tgc	**Arg R** cga	Phe F ttc	Asp D gac	Leu L ttg	Val V gtc	Val V gtg

[a] Positions in bold are according to the IMGT unique numbering for C domain [141]; between parentheses, exon numbering [37], in italics, Bur numbering [160]. Mutated nucleotides between codons are undelined. [b] The allotype A2m3 was identified serologically on the C-terminal region (CH3 and/or CHS) of TOU II-5 (Erna van Loghem, GL, and MPL). (With permission from M-P. Lefranc and G. Lefranc, LIGM, Founders and Authors of IMGT®, the international ImMunoGeneTics information system®, https://www.imgt.org (accessed on 29 May 2023)).

"Alignments of alleles of *Homo sapiens* IGHA2" is available in IMGT Repertoire [114] (Supplementary Table S10).

8. Gm Haplotypes

8.1. Gm (or Gm–Am) Haplotype Definition

Gm allotypes are inherited in fixed combinations called "Gm haplotypes" or "Gm–Am haplotypes" (if A2m allotypes are tested) owing to the linkage of the IGHC genes within a cluster in the IGH locus [30–36]. Haplotypes have a low frequency of crossovers; however, crossover events and gene conversions [84,86,87,90] have occurred during evolution, resulting in characteristic haplotypes present in diverse populations, hence the usefulness of the allotype system in population studies. Equal or unequal crossovers, the later generating gene duplication (or expansion) or, in contrast, gene deletion (or contraction) in the IGH locus, have been demonstrated [81–83,86,89,91,92,94,95], and they are now commonly named copy number variation (CNV) [161,162].

8.2. Description of the Main Gm Haplotypes

The G1m, G2m, and G3m alleles are inherited in fixed combinations or Gm haplotypes. Table 11 shows the eleven most prevalent Gm haplotypes.

Table 11. Prevalent Gm haplotypes in populations [2] and this paper.

Populations	Prevalent Gm Haplotypes [a]		
	Gm Haplotypes	**Simplified Form [b]**	**Complete Description (WHO/IMGT Nomenclature)**
Caucasoid	A	Gm5*;3;23	Gm5,10,11,13,14,26,27;3;23
	B	Gm5*;3;..	Gm5,10,11,13,14,26,27;3;..
Caucasoid and Mongoloid	C	Gm21*;17,1;..	Gm21,26,27,28;17,1;..
	D	Gm21*;17,1,2;..	Gm21,26,27,28;17,1,2;..
Negroid	E	Gm5*;17,1;..	Gm5,10,11,13,14,26,27;17,1;.. (+G1m28) [c]
	F	Gm6*;17,1;..	Gm5,6,10,11,14,26,27;17,1;.. (+G1m28) [c]

Table 11. *Cont.*

Populations	Prevalent Gm Haplotypes [a]		
	Gm Haplotypes	**Simplified Form [b]**	**Complete Description (WHO/IMGT Nomenclature)**
	G [c]	Gm24*;17,1;..	Gm5,6,11,24,26;17,1;.. (+G1m28) [c]
Khoisan [d]	H	Gm15*;17,1;..	Gm10,11,13,15,27;17,1;..
Mongoloid	I	Gm16*;17,1;..	Gm10,11,13,15,16,27;17,1;..
	J	Gm5*;3,1;23	Gm5,10,11,13,14,26,27;3,1;23
	K	Gm5*;3,1;..	Gm5,10,11,13,14,26,27;3,1;..

[a] Prevalent haplotypes are characteristic of given populations. This does not mean that they are totally absent from other populations. They can be found to frequency usually <0.01 and represent rare alleles without miscegenation. [b] The current simplified form of the Gm haplotypes only contains one number for the G3m allele. 24* was previously designated as 6,24* and 16* as 15,16* [c] The presence of the G1m28 allotype [80] is frequently observed in association with haplotypes E, F, and G. In contrast, the presence of G1m27 can only be confirmed in homozygotes for haplotype G (haplotype G is negative for G3m27, whereas haplotypes E and F are positive for G3m27) [80,90]. As the assignment to one or the other haplotype in heterozygous individuals is not possible in usual typing, G1m28 allotype is usually indicated as "+G1m28" in genotype description. In homozygous individuals, as demonstrated in [80], the haplotype is Gm24*;17,1,27,28;.. in Lat IV-5 and Gm6*;17,1,27,28;.. in Sno. The G1m28 also explains the uncommon haplotypes found in Tunisian families [78,79,86]. [d] The Khoisan population regroups the San (or Bushmen), who are native people and hunters/gatherers of southwestern Africa, and the Khoikhoi (or Hottentots), pasturalists who had lived in southern Africa since the 5th century AD. (With permission from M-P. Lefranc and G. Lefranc, LIGM, Founders and Authors of IMGT®, the international ImMunoGeneTics information system®, https://www.imgt.org (accessed on 29 May 2023)).

