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Review Article

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ABSTRACT

The genes that code for major histocompatibility complex (MHC) molecules, the antibody (immunoglobulins) and the T-cell receptor occur in multiple forms which helps to create diversity. This review describes polygeny as seen in the MHC and the antibody/TCR genes and how they generate diversity. Also described is the organisation, gene structure, pattern of inheritance, and regulation of transcription of MHC and antibody/TCR genes. The differences and similarities between the MHC and antibody/TCR genes genes are also highlighted.

INTRODUCTION

The genes of the major histocompatibility complex (MHC), the T-cell receptor and antibody (Immunoglobulin) encode for the MHC molecules, TCR and Ig respectively which all take part in the immune response. The TCR and the Ig bind pathogens and antigens, but the TCR can only bind antigens as processed peptides on antigen presenting cells which are bound to MHC molecules. MHC molecules are expressed on most cells of the body.

These molecules or receptors all function together to achieve the purpose of mounting an immune response against invading pathogens, because of this oneness of purpose, the molecules and the genes that code for them share some basic features, though with some differences. The TCR and antibody receptor also known as B- cell receptor (BCR) are basically the same in their structure, function and the genes that encode for them. The MHC molecule however, shows some basic differences from the TCR and BCR, in function, structure, and the genes which code for them.

Basis For Variability Between MHC Genes And The Antibody/TCR Genes

Multiplicity of genes (polygeny)

Both the MHC and antibody/TCR genes have several genes which have been said to result from gene duplication and mutations, as an evolutionary measure [Yeager and Hughes, 1991; Ohno, 1970]. This helps in creating diversity for the MHC and antibody/TCR genes, the similarities and differences between both types are discussed below.

MHC Genes

About 224 gene loci have been identified for the MHC [The MHC Consortium, 1999]; these gene loci are located on the long arm of chromosome 6; between 6p21.1 and 6p21.3 in humans (Dausset, 1981). They span over 4 centimorgans or 4 megabase pair of DNA [Stephens *et al*, 1999] and about 2 centimorgans of DNA on chromosome 17 inmice [Steinmetz and Hood, 1983]. The genes are divided into three regions: class I genes on the telomeric end, the class II genes on the Centromeric end and the class III genes in between class I and class II genes [Trowsdale and Campbell, 1988]. The class I region contains the genes for the classical MHC I: HLA-A,

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HLA-B and HLA-C) [Guillemot *et al*, 1988]. It also contains the genes for the non-classical MHC I molecules which are HLA-D, HLA-G and HLA-E and HLA-F. The non-classical MHC molecules do not take part in antigen presentation (Koller *et al*, 1988). A total of about 17 related genes have been identified in human HLA -1 region (Lawlor *et al*, 1990) and 36 in mice class I region (K, D, L, 11 Qa-1, Qa-2, and Tl) (Koller *et al*, 1989). The class II region contain the loci for the for HLA-DR, HLA-DQ, and HLA-DP with 6 alpha (α) and 10 beta (β) genes which code for the MHC class II molecules [Andersson *et al*, 1987]. Other genes on the class II regions are DNA, DOB, DQB2, and DGA2 [Trowsdale and Campbell, 1992]. The class II region also contain some novel genes such as the collagen genes (COL11A2) [Hanson *et al*, 1989], KE3, KE5 [Abe *et al*, 1998], RING1, RING 2 and RING5 [Hanson *et al*, 1989;Abe *et al*, 1988]. The region also contains the genes for Tapasin, tap I, tap II, LMP3 and LMP7 (involved in antigen presentation by MHC I)[Herberg *et al*, 1998b], DAXX(which codes for an effector of FAS)[Chang *et al*, 1998], RGL2 (which codes for an effector of RAS)[Herberg *et al*, 1998a], and GM2 which has been recently found to be involved to influence MHC I antigen presentation in mice[Simmons *et al*, 1997b]. The class III region contain over 60 genes which are heterogeneous [The MHC Consortium, 1999]; most of the products coded for do not take part in the immune system. These genes include those of complement factors C4, C2, factor B, others are the genes for the tumour necrosis factor A and B, genes for the heat shock proteins (HSP70 1 and 2), CYP21, Lymphotoxins α and β, tenascine (TNX), Ig SF [Caroll *et al*, 1984; Caroll *et al*, 1985;C aroll *et al*, 1987;Sargent *et al*, 1989; Milner and Campbell, 1990; Schwaiger and Epplen, 1995].

