Immunology 6

Specificity 8

Specificity

- of immunoglobulin molecule on B cell – BCR
- of receptor on T cell – TCR

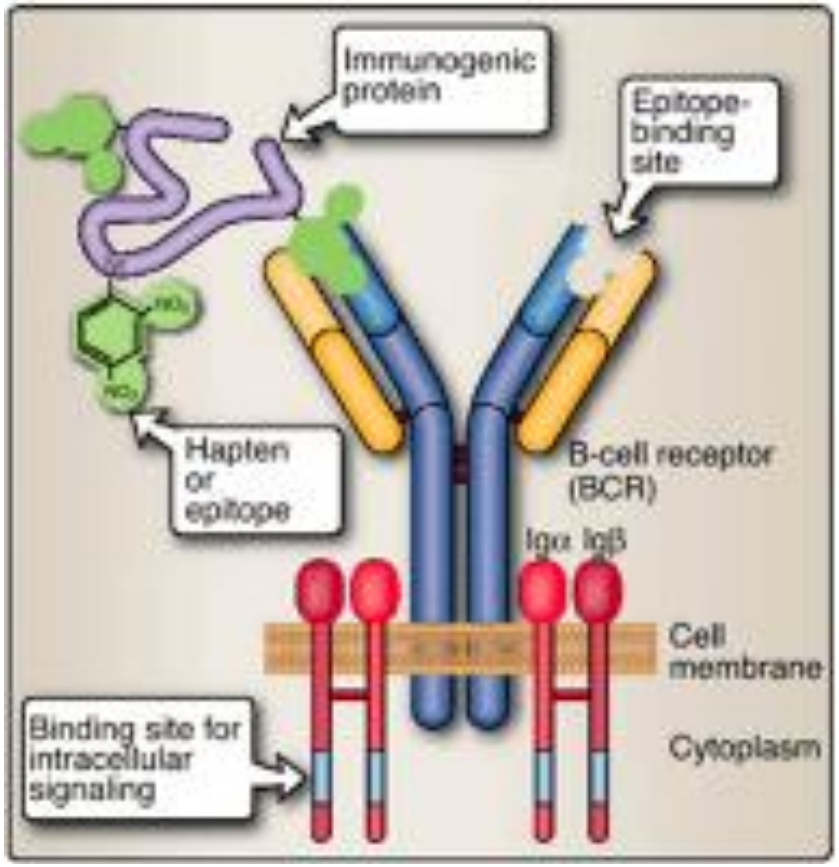
is defined and produced before their exposition to antigen

Number of specificities of BCR and TCR overpasses the number of genes on human chromosomes

Limited amount of genes can generate almost unlimited amount of specific BCR and TCR molecules

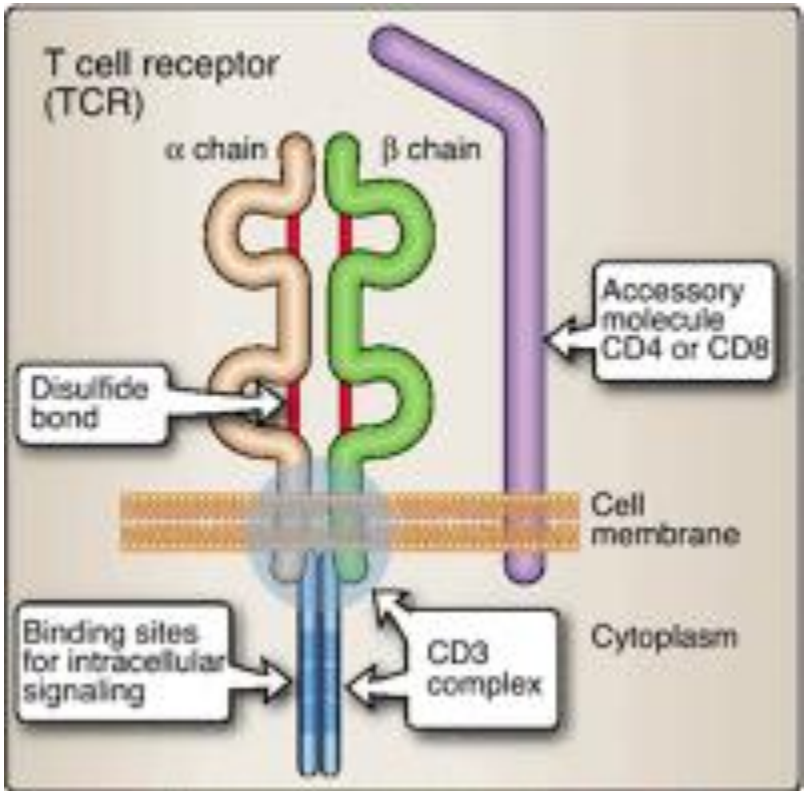
BCR – B cell receptor

- monomer of immunoglobulin
- light and heavy chains
- light – λ,κ
- heavy – ε,μ,δ,γ,α
- variable part – constant part



TCR

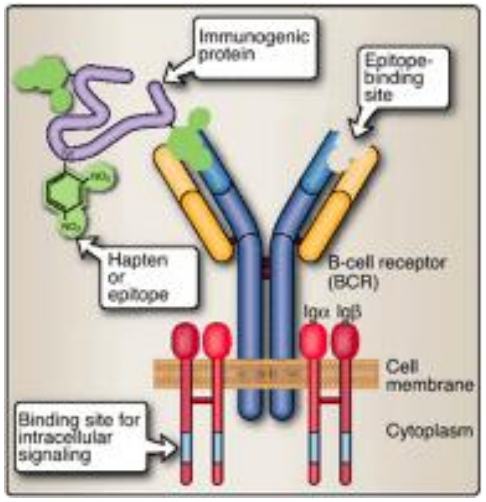
- structurally like immunoglobulin
- heterodimer consisting of αβ or δγ pair of chains.
- α γ -light
- δ β - heavy
- Variable and constant part



Genetic base of specificity

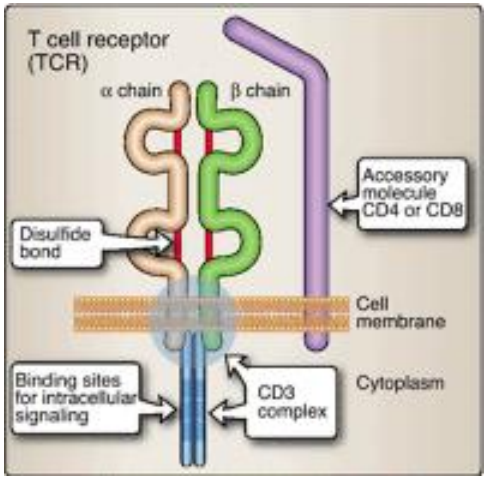
- Individual inherited set of genes from parents (maternal and paternal)
- in one individual there exist maternal or paternal formes of allels on different molecules of receptors or Ig (allotypes)