The nomenclature of the Gm haplotypes takes into account the IGHG gene order in the locus [81,98,99]. The Gm allotypes are written in the linkage order of the IGHG subclass genes, i.e., IGHG3, IGHG1, and IGHG2, with semicolons separating the subclasses and comas separating the allotypes; G2m23 is the only allotype defined on gamma 2, with two dots being used to indicate that a specimen was tested and found to be negative for G2m23 [30,31,35,36].

In haplotypes A and B, the G3m5* allele is inherited with the G1m3 allele with or without G2m23, respectively. In haplotypes C and D, the G3m21* allele is inherited with G1m17,1 or G1m17,1,2, respectively (without G2m23). In haplotypes E, F, G, and H, the G3m alleles (G3m5*, G3m6*, G3m24*, and G3m15*) differentiate the four haplotypes since they are all associated with the G1m17,1 allele (without G2m23). The haplotype I corresponds to Gm16*;17,1;.., whereas the haplotypes J and K correspond to the G3m5* allele inherited with the G1m3,1 allele with or without G2m23, respectively (Table 11). Less frequent Gm haplotypes include, for example, haplotypes L (Gm5*;17,1,2;..) and M (Gm21*;17,1;23), identified in Lebanese and Tunisian populations [30,35,36]. Correspondence of the Gm haplotypes A to M with previous designation is given in Appendix A (Table A1).

8.3. Prevalent Gm Haplotypes in Different Populations

The eleven most prevalent Gm haplotypes are differently represented in the Negroid, Khoisan, Caucasoid, and Mongoloid populations (Table 11). Thus, Gm5*;3;23 [A] and Gm5*;3;.. [B] are only typical of the Caucasoid populations. Two haplotypes, Gm21*;17,1;.. [C] and Gm 21*;17,1,2;.. [D], are shared by the Caucasoid and Mongoloid populations. A unique set of haplotypes characterizes the Negroid populations: Gm5*;17,1,.. [E], Gm6*;17,1;.. [F], and Gm24*;17,1,.. [G]. The haplotype Gm15*;17,1;.. [H] (with or without G3m16) is characteristic of the Khoisan population of southern Africa. Three Gm haplotypes only occur in the Mongoloid populations: Gm16*;17,1;.. [I], largely in the northern hemisphere, and Gm5*;3,1;23 [J] and Gm5*;3,1;.. [K] in the southern hemisphere.

Haplotypes E, F, and G in the Negroid populations have been found with G1m27 and G1m28 on gamma1 (demonstrated on isolated chains of Lat-IV-5 (haplotype G) and Sno (haplotype F) [80].

8.4. From Gm Phenotypes to Gm Genotypes and Haplotypes

Gm phenotypes and deduced Gm genotypes and haplotypes from the Tunisian population [36] are shown as examples in Table 12. The observed diversity (26 phenotypes and 28 deduced Gm genotypes contributed by 8 Gm haplotypes) is explained by the geographical localization of Tunisia at the carrefour of many population migrations and civilizations (Table 12).

Table 12. Gm phenotypes observed in the Tunisian populations and deduced Gm genotypes with contributing Gm haplotypes [2] and this paper.