Antibody/TCR genes

The genes for TCR are located on four loci; TCR-α (TRCA), TCR-β (TRCB), TCR-γ (TRCG), and TCR-δ (TRCD) which code for the α, β, γ and δ chains respectively TRCA is located on chromosome 14; TRCD is embedded within the TRCA locus.The TRCG locus and the TRCB is on chromosome 7 (chromosome 13 for mice)[LeFranc and LeFranc, 2001a]. The antibody genes loci are the IGH, IGλ, and IGκ which code for the heavy chain, the lambda and kappa light chains respectively. These gene loci are located on separate chromosomes; chromosome 2 for IGk, chromosome 22 for IGλ and chromosome 14 for IGH [LeFranc and LeFranc, 2001b]. The gene loci for both the TCR and the antibody contain multiple gene segments which are non-contiguous. The TCRA contain 70 variable (V) gene segments, 61 joining (J) segments and 1 C segment[Toyonaga *et al*. 1985; Roman- Roman *et al*, 1991], TCRB contain 67 V gene segments, 13 J genes, 1 D gene segment[Rowen *et al*, 1996], TCRG contains 14 V gene segments, 3J[LeFranc *et al*, 1986], TCRD locus consists of 3D gene segments, 4 J gene segments, and 1 C gene segment[LeFranc, 2000]. The antibody gene loci for the light chain kappa contains 40 V gene segments and 5 J segments, that for the lambda light chain has 30 V gene segments and 4 J segments. The heavy chain genes consist of 40 V, 25 D and 6 J gene segments [LeFranc and LeFranc, 2001b; Giudicelli, 2005].

One difference here between MHC and antibody/TCR genes is that the gene loci for the MHC are all located within one chromosome as a complex linked together in clusters, except for the gene that codes for beta2 micro globulin (2m) chain which is located on chromosome 15 [Tait, 1996]. On the other hand, for the antibody/TCR genes, the gene loci which code for the different polypeptide chains are located on different chromosomes and are non-contiguous. As stated earlier, one common similarity between the MHC and the antibody/TCR gene sequences is in the duplication of genes or presence of multiple genes. The reason for this is to create diversity to meet up with the challenge of different antigens. Some of these genes are not functional (pseudogenes), but while the MHC genes are complete gene loci, that for the antibody/TCR are segments within loci which have to be re-arranged to form complete coding sequences. The MHC also contains a lot of other genes which have functions not related to antigen presentation but useful in the immune system, and some that code for products that play different role in antigen processing, like the Tapasin gene which codes for Tapasin involved in the transport of peptides being processed in the MHC molecule. Other genes found in the MHC code for products which do not have immune functions.

Gene organization

MHC

The MHC is composed of long stretches of DNA which vary in their guanosine (G) + cytosine (C) content, the G + C content determines the density of the chromosomes [Bernadi, 1993; Craig and Bickmore, 1993]. The MHC is quite dense, one of the densest known, with about 1 gene per 12.9 kb in the class III regions (the class III region being the densest) [Carroll *et al*, 1985]. The class I gene loci occupy approximately 1.1 mbp[Schimidt and Orr,1991] at the telomeric end [Trowsdale and Campbell, 1988], with HLA-A being about 0.8mbp from HLA-C and HLA -B being 0.2mbp from HLA-C.HLA-E is between HLA-A and HLA-C, while HLA-G and HLA-F are telomeric to HLA-A [Schimidt and Orr,1991]. The class II loci occupy 1mbp of DNA and are Centromeric[Hardy *et al*, 1986] while the class III region occupy 1.1mbp of DNA and is central [Carroll *et al*, 1985; Carroll *et al*, 1987].

