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B-cell antibody class switchings are pressuromodulated events: Part II, gene recombination

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Abstract

Background: The *esebssiwaagoT*$_Q$ method is applicable for the of study cell gene recombination events as the *esebssiwaagoT*$_Q$ is a measure of the intracellular pressure required to establish a horizontal reading frame for alignment of a gene and its intergene bases for maximal transcription and recombination enzyme activity. B-cell differentiation stages have recently been studied by gene *esebssiwaagoT*$_Q$-based pressuromodulation mapping. In this study, the B-cell differentiation stage pressuromodulation map is utilized as a template to simulate B-cell immunoglobulin locus recombination events that take place in the pressuromodulated state in vivo.

Methods: Chromosome 14 (–) strand location 105,566,277 and 106,879,844 germline genes were recombined after determination of gene *esebssiwaagoT*$_Q$s *with respect to* the germline, and then recombined genes were recombined further after determination of gene *esebssiwaagoT*$_Q$s *with respect to* rearranged configurations. For both alleles, first, *IGHD_-_* to *IGHJ_* was performed, and then *IGHV_-_* to *IGHD_-_-IGHJ_* was performed. For Allele 1 (IGHM), internal consensus recognition sequence (iCSR) and further CSR isotype switchings were performed; and for Allele 2 (IGHD), homologous recombination was performed and initial allelic exclusion determined.

Results: First, the *esebssiwaagoT*$_Q$ of a joining (*J_*) and diversity (*D_-_*) gene in its native germline configuration is the basis for predictable subsequent gene rearrangement. Second, *D_-_* to *J_* gene recombination events are bi-allelic and mutually exclusive. Third, the entire process from beginning to end depends on the grade of the pressuromodulation effect, and as per the classical pathway it is an antigen presenting cell (APC)-dependent CD4R+ T-cell-mediated B-cell polarization process. Fourth, CD4R+ T-cells are positively pressuromodulated, while B-cells are subject to the effect of both positive and negative forms of antigen pressuromodulation. And fifth, B-cell to plasma cell transformation and the extra-nodal periphery/tissue nidus phase take place in the presence of antigen load and either positive or negative pressuromodulation of the cell to its recombined antibody gene expression intracellular pressure.

Conclusions: B-cell gene recombination rearrangement events can be predicted with a reasonable degree of certainty. It is envisioned that further *esebssiwaagoT*$_Q$-based study of the remaining B-cell variability gene recombinations isotype switching events will further our understanding of pressuromodulated basis for antigen selection including the evolutionary underpinnings of.

Keywords: Horizontal alignment, *esebssiwaagoT*$_Q$, Pressurotopic, Anisotropy, Mesotropy, Stabilizing isotropy, Supra-pressuromodulated gene, Infra-pressuromodulated gene, Pressuromodulator, Cell polarization, V(D)J gene rearrangement, Internal, Consensus sequence recognition, Homologous recombination, Initial allelic exclusion, Immunoglobulin, Classical pathway, Non-classical pathway

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Background

Gene transcription is a pressuromodulated process, pressurotopic [1–3]. B-cell maturation has recently been studied by gene *esebssiwaagoT*$_Q$-based pressuromodulation mapping of B-cell differentiation stage markers [4]. The *esebssiwaagoT*$_Q$-based pressuromodulation map of B-cell differentiation stage genes accurately simulates B-cell maturation in vivo and applies to both the classical B-cell maturation pathway (2-allele T-cell mediated pressuromodulation effect pathway) and the parallel alternative non-classical B-cell maturation pathway (1-allele T-cell independent antigen-mediated pressuromodulation effect pathway).

The classical 2-allele T-cell dependent B-cell maturation pathway involves three phases.

The first phase is the antigen presenting cell (APC)-more primed CD4R+ CD40LG T-cell-mediated CD40R B-cell cell membrane (CM) polarization effect or less primed T-cell-mediated polarization effect myeloid bone marrow phase until the Immature B-cell stage (CM IgM+), during which there is Allele 1 (IGHM) VDJ and internal consensus sequence recognition (iCSR) (CM IgM+) and after which there is Allele 2 (IGHD) VDJ.

The second phase is the CD4R+ CD40LG T-cell-mediated CD40R B-cell polarization effect lymph node phase until either the Mature naïve B-cell (CM IgM+ IgD+ or IgM+ IgM+) or Evolved mature naïve B-cell (CM IgG_ + IgG_+) stage, during which there is Allele 2 (IGHD) post-V(D)J homologous recombination (HR) or initial allelic exclusion followed by delayed IgM iCSR and primary, secondary or further CSR isotype switching [5].

And, the third phase is the T-cell independent B-cell CM receptor antigenic pressuromodulation effect-mediated extra-nodal periphery/tissue nidus secretory antibody phase upon exposure to either positive pressuromodulator antigens or negative pressuromodulator antigens, during which there is transformation from B-cell to B-pre-plasma cell followed by B-plasma cell node exiting diapedesis as a secretory long-lived B-plasma cell/plasmablast [6, 7].

The parallel alternate non-classical 1-allele T-cell independent B-cell maturation pathway involves two phases, the myeloid bone marrow phase during acute exposure to antigenic positve pressuromodulators, when the T-cell is out of intracellular pressure window for *CD40LG* expression, making the myeloid phase a T-cell independent process; and then the extra-nodal periphery/tissue nidus secretory anibody B-plasma cell phase, which is also a T-cell independent pressuromodulator antigen dependent process.

The non-classical pathway myeloid bone marrow phase involves B-cell CM toll-like receptor (TLR)-mediated endocytosis for example, which substitutes for the T-cell-mediated B-cell polarization pressuromodulation effect in oscillating B-cell intracellular pressure in the marrow [⊂ 0.26 *esebssiwaagoT*$_Q$ units (*CD40*) 0.36–0.41 *esebssiwaagoT*$_Q$ units (*PRDM1*–0.41) 0.10–0.14 *esebssiwaagoT*$_Q$ units ⊃] [4] through the Mature naïve B-cell stage (CM IgM+ IgD-). Thus, during the marrow phase, there is Allele 1 (IGHM) VDJ, iCSR (CM IgM+) and Allele 2 (IGHD) VDJ, which results in a circulating Allele 1 IgM+ only Mature (naïve) B-cell [8].

And, the non-classical pathway T-cell independent extra-marrow periphery/tissue nidus phase results in the IgM+ only (IgM+ IgD-) secretory B-plasma cell or in a further CSRing B-cell and a Ig_+ only (Ig_+ IgD-) secretory B-plasma cell, both short-lived B-plasma cells/plasmablasts [6, 9].

The general intervals of B-cell gene recombination events are shown on the recently developed B-cell differentiation stage pressuromodulation map [4], as are general intervals of internal consensus sequence recognition (iCSR), homologous recombination and further CSR antibody isotype switchings. Thus, the B-cell differentiation stage pressuromodulation map serves as a template for predicting B-cell gene rearrangement events.

B-cell gene recombination events can be predicted for both B-cell differentiation pathways when the following points are considered:

(1) The discordant mechanisms of the recombination enzyme actions on DNA segments, (a) RAG1 and RAG2 recombinases facilitate the excision of intervening variability (*V_-_*), diversity (*D_-_*) and joining (*J_*) genes, where V(D)J recombination does not require an *esebssiwaagoT*$_Q$ match [4] because the mechanism is as such [10], while (b) AICDA and APOBEC3A-G cytidine deaminases facilitate the excision of intervening heavy chain (*IGH_*) genes, where iCSR [10, 11], CSR recombination [10, 12, 13] and B-cell homologous recombination [14] do require an *esebssiwaagoT*$_Q$ match [4];

(2) B-cell gene recombination begins at greater intracellular pressure on Allele 1 (IGHM) and results in earlier assembly and presentation of IgM on the cell membrane (CM) as compared to Allele 2 (IGHD);

(3) *D_-_* to *J_* gene rearrangement process of the VDJ [10, 15–17] is a limited step process for each allele and the number of steps depend on the grade of the positive antigen pressuromodulation effect;

(4) non-functional *D_-_* genes are not present in the VDJ [18], as they serve only the purpose of being stepping stone recombination genes for 2-step *D_-_* to *J_*, and include *IGHD1–20 (nf)*, *IGHD4–11 (nf)* and *IGHD5–18 (nf)* with the exception of *IGHD7–27 (nf)*, which does not participate; and

(5) the percentage of V(D)J *IGHJ_* genes [18] for Allele 1 (IGHM) 2-step *D_-_* to *J_* is 40% (*IGHJ6*) and Allele 1 (IGHM) 1-step *D_-_* to *J_* is 10% (*IGHJ5*), and for Allele 2 (IGHD) 2-step *D_-_* to *J_* is 32% (*IGHJ4*) and Allele 2 (IGHD) 1-step *D_-_* to *J_* is 8.5% (*IGHJ3*), ~ 1.5% (*IGHJ2*) and 8.5% (*IGHJ1*).

In this study, B-cell gene recombination is studied by determining germline gene *esebssiwaagoT*$_Q$s, and rearranging germline genes to simulate actual pressuromodulated in vivo gene recombination events including (1) *IGHD_-_* to *IGHJ_*, (2) *IGHV_-_* to *IGHD_-_-IGHJ_*, (3) internal consensus sequence recognition (iCSR) for Allele 1 (IGHM) and homologous recombination or initial allelic exclusion for Allele 2 (IGHD); and (4) further CSR isotype switchings for Allele 1 (IGHM) or for both alleles.

Methods

Data mining

Locations of germline Ig heavy chain locus genes between chromosome 14 (−) strand location 105,566,277 and 106,879,844 [19], as well as locations of downstream and upstream genes were mined at GeneCards (https://www.genecards.org/) genomic neighborhood GeneLoc genome locator database and at LNCipedia.org database (http://www.lncipedia.org/), pseudogenes included and enhancers excluded [2, 4] (Additional file 1: Table S1).

The 5′ - > 3′ direction episodic sub-episode sums split-integrated weighted average-averaged gene overexpression tropy quotient (*esebssiwaagoT*$_Q$) method and overall approach to gene rearrangement

The downstream and upstream intergene base distances were tabulated, and then the final 5′ - > 3′ *esebssiwaagoT*$_Q$ (fract) for each gene was calculated in upstream anisotropic, upstream mesotropic, downstream anisotropic and downstream mesotropic parts. First, the 3′ - > 5′ and 5′ - > 3′ direction paired point tropy quotients (*prpT*$_Q$s; fract) were determined. Second, initial anisotropic and mesotropic sub-episode blocks (SEB; ASEB, MSEB) were determined, which are constant per episode *where* the number of initial SEBs for establishing a gene category with 100% sensitivity and 100% specificity (100% accuracy) are 5 initial SEBs for an Episode 2 category gene, 7 initial SEBs for an Episode 3 category gene, 9 initial SEBs for an Episode 4 gene, 11 initial SEBs for an Episode 5 gene, 13 initial SEBs for an Episode 6 gene. Third, on the basis of the initial SEBs, the final anisotropic and mesotropic sub-episode blocks (SEB; ASEB, MSEB) were determined, which are variable. And fourth, the 5′ - > 3′ direction *esebssiwaagoT*$_Q$s to the final *esebssiwaagoT*$_Q$ were determined, *where* a gene with an anisotropic final *esebssiwaagoT*$_Q$ for < 0.25 is an infra-pressuromodulated gene (Infra gene), and *where* a gene with a mesotropic final *esebssiwaagoT*$_Q \geq 0.25 < 0.75$ is a supra-pressuromodulated gene (Supra gene). The detailed *esebssiwaagoT*$_Q$ method is in references [2, 4].

Germline genes were recombined after determination of gene *esebssiwaagoT*$_Q$s *with respect to* the germline, and recombined genes were recombined further after determination of gene *esebssiwaagoT*$_Q$s *with respect to* the rearranged configuration. For both alleles, first, *IGHD_-_* to *IGHJ_* recombination was performed, and then *IGHV_-_* to *IGHD_-_-IGHJ_* recombination was performed. For Allele 1 (IGHM), internal consensus sequence recognition (iCSR) and further CSR isotype switchings were performed; and for Allele 2 (IGHD), homologous recombination was performed and initial allelic exclusion determined.

Gene *esebssiwaagoT*$_Q$-based simulation of 2-step and 1-step *IGHD_-_* and *IGHJ_* recombinations for allele 1 (IGHM) and allele 2 (IGHD)

For both alleles, 2-step (1, 2a, 2b) and 1-step D_-_↔ J_ recombination simulations were performed.