Exclusion of allels

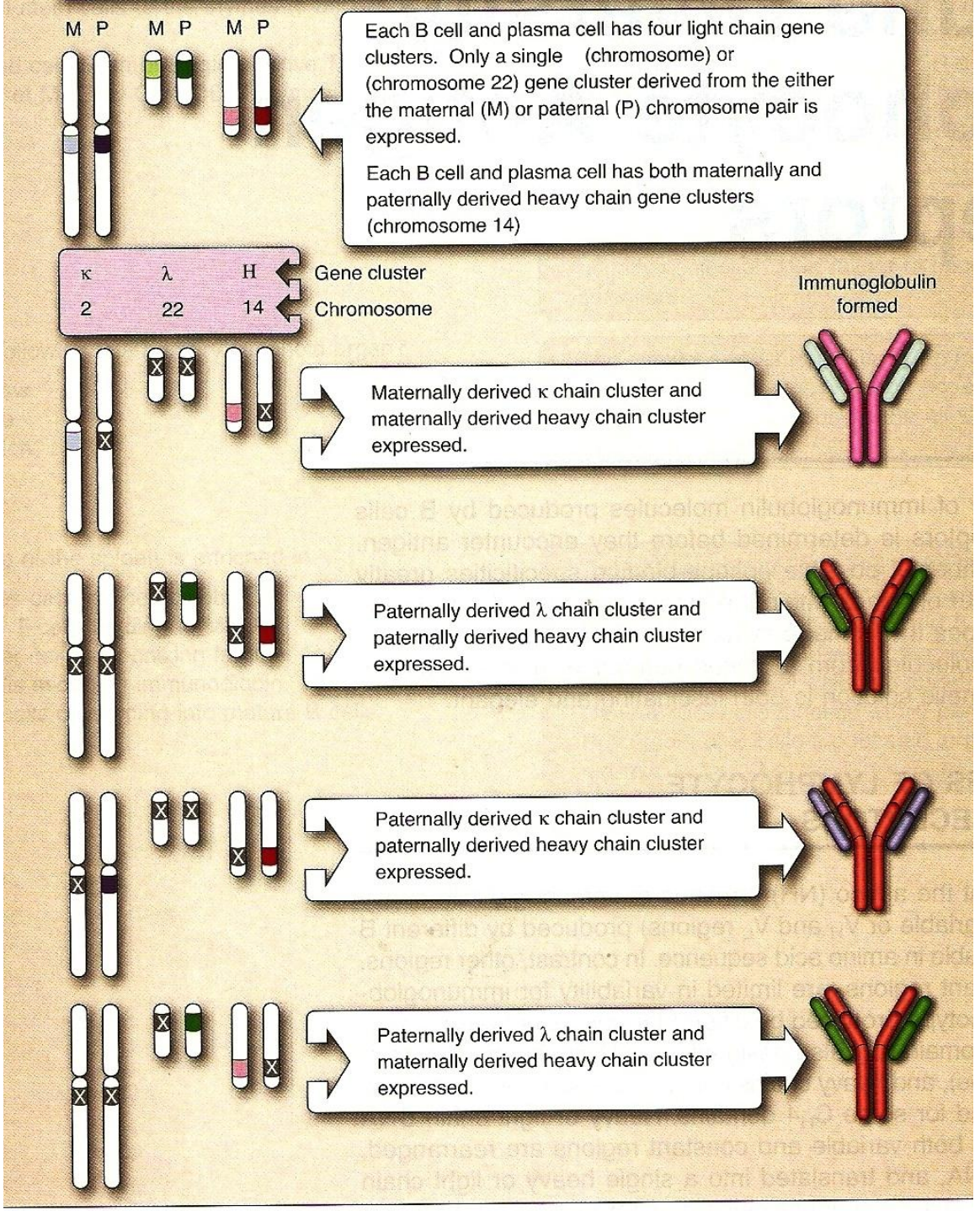


- only kappa or lambda light chains from father or mather
- maternal or paternal heavy chain

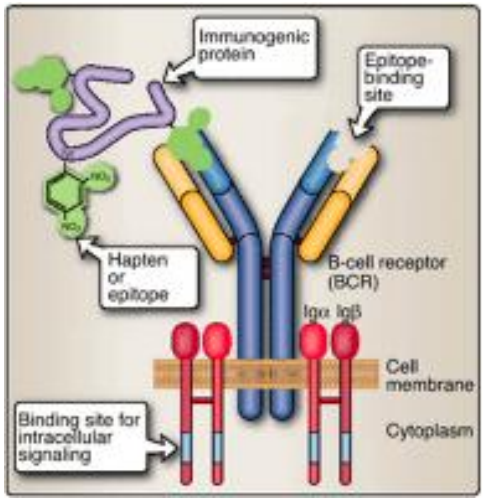
- For genes encoding TCR
  αβ a γδ
  (α or γ for light
  β or δ for heavy)



Exclusion of allels



Antigen specific receptores on lymphocytes



- Domains - NH ends of variable parts of heavy and light chains on B lymphocytes differs in different sequencies of aminoacids
- Domains - C ends – of constant parts have limited variability in the same isotype produced by different B or plasma cells

Genetic base of specificity

- Sequence of aminoacids is – encoded by genes od DNA localised on chromozomes– *overload of genes* =>
- Aminoacids are encoded on several chromosomes: 2, 22, 14 for BCR
  14 and 7 for TCR
- In chromosomal locuses V, J, C – for light
  V, D, J, C – for heavy

Genetic base of specificity

- Genes are
  - rearraged,
  - transcribed to mRNA
  - translated to the single light and single heavy chaine polypeptide