Antibody/TCR

The organisation of the antibody/TCR genes is different from that of the MHC genes, and they do not have the level and pattern of gene density described for the MHC. The TCRD gene segments are located within the TCRA gene loci on chromosome 14q11-12, between its V and J gene segments [LeFranc and LeFranc, 2001a]. The J gene segments are spread over an 800kb of DNA [Toyonaga *et al*, 1985; Roman-Roman *et al*, 1991]. The TCRB loci is at position 7q32-35[Tait, 1996] , its V gene are grouped into 23 families based on their nucleotide sequence identity [Toyonaga and Mak, 1987] while the C, J and D gene segments associate as clusters known as the D-J-C clusters[Arden *et al*,1995] . The TCRB spans over 900kb of DNA in humans [Lai *et al*, 1988]. The TCRG gene loci also have a J-C cluster, with its V-gene segment grouped into 4 families [Hodges *et al*, 2003]. It is located at position 7p15 [Giudicelli *et al*, 2005] and spans over 160kb of DNA [Fox *et al*, 1987]. For the IG genes, the VH loci lie close to the

telomere of chromosome 14[Matsuda *et al*, 1998], spanning about 1.5mb of DNA and close to the DH loci [Chevillard *et al*, 2002]. The DH gene segments are distributed over a 86kb of DNA [Degner –Leisso and Feeney, 2010]. The CH gene clusters that are functional are located within 300-320 kb of DNA [Bottaro *et al*, 1989].

Gene structure

MHC

The cDNA of the MHC I genes are split into 8 exons. The exons code for the different domain of the MHC molecule; the first exon codes for a leader or signal peptide which initiates transcription, the second, third and fourth exons code for the 1,2, and 3 domains, while the 6th, 7th and 8th exons code for the transmembrane and cytoplasmic domain[Tait, 1996].

Antibody/TCR

The genes of the antibody/TCR do not have the large number of exons contained in the MHC genes. The D and J gene segments of the antibody/TCR have very small coding regions which are about 8-37bp and 37-69bp [Lane *et al*, 2010]. The V gene segments consist of only 2 exons; the leader exon and the V- exon [LeFranc and LeFranc, 2001b], separated by introns. They also have a recombination signal sequence (RSS) located 3' of the V-genes, 5' of J-gene and both sides of the D-gene segments. The RSS is a non-coding sequence of a heptamer, nonamer and a spacer. The RSS guides the gene re-arrangement process. This RSS is not present in the MHC genes and is in fact absent from other conventional genes [LeFranc and LeFranc, 2001a; LeFranc and LeFranc, 2001b]. The CH genes however, consist of several exons with 1 exon coding for each CH domain and another for the hinge region [Flanagan and Rabbitts, 1982; Rabbitts *et al*, 1981]. The CH genes are also preceded by a Switch (S) gene needed for isotope switch [Shimizu and Honjo, 1984]. This is also not present in the MHC genes. The exons of the different gene segments are re-arranged, with the splicing of the introns to form the complete coding sequence for the receptors. The V-region exon codes for the complementarity determining region 1 and 2 (CDR1 and 2), the D exon codes for CDR3 [Tonegawa, 1983].

Pattern of inheritance and expression

The genes of the MHC are inherited and expressed in a co-dominant fashion so the alleles on both chromosomes code for a protein product with heterozygosity in most cases [Tait, 1996]. The pattern of expression is different for antibody/TCR genes, usually only one allele is expressed. Successful and productive re-arrangement for the gene that codes for a particular polypeptide chain on one chromosome switches off that on the other chromosome -allelic exclusion. [Alt *et al*, 1993].

Regulation of gene transcription

MHC

The regulation of transcription of the MHC genes is at the transcriptional level and consists of a conserved upstream 5' flanking sequence elements; this is proximal to the promoter region. These elements are the W, S, Z X(X1 and X2), and Y boxes [Choi *et al*, 2011]. They are located about 100-200bp upstream of the transcription start site, and are shared by both class I and class II genes [55]. They provide binding sites for nuclear binding proteins; NF-, CREB, and RFX: RFXS, RFXAP, RFX-B/RFXANK [Reith and Mach, 2001; Ting and Trowsdale, 2002]. The MHC genes are also regulated by an enhancer A, IFN-stimulatory response element (ISRE), site α, and an enhancer β (enhB). Site α is located within the first 250bp of the promoter [Vanden- Elsen *et al*, 1998; Ting and Baildwin, 1993].

One striking difference between gene transcription of MHC and antibody/TCR genes, is the presence of the master regulator class II transcription activator (CIITA). CIITA does not bind to DNA directly but interacts with NF-, RFX 5, and other transcription factors [Ting and Trowsdale, 2002;Steimle *et al*, 1993; Steimle *et al*, 1994]. Although, it was initially reported to regulate only class II genes, it has been recently reported to also regulate class I genes as well [Ting and Baildwin, 1993]. Another difference between MHC genes and antibody/TCR genes regulation is that the regulation of MHC genes are also cytokine (IFN-) driven, interacting with the ISRE [Vanden- Elsen *et al*, 1998].