For the 2-step D_-_↔ J_ stimulation: first, the non-functional (*nf*) germline genes were determined (Step 1 of 2) and the *IGHJ_* gene was determined (Step 1 of 2) to yield the recombined gene, *IGHD_-_ (nf)-IGHJ_*; second, the *esebssiwaagoT*$_Q$s for the remaining *IGHD_-_* and *IGHJ_* genes *with respect to IGHD_-_ (nf)-IGHJ_* were determined; and third, these genes *with respect to IGHD_-_ (nf)-IGHJ_*, the remaining *IGHD_-_ with respect to IGHD_-_ (nf)-IGHJ_* (Step 2a of 2) and *IGHJ_* genes *with respect to IGHD_-_ (nf)-IGHJ_* (Step 2a of 2) were recombined to yield the final step recombined gene, *IGHD_-_ -IGHJ_* (Step 2b of 2), ready for *IGHV_-_ ↔ IGHD_-_-IGHJ_*.

For the 1-step D_-_↔ J_ stimulation, the germline *IGHD_-_* and *IGHJ_* genes were recombined to yield the final recombined gene, *IGHD_-_ -IGHJ_* (Step 1of 1), ready for *IGHV_-_ ↔ IGHD_-_-IGHJ_*.

Gene *esebssiwaagoT*$_Q$-based simulation of *IGHV_-_* and *IGHD_-_-IGHJ_* recombinations for allele 1 (IGHM) and allele 2 (IGHD)

The most common variable genes were sampled. These genes included *IGHV1–3*, *IGHV3–23*, *IGHV4–28*, *IGHV3–48*, *IGHV4–59* and *IGHV4–61* with the exception of *IGHV5–51* [18]. The *IGHV_-_* to *IGHD_-_-IGHJ_* recombination events through further CSR isotype switching recombinations were performed for *V1–3*, *V3–23*, and *V5–51*.

Gene *esebssiwaagoT*$_Q$-based simulation of internal consensus recognition sequence (iCSR) recombination for allele 1 (IGHM)

For Allele 1 (IGHM) [11], internal consensus sequence recognition (iCSR) recombination was performed between *MIR4537*, *MIR4507/MIR4538* and *MIR4539 with*

respect to IGHV_-_-IGHD_-_-(IGHJ5)-IGHJ6. The complete recombined V(D)J gene is VDJ6 irrespective of whether it is the 1-step recombined *IGHV_-_ -D_-_-J5* gene or the 2-step recombined *IGHV_-_ -D_-_-J5-J6* gene.

Gene *esebssiwaagoT*$_Q$-based simulation of homologous recombination for allele 2 (IGHD) and determination of initial allelic exclusion

For Allele 2 (IGHD) [14], homologous recombination (HR) was performed between *IGHV_-_-IGHD_-_-(J1)–(J2)-(J3)-J4-(J5)-J6* (VDJ6) and *IGHD with respect to IGHV_-_ -IGHD_-_-(J1)–(J2)-(J3)-J4-(J5)-J6*. If there was no *esebssiwaagoT*$_Q$ match (gene *esebssiwaagoT*$_Q$ ± 0.015 units) for homologous recombination, then further CSR was performed (as in Allele 1).

Gene *esebssiwaagoT*$_Q$-based simulation of consensus recognition sequence (CSR) antibody isotype switchings for allele 1 (IGHM)

For Allele 1 (IGHM) isotype switching [12, 13], consensus sequence recognition (CSR) recombination was performed if there was an *esebssiwaagoT*$_Q$ match between a downstream Ig heavy chain gene *IGHG3*, *IGHG1*, *IGHA1*, *IGHG4*/*IGHG2*, *IGHE* and *IGHA2 with respect to VDJ6-IGHM* (± 0.015 units) and *VDJ6-IGHM* (± 0.015 units). If there was an *esebssiwaagoT*$_Q$ match with a downstream gene for example with *IGHG3*, then the *esebssiwaagoT*$_Q$s for each remaining downstream Ig heavy chain gene *IGHG1*, *IGHA1*, *IGHG4*/*IGHG2*, *IGHE* and *IGHA2 with respect to VDJ6-IGHG3* were determined, after which further *esebssiwaagoT*$_Q$ matches were determined and remaining downstream gene recombinations simulated.

Results

Germline *IGH_* genes

IGHA2 is a 3 episode, 7 initial SEB and final SEB gene that begins with a mesotropic SEB. *IGHA2* has one instance of non-contributory anisotropy. *IGHA2* is a 3 M (7) NCA gene with a final *esebssiwaagoT*$_Q$ of 0.10 (*0.099*).

IGHE is a 3 episode, 7 initial SEB and final SEB gene that begins with an anisotropic SEB. *IGHE* is a 3 A (7) gene with a final *esebssiwaagoT*$_Q$ of 0.11 *(0.111)*.

IGHG4*/*IGHG2 is a 2 episode, 5 initial SEB and final SEB gene that begins with a mesotropic SEB. *IGHG4/IGHG2* has one instance of non-contributory anisotropy. *IGHG4/IGHG2* is a 2 M (5) NCA gene with a final *esebssiwaagoT*$_Q$ of 0.16 (*0.163*).

IGHA1 is a 3 episode, 7 initial SEB and final SEB gene that begins with a mesotropic SEB. *IGHA1* is a 3 M (7) gene with a final *esebssiwaagoT*$_Q$ of 0.13 *(0.131)*.

IGHG1 is a 3 episode, 7 initial SEB and final SEB gene that begins with an anisotropic SEB. *IGHG1* is a 3 A (7) gene with a final *esebssiwaagoT*$_Q$ of 0.12 *(0.120)*.

IGHG3 is a 2 episode, 5 initial SEB and final SEB gene that begins with a anisotropic SEB. *IGHG3* is a 2 A (5) gene with a final *esebssiwaagoT*$_Q$ of 0.08 *(0.075)*.

IGHD is a 3 episode, 7 initial SEB and final SEB gene that begins with a mesotropic SEB. *IGHD* is a 3 M (7) gene with a final *esebssiwaagoT*$_Q$ of 0.09 *(0.092)*.

IGHM is a 3 episode, 7 initial SEB and final SEB gene that begins with anisotropic SEB. *IGHM* is a 3 A (7) gene with a final *esebssiwaagoT*$_Q$ of 0.09 *(0.088)*.

MIR4539 is a 3 episode, 7 initial SEB and final SEB gene that begins with a mesotropic SEB. *MIR4539* has one instance of non-contributory anisotropy. *MIR4539* is a 3 M (7) NCA gene with a final *esebssiwaagoT*$_Q$ of 0.08 *(0.076)*.

MIR4507/MIR4538 is a 3 episode, 7 initial SEB and final SEB gene that begins with an anisotropic SEB. *MIR4507/MIR4538* has one instance of non-contributory anisotropy. *MIR4507/MIR4538* is a 3 A (7) NCA gene with a final *esebssiwaagoT*$_Q$ of 0.08 *(0.081)*.

MIR4537 is a 3 episode, 7 initial SEB and final SEB gene that begins with a mesotropic SEB. *MIR4537* has one instance of non-contributory anisotropy. *MIR4537* is a 3 M (7) NCA gene with a final *esebssiwaagoT*$_Q$ of 0.06 *(0.064)* (Table 1, Additional file 2: Table S2).

Germline *IGHJ_* genes

IGHJ6 is a 3 episode, 7 initial SEB and final SEB gene that begins with an anisotropic SEB. *IGHJ6* is a 3 A (7) gene with a final *esebssiwaagoT*$_Q$ of 0.10 *(0.097)*.

IGHJ5 is a 3 episode, 7 initial SEB and final SEB gene that begins with an anisotropic SEB. *IGHJ5* is a 3 A (7) gene with a final *esebssiwaagoT*$_Q$ of 0.24 *(0.235)*.

IGHJ4 is a 3 episode, 7 initial SEB and final SEB gene that begins with a mesotropic SEB. *IGHJ4* has one instance of non-contributory anisotropy. *IGHJ4* is a 3 M (7) NCA gene with a final *esebssiwaagoT*$_Q$ of 0.11 *(0.110)*.

IGHJ3 is a 3 episode, 7 initial SEB and final SEB gene that begins with a mesotropic SEB. *IGHJ3* is a 3 M (7) gene with a final *esebssiwaagoT*$_Q$ of 0.11 *(0.112)*.

IGHJ2 is a 3 episode, 7 initial SEB and final SEB gene that begins with a mesotropic SEB. *IGHJ2* is a 3 M (7) gene with a final *esebssiwaagoT*$_Q$ of 0.11 *(0.114)*.

IGHJ1 is a 3 episode, 7 initial SEB and final SEB gene that begins with a mesotropic SEB. *IGHJ1* has one instance of non-contributory anisotropy. *IGHJ1* is a 3 M (7) NCA gene with a final *esebssiwaagoT*$_Q$ of 0.12 *(0.116)* (Table 2, Additional file 3: Table S3).

Table 1 Chromosome 14 (–) strand chromatin Ig heavy chain locus immunoglobin gene *esebssiwaagoT$_Q$*s for germline genes in native 5′- > 3′ chronology before gene rearrangement

Germline Gene[a]	Germline gene locus[a]	Total no. of transcribed bases at gene locus or n/a (episode category)[b]	Initial no. of sub-episode blocks (converted final no. of sub-episode blocks, or n/a)	Germline gen e 2-digit (*3-digit*) *esebssiwaagoT$_Q$*	Predicted gene recombination *wrt* allele 1 (IGHM), allele 2 (IGHD), both, or neither
IGHA2	*IGHA2*	1508 (3)	7 (n/a)	0.10 *(0.099)*	Allele 1; Allele 2 after initial allelic exclusion
IGHE	*ENSG00000227468/IGHE/ENSG00000254140*	7667 (3)	7 (n/a)	0.11 *(0.111)*	Allele 1; Allele 2 after initial allelic exclusion
IGHG4 & IGHG2	*lnc-JAG2–1/IGHG4 /IGHG2/ ENSG00000253364*	30,527 (2)	7 (5)	0.16 *(0.163)*	Allele 1; Allele 2 after initial allelic exclusion
IGHA1	*IGHA1*	1548 (3)	7 (n/a)	0.13 *(0.131)*	Allele 1; Allele 2 after initial allelic exclusion
IGHG1	*IGHG1*	6729 (3)	7 (n/a)	0.12 *(0.120)*	Allele 1; Allele 2 after initial allelic exclusion
IGHG3	*GC14M105753/IGHG3*	20,987 (2)	7 (5)	0.08 *(0.075)*	Allele 1; Allele 2 after initial allelic exclusion
IGHD	*IGHD*	8914 (3)	7 (n/a)	0.09 *(0.092)*	Allele 2 HR except in initial allelic exclusion
IGHM	*IGHM*	6729 (3)	7 (n/a)	0.09 *(0.088)*	Allele 1; Allele 2 after initial allelic exclusion
MIR4539	*MIR4539*	60 (3)	7 (n/a)	0.08 *(0.076)*	iCSR for Allele 1 (IGHM); Allele 2 (IGHD) delayed iCSR after initial allelic exclusion
MIR4507 & MIR4538	*MIR4507/ MIR4538*	119 (3)	7 (n/a)	0.08 *(0.081)*	iCSR for Allele 1 (IGHM); Allele 2 (IGHD) delayed iCSR after initial allelic exclusion
MIR4537	*MIR4537*	70 (3)	7 (n/a)	0.06 *(0.064)*	iCSR for Allele 1 (IGHM); Allele 2 (IGHD) delayed iCSR after initial allelic exclusion

[a]only Ig genes and gene loci included, non-coding RNA genes (processed pseudogenes) excluded [b] > 11,864 ≤ 265,005 total transcribed bases, Episode category 2 gene; Episode category 3 gene bases, ≤ 11,864 total transcribed bases, Episode category 3 gene

Germline non-functional *IGHD1–20 (nf)* gene for allele 1 (IGHM) 2-step (1 of 2) recombination

IGHD1–20 (nf) is a 3 episode, 7 initial SEB and 7* final SEB gene that begins with an anisotropic SEB. *IGHD1–20 (nf)* has one instance of non-contributory anisotropy at the ending. *IGHD1–20 (nf)* is a 3 A [7 (+ 2): 7*] NCA* gene with a final *esebssiwaagoT*$_Q$ of 0.41 *(0.406)* (Table 3, Additional file 4: Table S4; Table 4).

