From HGM10 (1989) to HGM 2010: IG and TR gene concept and IMGT/GENE-DB

Véronique Giudicelli and Marie-Paule Lefranc

IMGT®, the international ImMunoGeneTics information system®, Laboratoire d'ImmunoGénétique Moléculaire LIGM, Université Montpellier 2, Institut de Génétique Humaine IGH, CNRS UPR 1142, 141 rue de la Cardonille, F-34396 Montpellier cedex 05, France

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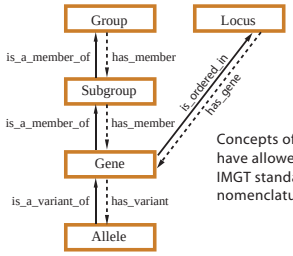
The immunoglobulin (IG) and T cell receptor (TR) major loci span about 6 Megabases (Mb) of the human genome on chromosomes 2, 7, 14 and 22. There are seven major loci: three IG loci (IGH, IGK, IGL) and four TR loci (TRA, TRB, TRG, TRD), with a distinct repartition of the variable (V), diversity (D), joining (J) and constant (C) genes. The human genome comprises a total number of 610-667 IG and TR genes (373-424 IG and 237-243 TR), depending on the haplotypes, per haploid genome [1, 2] of which 531-588 genes are located in the major loci (distributed in 369-418 V, 32 D, 105-109 J and 25-29 C genes). There are also 79 orphons (70 IG and 9 TR) including two processed IG genes, outside the major loci. The number of functional IG and TR genes is 308-356 (137-171 IG and 172-185 TR) per haploid genome. All these genomic data are managed in the IMGT® gene database, IMGT/GENE-DB [3], according to the axioms and concepts of IMGT-ONTOLOGY [4]. In May 2010, IMGT/GENE-DB manages 683 human genes and 1254 alleles (including 16 non-mapped genes).

[1] Lefranc M.-P. and Lefranc G., The Immunoglobulin FactsBook, Academic Press, London, 458 pages (2001).
[2] Lefranc M.-P. and Lefranc G., The T cell receptor FactsBook, Academic Press, London, 398 pages (2001).
[3] Giudicelli V. et al. Nucleic Acids Res., 33, D256-261 (2005).
[4] Duroux, P. et al. IMGT-Kaleidoscope, the Formal IMGT-ONTOLOGY paradigm. Biochimie, 90, 570-583 (2008)

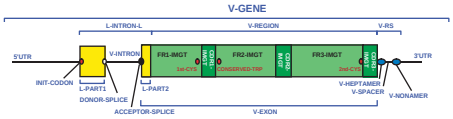
IMGT-ONTOLOGY AXIOMS AND CONCEPTS

CLASSIFICATION



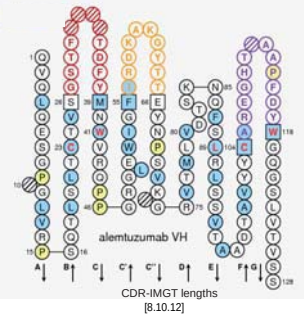
Concepts of classification have allowed to define the IMGT standardized nomenclature for IG and TR.

DESCRIPTION



Concepts of description provide the standardized labels and the rules to annotate the IG and TR sequences and 3D structures.

NUMEROTATION



CDR-IMGT lengths [8.10.12]

The concepts 'IMGT unique numbering' and its graphical representation, the 'IMGT Collier de Perles' determine the principles of a unique numbering for variable and constant domains of IG and TR. They allow to delimit the framework and complementarity determining regions. They represent a major breakthrough and are the flaship of IMGT® since they allow to bridge the gap between sequences and structures.

IMGT/GENE-DB DATABASE

IMGT/GENE-DB, the IMGT® genome database, was developed to standardize and classify the IG and TR gene data and to manage the related knowledge. Human IG and TR IMGT reference sequences, after approval by HGNC, were provided to NCBI Entrez Gene, EBI Ensembl and Wellcome Trust Sanger Institute Vega, for genome annotation. The translation of the IG and TR constant genes was provided to UniProt in 2008.

IMGT/GENE-DB provides links to IMGT® sequence database (IMGT/LIGM-DB) and 3D structure database (IMGT/3Dstructure-DB), to IMGT® tools for sequences (IMGT/V-QUEST, IMGT/DomainGapAlign, etc.), genomic data (IMGT/GeneFrequency, etc.), structural data (IMGT/DomainDisplay, etc.), and to IMGT Repertoire Web resources (Chromosomal localizations, Locus representations, Gene tables, etc.).