Antibody/TCR

The antibody/TCR gene promoters are located 5' of the V gene segments, it is brought close to enhancers 3' of the C-gene during recombination [Nelsen and Sen, 1992]. They are said to require the regulation of enhancers to be active. Transcription is thus required for recombination and transcription [Diamond *et al*, 1989], as different from MHC. Unlike the compact multicomponent motif with 4 sub-elements seen in the MHCgenes [Choi *et al*, 2011], the IG promoters contain different conserved octamer motifs at different sites and their binding elements [Nelsen and Sen, 1992]. Other sequence elements are conservedheptanucleotide sequence close to the octamersite. For TCR genes, conserved decamer motifs located 100bp from the TSS, and enhancers provide binding sites for the nuclear protein binding elements such as CREB- ATF, GATA-3, LEF-1/TCF-1, and Ets-1[Gottsschalk and Leoden, 1990; Anderson *et al*, 1989; Anderson *et al*, 1988].

Generation of diversity

This is one area where the MHC and antibody/TCR genes show a great deal of variability. Though both have the same purpose of generating a wide range of antigen binding sites to meet up with the challenge of the number of pathogens, but they do this via different mechanisms.

MHC Genes

Diversity here is generated at the population level as against that in antibody/TCR where it is generated at the individual level. There are multiple alleles for each MHC isoform within a population. Polymorphism is the mechanism by which diversity is generated by MHC genes. MHC genes are said to be extremely polymorphic and this greatly increases the diversity [Trowsdale 1993; Steinmetz, 1986]. As many as 100 alleles or more has been estimated per locus of the MHC genes in certainspecies [Klein, 1986]. Substitutions are mostly non-synonymous [Hughes and Nei, 1989]. Polymorphisms are more in the peptide-binding residues (exons 2 and 3 for class I and exon 2 for class II genes) and determine the variability seen in the 1 and 2 domains of the MHC I molecules and the 1, 1 domains of the MHC II molecules [Hughes and Nei, 1989].

This variability determines the peptide binding specificities. The difference in nucleotide substitution of different MHC alleles may be as much as 20 or more, with this also reflecting in the amino acid differences of the products they code [Rammensee *et al*, 1997].

Polymorphisms is said to be strongly selected by evolutionary pressures, and the mechanisms attributed are accumulation of point mutations, insertions and deletions. It has also been attributed to homologous equal recombination events and unequal crossing between different genes. Other genetic mechanisms such as gene conversion where there is a transfer of sequences between alleles in a non-reciprocal manner, has also been described to be a mechanism of generating polymorphism and diversity in the MHC genes [Steinmetz,1986]. Gene conversion is a process also involved in the generation of diversity in the Ig genes of some species. Some other workers however, have ruled it out as having a diversifying effect on the polymorphism seen in the MHC genes [Klein *et al*, 2007] .

Polymorphism is maintained by the selective advantage given to heterozygous alleles, because heterozygosity leads to better immune responses [Hughes and Nei, 1988]. Maintenance of polymorphism can also be disease-driven where a new allele or over dominance is given a selective advantage by its ability to cope with certain pathogens [Howard, 1991].

Antibody/TCR

Although polymorphism may contribute to diversity [Reyburn *et al*, 1993], the main mechanism by which the antibody/TCR genes generate diversity is by gene re- arrangement. The gene segments on the chromosome recombine with the splicing of intervening introns to form an exon which would code for the complete chain. Since there are multiple copies of the gene segments, random selection and re-arrangement results in diverse antigen receptors, this is known as combinatorial diversity. [Alt *et al*, 1992]. The heavy chain gene is re-arranged first, followed by the light chain. The process is guided by the RSS, which has a 12bp spacer or a 23bp spacer. Genes bound by a 12bp spacer can only re-arrange to gene segments bound by a 23bp spacer, thus DH joins to JH gene segments before it is re-arranged to the VH gene to form the complete coding sequence for the variable region of the heavy chain [Sakano *et al*, 1979]. The same process applies for the light chain but without the DH gene segment. This process is also made possible by enzymes- the V (D) J recombinase, and the RAG 1 and RAG 2 enzymes which are lymphoid specific [Ohno, 1970;Sakano *et al*, 1979].