Germline functional *IGHD_-_* genes un-involved in the 1st step of 2-step allele 1 (IGHM) recombination

IGHD6–19 is a 3 episode, 7 initial and 5 final SEB gene that begins with a mesotropic SEB. *IGHD6–19* has one instance of anisotropy converted-to-mesotropy, and one instance of indirect stIsotropy for mesotropy. *IGHD6–19* is a 3 M [7(− 2): 5] ACM stIMfA gene with a final *esebssiwaagoT*$_Q$ of 0.31 *(0.309)*.

IGHD4–17 is a 3 episode, 7 initial and 9 final SEB gene that begins with an anisotropic SEB. *IGHD4–17* has one instance of anisotropy converted-to-mesotropy. *IGHD4–17* is a 3 A [7 (+ 2): 9] ACM with a final *esebssiwaagoT*$_Q$ of 0.31 *(0.310)*.

IGHD3–16 is a 3 episode, 7 initial and final SEB gene that begins with a mesotropic SEB. *IGHD3–16* has one instance of non-contributory anisotropy. *IGHD3–16* is a 3 M (7) NCA gene with a final *esebssiwaagoT*$_Q$ of 0.31 *(0.308)*.

IGHD3–10 is a 3 episode, 7 initial and final SEB gene that begins with an anisotropic SEB. *IGHD3–10* has one instance of anisotropy converted-to-mesotropy, and non-contributory reverse/stIsotropy. *IGHD3–10* is a 3 A (7) ACM NCstI gene with a final *esebssiwaagoT*$_Q$ of 0.34 *(0.342)*.

IGHD2–8 is a 3 episode, 7 initial and final SEB gene that begins with a mesotropic SEB. *IGHD2–8* has one instance of non-contributory reverse/ stIsotropy. *IGHD2–8* is a 3 M (7) NCstI gene with a final *esebssiwaagoT*$_Q$ of 0.30. *(0.295)*.

IGHD2–2 is a 3 episode, 7 initial and final SEB gene that begins with a mesotropic SEB. *IGHD2–2* has one instance of non-contributory reverse/ stIsotropy. *IGHD2–2* is a 3 M (7) NCstI gene with a final *esebssiwaagoT*$_Q$ of 0.30 (*0.301*) (Table 3, Additional file 4: Table S4; Table 4).

Germline non-functional *IGHD4–11 (nf)* gene and *IGHD5–8 (nf)* for allele 2 (IGHD) 2-step (1 of 2) recombination

IGHD4–11(nf) is a 3 episode, 7 initial SEB and final SEB gene that begins with an anisotropic SEB. *IGHD4–11(nf)* has one instance of anisotropy converted-to-mesotropy *IGHD4–11(nf)* is a 3 A (7) ACM gene with a final *esebssiwaagoT*$_Q$ of 0.29 *(0.293)*.

IGHD5–18 (nf) is a 3 episode, 7 initial and 6 final SEB gene that begins with a mesotropic SEB. *IGHD5–18 (nf)* has one instance of a non-contributory anisotropy, and one instance of indirect stIsotropy for anisotropy. *IGHD5–18 (nf)* is a 3 M [7 (− 3): 4] NCA stIMfA gene with a final *esebssiwaagoT*$_Q$ 0.25 *(0.254)* (Table 3, Additional file 4: Table S4; Table 5).

Germline functional *IGHD_-_* genes un-involved in the 1st step of 2-step allele 2 (IGHD) recombination

IGHD3–9 is a 3 episode, 7 initial and 3 final SEB gene that begins with a mesotropic SEB. *IGHD3–9* has one instance of anisotropy converted-to-mesotropy, one instance of non-contributory anisotropy, and one instance of non-contributory reverse/stIsotropy. *IGHD3–9* is a 3 M [7 (− 4): 3] ACM NCA NCstI gene with a final *esebssiwaagoT*$_Q$ of 0.24 *(0.239)*.

IGHD1–7 is a 3 episode, 7 initial and 5 final SEB gene that begins with an anisotropic SEB. *IGHD1–7* has one instance of anisotropy converted-to-mesotropy, one instance of non-contributory anisotropy, and non-contributory reverse/stIsotropy. *IGHD1–7* is a 3 A [7 (− 2): 5] ACM NCA NCstI gene with a final *esebssiwaagoT*$_Q$ of 0.28 *(0.276)*.

Table 2 Chromosome 14 (–) strand chromatin Ig heavy chain locus joining gene *esebssiwaagoT*$_Q$s for germline genes in native 5′- > 3′ chronology before gene rearrangement

Germline Gene[a]	Germline gene locus[a]	Total no. of transcribed bases at gene locus or n/a (episode category)[b]	Initial no. of sub-episode blocks (converted final no. of sub-episode blocks, or n/a)	Germline gen e 2-digit (*3-digit*) *esebssiwaagoT*$_Q$	Predicted gene recombination *wrt* allele 1 (IGHM), allele 2 (IGHD), both, or neither
IGHJ6	*IGHJ6*	65 (3)	7 (n/a)	0.10 *(0.097)*	Allele 1 (D → J step 2 of 2 for IGHM)
IGHJ5	*IGHJ5*	53 (3)	7 (n/a)	0.24 *(0.235)*	Allele 1 (D → J step 1 of 1 & step 1 of 2 for IGHM)
IGHJ4	*IGHJ4*	50 (3)	7 (n/a)	0.11 *(0.110)*	Allele 2 (D → J step 2 of 2 for IGHD)
IGHJ3	*IGHJ3*	52 (3)	7 (n/a)	0.11 *(0.112)*	Allele 2 (D → J step 1 of 1 for IGHD)
IGHJ2	*IGHJ2*	55 (3)	7 (n/a)	0.11 *(0.114)*	Allele 2 (D → J step 1 of 1 & step 1 of 2 for IGHD)
IGHJ1	*IGHJ1*	54 (3)	7 (n/a)	0.12 *(0.116)*	Allele 2 (D → J step 1 of 1 for IGHD)

[a]only Ig genes and gene loci included, non-coding RNA genes (processed pseudogenes) excluded [b] > 11,864 ≤ 265,005 total transcribed bases, Episode category 2 gene; Episode category 3 gene bases, ≤ 11,864 total transcribed bases, Episode category 3 gene

Table 3 Chromosome 14 (–) strand chromatin Ig heavy chain locus diversity gene *esebssiwaagoT$_Q$*s for germline genes in native 5′- > 3′ chronology before gene rearrangement

Germline Gene 1 nf	Germline gene locus[a]	Total no. of transcribed bases at gene locus or n/a (episode category)[b]	Initial no. of sub-episode blocks (converted final no. of sub-episode blocks, or n/a)	Germline gene 2-digit (*3-digit*) *esebssiwaagoT$_Q^c$*	Predicted gene recombination *wrt* allele 1 (IGHM), allele 2 (IGHD), both, or neither
IGHD7–27[c]	*IGHD7–27*	11 (3)	7 (n/a)	0.17 *(0.165)*[c]	Neither allele 1 nor allele 2
IGHD1–26	*IGHD1–26*	20 (3)	7 (n/a)	0.22 *(0.217)*	Allele 2 (D → J step 1 of 1 for IGHD)
IGHD6–25	*IGHD6–25*	18 (3)	7 (n/a)	0.17 *(0.172)*	Allele 2 (D → J step 1 of 1 for IGHD)
IGHD5–24, IGHD4–23 & IGHD3–22	*lnc-BRF1–1 {IGHD5–24; IGHD4–23; IGHD3–22)*	2856 (3)	7 (5)	0.22 *(0.216)*	Allele 2 (D → J step 1 of 1 for IGHD)
IGHD2–21	*IGHD2–21*	28 (3)	7 (n/a)	0.20 *(0.205)*	Allele 2 (D → J step 1 of 1 for IGHD)
IGHD1–20[nf]	*IGHD1–20*	17 (3)	7 (7)	0.41 *(0.406)*	Allele 1 non-functional (D → J step 1 of 2 for IGHM)
IGHD6–19	*IGHD6–19*	21 (3)	7 (5)	0.31 (*0.309*)	Allele 1 (D → J step 2 of 2 for IGHM *wrt IGHJ5-IGHD1–20*)
IGHD5–18[nf]	*IGHD5–18*	20 (3)	7 (4)	0.25 *(0.254)*	Allele 2 non-functional (D → J step 1 of 2 for IGHD)
IGHD4–17	*IGHD4–17*	16 (3)	7 (9)	0.31 *(0.310)*	Allele 1 (D → J step 2 of 2 for IGHM *wrt IGHJ5-IGHD1–20*)
IGHD3–16	*IGHD3–16*	37 (3)	7 (n/a)	0.31 *(0.308)*	Allele 1 (D → J step 2 of 2 for IGHM *wrt IGHJ5-IGHD1–20*)
IGHD2–15	*IGHD2–15*	31 (3)	7 (n/a)	0.29 *(0.294)*	Allele 1 (D → J step 1 of 1 for IGHM
IGHD1–14	*IGHD1–14*	17 (3)	7 (n/a)	0.29 *(0.292)*	Allele 1 (D → J step 1 of 1 for IGHM
IGHD6–13	*IGHD6–13*	21 (3)	7 (n/a)	0.29 *(0.286)*	Allele 2 (D → J step 1 of 1 for IGHM
IGHD5–12	*IGHD5–12*	23 (3)	7 (n/a)	0.22 *(0.218)*	Allele 2 (D → J step 1 of 1 for IGHD)
IGHD4–11[nf]	*IGHD4–11*	16 (3)	7 (n/a)	0.29 *(0.293)*	Allele 2 non-functional (D → J step 1 of 2 for IGHD)
IGHD3–10	*IGHD3–10*	31 (3)	7 (n/a)	0.34 *(0.342)*	Allele 1 (D → J step 2 of 2 for IGHM *wrt IGHJ5-IGHD1–20*)
IGHD3–9	*IGHD3–9*	31 (3)	7 (3)	0.24 *(0.239)*	Allele 2 (D → J step 2 of 2 for IGHD *wrt IGHJ2–IGHD4–11*)
IGHD2–8	*IGHD2–8*	31 (3)	7 (n/a)	0.30 *(0.295)*	Allele 1 (D → J step 2 of 2 for IGHM *wrt IGHJ5-IGHD1–20*)
IGHD1–7	*IGHD1–7*	17 (3)	7 (5)	0.28 *(0.276)*	Allele 2 (D → J step 2 of 2 for IGHD *wrt IGHJ2–IGHD4–11*)
IGHD6–6	*IGHD6–6*	18 (3)	7 (n/a)	0.27 *(0.275)*	Allele 2 (D → J step 2 of 2 for IGHD *wrt IGHJ2–IGHD4–11*)
IGHD5–5	*IGHD5–5*	20 (3)	7 (n/a)	0.23 *(0.233)*	Allele 2 (D → J step 2 of 2 for IGHD *wrt IGHJ2-IGHD5–18*)
IGHD4–4	*IGHD4–4*	16 (3)	7 (n/a)	0.26 *(0.258)*	Allele 2 (D → J step 2 of 2 for IGHD *wrt IGHJ2–IGHD4–11*)
IGHD3–3	*IGHD3–3*	31 (3)	7 (9)	0.24 *(0.243)*	Allele 1 (D → J step 2 of 2 for IGHD *wrt IGHJ2-IGHD4–11*)
IGHD2–2	*IGHD2–2*	31 (3)	7 (n/a)	0.30 *(0.301)*	Allele 1 (D → J step 2 of 2 for IGHM *wrt IGHJ5-IGHD1–20*)
IGHD1–1	*IGHD1–1*	17 (3)	7 (7)	0.23 *(0.233)*	Allele 2 (D → J step 2 of 2 for IGHD *wrt IGHJ2-IGHD5–18*)

[a]only Ig genes and gene loci included, non-coding RNA genes (processed pseudogenes) excluded [b] > 11,864 ≤ 265,005 total transcribed bases, Episode category 2 gene; Episode category 3 gene bases, ≤ 11,864 total transcribed bases, Episode category 3 gene. [c]nadir *esebssiwaagoT$_Q$* for step 1 D-to-J recombination [IGHD7–27 *esebssiwaagoT$_Q$* at 0.17 (*0.165*)]; *nf* non-functional (*IGHD1–20*, *IGHD5–18*, *IGHD4–11*)

Table 4 Chromosome 14 (–) strand chromatin Ig heavy chain locus diversity (D)-to-joining (J) recombination sequence for allele 1 (IGHM) before VDJ