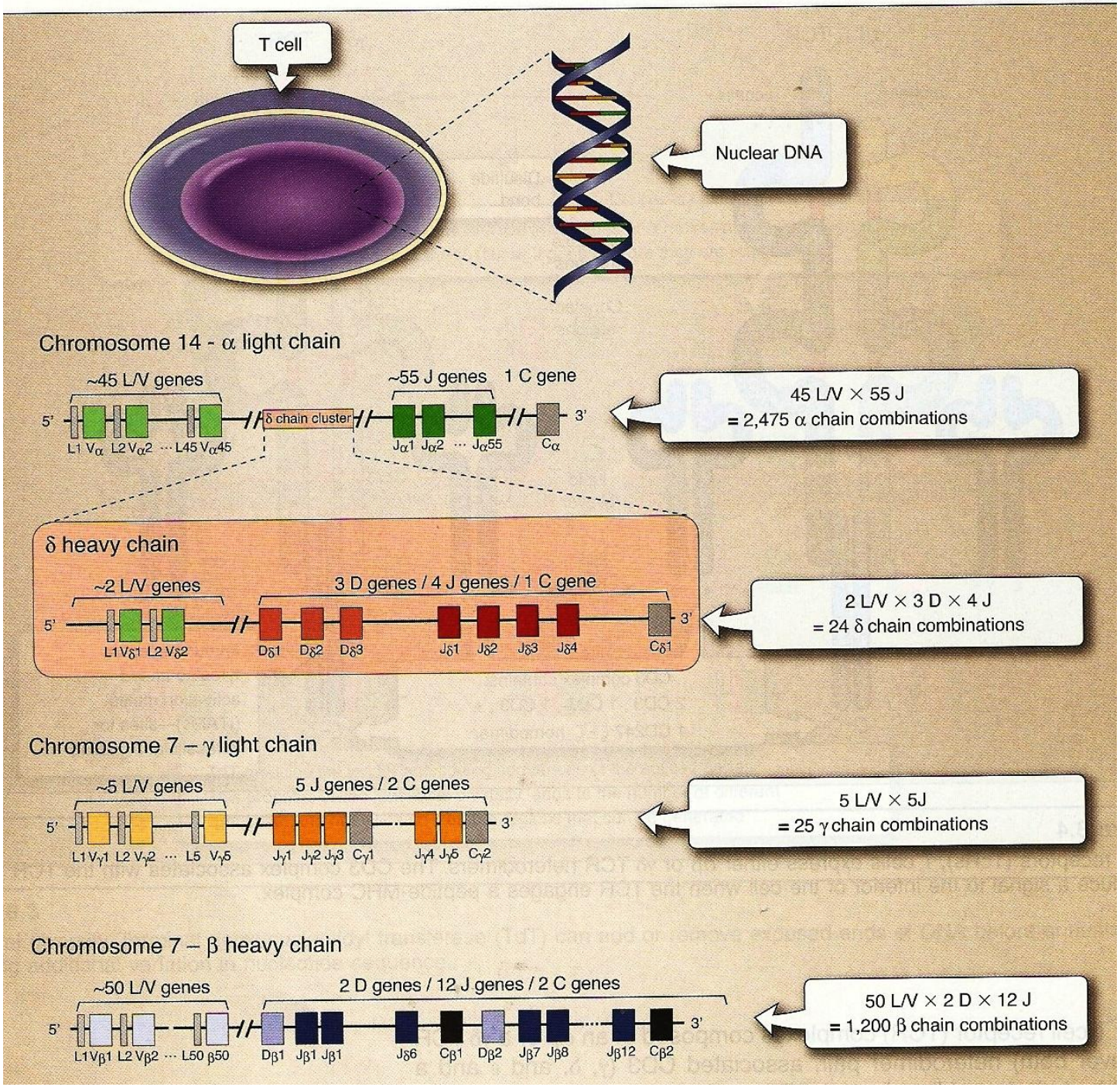
Gene rearrangement, deletion, mutation

- Every individuuam is able to produce

  10^{15} epitope-specific receptors

Rearrangement is responsible of ennorme variability of epitop-specific part on variable domaines of heavy and light chains $V_L V_H$ on BCR and TCR

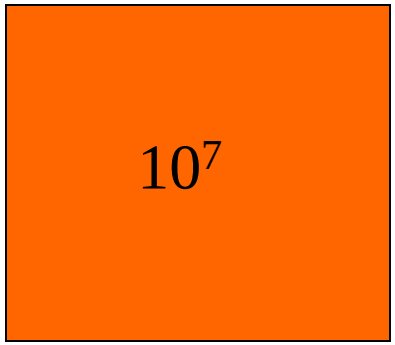
- It arrises by deletion of existing nucleotides genes in a segment of DNA on chromosome encoding this individual receptor molecule


T cell
Nuclear DNA
Chromosome 14 - α light chain
~45 L/V genes
~55 J genes
1 C gene
5'
δ chain cluster
3'
L1 Vα L2 Vα2 ··· L45 Vα45
Jα1 Jα2 ··· Jα55
Cα
45 L/V × 55 J
= 2,475 α chain combinations
δ heavy chain
~2 L/V genes
3 D genes / 4 J genes / 1 C gene
5'
3'
L1 Vδ1 L2 Vδ2
Dδ1 Dδ2 Dδ3
Jδ1 Jδ2 Jδ3 Jδ4
Cδ1
2 L/V × 3 D × 4 J
= 24 δ chain combinations
Chromosome 7 – γ light chain
~5 L/V genes
5 J genes / 2 C genes
5'
3'
L1 Vγ1 L2 Vγ2 ··· L5 Vγ5
Jγ1 Jγ2 Jγ3 Cγ1
Jγ4 Jγ5 Cγ2
5 L/V × 5J
= 25 γ chain combinations
Chromosome 7 – β heavy chain
~50 L/V genes
2 D genes / 12 J genes / 2 C genes
5'
3'
L1 Vβ1 L2 Vβ2 ··· L50 β50
Dβ1 Jβ1 Jβ1
Jδ6 Cβ1 Dβ2 Jβ7 Jβ8
Jβ12 Cβ2
50 L/V × 2 D × 12 J
= 1,200 β chain combinations