A form of recombination also occurs for MHC genes but this occurs at some preferred sites known as hot spots, and it involves the shuffling of chromosomal segments to form new allelic variants (polymorphism). This however, does not follow the same process as that of the lymphocyte gene segment re-arrangements, but is made possible by linkage disequilibrium where the loci are linked close enough to allow for these recombinations to occur with the presence of the hot spots [Steinmetz, 1986]. Another mechanism of generating diversity under antibody/TCR gene rearrangement is junctional diversity. Random cleavage of the coding sequence and imprecise joining of the strands during the re-arrangement process, is followed by the addition of palindromic nucleotides and non- templated nucleotides at the junctions between the gene segments.Junctional diversity contributes to the diversity of the CDR3 region and is absent in the MHC genes [Hodges *et al*, 2003] .

The third mechanism by which Ig genes generate diversity is by somatic hyper mutation, this process is also absent in the TCR genes and does not occur in the MHC genes. It occurs when B-cells are exposed to antigen, point mutations are introduced into the V-region of the re-arranged genes. The resulting V- region differs from the initial V-region by a single amino acid sequence, thus creating more diversity. Although the mechanism is not yet well understand, the point mutations are said to occur preferentially at certain sites ("hot spots") with a characteristic 4-5 nucleotide motif [Berek and Milstein, 1987]. The process requires enhancers and transcription promoters [Betz *et al*, 1994] and catalysed by the enzyme activation induced cytidinedeaminase (AID) [Muramatsu *et al*, 1999].

The fourth mechanism also occurs is class switching, the default Ig expressed with B-cell, which is the soluble IgM is switched to either to another class. This is achieved by the detachment of the VH-region from the CH region, and joining it another C-region of the particular H chain type required at that particulartime [Manis *et al*, 2002]. Gene conversion, a process described above for MHC genes, has also been described for chicken immunoglobulin genes. Here, blocks of amino acid sequences in the V-region are replaced by sequences from V-regions ofpseudo genes [.Ota and Nei, 1995]

References

1. Yeager, M., and Hughes, A L. (1991) Evolution of the mammalian MHC: Natural selection, recombination and convergent evolution. Immunol Rev, 167:45-58.
2. Ohno, S. (1970) Evolution by gene duplication. Berlin: Springer-Verlag; ISBN 0-04-575015-7.
3. The MHC Consortium (1999). Complete sequence and gene map of a human MHC. Nature, 401: 921-923.
4. Dausset, J. (1981). The MHC in man. Science, new series, 213(4515):1469- 1474.
5. Stephens, R., Horton, R., Humphray, S., and Beck, S. (1999) Gene organisation, sequence variation and isochore structure at the Centromeric boundary of the human MHC. J MolBiol, 291:789- 799.
6. Steinmetz, M., and Hood, L. (1983) Genes of the MHC in mouse and man. Science, New series, 222(4625):727-733.
7. Trowsdale, J., and Campbell, R D. (1988) Physical map of the human HLA region. Immunology Today, 9:34-35.
8. Guillemot F *et al*. (1988) MHC antigen genes In: Molecular Immunology(Ed. By B.D Harnes and D. M Glover), p81. IRL press, Oxford.
9. Koller, B.H., Geraghty, D., Shimizu, Y., DeMars, R., and Orr, H. (1988) HLA-E, a novel HLA class I gene expressed in resting T- lymphocytes. J. Immunol, 141:897-904.