Germline gene	Germline gene episode category, initial no. of sub-episode blocks (converted final no. of sub-episode blocks, or n/a)[1]	Germline gene 2-digit (*3-digit*) *esebssiwaagoT*$_Q$	*with respect to* Non-germline recombined gene (Step 1 of 2)	Non-germline gene, or n/a	Non-germline gene category, initial no. of sub-episode blocks (converted final no. of sub-episode blocks, or n/a)[a]	Non-germline gene 2-digit *(3-digit) esebssiwaagoT*$_Q$	Step (1 of 1, or 2a, 2b of 2)[b]
IGHD1–20 (nf)*	7 (7)	0.41 *(0.406)*	*IGHD1–20- IGHJ5* (1 of 2)	*IGHD3–10*	7 (5)	0.40 *(0.402)*	2a of 2
IGHD3–10	7 (n/a)	0.34 *(0.342)*		*IGHJ6*	7 (n/a)	0.10 *(0.101)*	2a of 2
IGHJ5	7 (n/a)	0.24 *(0.235)*		*IGHD3–10-IGHJ6*	7 (5)	0.23 *(0.231)*	2b of 2
IGHD1–20 (nf)*	7 (7)	0.41 *(0.406)*	*IGHD1–20- IGHJ5* (1 of 2)	*IGHD4–17*	7 (n/a)	0.15 *(0.150)*	2a of 2
IGHD4–17	7 (9)	0.31 *(0.310)*		*IGHJ6*	7 (n/a)	0.10 *(0.101)*	2a of 2
IGHJ5	7 (n/a)	0.24 *(0.235)*		*IGHD4–17-IGHJ6*	7 (n/a)	0.13 *(0.130)*	2b of 2
IGHD1–20 (nf)*	7 (7)	0.41 *(0.406)*	*IGHD1–20- IGHJ5* (1 of 2)	*IGHD6–19*	7 (n/a)	0.23 *(0.233)*	2a of 2
IGHD6–19	7 (5)	0.31 (*0.309*)		*IGHJ6*	7 (n/a)	0.10 *(0.101)*	2a of 2
IGHJ5	7 (n/a)	0.24 *(0.235)*		*IGHD6–19-IGHJ6*	7 (5)	0.19 *(0.194)*	2b of 2
IGHD1–20 (nf)*	7 (7)	0.41 *(0.406)*	*IGHD1–20- IGHJ5* (1 of 2)	*IGHD3–16*	7 (5)	0.18 *(0.177)*	2a of 2
IGHD3–16	7 (n/a)	0.31 *(0.308)*		*IGHJ6*	7 (n/a)	0.10 *(0.101)*	2a of 2
IGHJ5	7 (n/a)	0.24 *(0.235)*		*IGHD3–16-IGHJ6*	7 (n/a)	0.23 *(0.233)*	2b of 2
IGHD1–20 (nf)*	7 (7)	0.41 *(0.406)*	*IGHD1–20-IGHJ5* (1 of 2)	*IGHD2–2*	7 (n/a)	0.30 *(0.296)*	2a of 2
IGHD2–2	7 (n/a)	0.30 *(0.301)*		*IGHJ6*	7 (n/a)	0.10 *(0.101)*	2a of 2
IGHJ5	7 (n/a)	0.24 *(0.235)*		*IGHD2–2-IGHJ6*	7 (3)	0.30 *(0.297)*	2b of 2
IGHD1–20 (nf)*	7 (7)	0.41 *(0.406)*	*IGHD1–20- IGHJ5* (1 of 2)	*IGHD2–8*	7 (n/a)	0.24 *(0.238)*	2a of 2
IGHD2–8	7 (n/a)	0.30 *(0.295)*		*IGHJ6*	7 (n/a)	0.10 *(0.101)*	2a of 2
IGHJ5	7 (n/a)	0.24 *(0.235)*		*IGHD2–8-IGHJ6*	7 (n/a)	0.20 *(0.196)*	2b of 2
IGHD2–15	7 (n/a)	0.29 *(0.294)*	n/a	*IGHD2–15- IGHJ5*	7 (n/a)	0.25 *(0.251)*	1 of 1
IGHJ5	7 (n/a)	0.24 *(0.235)*					
IGHD1–14	7 (n/a)	0.29 *(0.292)*	n/a	*IGHD1–14- IGHJ5*	7 (n/a)	0.15 *(0.149)*	1 of 1
IGHJ5	7 (n/a)	0.24 *(0.235)*					
IGHD6–13	7 (n/a)	0.29 *(0.286)*	n/a	*IGHD6–13- IGHJ5*	7 (9)	0.20 *(0.205)*	1 of 1
IGHJ5	7 (n/a)	0.24 *(0.235)*					

[a]> 11,864 ≤ 265,005 total transcribed bases, Episode category 2 gene; Episode category 3 gene bases, ≤ 11,864 total transcribed bases, Episode category 3 gene. [b] > 11,864 ≤ 265,005 total transcribed bases, Episode category 2 gene; Episode category 3 gene bases, ≤ 11,864 total transcribed bases, Episode category 3 gene. [b]40% of D-to-J recombinations are 2-step (step 1, J5; step 2 J6) and 10% of D-to-J recombinations are 1-step (step-1, J5 only). **nf* Non-functional

Table 5 Chromosome 14 (–) strand chromatin Ig heavy chain locus diversity (D)-to-joining (J) recombination sequence for allele 2 (IGHD) before VDJ

Germline gene	Germline gene episode category, initial no. of sub-episode blocks (converted final no. of sub-episode blocks, or n/a)[a]	Germline gene 2-digit (*and 3-digit*) *esebssiwaagoT*$_Q$	*with respect to* Non-germline recombined gene (Step 1 of 2)	Non-germline gene, or n/a	Non-germline gene category, initial no. of sub-episode blocks (converted final no. of sub-episode blocks, or n/a)[a]	Non-germline gene 2-digit *(and 3-digit) esebssiwaagoT*$_Q$	Step (1 of 1, or 2a, 2b of 2)[b]
IGHD4–11 (nf)[c]	7 (n/a)	0.29 *(0.293)*	*IGHD4–11- IGHJ2* (1 of 2)	*IGHD1–7*	7 (n/a)	0.31 *(0.311)*	2a of 2
IGHD1–7	7 (5)	0.28 *(0.276)*		*IGHJ4*	7 (9)	0.19 *(0.193)*	2a of 2
IGHJ2	7 (n/a)	0.11 *(0.114)*		*IGHD1–7-IGHJ4*	7 (5)	0.35 *(0.350)*	2b of 2
IGHD4–11 (nf)[c]	7 (n/a)	0.29 *(0.293)*	*IGHD4–11- IGHJ2* (1 of 2)	*IGHD6–6*	7 (5)	0.27 (*0.266*)	2a of 2
IGHD6–6	7 (n/a)	0.27 *(0.275)*		*IGHJ4*	7 (9)	0.19 *(0.193)*	2a of 2
IGHJ2	7 (n/a)	0.11 *(0.114)*		*IGHD6–6-IGHJ4*	7 (9)	0.25 (0.249)	2b of 2
IGHD4–11 (nf)[c]	7 (n/a)	0.29 *(0.293)*	*IGHD4–11-IGHJ2* (1 of 2)	*IGHD4–4*	7 (n/a)	0.27 *(0.268)*	2a of 2
IGHD4–4	7 (n/a)	0.26 *(0.258)*		*IGHJ4*	7 (9)	0.19 *(0.193)*	2a of 2
IGHJ2	7 (n/a)	0.11 *(0.114)*		*IGHD4–4-IGHJ4*	7 (n/a)	0.33 *(0.332)*	2b of 2
IGHD4–11 (nf)[c]	7 (n/a)	0.29 *(0.293)*	*IGHD4–11- IGHJ2* (1 of 2)	*IGHD3–3*	7 (n/a)	0.16 *(0.156)*	2a of 2
IGHD3–3	7 (9)	0.24 *(0.243)*		*IGHJ4*	7 (9)	0.19 *(0.193)*	2a of 2
IGHJ2	7 (n/a)	0.11 *(0.114)*		*IGHD3–3-IGHJ4*	7 (9)	0.26 *(0.258)*	2b of 2
IGHD4–11 (nf)[c]	7 (n/a)	0.29 *(0.293)*	*IGHD4–11- IGHJ2* (1 of 2)	*IGHD3–9*	7 (n/a)	0.33 *(0.332)*	2a of 2
IGHD3–9	7 (3)	0.24 *(0.239)*		*IGHJ4*	7 (9)	0.19 *(0.193)*	2a of 2
IGHJ2	7 (n/a)	0.11 *(0.114)*		*IGHD3–9-IGHJ4*	7 (n/a)	0.32 *(0.324)*	2b of 2
IGHD5–18 (nf)[c]	7 (4)	0.25 *(0.254)*	*IGHD5–18- IGHJ4* (1 of 2)	*IGHD5–5*	7 (n/a)	0.31 *(0.308)*	2a of 2
IGHD5–5	7 (n/a)	0.23 *(0.233)*		*IGHJ4*	7 (n/a)	0.17 *(0.165)*	2a of 2
IGHJ2	7 (n/a)	0.11 *(0.114)*		*IGHD5–5-IGHJ4*	7 (3)	0.30 *(0.297)*	2b of 2
IGHD5–18 (nf)[c]	7 (4)	0.25 *(0.254)*	*IGHD5–18- IGHJ4* (1 of 2)	*IGHD1–1*	7 (n/a)	0.25 *(0.250)*	2a of 2
IGHD1–1	7 (7)	0.23 *(0.233)*		*IGHJ4*	7 (n/a)	0.17 *(0.165)*	2a of 2
IGHJ2	7 (n/a)	0.11 *(0.114)*		*IGHD1–1-IGHJ4*	7 (6)	0.34 *(0.340)*	2b of 2
IGHD5–24/ IGHD4–23/ IGHD3–22	7 (5)	0.22 *(0.216)*	n/a	*IGHD5–24/ IGHD4–23/ IGHD3–22- IGHJ1*	7 (n/a)	0.16 *(0.161)*	1 of 1
IGHJ1	7 (n/a)	0.12 *(0.116)*					
IGHD1–26	7 (n/a)	0.22 *(0.217)*	n/a	*IGHD1–26-IGHJ1*	7 (n/a)	0.13 *(0.130)*	1 of 1
IGHJ1	7 (n/a)	0.12 *(0.116)*					
IGHD2–21	7 (n/a)	0.20*(0.205)*	n/a	*IGHD2–21- IGHJ1*	7 (6)	0.21*(0.206)*	1 of 1
IGHJ1	7 (n/a)	0.12 *(0.116)*					
IGHD6–25	7 (n/a)	0.17 *(0.172)*	n/a	*IGHD6–25 IGHJ1*	7 (n/a)	0.23 *(0.233)*	1 of 1
IGHJ1	7 (n/a)	0.12 q*(0.116)*					

Table 5 Chromosome 14 (–) strand chromatin Ig heavy chain locus diversity (D)-to-joining (J) recombination sequence for allele 2 (IGHD) before VDJ *(Continued)*

Germline gene	Germline gene episode category, initial no. of sub-episode blocks (converted final no. of sub-episode blocks, or n/a)[a]	Germline gene 2-digit (*and 3-digit*) *esebssiwaagoT*$_Q$	*with respect to* Non-germline recombined gene (Step 1 of 2)	Non-germline gene, or n/a	Non-germline gene category, initial no. of sub-episode blocks (converted final no. of sub-episode blocks, or n/a)[a]	Non-germline gene 2-digit *(and 3-digit) esebssiwaagoT*$_Q$	Step (1 of 1, or 2a, 2b of 2)[b]
IGHD5–12	7 (n/a)	0.22 *(0.218)*	n/a	*IGHD5–12_ IGHJ2*	7 (5)	0.35 *(0.347)*	1 of 1
IGHJ2	7 (n/a)	0.11 *(0.114)*					
IGHD5–24/ IGHD4–23/ IGHD3–22	7 (5)	0.22 *(0.216)*	n/a	*IGHD5–24/ IGHD4–23/ IGHD3–22- IGHJ3*	7 (n/a)	0.15 *(0.147)*	1 of 1
IGHJ3	7 (n/a)	0.11 *(0.112)*					
IGHD1–26	7 (n/a)	0.22 *(0.217)*	n/a	*IGHD1–26- IGHJ3*	7 (6)	0.11 *(0.114)*	1 of 1
IGHJ3	7 (n/a)	0.11 *(0.112)*					
IGHD2–21	7 (n/a)	0.20 *(0.205)*	n/a	*IGHD2–21- IGHJ3*	7 (n/a)	0.13 *(0.130)*	1 of 1
IGHJ3	7 (n/a)	0.11 *(0.112)*					
IGHD6–25	7 (n/a)	0.17 *(0.172)*	n/a	*IGHD6–25_ IGHJ3*	7 (5)	0.20 *(0.195)*	1 of 1
IGHJ3	7 (n/a)	0.11 *(0.112)*					

[a]> 11,864 ≤ 265,005 total transcribed bases, Episode category 2 gene; Episode category 3 gene bases, ≤ 11,864 total transcribed bases, Episode category 3 gene. [b]32% of D-to-J recombinations are 2-step (step 1, J2; step 2 J4), 18% of D-to-J recombinations are 1-step (either J1 or J3), and ~ 1.5% of D-to-J recombinations are 1-step (step 1, J2 only). [c]*nf* Non-functional

IGHD6–6 is a 3 episode, 7 initial and final SEB gene that begins with a mesotropic SEB. *IGHD6–6* has one instance of indirect stIsotropy for mesotropy. *IGHD6–19* is a 3 M (7) stIMfM gene with a final *esebssiwaagoT*$_Q$ of 0.27 *(0.275)*.