Gm Phenotypes [a]	Deduced Gm Genotypes with Contributing Gm Haplotypes	Observed [b]
5,10,11,13,14,26,27;3;23	A/A ou A/B	117
5,10,11,13,14,26,27;3;..	B/B	7
5,10,11,13,14,21,26,27,28;1,3,17;23	A/C	93
5,10,11,13,14,21,26,27,28;1,3,17;..	B/C	17
5,10,11,13,14,26,27;1,3,17;23	A/E	45
5,10,11,13,14,26,27;1,3,17;..	B/E	8
5,6,10,11,13,14,24,26,27;1,3,17;23	A/G	3
5,6,10,11,13,14,24,26,27;1,3,17;..	B/G	1
5,6,10,11,13,14,26,27;1,3,17;23	A/F	4
21,26,27,28;1,17;23	C/M	2
21,26,27,28;1,17;..	C/C	18
5,10,11,13,14,21,26,27,28;1,17;23	E/M	2
5,10,11,13,14,21,26,27,28;1,17;..	C/E	13
5,10,11,13,14,21,26,27,28;1,2,3,17;23	A/D	17
5,10,11,13,14,21,26,27,28;1,2,3,17;..	B/D	2
21,26,27,28;1,2,17;23	D/M	1
21,26,27,28,1,2,17;..	D/D ou C/D	6
5,10,11,13,14,21,26,27,28;1,2,17;..	D/E	3
5,10,11,13,14,26,27;1,17;..	E/E	1
5,6,10,11,13,14,24,26,27;1,17;..	E/G	1
5,6,10,11,13,14,26,27;1,17;..	E/F	1
5,6,11,21,24,26,27,28;1,17;..	C/G	1
5,6,10,11,14,21,26,27,28;1,17;..;23	C/F	1
10,11,13,15,16,21,26,27,28;1,17,..	C/I	1
5,10,11,13,14,15,16,26,27;1,3,17	A/I	1
5,10,11,13,14,15,16,26,27;1,3,17;..	B/I	1
Total		367

[a] In Gm phenotypes, allotypes are given in increasing numbers in the order G3m, G1m, and G2m and separated by semi-colons between chains of different subclasses. [b] Five unusual phenotypes, each one found in one individual, were the starting point of familial studies and are not included in this table [36]. (With permission from M-P. Lefranc and G. Lefranc, LIGM, Founders and Authors of IMGT®, the international ImMunoGeneTics information system®, https://www.imgt.org (accessed on 29 May 2023)).

8.5. Gm Haplotype Frequency in Different Populations

Gm haplotype frequencies from different populations are shown, as examples, in Table 13.

Table 13. Gm haplotype frequencies among Middle Eastern, European, African, and Asian populations [2] and this paper.

Populations [a]	Gm Haplotypes								References
	Caucasoid				Negroid Khoisan		Mongoloid		
	A,B	C	D	E	F,G	H	I	J,K	
Tunisia	0.602–0.618	0.226–0.243	0.025–0.051	0.083–0.101	0.018–0.022	-	0.004–0.007	-	[36]
Lebanon	0.692–0.748	0.137–0.197	0.007–0.033	0.007–0.053	0.000–0.037	-	0.013–0.042	-	[30,32,35]
Hungary Czechoslovakia	0.776–0.777	0.138–0.147	0.049–0.076	0.005–0.013	0.005–0.013	-	0.005–0.014	-	[53,54]
Austria Germany Italy Sardinia	0.725–0.831	0.120–0.190	0.049–0.085	-	-	-	-	-	[44,50,57]
Ethiopia Sidamos	0.157	0.236	0.018	0.400	0.135	0.027	0.027	-	[49]
Angola	-	-	-	0.793	0.207	-	-	-	[43]
Mozambique	-	-	-	0.716	0.260	0.024	-	-	[43]
San	-	0.120	-	0.295	0.030	0.555	-	-	[55]
Khoikhoi	-	-	0.048	0.429	0.190	0.333	-	-	[55]
Japan	-	0.437	0.151	-	-	-	0.261	0.151	[74]

[a] More information on these populations and other populations are available in [1] and in the original references. See also [30–71].

9. Km Allotypes

9.1. Definition

Allotypes have been identified for the human IGKC gene and are designated as Km (for "kappa marker") (previously Inv) [25,26].

There are three kappa chain allotypes designated Km1, Km2, and Km3 that define three alleles. In 1961, Ropartz described the first IG light-chain allotype Inv(a) [25], now called Km2. One year later, the Inv(l) allotype, now called Km1, was described by the same group [26]. In 1962, Steinberg et al., described the third Km allotype, Inv(b) [27], now called Km3. They found that sera negative for Km1 and Km2 were always positive for Km3 and that sera negative for Km3 were always positive for Km1 and mostly also for Km2. Thus, the three Km allotypes define three alleles: Km3, Km1,2, and Km1.

9.2. Km Allotype Determination, Km Phenotypes, and Km Genotypes

The three Km allotypes, namely Km1, Km2, and Km3, are determined by the hemagglutination inhibition technique [30,33,34,36]. Given the rarity of anti-Km2 and anti-Km3 reagent antibodies, only the Km1 allotype is tested in most of the population studies. Km genotypes and observed phenotypes depend on the number of tested allotypes. In Table 14 are shown the following:

- The six Km genotypes defined by their Km alleles;
- The five Km phenotypes observed when sera are tested for the three allotypes Km1, Km2, and Km3;
- The three Km phenotypes observed when sera are only tested for allotypes Km1 and Km2;
- The two Km phenotypes observed when sera are only tested for allotype Km1.