10. Lawlor, D.A., Zemmour, J., Ennis, P.D., and Parham, P. (1990) Evolution of class I MHC genes and proteins: from natural selection to thymic selection. Annu Rev Immunol, 8:23-63
11. Koller, B. H., Geraghty, D. E., Demars, R., Duvick, L., Rich, S. S.,and Orr, H. T. (1989) Chromosomal organisation of the human MHC class I gene family. *Journal of Experimental Medicine*, 169:469-80
12. Andersson, G., Larhammar, D., Widmark, E., Servenius, B., Peterson, P.A., and Rask, L. (1987) Class II genes of the human MHC. Organisation and evolutionary relationship of DRβ genes. J Biol Chem. 262:8748.
13. Trowsdale, J., and Campbell, R. D. (1992) Complexity in the MHC. Eur J Immunol., 19:43-55.
14. Hanson, I. M., Gorman, P., Lui, V. C. H., Cheah, K. S. E., Solomon, E., and Trowsdale, J. (1989). the human pro-a2 (X1) collagen gene (C0LIIA2) maps to the Centromeric border of the MHC. Genomics, 5:925-931
15. Abe K., Wei J.F., Wei F.S., Hsu Y.C. Uehara H., ArtztK.,and Bennett D. (1988) Searching for coding sequences in the mammalian genome: the H-2K region of the mouse MHC is replete with genes expressed in the embryos. EMBO J, 7:3441-3449.
16. Herberg J.A., Sgouros J., Jones T., Copeman J., Humphray S.J., Sheer, D., Cresswell, P., Beck, S., and Trowsdale, J. (1998b) Genomic analysis of the Tapasin gene located close to the TAP loci in the MHC. Eur J Immunol, 28:459-467.
17. Chang, H. Y., Nishitoh, H., Yang, X., Ichijo, H., Baltimore, D. (1998). Activation of apoptosis signal regulating kinase 1 (ASK 1) by the adapter protein DAXX. Science, 28:1860-1863.
18. Herberg, J. A., Beck, S. and Trowsdale, J (1998a) TAPASIN, DAXX, RGL2, HKE2 and 4 new genes (RING1, 3-5) from a dense cluster at the Centromeric end of the MHC. J MolBiol, 277:839-857.
19. Simmons, W. A., Roopenian, D. C., Summerfield, S. G., Jones, R. C., Galocha, B., Christianson, G. J., *et al*. (1997b) A new MHC locus that influences class I peptide presentation. Immunity, 7:641-651.
20. Carroll, M.C., Campbell, R.D., Bentley, D.R., Porter, R.R. (1984) A molecular map of the human MHC III region linking complement genes C4, C2 and factor B. Nature,307(5948):237-41.
21. Carroll, M.C., Campbell, R.D., Porter, R.R. (1985) Mapping of the steroid 21-hydroxylase genes adjacent to complement component C4 genes in the HLA, the MHC in man. ProcNatlAcadSci USA, 82(4):521-525
22. Carroll, M.C., Katzman, P., Alicot, E.M., Koller, B.H., Geraghty, D.E., Orr, H.T., Strominger, J.L., Spies, T. (1987). A linkage map of the MHC including the TNF genes. ProcNatlAcadSci USA, 84(23):8535-39.
23. Sargent, C.A., Dunham, I., Trowsdale, J., Campbell, R.D. (1989) Human MHC contains genes for the major Heat shock proteins HSP70. Proc Natl Acad Sci USA, 86(6):1968-72.
24. Milner, C .M. and Campbell, R. D. (1990) Structure and expression of the 3 MHC- linked HSP 70 genes. Immunogenetics, 32(4):242-51.
25. Schwaiger, F .W. and Epplen, J. T. (1995) Exonic MHC- DRB Polymorphisms and intronic simple repeat sequences: Janus' faces of DNA sequence evolution. Immunological Reviews, 143:199-224.
26. LeFranc M P, LeFranc G: The TCR facts book. Academic Press, London UK; 2001a:398.
27. LeFranc M P, LeFranc G: The Immunoglobulin Facts book. Academic press; 2001b: 1-458.
28. Toyonaga, B., Yoshikai, Y., Vadasz, V., Chin, B and Mak, T.W. (1985) Organisation and Sequences of the V, J and C region genes of the human TCR α- chain. Nature, 310:837-40.
29. Roman-Roman, S., Ferradini, L., Azocar, J., Genevée, C., Hercend, T., Triebel, F. (1991) Studies on the human TCR α/β V-region gene. I. identification of 7 additional V-α subfamilies and 14 J α gene segments. Eur J Immunol, 21:927-33.
30. Rowen, L., Koop, B.F., Hood, L. (1996) The complete 685-kb DNA sequence of the human β TCR locus. Science, 272:1755-62.
31. LeFranc, M.P., Forster, A., Baer, R., Stinson, M.A., Rabbitts, T.H. (1986) Diversity and re-arrangement of the human T-cell re-arranging gamma genes: 9 germ line variable genes belonging to 2 subgroups. Cell, 45:237-46.
32. LeFranc M P. (2000) Locus maps and genomic repertoire of the human TCR repertoire. The Immunologist, 8:72-8.
33. Giudicelli, V., Chaume, D., Lefranc, M.P. (2005) IMGT/Gene-DB: A comprehensive database for human and mouse Ig and TCR genes. Nucleic Acids Res, 33:D256-61
34. Tait, B. D. (1996) The Major Histocompatibility complex. Immunobiology, 6:121-136.
35. 35 Bernadi, G. (1993) The Isochore organisations of the human genome and its evolutionary history-A review. Gene, 135:57-66.
36. Craig J M, Bickmore W A. (1993) Chromosome bands- flavours to savour. Bioassays 15, 349-354.
37. Schimidt, C. M and Orr, H. T. (1991) A physical linkage map of the HLA-A,-G, -7.5p, and -F. Human Immunology, 31 (3): 180-185.
38. Hardy, D.A., Bell, J.I., Long, E.O., Lindsten, T., and McDevitt, H.O. (1986) Mapping of class II region of the human MHC by pulsed field gel electrophoresis. Nature, 323(6087):453-455.
39. Toyonaga, B., and Mak, T .W. (1987) Genes of the T-cell antigen receptors in normal and malignant T -cells. Annu Rev Immunol, 5: 585-620.
40. Arden, B., Clark, S.P., Kabelitz, D., Mak, T.W. (1995) Human TCR variable segments families. Immunogenetics, 42:455-500.
41. Lai, E., Concannon, P., and Hood, L. (1988). Conserved organisation of the human and murine TCR β- gene family. Nature, 331:543-46.
42. Hodges, E., Krishna, M.T., Pickard, C., Smith, J.L. (2003) Diagnostic role of tests for the TCR genes. J ClinPathol 56:1-11.