IGHD5–5 is a 3 episode, 7 initial and final SEB gene that begins with a mesotropic SEB. *IGHD5–5* has one instance of non-contributory reverse/stIsotropy. *IGHD5–5* is a 3 M (7) NCstI gene with a final *esebssiwaagoT*$_Q$ of 0.23 *(0.233)*.

IGHD4–4 is a 3 episode, 7 initial and final SEB gene that begins with a mesotropic SEB. *IGHD4–4* has two instances of non-contributory reverse/stIsotropy. *IGHD4–4* is a 3 M (7) NCstI × 2 gene with a final *esebssiwaagoT*$_Q$ of 0.26 *(0.258)*.

IGHD3–3 is a 3 episode, 7 initial and 9 final SEB gene that begins with a mesotropic SEB. *IGHD3–3* has one instance of non-contributory anisotropy, and one instance of non-contributory reverse/stIsotropy. *IGHD3–3* is a 3 M [7 (+ 2): 9] NCA NCstI gene with a final *esebssiwaagoT*$_Q$ of 0.24 *(0.243)*.

IGHD1–1 is a 3 episode, 7 initial SEB and 7* final SEB gene that begins with a mesotropic SEB. *IGHD1–1* has one instance of anisotropy converted-to-mesotropy preceding ending confirmation (anisotropic SEB no. 8), and three instances of non-contributory reverse/stIsotropy. *IGHD1–1* is a 3 M [7 (+ 1): 7*] ACM* NCstI gene with a final *esebssiwaagoT*$_Q$ of 0.23 *(0.233)* (Table 3, Additional file 4: Table S4; Table 5).

Germline non-functional *IGHD_-_* gene

IGHD7–27† is a 3 episode, 7 initial SEB and final SEB gene that begins with a mesotropic SEB. *IGHD7–27*† is a 3 M (7) gene with a final *esebssiwaagoT*$_Q$ of. 0.17 *(0.165)*† (Table 3, Additional file 4: Table S4).

Germline *IGHJ5* gene for allele 1 (IGHM) 2-step (1 of 2) recombination [and for allele 1 (IGHM) 1-step recombination]

IGHJ5 is a 3 A (7) gene with a final *esebssiwaagoT*$_Q$ of 0.24 (*0.235*) (Table 2, Additional file 3: Table S3; Table 4).

Germline non-functional *IGHD1–20 (nf)* gene for allele 1 (IGHM) 2-step (1 of 2) recombination

IGHD1–20 (nf) is a 3 A [7 (+ 2): 7*] NCA* gene with a final *esebssiwaagoT*$_Q$ of 0.41 *(0.406)* (Table 3, Additional file 4: Table S4; Table 4).

IGHJ6 gene *with respect to IGHD1–20 (nf)-IGHJ5* for allele 1 (IGHM) 2-step (2a of 2) recombination

IGHJ6 *with respect to IGHD1–20-IGHJ5* is a 3 episode, 7 initial and final SEB gene that begins with an anisotropic SEB. ***IGHJ6*** *with respect to IGHD1–20-IGHJ5* is a 3 A (7) gene with a final *esebssiwaagoT*$_Q$ of 0.10 *(0.101)* (Table 4, Additional file 5: Table S5).

IGHD_-_ genes *with respect to IGHD1–20 (nf)-IGHJ5* for allele 1 (IGHM) 2-step (2a of 2) recombination

IGHD3–10 *with respect to IGHD1–20-IGHJ5* is a 3 episode, 7 initial and 5 final SEB gene that begins with an anisotropic SEB. ***IGHD3–10*** *with respect to IGHD1–20-IGHJ5* has one instance of non-contributory anisotropy, and one instance of non-contributory reverse/stIsotropy. ***IGHD3–10*** *with respect to IGHD1–20-IGHJ5* is a 3 A [7(− 2): 5] NCA NCstI gene with a final *esebssiwaagoT*$_Q$ of 0.40 *(0.402)*.

IGHD4–17 *with respect to IGHD1–20-IGHJ5* is a 3 episode, 7 initial and final SEB gene that begins with a mesotropic SEB. ***IGHD4–17*** *with respect to IGHD1–20-IGHJ5* has one instance of non-contributory anisotropy. ***IGHD4–17*** *with respect to IGHD1–20-IGHJ5* is a 3 M (7) NCA gene with a final *esebssiwaagoT*$_Q$ of 0.15 *(0.150)*.

IGHD6–19 *with respect to IGHD1–20-IGHJ5* is a 3 episode, 7 initial and 3 final SEB gene that begins with a mesotropic SEB. ***IGHD6–19*** *with respect to IGHD1–20-IGHJ5* is a 3 M (7) gene with a final *esebssiwaagoT*$_Q$ of 0.23 *(0.233)*.

IGHD3–16 *with respect to IGHD1–20-IGHJ5* is a 3 episode, 7 initial and 5 final SEB gene that begins with a mesotropic SEB. ***IGHD3–16*** *with respect to IGHD1–20-IGHJ5* has one instance of anisotropy converted-to-mesotropy. ***IGHD3–16*** *with respect to IGHD1–20-IGHJ5* is a 3 M [7(− 2): 5] ACM gene with a final *esebssiwaagoT*$_Q$ of 0.18 *(0.177)*.

IGHD2–2 *with respect to IGHD1–20-IGHJ5* is a 3 episode, 7 initial and 3 final SEB gene that begins with a mesotropic SEB. ***IGHD2–2*** *with respect to IGHD1–20-IGHJ5* has one instance of non-contributory reverse/stIsotropy. *IGHD3–9* is a 3 M (7) NCstI gene with a final *esebssiwaagoT*$_Q$ of 0.30 *(0.296)*.

IGHD2–8 *with respect to IGHD1–20-IGHJ5* is a 3 episode, 7 initial and 3 final SEB gene that begins with a mesotropic SEB. ***IGHD2–8*** *with respect to IGHD1–20-IGHJ5* has one instance of non-contributory anisotropy, and one instance of non-contributory reverse/stIsotropy. ***IGHD2–8*** *with respect to IGHD1–20-IGHJ5* is a 3 M (7) NCA NCstI gene with a final *esebssiwaagoT*$_Q$ of 0.24 *(0.238)* (Table 4, Additional file 5: Table S5).

*IGHD_-_-IGHJ_* genes for allele 1 (IGHM) 2-step (2b of 2) recombination

IGHD3–10-IGHJ6 is a 3 episode, 7 initial and 5 final SEB gene that begins with an anisotropic SEB. *IGHD3–10-IGHJ6* has one instance of anisotropy converted-to-mesotropy. *IGHD3–10-IGHJ6* is a 3 A [7(− 2): 5] ACM gene with a final *esebssiwaagoT*$_Q$ of 0.23 *(0.231)*.

IGHD4–17-IGHJ6 is a 3 episode, 7 initial and final SEB gene that begins with a mesotropic SEB. *IGHD4–17-IGHJ6* has one instance of non-contributory

anisotropy. *IGHD4–17-IGHJ6* is a 3 M (7) NCA gene with a final *esebssiwaagoT*$_Q$ of 0.13 *(0.130)*.

IGHD6–19-IGHJ6 is a 3 episode, 7 initial and 5 final SEB gene that begins with a mesotropic SEB. *IGHD6–19-IGHJ6* has one instance of anisotropy converted-to-mesotropy. *IGHD6–19-IGHJ6* is a 3 M [7(− 2): 5] ACM gene with a final *esebssiwaagoT*$_Q$ of 0.19 *(0.194)*.

IGHD3–16-IGHJ6 is a 3 episode, 7 initial SEB and final SEB gene that begins with a mesotropic SEB. *IGHD3–16-IGHJ6* is a 3 M (7) gene with a final *esebssiwaagoT*$_Q$ of 0.23 *(0.233)*.

IGHD2–2-IGHJ6 is a 3 episode, 7 initial and 3 final SEB gene that begins with a mesotropic SEB. *IGHD2–2-IGHJ6* has one instance of non-contributory anisotropy, and one instance of indirect stIsotropy for anisotropy. *IGHD2–2-IGHJ6* is a 3 M [7(− 4): 3] NCA stIMfA gene with a final *esebssiwaagoT*$_Q$ of 0.30 *(0.297)*.

IGHD2–8-IGHJ6 is a 3 episode, 7 initial SEB and final SEB gene that begins with a mesotropic SEB. *IGHD2–8-IGHJ6* is a 3 M (7) gene with a final *esebssiwaagoT*$_Q$ of 0.20 *(0.196)* (Table 4, Additional file 5: Table S5).

Germline *IGHJ2* gene for allele 2 (IGHD) 2-step (1 of 2) [and for allele 2 (IGHD) 1-step recombination]

IGHJ2 is a 3 M (7) gene with a final *esebssiwaagoT*$_Q$ of 0.11 *(0.114)* (Table 2, Additional file 3: Table S3; Table 5).

Germline non-functional *IGHD_-_ (nf)* genes for allele 2 (IGHD) 2-step (1 of 2) recombination

IGHD4–11(nf) is a 3 A (7) ACM gene with a final *esebssiwaagoT*$_Q$ of 0.29 *(0.293)*.

IGHD5–18 (nf) is a 3 M [7 (− 3): 4] NCA stIMfA gene with a final *esebssiwaagoT*$_Q$ 0.25 *(0.254)* (Table 3, Additional file 4: Table S4; Table 5).

IGHJ4 gene *with respect to IGHD4–11 (nf)-IGHJ2* and *IGHJ4* gene *with respect to IGHD5–18 (nf)*-IGHJ2 for allele 2 (IGHD) 2-step (2a of 2) recombination

IGHJ4 *with respect to IGHD4–11-IGHJ2* is a 3 episode, 7 initial and 9 final SEB gene that begins with an mesotropic SEB. ***IGHJ4*** *with respect to IGHD4–11-IGHJ2* has one instance of anisotropy converted-to-mesotropy. ***IGHJ4*** *with respect to IGHD4–11-IGHJ2* is a 3 M [7(+ 2): 9] ACM with a final *esebssiwaagoT*$_Q$ 0.19 *(0.193)*.

IGHJ4 *with respect to IGHD5–18-IGHJ4* is a 3 episode, 7 initial SEB and final SEB gene that begins with a mesotropic SEB. ***IGHJ4*** *with respect to IGHD5–18-IGHJ4* is a 3 M (7) gene with a final *esebssiwaagoT*$_Q$ of 0.17 *(0.165)* (Table 5, Additional file 6: Table S6).

IGHD_-_ genes *with respect to IGHD_-_ (nf)-IGHJ2* for allele 2 (IGHD) 2-step (2a of 2) recombination

IGHD1–7 *with respect to IGHD4–11-IGHJ2* is a 3 episode, 7 initial and final SEB gene that begins with an anisotropic SEB. ***IGHD1–7*** *with respect to IGHD4–11-IGHJ2* has one instance of non-contributory reverse/stIsotropy. ***IGHD1–7*** *with respect to IGHD4–11-IGHJ2* is a 3 A (7) NCstI gene with a final *esebssiwaagoT*$_Q$ of 0.31 *(0.311)*.

IGHD6–6 *with respect to IGHD4–11-IGHJ2* is a 3 episode, 7 initial and 5 final SEB gene that begins with a mesotropic SEB. ***IGHD6–6*** *with respect to IGHD4–11-IGHJ2* has one instance of anisotropy converted-to-mesotropy, one instance of non-contributory anisotropy, and one instance of non-contributory reverse/stIsotropy. ***IGHD6–6*** *with respect to IGHD4–11-IGHJ2* is a 3 M [7(− 2): 5] ACM NCA NCstI gene with a final *esebssiwaagoT*$_Q$ of 0.27 *(0.266)*.