Genotype of TCR – V(D)J chromosome 14 and 7

- TCR: V, D, J gens: - for α = 45V/L x 55J
  - for β = 50V/L x 2D x 12J

1200 x 2475 = $3x10^6$

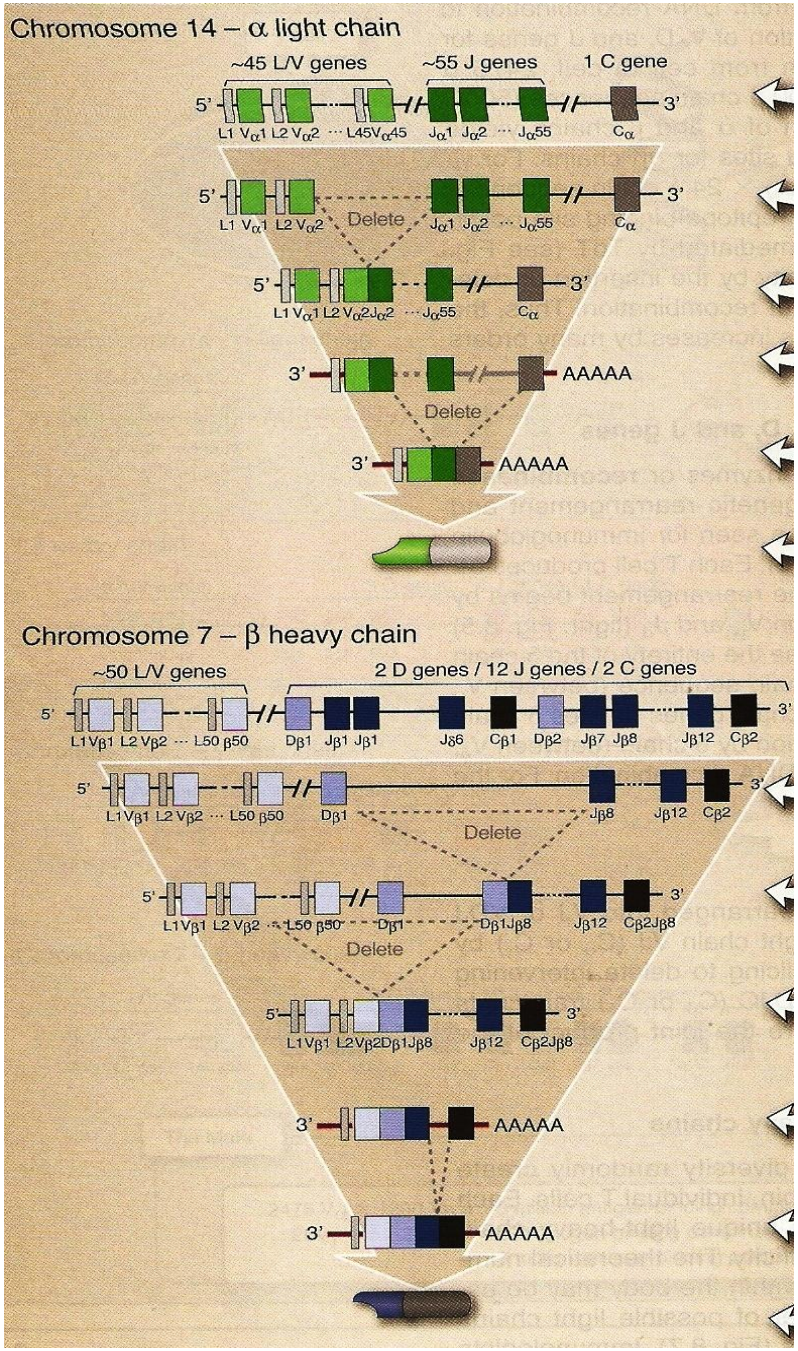


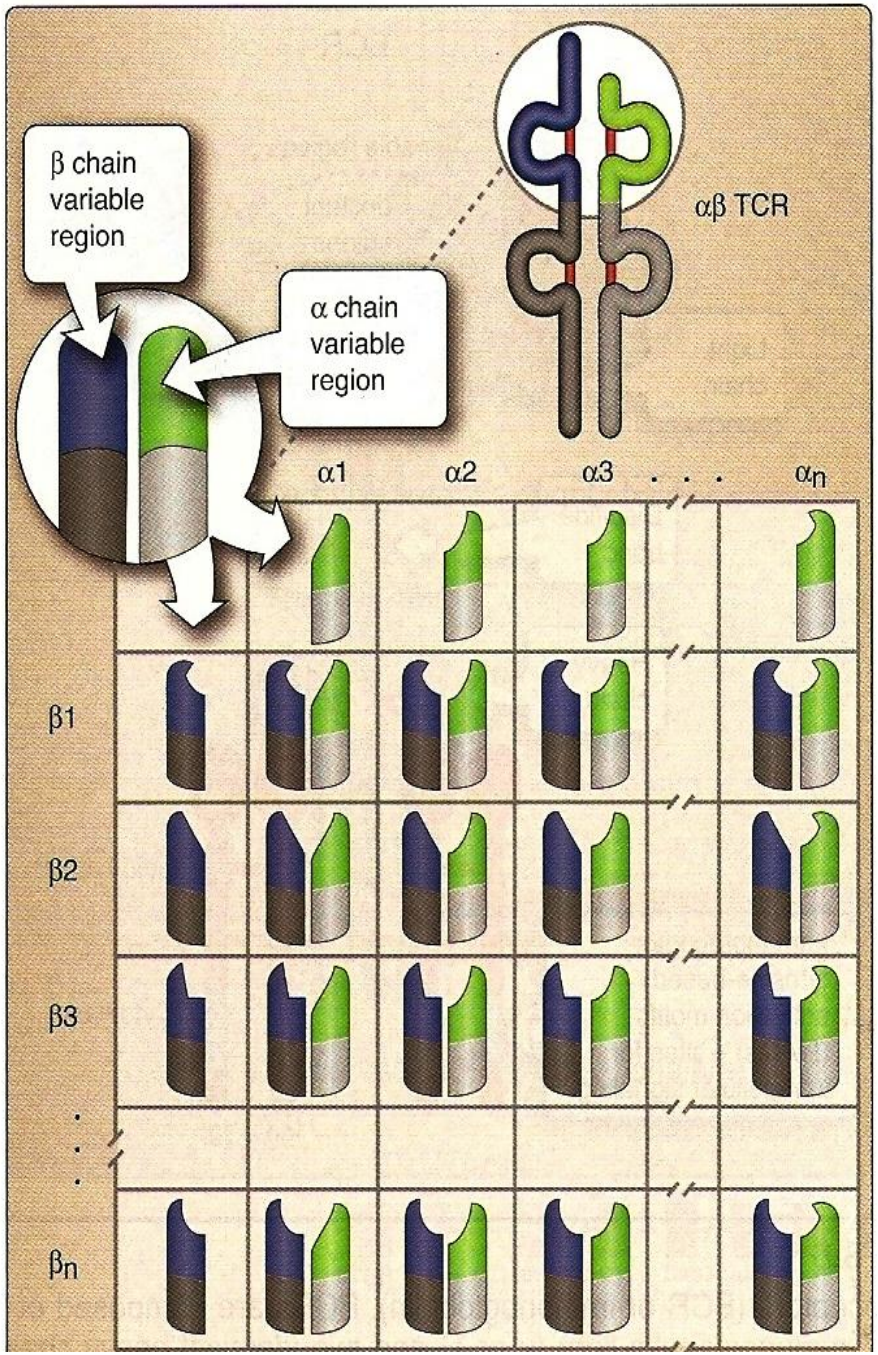
- for γ = 5V/L x 5J
- for δ = 2V/L x 3D x 4J

24 x 25 = 600

+ constant part coding + 20 junction part

TCR


Chromosome 14 – α light chain
~45 L/V genes
~55 J genes
1 C gene
5'
3'
L1 Vα1 L2 Vα2 ··· L45Vα45
Jα1 Jα2 ··· Jα55
Cα
Delete
L1 Vα1 L2 Vα2Jα2
AAAAA
Chromosome 7 – β heavy chain
~50 L/V genes
2 D genes / 12 J genes / 2 C genes
L1Vβ1 L2 Vβ2 ··· L50 β50
Dβ1 Jβ1 Jβ1
Jδ6 Cβ1 Dβ2 Jβ7 Jβ8
Jβ12 Cβ2
L1Vβ1 L2 Vβ2Dβ1Jβ8
Cβ2Jβ8