43. Fox, V. L., Strauss, W. M., Seidman, J. G (1987) Isolation and restriction map of the V-J interval of the human TCR γ-chain locus. Science, 237:1217-19.
44. Matsuda, F., Ishii, K., Bourvagnet, P., Kuma, K., Hayashida, H., Miyata, T., Honjo, T. (1998) The complete nucleotide sequence of the human Ig heavy chain V-region locus. J Exp Med 188:2151-2162.
45. Chevillard, C., Ozaki, J., Herring, C.D., and Riblet, R. (2002) A 3-mb yeast artificial chromosome contig spanning the C57BL mouse IgH locus. J Immunol, 168:5659-5666.
46. Degner –Leisso, S. C., and Feeney, A. J. (2010) Epigenetic and 3-dimensional regulation of V (D) J re-arrangement of Ig genes. Seminars in Immunology, 22: 346-352.
47. Bottaro A., Cariota, U., Demarchi, M., and Carbonara A.O. (1989) Pulsed-field gel analysis of human Ig heavy chain constant region gene deletions revealed the extent of unmapped regions within the locus. Genomics, 4:505-508.
48. Lane J *et al*. (2010) From IMGT-Ontology to IMGT/LIG motif: the IMGT standardised approach for Ig and TCR identification and description in large sequences. Bioinformatics, 11:223-239.
49. Flanagan, J. G., and Rabbitts, T. H. (1982) Arrangement of human Ig heavy chain C- region genes implies evolutionary duplication of a segment containing γ, ε, and α gene. Nature, 300: 709-713.
50. Rabbitts T H *et al*. (1981) Human Ig human heavy chain genes: evolution comparisms of Cμ, Cδ and Cγ genes and associated Switch sequences. Nucleic Acids Res, 9: 5409-4524.
51. Shimizu, A., and Honjo, T. (1984) Immunoglobulin class Switching. Cell, 36:801- 803.
52. Tonegawa S. (1983) Somatic generation of antibody diversity. Nature, 302:575-81.
53. Alt. F. W., Oltz, E.M., Young, F., Gorman, J., Tacciol,iG.,and Chen, J. (1992) V D J recombination. Immunology Today, 13:306-314.
54. Choi, N. M., Majumder, P., Boss, J.M. (2011) Regulation of MHC class II genes. Current Opinion in Immunology, 23: 81-87.
55. Reith, W and Mach, B. (2001) the bare lymphocyte syndrome and the regulation of MHC expression. Annu Rev Immunol, 19:331-373.
56. Ting, J. P., and Trowsdale, J. (2002) Genetic control of MHC class II expression. Cell, 109 Suppl.S21-33.
57. Vanden- Elsen, P. J., Peijnenburg, A., van Eggermond, M.C., and Gobin, S.J. (1998) Shared regulatory elements in the promoters oh MHC class I and class II genes. Immunology Today, 19(7): 308-312.
58. Ting, J. P., and Baildwin, A. S. (1993) Regulation of MHC gene expression. Current Opinion in Immunology, 5: 8-16.
59. Steimle, V., Otten, L.A., Zufferey, M., Mach, B. (1993) Complementation cloning of an MHC class transactivator mutated in hereditary MHC class II deficiency (aBLS). Cell, 75:135-146.
60. Steimle, V., Siegrist, C.A., Mottet, A., Lisowska-Grospierre, B., Mach, B. (1994) Regulation of MHC II expression by IFN mediated by the transactivator gene CIITA. Science, 265:106-109.
61. Nelsen, B., and Sen, R. J. (1992) Regulation of Immunoglobulin gene transcription. In: International cytology:A survey of cell biology.(ed. By Kwang W J) pg 121- 130. Academic Press.