IGHD4–4 *with respect to IGHD4–11-IGHJ2* is a 3 episode, 7 initial and final SEB gene that begins with a mesotropic SEB. ***IGHD4–4*** *with respect to IGHD4–11-IGHJ2* has one instance of non-contributory reverse/stIsotropy. ***IGHD4–4*** *with respect to IGHD4–11-IGHJ2* is a 3 M (7) NCstI gene with a final *esebssiwaagoT*$_Q$ of 0.27 *(0.268)*.

IGHD3–3 *with respect to IGHD4–11-IGHJ2* is a 3 episode, 7 initial and final SEB gene that begins with a mesotropic SEB. ***IGHD3–3*** *with respect to IGHD4–11-IGHJ2* has one instance of non-contributory reverse/stIsotropy. ***IGHD3–3*** *with respect to IGHD4–11-IGHJ2* is a 3 M (7) NCstI gene with a final *esebssiwaagoT*$_Q$ of 0.16 *(0.156)*.

IGHD3–9 *with respect to IGHD4–11-IGHJ2* is a 3 episode, 7 initial and final SEB gene that begins with a mesotropic SEB. ***IGHD3–9*** *with respect to IGHD4–11-IGHJ2* has one instance of anisotropy converted-to-mesotropy. ***IGHD3–9*** *with respect to IGHD4–11-IGHJ2* a 3 M (7) ACM gene with a final *esebssiwaagoT*$_Q$ of 0.33 *(0.332)*.

IGHD5–5 *with respect to IGHD5–18-IGHJ2* is a 3 episode, 7 initial and final SEB gene that begins with a mesotropic SEB. ***IGHD5–5*** *with respect to IGHD5–18-IGHJ2* has one instance of anisotropy converted-to-mesotropy, and one instance of non-contributory reverse/stIsotropy. ***IGHD5–5*** *with respect to IGHD5–18-IGHJ2* is a 3 M (7) ACM NCstI gene with a final *esebssiwaagoT*$_Q$ of 0.31 *(0.308)*.

IGHD1–1 *with respect to IGHD5–18-IGHJ2* is a 3 episode, 7 initial and final SEB gene that begins with a mesotropic SEB. ***IGHD1–1*** *with respect to IGHD5–18-IGHJ2* has one instance of non-contributory reverse/stIsotropy, and one instance of indirect stIsotropy for mesotropy. ***IGHD1–1*** *with respect to IGHD5–18-IGHJ2* is a 3 M (7) NCstI stIMfM gene

with a final *esebssiwaagoT*$_Q$ of 0.25 *(0.250)* (Table 5, Additional file 6: Table S6).

*IGHD_-_ -IGHJ_* genes for allele 2 (IGHD) 2-step (2b of 2) recombination

IGHD1–7-IGHJ4 is a 3 episode, 7 initial and 5 final SEB gene that begins with an anisotropic SEB. ***IGHD1–7-IGHJ4*** has one instance of anisotropy converted-to-mesotropy, and one instance of indirect stIsotropy for mesotropy. ***IGHD1–7-IGHJ4*** is a 3 A [7(− 2): 5] ACM stIMfM gene with a final *esebssiwaagoT*$_Q$ of 0.35 *(0.350)*.

IGHD6–6-IGHJ4 is a 3 episode, 7 initial and 9 final SEB gene that begins with a mesotropic SEB. *IGHD6–6-IGHJ4* has one instance of anisotropy converted-to-mesotropy. *IGHD6–6-IGHJ4* is a 3 M [7(+ 2): 9] ACM gene with a final *esebssiwaagoT*$_Q$ of 0.25 *(0.249)*.

IGHD4–4-IGHJ4 is a 3 episode, 7 initial and final SEB gene that begins with anisotropic SEB. *IGHD4–4-IGHJ4* has one instance of anisotropy converted-to-mesotropy. *IGHD4–4-IGHJ4* is a 3 A (7) ACM gene with a final *esebssiwaagoT*$_Q$ of 0.33 *(0.332)*.

IGHD3–3-IGHJ4 is a 3 episode, 7 initial and 9 final SEB gene that begins with a mesotropic SEB. *IGHD3–3-IGHJ4* has one instance of anisotropy converted-to-mesotropy. *IGHD3–3-IGHJ4* is a 3 M [7(+ 2): 9] ACM gene with a final *esebssiwaagoT*$_Q$ of 0.26 *(0.258)*.

IGHD3–9-IGHJ4 is a 3 episode, 7 initial and final SEB gene that begins with a mesotropic SEB. *IGHD3–3-IGHJ4* is a 3 M (7) gene with a final *esebssiwaagoT*$_Q$ of 0.32 *(0.324)*.

IGHD5–5-IGHJ4 is a 3 episode, 7 initial and 3 final SEB gene that begins with a mesotropic SEB. *IGHD5–5-IGHJ4* has one instance of a non-contributory anisotropy, and one instance of indirect stIsotropy for anisotropy. *IGHD5–5-IGHJ4* is a 3 M [7(− 4): 3] NCA stIMfA gene with a final *esebssiwaagoT*$_Q$ of 0.30 *(0.297)*.

IGHD1–1-IGHJ4 is a 3 episode, 7 initial and 6 final SEB gene that begins with an anisotropic SEB. *IGHD1–1-IGHJ4* has one instance of a non-contributory anisotropy. *IGHD1–1-IGHJ4* is a 3 A [7(− 1): 6] NCA gene with a final *esebssiwaagoT*$_Q$ of 0.34 (*0.340*) (Table 5, Additional file 6: Table S6).

Germline *IGHJ5* gene for allele 1 (IGHM) allele 1 (IGHM) 1-step recombination

IGHJ5 is a 3 A (7) gene with a final *esebssiwaagoT*$_Q$ of 0.24 *(0.235* (Table 2, Additional file 3: Table S3; Table 4).

Germline functional *IGHD_-_* genes for allele 1 (IGHM) 1-step recombination

IGHD2–15 is a 3 episode, 7 initial SEB and final SEB gene that begins with a mesotropic SEB. *IGHD2–15* has one instance of non-contributory anisotropy. *IGHD2–15* is a 3 M (7) NCA gene with a final *esebssiwaagoT*$_Q$ of 0.29 *(0.294)*.

IGHD1–14 is a 3 episode, 7 initial and final SEB gene that begins with an anisotropic SEB. *IGHD1–14* has two instances of anisotropy converted-to-mesotropy, and one instance of non-contributory anisotropy. *IGHD1–14* is a 3 A (7) ACM × 2 NCA with a final *esebssiwaagoT*$_Q$ of 0.29 *(0.292)*.

IGHD6–13 is a 3 episode, 7 initial and final SEB gene that begins with a mesotropic SEB. *IGHD6–13* has one instance of non-contributory anisotropy, and one instance of non-contributory reverse stIsotropy. *IGHD6–13* is a 3 M (7) NCA NCstI gene with a final *esebssiwaagoT*$_Q$ of 0.29 *(0.286)* (Table 3, Additional file 4: Table S4; Table 4).

IGHD_-_-IGHJ5 genes for allele 1 (IGHM) V-to-DJ after 1-step recombination

IGHD2–15-IGHJ5 is a 3 episode, 7 initial SEB and final SEB gene that begins with a mesotropic SEB. *IGHD2–15-IGHJ5* is a 3 M (7) gene with a final *esebssiwaagoT*$_Q$ of 0.25 *(0.251)*.

IGHD1–14-IGHJ5 is a 3 episode, 7 initial and 3 final SEB gene that begins with a mesotropic SEB. *IGHD1–14-IGHJ5* has one instance of anisotropy converted-to-mesotropy, and one instance of non-contributory anisotropy. *IGHD1–14-IGHJ5* is a 3 M (7) ACM NCA gene with a final *esebssiwaagoT*$_Q$ of 0.15 *(0.149)*.

IGHD6–13-IGHJ5 is a 3 episode, 7 initial and 9 final SEB gene that begins with an anisotropic SEB. *IGHD6–13-IGHJ5* has one instance of anisotropy converted-to-mesotropy, and one instance of non-contributory anisotropy. *IGHD6–13- IGHJ5* is a 3 A [7(+ 2): 9] ACM NCA gene with a final *esebssiwaagoT*$_Q$ of 0.20 *(0.205)* (Table 4, Additional file 5: Table S5).

Germline functional *IGHJ3, IGHJ2 and IGHJ1* genes for allele 2 (IGHD) 1-step recombination

IGHJ3 is a 3 M (7) gene with a final *esebssiwaagoT*$_Q$ of 0.11 *(0.112)*.

IGHJ2 is a 3 M (7) gene with a final *esebssiwaagoT*$_Q$ of 0.11 *(0.114)*.

IGHJ1 is a 3 M (7) NCA gene with a final *esebssiwaagoT*$_Q$ of 0.12 *(0.116)* (Table 2, Additional file 3: Table S3; Table 5).

Germline functional *IGHD_-_* genes for allele 2 (IGHD) 1-step recombination

IGHD1–26 is a 3 episode, 7 initial and final SEB gene that begins with an anisotropic SEB. *IGHD1–26* has two instances of non-contributory anisotropy. *IGHD1–26* is a 3 A (7) NCA × 2gene with a final *esebssiwaagoT*$_Q$ of 0.22 *(0.217)*.

IGHD6–25 is a 3 episode, 7 initial and final SEB gene that begins with an anisotropic SEB. *IGHD1–14 IGHD6–25* has one instance of anisotropy converted-to-mesotropy, and two instances of non-contributory anisotropy. *IGHD6–25* is a 3 A (7) ACM NCA × 2 with a final *esebssiwaagoT*$_Q$ 0.17 *(0.172)*.

IGHD5–24/IGHD4–23/IGHD3–22 is a 3 episode, 7 initial and 5 final SEB gene that begins with an anisotropic SEB. *IGHD5–24/IGHD4–23/IGHD3–22* has one instance of anisotropy converted-to-mesotropy, and one instance of non-contributory anisotropy. *IGHD5–24/IGHD4–23/IGHD3–22* is a 3 A [(7(− 2): 5] ACM NCA with a final *esebssiwaagoT*$_Q$ of 0.22 *(0.216)*.

IGHD2–21 is a 3 episode, 7 initial and final SEB gene that begins with a mesotropic SEB. *IGHD2–21* has one instance of non-contributory anisotropy. *IGHD2–21* is a 3 M (7) NCA with a final *esebssiwaagoT*$_Q$ of 0.20 *(0.205)*.

IGHD5–12 is a 3 episode, 7 initial SEB and final SEB gene that begins with a mesotropic SEB. *IGHJ3 IGHD5–12* is a 3 M (7) gene with a final *esebssiwaagoT*$_Q$ of 0.22 *(0.218)* (Table 3, Additional file 4: Table S4; Table 5).

*IGHD_-_-IGHJ_* genes for allele 2 (IGHD) V-to-DJ after 1-step recombination

IGHD5–24/IGHD4–23/IGHD3–22-IGHJ1 is a 3 episode, 7 initial and final SEB gene that begins with a mesotropic SEB. *IGHD5–24/IGHD4–23/IGHD3–22-IGHJ1* has one instance of indirect stIsotropy for mesotropy. *IGHD5–24/IGHD4–23/IGHD3–22-IGHJ1* is a 3 M (7) stIMfM gene with a final *esebssiwaagoT*$_Q$ of 0.16 *(0.161)*.

IGHD1–26-IGHJ1 is a 3 episode, 7 initial SEB and final SEB gene that begins with a mesotropic SEB. *IGHD1–26-IGHJ1* is a 3 M (7) gene with a final *esebssiwaagoT*$_Q$ of 0.13 *(0.130)*.

IGHD2–21-IGHJ1 is a 3 episode, 7 initial and 6 final SEB gene that begins with a mesotropic SEB. *IGHD2–21- IGHJ1* has two instances of non-contributory anisotropy. *IGHD2–21- IGHJ1* is a 3 M [7(− 1): 6] NCA × 2 gene with a final *esebssiwaagoT*$_Q$ of 0.21 *(0.206)*.

IGHD6–25-IGHJ1 is a 3 episode, 7 initial SEB and final SEB gene that begins with a mesotropic SEB. *IGHD6–25-IGHJ1* is a 3 M (7) gene with a final *esebssiwaagoT*$_Q$ of 0.23 *(0.233)*.

IGHD5–12-IGHJ2 is a 3 episode, 7 initial and 5 final SEB gene that begins with a mesotropic SEB. *IGHD5–12-IGHJ2* has one instance of non-contributory anisotropy. *IGHD5–12-IGHJ2* is a 3 M [7(− 2): 5] NCA gene with a final *esebssiwaagoT*$_Q$ of 0.35 *(0.347)*.