IMGT/GENE-DB entry for *Homo sapiens* IGHV1-3

- IMGT gene name and definition
  - IMGT gene name : *Homo sapiens* IGHV1-3
  - IMGT gene definition : Immunoglobulin heavy variable 1-3
- Chromosomal localization
  - Locus name : *Homo sapiens* IGH locus
  - Chromosome : 14
  - Chromosomal localization : 14q32.33
- Number of alleles: 2
- IMGT reference alleles :

An IMGT/GENE-DB entry includes IMGT gene name and definition, Chromosomal localization, Number of alleles, IMGT reference alleles, IMGT Repertoire links and table of annotated cDNA sequences in IMGT/LIGM-DB and, if available, protein structures in IMGT/3Dstructure-DB.

IGHV1-3 allele names	Gene functionality	R	T	Pr	IMGT/LIGM-DB reference sequences		
					Clone names	Accession numbers	Molecule type
IGHV1-3*01	F		+		VI-3b	X62109	gDNA
IGHV1-3*02	F				VI-3	X62107	gDNA

IGHV1-58 allele names	Gene functionality	IMGT/GENE-DB reference sequences (in FASTA format)				
		V-REGION			L-PART1+V-EXON	
		F+ORF+all P	F+ORF+in-frame P with IMGT gaps		F+ORF+all P	F+ORF+in-frame P
IGHV1-3*01	F	nucleotides	nucleotides	amino acids	nucleotides	amino acids
IGHV1-3*02	F					

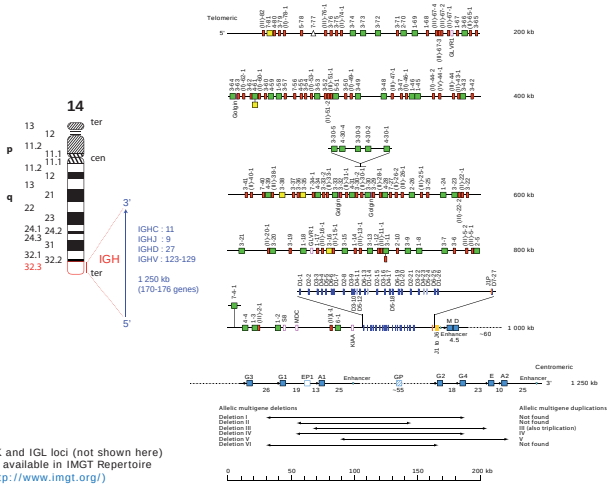
- IMGT Repertoire links :

Locus and genes	Proteins and alleles
Gene table	Alignment of alleles
Locus representation	Tables of alleles
Chromosomal representation	protein displays

- Annotated IMGT/LIGM-DB cDNA sequences for *Homo sapiens* IGHV1-3: 172
- Annotated IMGT/3Dstructure-DB structures for *Homo sapiens* IGHV1-3: 7

HUMAN IMMUNOGLOBULIN GENES

IGH locus at 14q32.3



IGK and IGL loci (not shown here) are available in IMGT Repertoire (http://www.imgt.org/)

Total number of IG genes

The human genome comprises 373-424 IG genes (303-354 genes located in the 3 major IG loci and 70 orphons), per haploid genome.

Locus	Major loci						Number of orphons	Total number of IG genes including orphons
	Chromosomal localization	V	D	J	C	Total number of genes		
IGH	14q32.33	123-129[b]	27	9	11[a]	170-176[b]	37[c]	207-213[b,c]
IGK	2p11.2	(40[d] or) 76[e]	0	5	1	(46[d] or) 82	26	(72[d] or) 108[e]
IGL	22q11.2	73-74[f]	0	7-11	7-11	87-96	7[g]	94-103[f]
Total number of genes		236-279	27	21-25	19-23	303-354	70	373-424

Number of functional IG genes

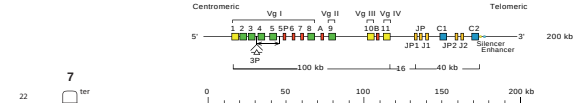
The functional IG genes (137-171 depending on the haplotypes) are located in the 3 major IG loci. Different molecular mechanisms (V-J and V-D-J rearrangements, N-diversity, and for IG, somatic hypermutations), unique to vertebrates, allow to create a huge repertoire of **2x10¹² IG** (or antibodies) per individual.