Table 14. Km genotypes and observed Km phenotypes depending on the tested Km allotypes ([2] and this paper).

Km Genotypes	Km Phenotypes		
	Sera Tested for Allotypes Km1, Km2, and Km3	**Sera Only Tested for Allotypes Km1 and Km2**	**Sera Only Tested for Allotype Km1**
Km1/Km1	Km1	Km1,-2	Km1
Km1/Km3	Km1,3		
Km1/Km1,2 or Km1,2/Km1,2	Km1,2	Km1,2	
Km1,2/Km3	Km1,2,3		
Km3/Km3	Km3	Km-1,-2	Km-1

9.3. Km Phenotypes and Km Allele Frequencies in Different Populations

The two allotypes Km1 and Km2 mostly co-occur and are present in 10–20% of Caucasoid [30,36,38,51], 40–60% of Negroid [63], and 30–60% of Mongoloid [61] populations (Table 15) [1].

Table 15. Km phenotype [2] and this paper.

Km Phenotype Frequency	Populations		
	Caucasoid	**Negroid**	**Mongoloid**
Km3	80–90	40–60	40–70
Km1,2	10–20	40–60	30–60

Km allele frequency in the different populations is given in Table 16.

Table 16. Km allele frequency [2] and this paper.

Km Allele Frequency	Populations		
	Caucasoid	**Negroid**	**Mongoloid**
Km3	0.90–0.94	0.80–0.50	0.80–0.50
Km1,2	0.06–0.08	0.20–0.50	0.20–0.50
Km1	0.01	0.01	0.01

Details on extensive Km analysis in populations from Lebanon (6076 alleles studied in eight different communities) and Tunisia (756 alleles) [30,35,36] are available in IMGT Repertoire, https://www.imgt.org/IMGTrepertoire/ (accessed on 23 June 2023) > Allotypes > *Homo sapiens* IGKC [114]. (With permission from M-P. Lefranc and G. Lefranc, LIGM, Founders and Authors of IMGT®, the international ImMunoGeneTics information system®, https://www.imgt.org (accessed on 29 May 2023)).

9.4. IMGT Correspondence between Km Alleles and IGKC Allele Names

Km allotypes correspond to amino acid changes in the C region of the kappa chain (C-KAPPA) at position IMGT 45.1 and 101 [163–165] (Figure 11) (IMGT Repertoire, https://www.imgt.org/IMGTrepertoire/ (accessed 23 June 2023) > Alignments of alleles > *Homo sapiens* IGKC) [114].

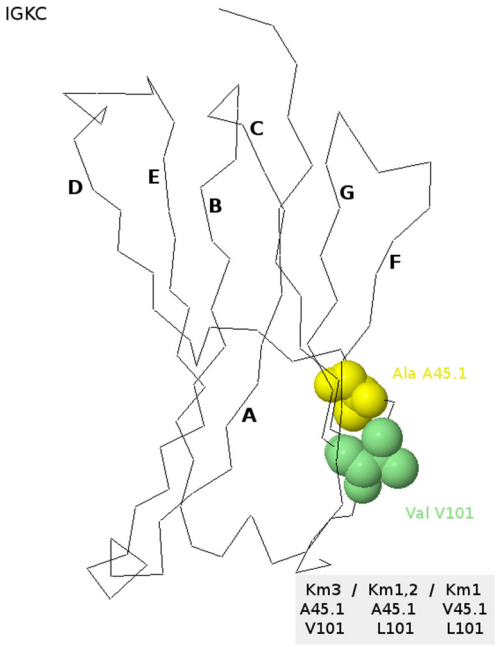

Figure 11. Three-dimensional structure of IGKC*01 ([2] and this paper). The C-KAPPA domain is from the b12 antibody (IMGT/3Dstructure-DB [143,144], code PDB:1hzh). The seven anti-parallel strands of the C-KAPPA (C-domain) are indicated by the letters A to G. The alanine Ala A45.1 (strand CD) and the valine Val V101 (strand F) are shown. The A45.1 and V101 correspond to the Km3 allotype. The A45.1 and L101 correspond to Km1,2 and the V45.1 and L101 to Km1. (With permission from M-P. Lefranc and G. Lefranc, LIGM, Founders and Authors of IMGT®, the international ImMunoGeneTics information system®, https://www.imgt.org (accessed on 29 May 2023).)