IGHD5–24/IGHD4–23/IGHD3–22-IGHJ3 is a 3 episode, 7 initial SEB and final SEB gene that begins with a mesotropic SEB. *IGHD5–24/IGHD4–23/IGHD3–22-IGHJ3* is a 3 M (7) gene with a final *esebssiwaagoT*$_Q$ of 0.15 *(0.147)*.

IGHD1–26-IGHJ3 is a 3 episode, 7 initial and 6 final SEB gene that begins with a mesotropic SEB. *IGHD1–26-IGHJ3* has one instance of non-contributory anisotropy. *IGHD1–14-IGHJ5* is a 3 M [7(− 1): 6] NCA gene with a final *esebssiwaagoT*$_Q$ of 0.11 *(0.114)*.

IGHD2–21- IGHJ3 is a 3 episode, 7 initial SEB and final SEB gene that begins with a mesotropic SEB. *IGHD2–21- IGHJ3* is a 3 M (7) gene with a final *esebssiwaagoT*$_Q$ of 0.13 (*0.130*).

IGHD6–25-IGHJ3 is a 3 episode, 7 initial and 5 final SEB gene that begins with an mesotropic SEB. *IGHD6–25-IGHJ3* has one instance of anisotropy converted-to-mesotropy. *IGHD6–25-IGHJ3* is a 3 M [7(− 2): 5] ACM with a final *esebssiwaagoT*$_Q$ of 0.20 *(0.195)* (Table 5, Additional file 6: Table S6).

Germline *IGHV_* genes

IGHV1–3/IGHV4–4§ *with respect to IGHJ_-IGHD_-_* is a 3 episode, 7 initial and variable final SEB gene that begins with either an anisotropic SEB or a mesotropic SEB. The final *esebssiwaagoT*$_Q$ is variable.

IGHV3–23 is a 3 episode, 7 initial SEB and final SEB gene that begins with an anisotropic SEB. *IGHV3–23* is a 3 A (7) gene with a final *esebssiwaagoT*$_Q$ of 0.33 *(0.332)*.

IGHV4–28 is a 3 episode, 7 initial and 5 final SEB gene that begins with a mesotropic SEB. *IGHV4–28* has one instance of anisotropy converted-to-mesotropy, and one instance of indirect stIsotropy for mesotropy. ***IGHV4–28*** is a 3 M [7 (− 2): 5] ACM stIMfM gene with a final *esebssiwaagoT*$_Q$ of 0.41 *(0.415)*.

IGHV3–48 is a 3 episode, 7 initial SEB and final SEB gene that begins with an anisotropic SEB. *IGHV3–48* is a 3 A (7) gene with a final *esebssiwaagoT*$_Q$ of 0.27 *(0.274)*.

IGHV5–51/IGHV3–53 is a 2 episode, 5 initial SEB and final SEB gene that begins with an anisotropic SEB. *IGHV5–51/IGHV3–53* has one instance of non-contributory anisotropy. *IGHV5–51/IGHV3–53* is a 2 A (5) NCA gene with a final *esebssiwaagoT*$_Q$ of 0.25 *(0.245)*.

IGHV4–59 is a 3 episode, 7 initial SEB and final SEB gene that begins with a mesotropic SEB. *IGHV4–59* is a 3 M (7) gene with a final *esebssiwaagoT*$_Q$ of. 0.34 *(0.336)*.

IGHV4–61 is a 3 episode, 7 initial SEB and final SEB gene that begins with a mesotropic SEB. *IGHV4–61* is a 3 M (7) gene with a final *esebssiwaagoT*$_Q$ of. 0.26 *(0.258)* (Table 6, Additional file 7: Table S7).

Ig heavy chain genes before iCSR and homologous recombination after *IGHV1–3-IGHD_-_-IGHJ6*

IGHV1–3- IGHD_-_-IGHJ6 is a 3 episode, 7 initial and 9* final SEB gene that begins with a mesotropic SEB. *IGHV1–3- IGHD_-_-IGHJ6* has one instance of

anisotropy converted-to-mesotropy, and one instance of indirect stIsotropy for anisotropy. *IGHV1–3- IGHD_-_-IGHJ6* is a 3 M [7(+ 2)(+ 1):9*] ACM stIMfA* gene with a final *esebssiwaagoT*$_Q$ 0.23 *(0.226)*.

MIR4537 *with respect to V1–3- D_-_-J6* is a 3 episode, 7 initial and final SEB gene that begins with an anisotropic SEB. ***MIR4537*** *with respect to V1–3-D_-_-*J6 is a 3 A (7) gene with a final *esebssiwaagoT*$_Q$ 0.25 *(0.251)*.

MIR4507/MIR4538 *with respect to V1–3-D_-_-J6* is a 3 episode, 7 initial and final SEB gene that begins with a mesotropic SEB. ***MIR4507/MIR4538*** *with respect to V1–3-D_-_-J6* is a 3 M (7) gene with a final *esebssiwaagoT*$_Q$ of 0.26 *(0.260)*.

MIR4539 *with respect to V1–3-D_-_-J6* is a 3 episode, 7 initial and final SEB gene that begins with a mesotropic SEB. ***MIR4539*** *with respect to V1–3-D_-_-J6* is a 3 M (7) gene with a final *esebssiwaagoT*$_Q$ of 0.27 *(0.268)*.

IGHD *with respect to V1–3- D_-_-J6* is a 3 episode, 7 initial and final SEB gene that begins with an anisotropic SEB. ***IGHD*** *with respect to V1–3-D_-_-J6* is a 3 A (7) gene with a final *esebssiwaagoT*$_Q$ of 0.20 *(0.198)* (Table 7, Additional file 8: Table S8).

Ig heavy chain genes after iCSR, homologous recombination and further CSRs after *IGHV1–3-IGHD_-_-IGHJ6*

V1–3-D_-_-J6-IGHM is a 2 episode, 5 initial and final SEB gene that begins with a mesotropic SEB. *V1–3-D_-_-J6-IGHM* is a 2 M (5) gene with a final *esebssiwaagoT*$_Q$ of 0.27 *(0.275)*.

V1–3-D_-_-IGHD is a 2 episode, 5 initial and final SEB gene that begins with a mesotropic SEB. *V1–3-D_-_-IGHD* is a 2 M (5) gene with a final *esebssiwaagoT*$_Q$ of 0.32 *(0.320)*.

V1–3-D_-_-IGHG3 is a 2 episode, 5 initial and 4 final SEB gene that begins with a mesotropic SEB. *V1–3-D_-_-IGHG3* has one instance of anisotropy converted-to-mesotropy. *V1–3-D_-_ -IGHG3* is a 2 M [5(− 1): 4] ACM gene with a final *esebssiwaagoT*$_Q$ of 0.31 *(0.306)*.

V1–3-D_-_-IGHG4 is a 2 episode, 5 initial and 5* final SEB gene that begins with an anisotropic SEB. *V1–3-D_-_-IGHG4* has one instance of anisotropy converted-to-mesotropy. *V1–3-D_-_-IGHG4* is 2 A [5(+ 1): 5] ACM* gene with a final *esebssiwaagoT*$_Q$ of 0.24 *(0.237)*.

V1–3-D_-_-IGHA2 is a 2 episode, 5 initial and 7 final SEB gene that begins with a mesotropic SEB. *V1–3-D_-_-IGHA2* has one instance of anisotropy converted-to-mesotropy. *V1–3-D_-_ -IGHA2* s a 3 M [5(+ 2): 7] ACM gene with a final *esebssiwaagoT*$_Q$ of 0.18 *(0.185)* (Table 7, Additional file 8: Table S8).

See Table 7 and Additional file 8: Table S8 for *with respect to V1–3-D_-_-IGHM*, *with respect to V1–3-D_-_-IGHD*, *with respect to V1–3-D_-_-IGHG3*, *with respect to V1–3-D_-_-IGHG4*, and *with respect to V1–3-D_-_-IGHA2* genes.

Ig heavy chain genes before iCSR and initial allelic exclusion after *IGHV3–23-IGHD_-_-IGHJ6*

IGHV3–23- IGHD_-_-IGHJ6 is a 3 episode, 7 initial and final SEB gene that begins with a mesotropic SEB. *IGHV3–23- IGHD_-_-IGHJ6* is a 3 M (7) gene with a final *esebssiwaagoT*$_Q$ of 0.29 *(0.285)*.

MIR4537 *with respect to V3–23-D_-_-J6* is a 3 episode, 7 initial and final SEB gene that begins with an anisotropic SEB. ***MIR4537*** *with respect to V3–23-D_-_-J6* is a 3 A (7) gene with a final *esebssiwaagoT*$_Q$ of 0.27 *(0.272)*.

MIR4507/MIR4538 *with respect to V3–23-D_-_-J6* is a 3 episode, 7 initial and final SEB gene that begins with

Table 6 Chromosome 14 (–) strand chromatin Ig heavy chain locus variability gene *esebssiwaagoT*$_Q$s for germline genes in native 5′- > 3′ chronology

Germline Gene[1a,b]	Germline gene locus[1a]	Total no. of transcribed bases at gene locus or n/a (episode category)[2]	Initial no. of sub-episode blocks (converted final no. of sub-episode blocks, or n/a)	Germline gene 2-digit (*3-digit*) *esebssiwaagoT*$_Q$, or n/a
IGHV1–3 & IGHV4–4[§]	*lnc-AL901608.1–10/IGHV1–3/ IGHV4–4*[§]	10,439 (3)	7 (varies)	varies
IGHV3–23	*IGHV3–23*	535 (3)	7 (n/a)	0.33 *(0.332)*
IGHV4–28	*IGHV4–28*	507 (3)	7 (n/a)	0.41 *(0.415)*
IGHV3–48	*IGHV3–48*	535 (3)	7 (n/a)	0.27 *(0.274)*
IGHV5–51 & IGHV3–53	*GC14M107956/ lnc-AL901608.1–17 {IGHV5–51/IGHVIII-51–1 (pseudogene)/ IGHVII-51–2 (pseudogene)/ IGHV3–52 (pseudogene)/ IGHV3–53*	23,464 (2)	7 (5)	0.25 *(0.245)*
IGHV4–59	*IGHV4–59*	577 (3)	7 (n/a)	0.34 *(0.336)*
IGHV4–61	*IGHV4–61*	539 (3)	7 (n/a)	0.26 *(0.258)*

[1a] only Ig genes and gene loci included, non-coding RNA genes (processed pseudogenes) excluded [b]sample set of variability genes. [2]> 11,864 ≤ 265,005 total transcribed bases, Episode category 2 gene; Episode category 3 gene bases, ≤ 11,864 total transcribed bases, Episode category 3 gene. [§]*lnc-AL901608.1-10/IGHV1-3/IGHV4-*4 gene locus *esebssiwaagoT*$_Q$ is *D_-_ -J_* location dependent

Table 7 Chromosome 14 (–) strand chromatin Ig heavy chain locus recombination sequence for both alleles after *IGHV1-3-IGHD_-_-IGHJ6*