Locus	Locus size (kb)	V	D	J	C	Number of functional IG genes
IGH	1250	38-46	23	6	9[a]	76-84
IGK	1820	34-38	0	5	1	40-44
	500	17-19[d]				23-25[d]
IGL	1050	29-33	0	5	4-5	38-43
Total of functional IG genes		101-117	23	16	14-15	137 -171
		84-98[d]				

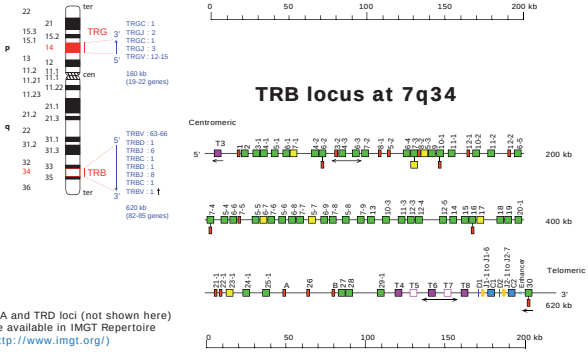
[a] Allelic IGHC multigene deletions, duplications and triplications have been described in healthy individuals. The number of IGHC genes is 5 (deletions I, III, and V), 6 (deletions IV and VI), or 8 (deletion II), per haploid genome.
In haplotypes with multigene duplication or triplication, the exact number of functional IGHC genes per haploid genome is not known.
[b] Not included 9 non-mapped IGHV genes.
[c] Included the IGHC processed gene, IGHEP2, localized on chromosome 9 (9p24.2-24.1).
[d] Number of genes in the rare IGKV haplotype without the distal V-CLUSTER.
[e] Not included 6 non-mapped IGKV genes.
[f] Not included one non-mapped IGLV gene.
[g] Included the IGLJ-C/OR18 processed gene, localized on chromosome 18 (18p11.31).

HUMAN T CELL GENES

TRG locus at 7p14



TRB locus at 7q34



TRA and TRD loci (not shown here) are available in IMGT Repertoire (http://www.imgt.org/)

Total number of TR genes

The human genome comprises 237-243 TR genes (228-234 genes located in the 4 major TR loci and 9 orphons), per haploid genome.

Locus	Major loci						Number of orphons	Total number of TR genes including orphons
	Chromosomal localization	V	D	J	C	Total number of genes		
TRA	14q11.2	54[a]	0	61	1	116[a]	0	116[a]
TRB	7q34	64-67	2	14	2	82-85	9	91-94
TRG	7p14	12-15	0	5	2	19-22	0	19-22
TRD	14q11.2	3 (8[a])	3	4	1	11 (16[a])	0	11 (16[a])
Total number of genes		133-139	5	84	6	228-234	9	237-243

Number of functional TR genes

The functional TR genes (172-185 depending on the haplotypes) are located in the 4 major TR loci. Different molecular mechanisms (V-J and V-D-J rearrangements, N-diversity), unique to vertebrates, allow to create a huge repertoire of **2x10¹² TR[d]** per individual.

Locus	Locus size (kb)	V	D	J	C	Number of functional TR genes
TRA	1000	43-45[a]	0	50	1	94-96[a]
TRB	620	40-48	2	11-13	2	56-65
TRG	160	4-6	0	5	2	11-13
TRD	60[b] (530[c])	3 (7-8[a])	3	4	1	11 (15-16[a])
Total of functional TR genes		90-102	5	71-72	6	172-185

[a] Including 5 TRAV/TRADV genes. These 5 genes are counted only once when both TRA and TRD loci are considered together: the number of functional TRAV and TRDV genes is 46-48 and the total number of functional genes is 105-107.
[b] Size of the cluster from TRDV2 to TRDV3.
[c] Distance between the most 5' TRAV/DV gene (TRAV14/DV4) and the most 3' gene of the TRD locus (TRDV3).
[d] Taking into account the rearrangement with 2 or 3 TRDD (4 possible combinations: D1,D2; D1,D3; D2,D3; D1,D2,D3).

IMGT founder and director: Marie-Paule Lefranc (Marie-Paule.Lefranc@igh.cnrs.fr)
Bioinformatics manager: Véronique Giudicelli (Veronique.Giudicelli@igh.cnrs.fr)
Computer manager: Patrice Duroux (Patrice.Duroux@igh.cnrs.fr)
Interface design: Chantal Ginestoux (Chantal.Ginestoux@igh.cnrs.fr)
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