β chain variable region
α chain variable region
αβ TCR
α1
α2
α3
αn
β1
β2
β3
βn

Genotype of BCR chromosomes 2 (κL), 22 (λL) a 14 (H)

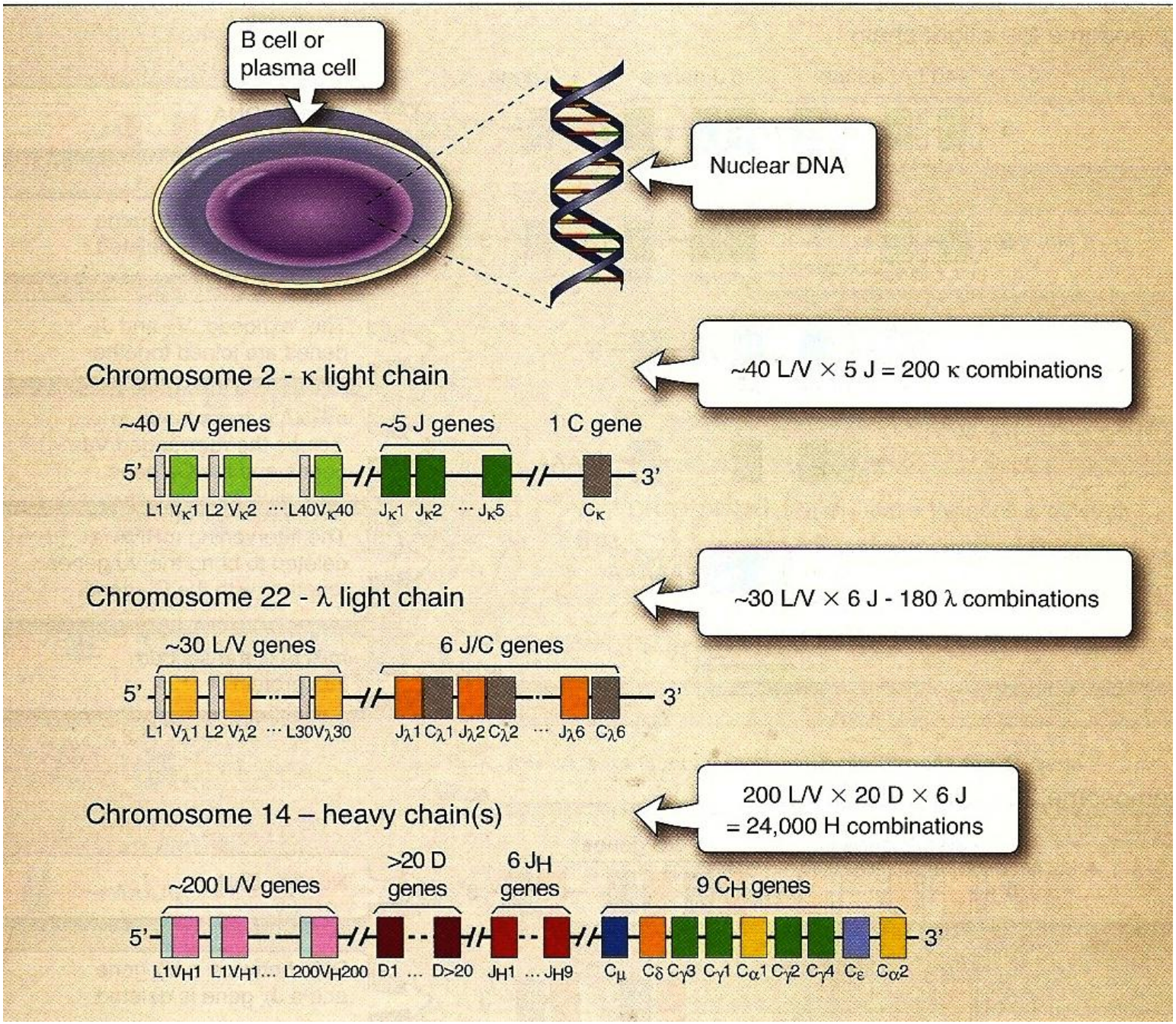
Rearrangement of genes for Ig

- happens in early stages of B lymphocyte evoluiton
- leads to formation of variable parts, that can recognise majority of antigenic structures ever present

- 1 B cell = 1 isotype, 1 specificity (constant)

↓

class switch


B cell or plasma cell
Nuclear DNA
Chromosome 2 - κ light chain
~40 L/V × 5 J = 200 κ combinations
~40 L/V genes
~5 J genes
1 C gene
5'
3'
L1 Vκ1 L2 Vκ2 ··· L40Vκ40
Jκ1 Jκ2 ··· Jκ5
Cκ
Chromosome 22 - λ light chain
~30 L/V × 6 J - 180 λ combinations
~30 L/V genes
6 J/C genes
5'
3'
L1 Vλ1 L2 Vλ2 ··· L30Vλ30
Jλ1 Cλ1 Jλ2 Cλ2 ··· Jλ6 Cλ6
Chromosome 14 – heavy chain(s)
200 L/V × 20 D × 6 J
= 24,000 H combinations
~200 L/V genes
>20 D genes
6 JH genes
9 CH genes
5'
3'
L1VH1 L1VH1... L200VH200
D1 ... D>20
JH1 ... JH9
Cμ Cδ Cγ3 Cγ1 Cα1 Cγ2 Cγ4 Cε Cα2