Km1 correlates with valine at position 45.1 (".1" for first position in the transverse CD strand [141]) (IGKC Val V45.1) and leucine at position 101 (IGKC Leu L101). Km1,2 correlates with alanine at position 45.1 (IGKC Ala A45.1) and leucine at position 101 (IGKC Leu L101), and Km3, the most frequent allotype, correlates with alanine at position 45.1 (IGKC Ala A45.1) and valine at position 101 (IGKC Val V101). Correspondence between Km alleles and IGKC allele names are shown in Table 17.

Table 17. Correspondence between Km alleles and IGKC alleles [2] and this paper.

Km Alleles	**IGKC Alleles**	**Amino Acid Positions** [a]		
		IMGT	**45.1**	**101**
		Exon	**(46)**	**(84)**
		Eu/Kabat	***153***	***191***
Km3	IGKC*01, IGKC*02, IGKC*03, IGKC*05		Ala g<u>c</u>c	Val g<u>t</u>c
Km1,2	IGKC*04		Ala g<u>c</u>c	Leu <u>c</u>tc
Km1	IGKC*06 [b]		Val (g<u>t</u>c)	Leu (<u>c</u>tc)

[a] Positions in bold are according to the IMGT unique numbering for C domain [141]; between parentheses, IMGT exon numbering [37]; in italics, Eu/Kabat numbering. Mutated nucleotides between codons are underlined. [b] IGKC*06 (not sequenced at the nucleotide level) corresponds to Km1 allele and has amino changes A45.1 > V and V101 > L (compared to IGKC*01). The expected codons (shown between parentheses) are gtc (V45.1) and ctc (L101), respectively [2]. (With permission from M-P. Lefranc and G. Lefranc, LIGM, Founders and Authors of IMGT®, the international ImMunoGeneTics information system®, https://www.imgt.org (accessed on 29 May 2023)).

The Km alleles comprise Km3, which corresponds to four IGKC alleles, namely IGKC*01, *02, *03, and *05; Km1,2, which corresponds to the IGKC*04 allele; and Km1, which corresponds to the IGKC*06 allele. Correspondence between C numberings is available in IMGT Scientific chart [114] (Supplementary Table S2). "Alignments of alleles of *Homo sapiens* IGKC" is available in IMGT Repertoire [114] (Supplementary Table S11).

10. Discussion

Using the IMGT Scientific chart rules [114] and the IMGT unique numbering for C-domain [141], the 20 Gm, 3 Am, and 3 Km allotypes have been described with their combinations in Gm, Am, and Km alleles and their linkage in Gm–Am haplotypes ([2] and this paper). The standard IMGT concepts of description (labels), of classification (nomenclature, gene and allele names), and of numerotation (IMGT unique numbering, IMGT Colliers de Perles) have been used to bridge sequences and structures of the IG constant (C) domain of the heavy (gamma1, gamma2, gamma3, and alpha2) and light (kappa) chains to the IGHC and IGKC gene alleles and 3D domain structures [114,141]. As Gm, Am, and Km allotypes are identified serologically, they bring a fundamental unique property, which is the correlation between allotype amino acid changes and immunogenicity. They therefore represent a major system for understanding immunogenicity of the polymorphic IG chains in relation to amino acid and conformational changes. This standardized approach has been fundamental in the molecular characterization of the human IGHC genes (gene polymorphism or alleles [84,85,88,93,96,97], restriction fragment length polymorphism (RFLP) and A2m [85], RFLP and Gm [100–103,105,106], and IG heavy-chain structure in domains [161]) and of the IGH locus (IGHC gene order [98,99], gene conversion [84,87,90], and copy number variation (CNV) [162]), with allotypes providing unique clues to be explored. It is the absence of the G1m allotype that was the starting point of the discovery of multigene deletions in healthy individuals [81–83,89,91,92,94,95], of the IGHC gene order in humans [161,162], and of the move to molecular biology with the sequencing of many IG genes, followed by the full description of the *Homo sapiens* T-cell receptor gamma (TRG) locus and, in 1989, the entry of the *Homo sapiens* IG and TR genes in the Human Gene Mapping 10 (HGM 10) database, the creation of IMGT, and the founding of immunoinformatics [114]. Given the diversity and complexity of the IG and TR genes, knowledge of natural data such as allotypes and IG chain immunogenicity opens the way for immunoinformatics of personalized therapeutic antibodies and engineered variants.