62. Diamond D J *et al* (1989) Lineage-specific expression of a TCR V-gene promoter controlled by upstream sequences. J Exp Med, 169:1213-31.
63. Gottsschalk, L. R and Leoden, J .M. (1990). Identification and functional characterisation of the human TCR β-gene transcriptional enhancer: common nuclear proteins interact with the transcriptional regulatory elements of the TCR α and β genes. Mol Cell Biol, 10:5486-95.
64. Anderson, S. J., Miyake, S., Loh, D.Y. (1989) Transcription from a murine TCR Vβ promoter depends on a conserved decamer motif similar to the Cyclic AMP response element. Mol Cell Biol, 9:4835-45.
65. Anderson, S.J., Chou, H.S., Loh, D.Y. (1988) A conserved sequence in the TCR β-chain promoter region. ProcNatlAcadSci USA, 85:3551-54.
66. Trowsdale, J. (1993) Genomic structure and function in the MHC. TIG, 9(4):117-122.
67. Steinmetz, M. (1986) The MHC: organisation and evolution. Clinical Immunology newsletter, 7(9): 134-137.
68. Klein, J. (1986) Natural history of the MHC. Wiley and sons, New York: 1986.
69. Hughes, A. L and Nei, M. (1989) Nucleotide substitution at the MHC class II loci: evidence for overdominantselection. ProcNatlAcadSci USA, 86:958-962.
70. Rammensee, H., Bachmann, .J, Emmerich, N.P., Bacho,r O.A., Stevanović, S.(1999) SYFPEITHI: database for MHC ligands and peptide motifs Immunogenetics. 199950(3-4):213-9.
71. Klein, J., Sato, A., Nikolaidis, N. (2007) MHC, TSP, and the origin of species: From Immunogenetics to evolutionary genetics. Annu Rev Genet, 41:281-304.
72. Hughes, A. L., and Nei, M. (1988) Nature (London) 335:167-170.
73. Howard J C. (1991) Disease and evolution. Nature, 352:565-567.
74. Reyburn, H., Cornélis, F., Russell, V., Harding, R., Moss, P., Bell, J. (1993) Allelic polymorphism of human TCR Vα-gene segments. Immunogenetics, 38:287-91.
75. Sakano, H., Hüppi, K., Heinrich, G., Tonegawa, S. (1979) Sequences at the somatic recombination sites of Ig L- chain genes. Nature, 280:288-294.
76. Berek, C., and Milstein, C. (1987) Mutation drift and repertoire shift in the maturation of the immune response. Immunol Rev, 16:23-41.
77. Betz, A.G., Milstein, C., González-Fernández, A., Pannell, R., Larson, T., Neuberger, M.S.(1994) Elements regulating the somatic hyper mutation of an

Ig κ gene: critical role for introns enhancer/matrix attachment region. Cell, 778:239-48.

78. Muramatsu, M., Sankaranand, V.S., Anant, S., Sugai, M., Kinoshita, K., Davidson, N.O., Honjo, T. (1999) Specific expression of AID, a novel member of RNA-editing deaminase family in germinal centre B-cells. J BiolChem, 274(26):18470-76.
79. Manis, J. P., Tian, M., Alt, F.W. (2002). Mechanism and control of class switch recombination. Trends Immunol, 23:31-39.
80. Ota, T., and Nei, M. (1995) Evolution of the Ig VH pseudogenes in chickens. MolBiolEvol, 12: 94-102.

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