Genes encoding BCR

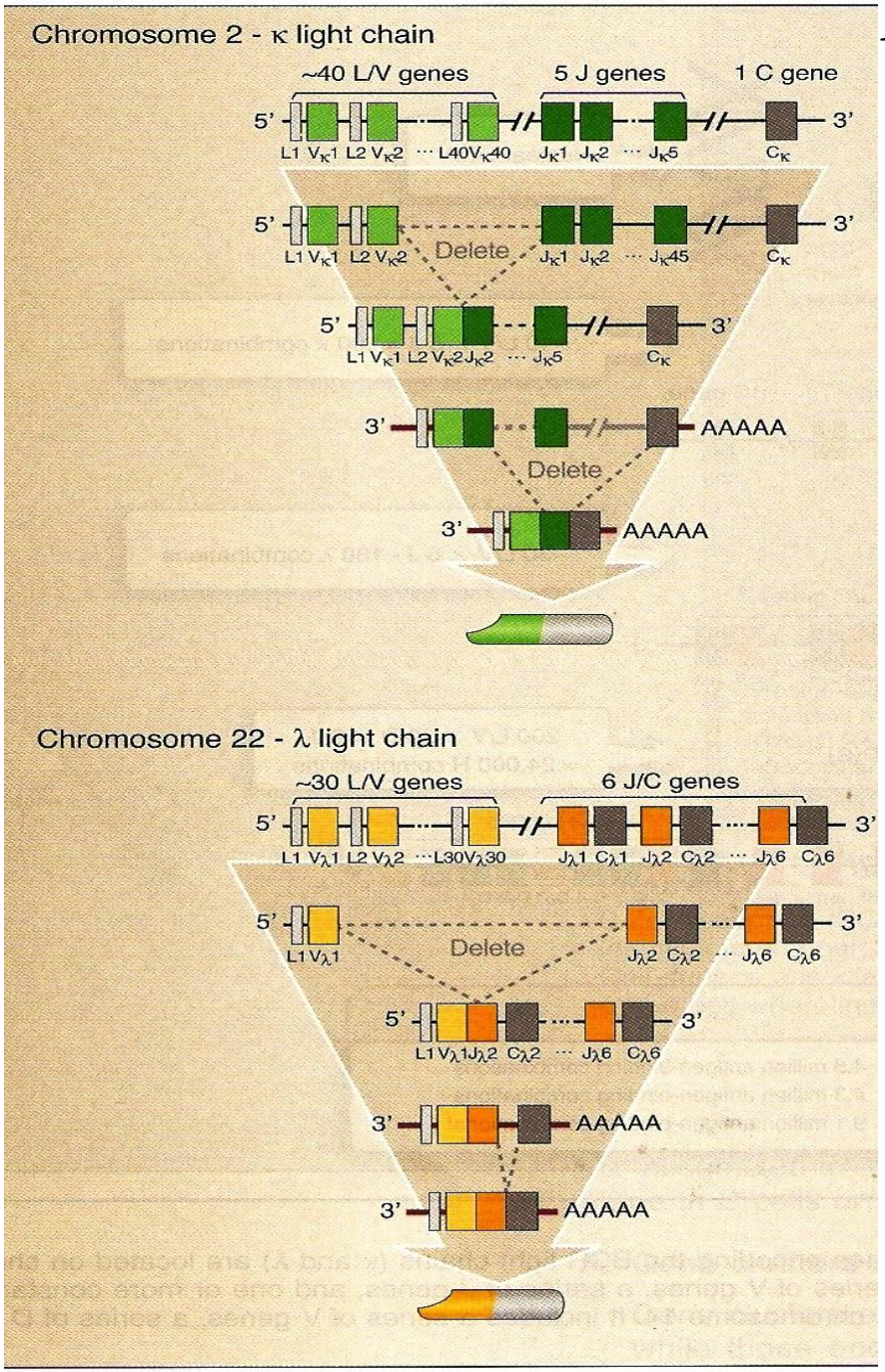
- Chromosome 2 – κ light – 40V x 5J x 1C = 200
- Chromosome 22 – λ light – 30V x 6J(C) = 80
- Chromosome 14 – heavy - 200V x 20D x 6J = 24 000 = 9,1 x 10^6

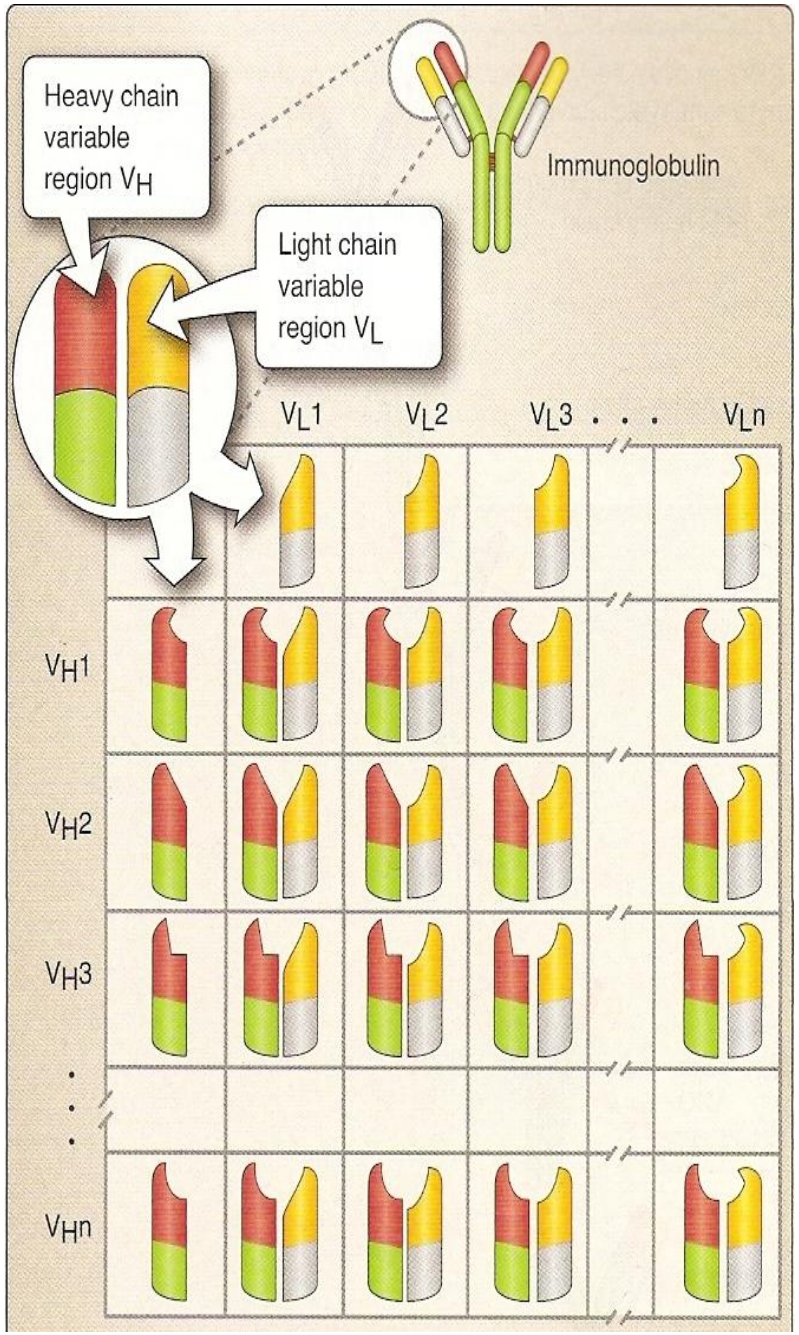
+

- encoding of constant parts 9C (α1, α2, γ1, γ2, γ3, γ4, μ, δ, ε)