The most prevalent Gm alleles in different populations are shown in Table A2. This type of information is of interest for the design of therapeutical monoclonal antibodies if the target has a geographical distribution. For a frequent Gm allele in populations, several IGHG alleles may be found that differ only at the level of the nucleotide sequence, as illustrated for the G1m alleles in Appendix B (Table A2). A first example is the G1m17,1 allele encoded by four alleles, IGHG1*01, IGHG1*02, IGHG1*05, and IGHG1*09, which only differ at the nucleotide level. A second example is the G1m3 allele encoded by the two alleles IGHG1*03 and IGHG1*06. In an attempt to reduce the risk of anti-G1m1 antibodies interfering with therapy, Carter et al. [166] engineered the trastuzumab heavy chain with two amino acid changes, IGHG1 CH3 D12 > E and L14 > M, to convert the G1m1 allotype to the isoallotype nG1m1, with the resulting gamma1 chain being Gm17, nG1m1. This variant, designated as IGHG1*03v (Table A2) (or, using the generic description: IGHG1*03v, G1m3 > G1m17, nG1m1 (CH1 R120 > K, CH3 E12, M14)), is frequently used in antibody engineering. It has a lysine K120 in CH1 (G1m17) and the E12 and M14 in CH3 (nG1m1). The second engineered variant, IGHG1*01v, corresponds to the natural G1m3,1, nGm17 allele and to the IGHG1*08 allele found in Mongoloid populations. Appendix C (Materials A1 to A10) provides complementary information from the IMGT Repertoire (IG and TR) on allotypes Gm, Km, and Am and isotypes IGLC.

As amino acids of all Gm allotypes have been defined, it becomes possible to assign the nucleotide sequence of the IGHG allele(s) to it. It is the presence of a leucine (instead of the usual valine) on a peptide obtained from a LC-MS screening for Fc allelic variants [167]

and unambiguously identified as the leucine characteristic of the G1m27 that led to the assignment of the IGHG1*04 allele to the G1m17,1,27 allele, which was detected serologically. Mass spectrometry detection of G3m and IGHG3 alleles has been performed for the follow-up of differential mother and neonate IgG3 [168], and molecular validation of the proteomic results has been performed by sequencing [169]. The use of the IMGT unique numbering for C domain in the study of allotypes and the recent motif description of engineered variants modifying the effector and structural properties of the therapeutical antibodies [170] contribute to bridging genes, sequences, structures, and functions despite their diversity and heterogeneity.

Supplementary Materials: Table S1: IMGT Scientific chart > Correspondence between the IMGT unique numbering for C-DOMAIN, the IMGT exon numbering, the EU and Kabat numberings: Human IGHG: https://www.imgt.org/IMGTScientificChart/Numbering/Hu_IGHGnber.html (accessed on 28 June 2023). Table S2: IMGT Scientific chart > Correspondence between the IMGT unique numbering for C-DOMAIN, the IMGT exon numbering, the EU and Kabat numberings: Human IGKC: https://www.imgt.org/IMGTScientificChart/Numbering/Hu_IGKCnber.html (accessed on 28 June 2023). Table S3: IMGT Education > Aide-mémoire > IMGT classes of the 20 common amino acids. https://www.imgt.org/IMGTeducation/Aide-memoire/_UK/aminoacids/IMGTclasses.html (accessed on 28 June 2023). Table S4: IMGT Repertoire (IG and TR) > Protein displays: human (*Homo sapiens*) IGHC. https://www.imgt.org/IMGTrepertoire/Proteins/proteinDisplays.php?species=human&latin=Homo%20sapiens&group=IGHC (accessed on 28 June 2023). Table S5: IMGT Repertoire (IG and TR) > Protein display: Human IGH C-REGIONs https://www.imgt.org/IMGTrepertoire/Proteins/protein/human/IGH/IGHC/Hu_IGHCallgenes.html (accessed on 28 June 2023). Table S6: IMGT Repertoire (IG and TR) > Alignment of alleles: human (*Homo sapiens*) IGHG1. https://www.imgt.org/IMGTrepertoire/Proteins/alleles/index.php?species=Homo%20sapiens&group=IGHC&gene=IGHG1 (accessed on 23 June 2023). Table S7: IMGT Repertoire (IG and TR) > Alignment of alleles: human (*Homo sapiens*) IGHG2. https://www.imgt.org/IMGTrepertoire/Proteins/alleles/index.php?species=Homo%20sapiens&group=IGHC&gene=IGHG2 (accessed on 23 June 2023). Table S8: IMGT Repertoire (IG and TR) > Alignment of alleles: human (*Homo sapiens*) IGHG3. https://www.imgt.org/IMGTrepertoire/Proteins/alleles/index.php?species=Homo%20sapiens&group=IGHC&gene=IGHG3 (accessed on 23 June 2023). Table S9: IMGT Repertoire (IG and TR) > Alignment of alleles: human (*Homo sapiens*) IGHG4. https://www.imgt.org/IMGTrepertoire/Proteins/alleles/index.php?species=Homo%20sapiens&group=IGHC&gene=IGHG4 (accessed on 23 June 2023). Table S10: IMGT Repertoire (IG and TR) > Alignment of alleles: human (*Homo sapiens*) IGHA2. https://www.imgt.org/IMGTrepertoire/Proteins/alleles/index.php?species=Homo%20sapiens&group=IGHC&gene=IGHA2 (accessed on 23 June 2023). Table S11: IMGT Repertoire (IG and TR) > Alignment of alleles: human IGKC. https://www.imgt.org/IMGTrepertoire/Proteins/alleles/index.php?species=Homo%20sapiens&group=IGKC&gene=IGKC (accessed on 23 June 2023).