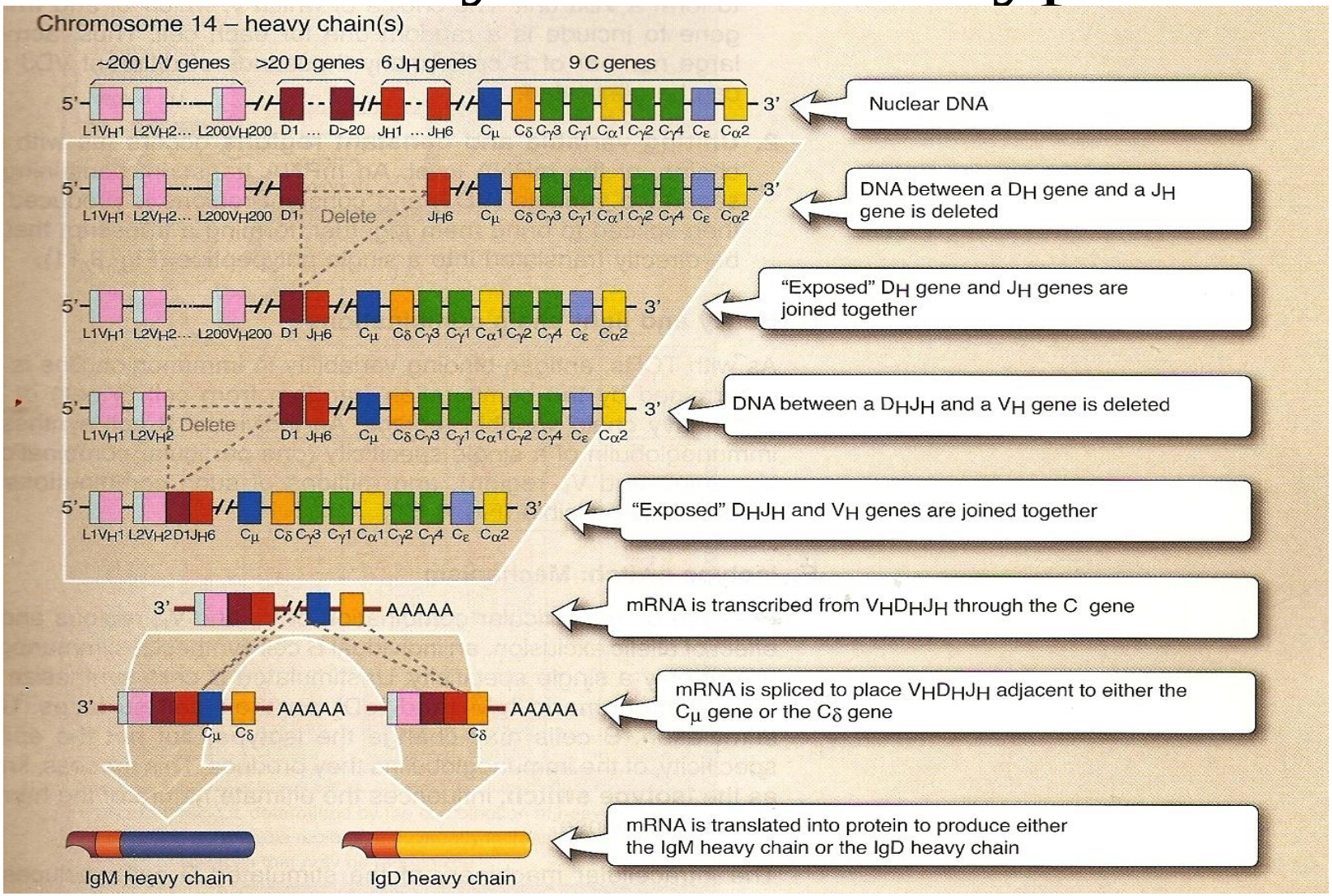
10^8

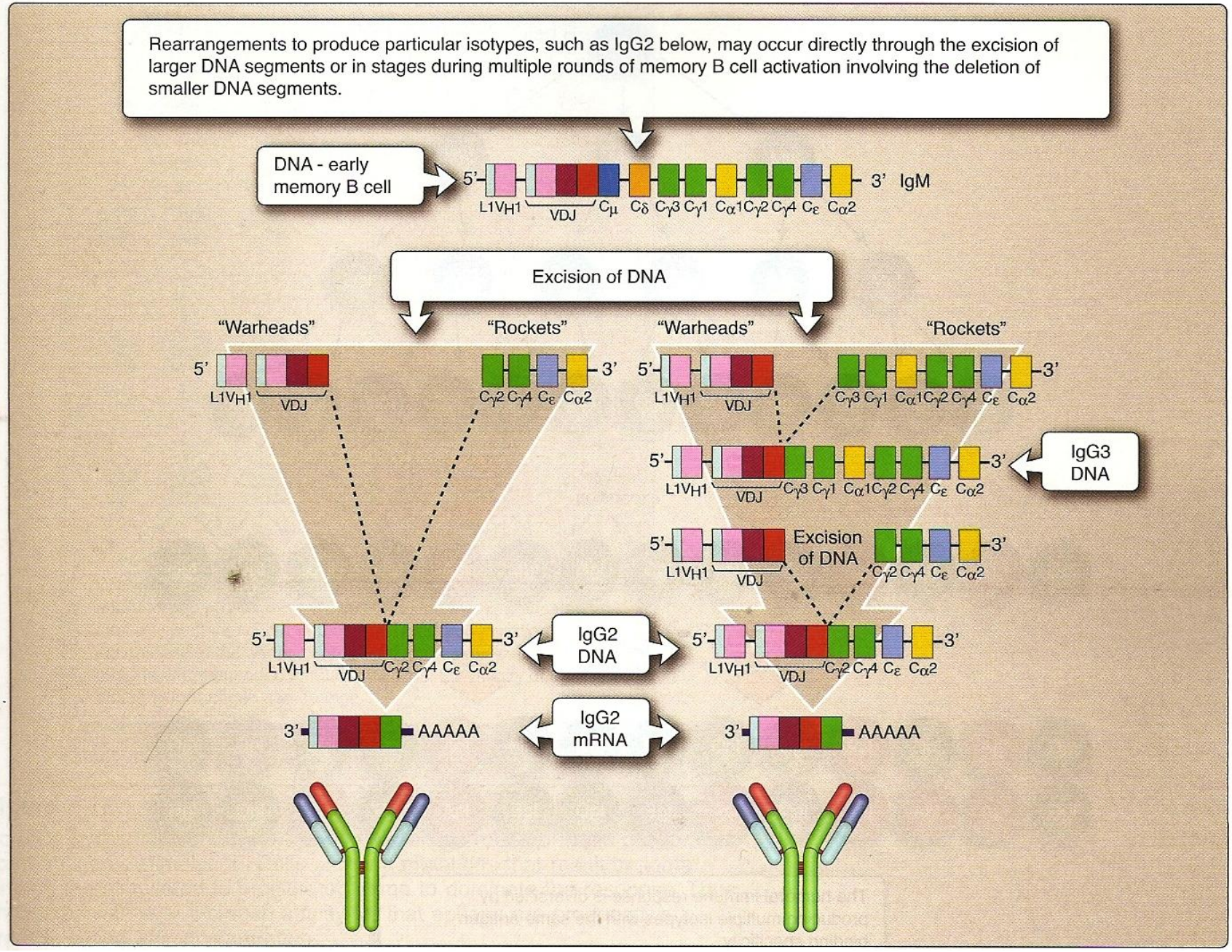
BCR


Chromosome 2 - κ light chain
~40 L/V genes
5 J genes
1 C gene
5'
3'
L1 Vκ1 L2 Vκ2 ··· L40Vκ40
Jκ1 Jκ2 ··· Jκ5
Cκ
Delete
Jκ45
L1 Vκ1 L2 Vκ2Jκ2 ··· Jκ5
AAAAA
Chromosome 22 - λ light chain
~30 L/V genes
6 J/C genes
L1 Vλ1 L2 Vλ2 ··· L30Vλ30
Jλ1 Cλ1 Jλ2 Cλ2 ··· Jλ6 Cλ6
L1 Vλ1
L1 Vλ1Jλ2 Cλ2 ··· Jλ6 Cλ6


Heavy chain variable region VH
Light chain variable region VL
Immunoglobulin
VL1
VL2
VL3 . . .
VLn
VH1
VH2
VH3
VHn

Rearrangement of genes for heavy chains - isotype

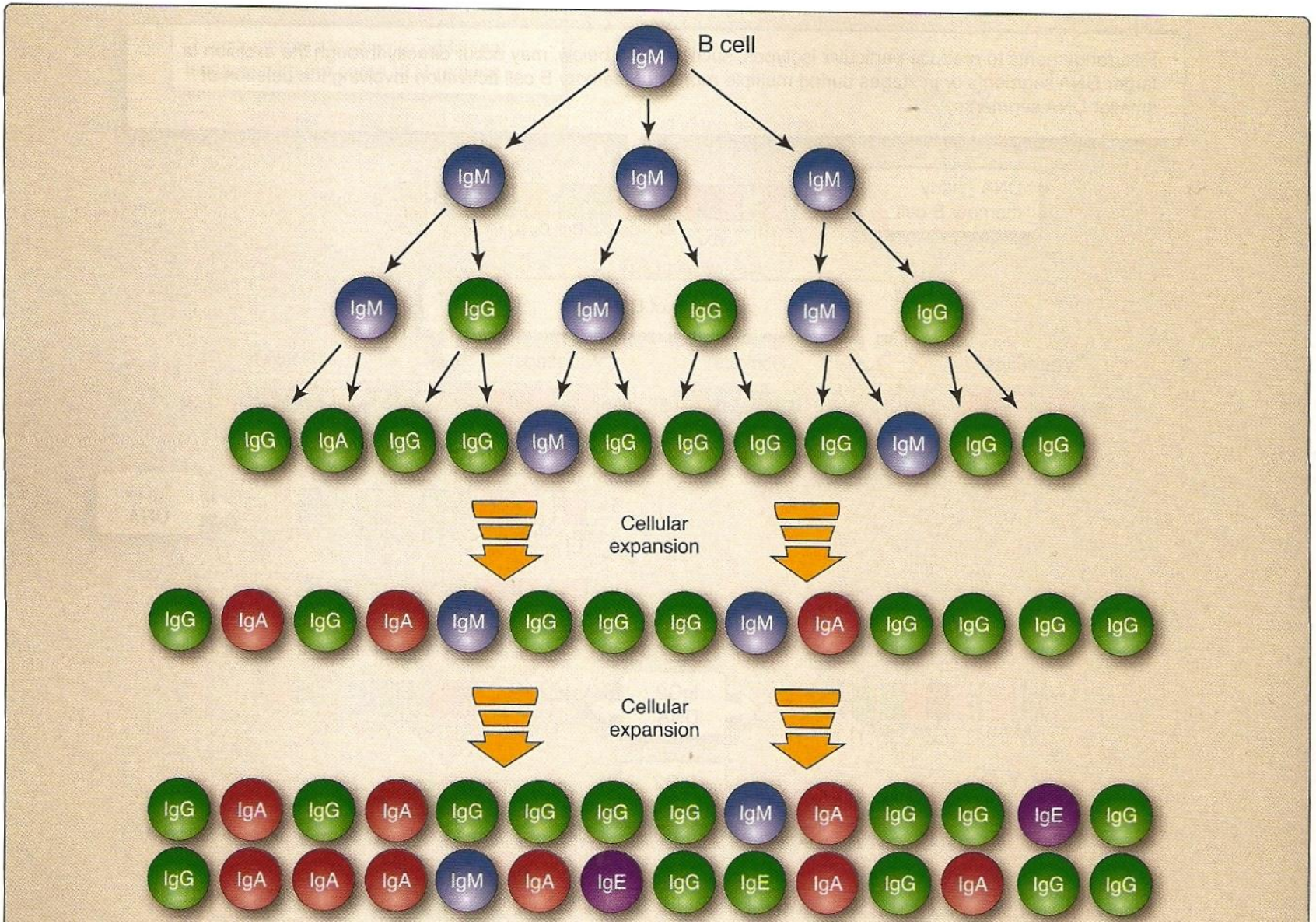



Rearrangements to produce particular isotypes, such as IgG2 below, may occur directly through the excision of larger DNA segments or in stages during multiple rounds of memory B cell activation involving the deletion of smaller DNA segments.
DNA - early memory B cell
5'
3'
IgM
L1VH1
VDJ
Cμ
Cδ
Cγ3
Cγ1
Cα1
Cγ2
Cγ4
Cε
Cα2
Excision of DNA
"Warheads"
"Rockets"
"Warheads"
"Rockets"
IgG3 DNA
Excision of DNA
IgG2 DNA
IgG2 mRNA
AAAAA
AAAAA

Class swich

- can happen suddenly or by exposition of the same type of antigens repeatedly to memory B cells
- Memory B cells – not every B cell that is exposed to the antigen change to plasma cell and start to produce Ig (IgM) at once. Some change to B memory cells and produce Ig after the next chalange (IgM,IgG)

Class switch



Somatic hypermutation
Affinity maturation

- B cells
- Multiple round of rapid proliferation
- Cells with mutation result in tighter binding and are
- stimulated to proliferate and will dominate.
- Antibodies with increased affinity are produced