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Appendix A

Table A1. Gm haplotypes (WHO/IMGT nomenclature) and correspondence with previous designation [2] and this paper.

Gm Haplotypes	Gm Haplotypes [a] (WHO/IMGT Nomenclature)	Previous Designation [b]
A	Gm5*;3;23	Gmb*;f;n
B	Gm5*;3;..	Gmb*;f;..
C	Gm21*;17,1;..	Gmg*;z,a;..
D	Gm21*;17,1,2;..	Gmg*;z,a,x;..
E	Gm5*;17,1;..	Gmb*;z,a;..
F	Gm6*;17,1;..	Gmc3*;z,a;..
G	Gm24*;17,1;..	Gmc5*;z,a;..
H	Gm15*;17,1;..	Gms*;z,a;..
I	Gm16*;17,1;..	Gmt*;z,a;..
J	Gm5*;3,1;23	Gmb*;f,a;n
K	Gm5*;3,1;..	Gmb*;f,a;..
L	Gm5*;17,1,2;..	Gmb*;z,a,x;..
M	Gm21*;17,1;23	Gmg*;z,a;n

[a] 24* was previously designated as 6,24*, and 16* as 15,16*. [b] c5* was previously designated as c3, c5*, and t* as s,t*.

Appendix B

Table A2. G1m allotypes and IGHG1 alleles in populations, and engineered. Correspondence between the IGHG1 alleles and G1m alleles, including engineered variants IGHG1*01v and IGHG1*03v (in red) used in therapeutical antibodies [2] and this paper.

IGHG1 Alleles	G1m Alleles [a]		IMGT Amino Acid Positions [b]								Populations [2] and This Paper
			CH1		CH3						
	Allotypes	Isoallotype [c]	103	120	12	14	101	110	115	116	
				G1m17/ nG1m17	G1m1/ nG1m1		/G1m27	/G1m2	/G1m28	-	
				G1m3 [d]							
IGHG1*01, IGHG1*02, IGHG1*05, IGHG1*09	G1m17,1		I	**K**	**D**	**L**	V	A	H	Y	Caucasoid Negroid Mongoloid
IGHG1*03, IGHG1*06	G1m3	*nG1m1*, *nG1m17*	**I**	**R**	E	M	V	A	H	Y	Caucasoid
IGHG1*04	G1m17,1,27		I	**K**	**D**	**L**	**I**	A	H	Y	Negroid
IGHG1*07	G1m17,1,2		I	**K**	**D**	**L**	V	**G**	H	Y	Caucasoid Mongoloid
IGHG1*08	G1m3,1	*nG1m17*	**I**	**R**	**D**	**L**	V	A	H	Y	Mongoloid
IGHG1*05p [e]	G1m17,1,28		I	**K**	**D**	**L**	V	A	**R**	**Y**	Negroid
IGHG1*06p [e]	G1m17,1,27,28		I	**K**	**D**	**L**	**I**	A	**R**	**Y**	Negroid
IGHG1*09p [e]	G1m17	*nG1m1*	**I**	**K**	E	M	V	A	H	Y	Caucasoid
IGHG1*01v	G1m3,1	*nG1m17*	**I**	**R**	**D**	**L**	V	A	H	Y	engineered
IGHG1*03v	G1m17	*nG1m1*	I	**K**	E	M	V	A	H	Y	engineered

[a] In Negroid populations, the G1m17,1 allele frequently includes G1m27 and/or G1m28, leading to three additional G1m. alleles, G1m17,1,27, G1m17,1,28 and G1m17,1,27,28 [2]. [b] Amino acids corresponding to G1m allotypes are shown in bold. [c] The nG1m1 and nG1m17 isoallotypes present on the Gm1-negative and Gm-17 negative gamma-1 chains (and on other gamma chains) are shown in italics. [d] The presence of R120 is detected by anti-nG1m17 antibodies whereas the simultaneous presence of I103 and R120 on the gamma1 chains is detected by anti-Gm3 antibodies [2]. [e] IGHG1*05p, IGHG1*06p, IGHG1*09p amino acids are expected [83] but not yet sequenced at the nucleotide level and therefore these alleles are not shown in IMGT Repertoire (IG and TR) Alignments of alleles. The definitive allele number will be assigned by chronological order following the availability of the nucleotide sequences. Allotypes on CH1 include G1m17 K120 (blue) vs. nG1m17, G1m3 R120 (dark blue). Allotypes on CH3 include G1m1 D12, L14 (yellow) vs. nG1m1 E12 M14 (pale yellow), G1m27 I101 (green), G1m2 G110 (purple), G1m28 R115, Y116 (orange).

Appendix C. IMGT Repertoire (IG and TR): Allotypes Gm, Km and Am and Isotypes IGLC

Material A1: IMGT Repertoire (IG and TR) > Allotypes: Human (*Homo sapiens*) IGHC > G1m allotypes: https://www.imgt.org/IMGTrepertoire/Proteins/allotypes/human/IGH/IGHC/G1m_allotypes.html (accessed on 28 June 2023).

Material A2: IMGT Repertoire (IG and TR) > Allotypes: Human (*Homo sapiens*) IGHC > G2m allotypes: https://www.imgt.org/IMGTrepertoire/Proteins/allotypes/human/IGH/IGHC/G2m_allotypes.html (accessed on 28 June 2023).

Material A3: IMGT Repertoire (IG and TR) > Allotypes: Human (*Homo sapiens*) IGHC > G3m allotypes: https://www.imgt.org/IMGTrepertoire/Proteins/allotypes/human/IGH/IGHC/G3mallotypes.html (accessed on 28 June 2023).

Material A4: IMGT Repertoire (IG and TR) > Allotypes: Human (*Homo sapiens*) IGHC > A2m allotypes: https://www.imgt.org/IMGTrepertoire/Proteins/allotypes/human/IGH/IGHC/A2mallotypes.html (accessed on 28 June 2023).

Material A5: IMGT Repertoire (IG and TR) > Allotypes: Human (*Homo sapiens*) IGHC > Em allotype: https://www.imgt.org/IMGTrepertoire/Proteins/allotypes/human/IGH/IGHC/Em%20allotype.html (accessed on 28 June 2023).

Material A6: IMGT Repertoire (IG and TR) > Allotypes: Human (*Homo sapiens*) IGHC > Part 1—Gm allotypes and Gm haplotypes https://www.imgt.org/IMGTrepertoire/Proteins/allotypes/human/IGH/IGHC/Hu_IGHCallotypes1.html (accessed on 28 June 2023).

Material A7: IMGT Repertoire (IG and TR) > Allotypes: Human (*Homo sapiens*) IGHC > Part 2—Prevalent Gm haplotypes of the human IGHG3, IGHG1 and IGHG2 alleles in different populations https://www.imgt.org/IMGTrepertoire/Proteins/allotypes/human/IGH/IGHC/Hu_IGHCallotypes2.html (accessed on 28 June 2023).

Material A8: IMGT Repertoire (IG and TR) > Allotypes: Human (*Homo sapiens*) IGHC > Part 3—*Bam*HI-*Sac*I RFLP alleles, BS haplotypes and Gm haplotypes https://www.imgt.org/IMGTrepertoire/Proteins/allotypes/human/IGH/IGHC/Hu_IGHCallotypes3.html (accessed on 28 June 2023).

Material A9: IMGT Repertoire (IG and TR) > Allotypes: Human (*Homo sapiens*) IGKC > Km allotypes https://www.imgt.org/IMGTrepertoire/Proteins/allotypes/human/IGK/IGKC/Hu_IGKCallotypes.html (accessed on 28 June 2023).

Material A10: IMGT Repertoire (IG and TR) > Isotypes: Human (*Homo sapiens*) IGLC > IGLC isotypes https://www.imgt.org/IMGTrepertoire/Proteins/isotypes/human/IGL/IGLC/Hu_IGLCisotypes.html (accessed on 28 June 2023).

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