Gene *with respect to*, or n/a	Gene (no. of transcribed gene bases, or n/a)	Total no. of transcribed bases at gene locus, or n/a (episode category)[a, g3, g4g2, e]	Initial no. of sub-episode blocks (converted final no. of sub-episode blocks, or n/a)	2-digit *esebssiwaagoT$_Q$* (*and 3-digit*) *esebssiwaagoT$_Q$*	*esebssiwaagoT$_Q$* match (yes, no)[b,c]	Match recombination gene for further recombination, location upstream & downstream of, or n/a
n//a	***V1–3-D_-_-J6*** (n./a)	n/a (3)	7 (9)	0.23 *(0.226)*	yes	HR upstream of IGHD (Allele 2)
V1–3- D_-_-J6	*MIR4537* (70)	70 (3)	7 (n/a)	0.25 *(0.251)*	no	n/a
V1–3- D_-_-J6	*MIR4507/MIR4538* (119)	119 (3)	7 (n/a)	0.26 *(0.260)*	yes	iCSR with intergene bases of MIR4539 (Allele 1)
V1–3- D_-_-J6	*MIR4539* (60)	60 (3)	7 (n/a)	0.27 *(0.268)*	yes	iCSR with intergene bases of MIR4507 (Allele 1)
V1–3- D_-_-J6	*IGHD* (8914)	8914 (3)	7 (n/a)	0.20 *(0.198)*	yes	HR downstream of *IGHV1–3- IGHD_-_-IGHJ6* (Allele 2)
n/a	***V1–3-D_-_ -J6-IGHD*** (n/a)	22,039 (2)	5 (n/a)	**0.32 *(0.320)***	n/a	n/a
n/a	***V1–3-D_-_ -J6-IGHM*** (n/a)	18,279 (2)	5 (n/a)	**0.27 (*0.275*)**	yes	upstream of IGHG3 & IGHA2 to upstream of IGHM CSRs
V1–3-D_-_ -J6-IGHM	*IGHG3* (5492)	20,987[g3] (2)	5 (n/a)	0.27 *(0.271)*	yes	primary CSR
V1–3-D_-_ -J6-IGHM	*IGHG1* (6729)	6729 (3)	7 (8)	0.17 *(0.173)*	no	n/a
V1–3-D_-_ -J6-IGHM	*IGHA1* (1548)	1548 (3)	7 (9)	0.22 *(0.222)*	no	n/a
V1–3-D_-_ -J6-IGHM	*IGHG4/ IGHG2* (1726; 1739)	30,527[g4g2] (2)	5 (n/a)	0.22 *(0.215)*	no	n/a
V1–3-D_-_ -J6-IGHM	*IGHE* (1788)	7667[e] (3)	7 (9)	0.22 *(0.222)*	no	n/a
V1–3-D_-_ -J6-IGHM	*IGHA2* (1508)	1508 (3)	7 (n/a)	0.26 *(0.258)*	yes	primary CSR (final)
n/a	***V1–3-D_-_ -J6-IGHG3*** (n/a)	n/a (2)	5 (4)	**0.31 *(0.306)***	yes	only upstream of IGHG4/IGHG2 to upstream of IGHG3 CSR
V1–3-D_-_ -J6-IGHG3	*IGHG1* (6729)	6729 (3)	7 (n/a)	0.19 *(0.190)*	no	n/a
V1–3-D_-_ -J6-IGHG3	*IGHA1* (1548)	1548 (3)	7 (n/a)	0.16 *(0.161)*	no	n/a
V1–3-D_-_ -J6-IGHG3	*IGHG4/ IGHG2* (1726; 1739)	30,527[g4g2] (2)	5 (n/a)	0.33 *(0.325)*	yes	secondary CSR
V1–3-D_-_ -J6-IGHG3	*IGHE* (1788)	7667 (3)	7 (n/a)	0.21 *(0.211)*	no	n/a
V1–3-D_-_ -J6-IGHG3	*IGHA2* (1508)	1508 (3)	7 (n/a)	0.23 *(0.226)*	no	n/a
—	**no *V1–3-D_-_ -J6-IGHG1***	—	—	—	—	—
no *V1–3-D_-_ -J6-IGHG1*	*IGHA1* (1548)	1548 (3)	7 (-)	n/a	n/a	tertiary CSR not applicable (n/a)
no *V1–3-D_-_ -J6-IGHG1*		30,527[g4g2] (2)	5 (-)	n/a	n/a	tertiary CSR not applicable (n/a)

Table 7 Chromosome 14 (–) strand chromatin Ig heavy chain locus recombination sequence for both alleles after *IGHV1-3-IGHD_-_-IGHJ6 (Continued)*

Gene *with respect to*, or n/a	Gene (no. of transcribed gene bases, or n/a)	Total no. of transcribed bases at gene locus, or n/a (episode category)[a, g3, g4g2, e]	Initial no. of sub-episode blocks (converted final no. of sub-episode blocks, or n/a)	2-digit *esebssiwaagoT*$_Q$ (*and 3-digit*) *esebssiwaagoT*$_Q$	*esebssiwaagoT*$_Q$ match (yes, no)[b,c]	Match recombination gene for further recombination, location upstream & downstream of, or n/a
	IGHG4/ IGHG2 (1726; 1739)					
no *V1–3-D_-_ -J6-IGHG1*	*IGHE* (1788)	7667 (3)	7 (–)	n/a	n/a	tertiary CSR not applicable (n/a)
no *V1–3-D_-_ -J6-IGHG1*	*IGHA2* (1508)	1508 (3)	7 (–)	n/a	n/a	tertiary CSR not applicable (n/a)
—	**no *V1–3-D_-_ -J6-IGHA1***	—	—	—	—	—
no *V1–3-D_-_ -J6-IGHA1*	*IGHG4/ IGHG2 (1726; 1739)*	30,527[g4g2] (2)	5 (-)	n/a	n/a	tertiary CSR not applicable (n/a)
no *V1–3-D_-_ -J6-IGHA1*	*IGHE* (1788)	7667[e] (3)	7 (–)	n/a	n/a	tertiary CSR not applicable (n/a)
no *V1–3-D_-_ -J6-IGHA1*	*IGHA2* (1508)	1508 (3)	7 (–)	n/a	n/a	tertiary CSR not applicable (n/a)
n/a	***V1–3-D_-_ -J6-IGHG4*** (n/a)	n/a (2)	5 (5)	**0.24 *(0.237)***	yes	upstream of IGHE & IGHA2 to upstream of IGHG4 CSR
V1–3-D_-_ -J6-IGHG4	*IGHE* (1788)	7667 (3)	7 (n/a)	0.19 *(0.187)*	no	n/a
V1–3-D_-_ -J6-IGHG4	*IGHA2* (1508)	1508 (3)	7 (n/a)	0.23 *(0.226)*	yes	tertiary CSR (final)
—	**no *V1–3-D_-_ -J6-IGHE***	—	—	—	—	—
no *V1–3-D_-_ -J6-IGHE*	*IGHA2* (1508)	1508 (3)	7 (–)	n/a	n/a	quaternary CSR not applicable (n/a)
n/a	***V1–3-D_-_ -J6-IGHA2*** (n/a)	n/a (2)	5 (7)	**0.18 *(0.185)***	n/a	n/a

[a] *lnc-AL901608.1–10* (106,003,045–106,013,483): *IGHV1–3* gene locus transcribed bases = 8389 [*IGHV1–3* (Ig heavy variable 1–3) (106,005,095–106,005,574)/remaining *lnc-AL901608.1–10* (106,005,575–106,013,483)/*IGHV4–4* (Ig heavy variable 4–4) (106,011,922–106,012,420)]. [b] > 11,864 ≤ 265,005 total transcribed bases, Episode category 2 gene; Episode category 3 gene bases, ≤ 11,864 total transcribed bases, Episode category 3 gene. [c] *esebssiwaagoT*$_Q$ match if gene *esebssiwaagoT*$_Q$ ± 0.015 units [g3)] *GC14M105753/IGHG3*. [g4g2)] *lnc-JAG2–1/IGHG4/IGHG2/ENSG00000253364* [e)] *ENSG00000227468/IGHE/ENSG00000254140*

a mesotropic SEB. ***MIR4507/MIR4538*** *with respect to V3–23-D_-_-J6* is a 3 M (7) gene with a final *esebssiwaagoT*$_Q$ of 0.28 *(0.277)*.

MIR4539 *with respect to V3–23-D_-_-J6* is a 3 episode, 7 initial and 5 final SEB gene that begins with a mesotropic SEB. ***MIR4539*** *with respect to V3–23-D_-_-J6* has one instance of anisotropy converted-to-mesotropy. ***MIR4539*** *with respect to V3–23-D_-_-J6* is a 3 M [7(− 2): 5] ACM gene with a final *esebssiwaagoT*$_Q$ of 0.23 *(0.232)*.

IGHD *with respect to V3–23-D_-_-J6* is a 3 episode, 7 initial and 8 final SEB gene that begins with an anisotropic SEB. ***IGHD*** *with respect to V3–23-D_-_-J6* has one instance of anisotropy converted-to-mesotropy. ***IGHD*** *with respect to V3–23-D_-_-J6* is a 3 A [7 (+ 1): 8] ACM 3 A (7) gene with a final *esebssiwaagoT*$_Q$ of 0.22 *(0.218)* (Table 8, Additional file 9: Table S9).

Ig heavy chain genes after iCSR and further CSRs following *IGHV3–23-IGHD_-_-IGHJ6*

V3–23-D_-_-J6–IGHM is a 3 episode, 7 initial and final SEB gene that begins with a mesotropic SEB. *V3–23-D_-_-J6-IGHM* is a 3 M (7) gene with a final *esebssiwaagoT*$_Q$ of. 0.28 *(0.277)*.

V3–23-D_-_-J6-IGHG1 is a 2 episode, 5 initial and final SEB gene that begins with a mesotropic SEB. *V3–23-D_-_-J6-IGHG1* has one instance of anisotropy converted-to-mesotropy. *V3–23-D_-_-J6-IGHG1* is 2 M (5) ACM gene with a final *esebssiwaagoT*$_Q$ of 0.26 *(0.256)*.

V3–23-D_-_-J6-IGHA1 is a 3 episode, 7 initial and final SEB gene that begins with a mesotropic SEB. *V3–23-D_-_-J6-IGHA1* has one instance of anisotropy converted-to-mesotropy. *V3–23-D_-_-J6-IGHA1* is 3 M (7) ACM gene with a final *esebssiwaagoT*$_Q$ of 0.17 *(0.171)*.

V3–23-D_-_-J6-IGHE is a 3 episode, 7 initial and final SEB gene that begins with a mesotropic SEB. *V3–23-D_-_-J6-IGHE* is a 3 M (7)) gene with a final *esebssiwaagoT*$_Q$ of. 0.21 *(0.205)*.

V3–23-D_-_-J6-IGHA2 is a 2 episode, 5 initial and 7 final SEB gene that begins with an anisotropic SEB. *V3–23-D_-_-J6-IGHA2* s a 3 A (7) gene with a final *esebssiwaagoT*$_Q$ of 0.21 *(0.208)* (Table 8, Additional file 9: Table S9).

See Table 8 and Additional file 9: Table S9 for *with respect to V3–23-D_-_-J6-IGHM*, *with respect to V3–23-D_-_-J6-IGHG1*, *with respect to V3–23-D_-_-J6-IGHA1*, *with respect to V3–23-D_-_-J6-IGHE*, and *with respect to V3–23-D_-_-J6-IGHA2* genes.

Ig heavy chain genes before iCSR and initial allelic exclusion after *IGHV5–51-IGHD_-_-IGHJ6*

IGHV5–51-IGHD_-_-IGHJ6 is a 2 episode, 5 initial and final SEB gene that begins with a mesotropic SEB. *IGHV5–51-IGHD_-_-IGHJ6* is a 2 M (5) gene with a final *esebssiwaagoT*$_Q$ of 0.23 *(0.233)*.

MIR4537 *with respect to V5–51-D_-_-J6* is a 3 episode, 7 initial and final SEB gene that begins with a mesotropic SEB. ***MIR4537*** *with respect to V5–51-D_-_-J6* is a 3 M (7) gene with a final *esebssiwaagoT*$_Q$ of 0.15 *(0.152)*.

MIR4507/MIR4538 *with respect to V5–51-D_-_-J6* is a 3 episode, 7 initial and final SEB gene that begins with an anisotropic SEB. ***MIR4507/MIR4538*** *with respect to V5–51-D_-_-J6* is a 3 A (7) gene with a final *esebssiwaagoT*$_Q$ of 0.15 *(0.155)*.

MIR4539 *with respect to V5–51-D_-_-J6* is a 3 episode, 7 initial and final SEB gene that begins with a mesotropic SEB. ***MIR4539*** *with respect to V5–51-D_-_-J6* is a 3 M (7) gene with a final *esebssiwaagoT*$_Q$ of 0.16 *(0.159)*.

IGHD *with respect to V5–51-D_-_-J6* is a 3 episode, 7 initial and 9 final SEB gene that begins with an anisotropic SEB. ***IGHD*** *with respect to V5–51-D_-_-J6* has one instance of anisotropy converted-to-mesotropy. ***IGHD*** *with respect to V3–51-D_-_-J6* is a 3 A [7(+ 2): 9] ACM gene with a final *esebssiwaagoT*$_Q$ of 0.17 *(0.169)* (Table 9, Additional file 10: Table S10).

Ig heavy chain genes after iCSR and further CSRs following *IGHV5–51-IGHD_-_-IGHJ6*

V5–51-D_-_-J6-IGHM is a 2 episode, 5 initial and final SEB gene that begins with an anisotropic SEB. *V5–51-D_-_-J6-IGHM* is a 2 A (5) gene with a final *esebssiwaagoT*$_Q$ of.0.16 *(0.165)*.

V5–51-D_-_-J6-IGHG1 is a 2 episode, 5 initial and final SEB gene that begins with a mesotropic SEB. *V5–51-D_-_-J6-IGHG1* has one instance of anisotropy converted-to-mesotropy. *V5–51-D_-_-J6-IGHG1* is 2 M (5) ACM gene with a final *esebssiwaagoT*$_Q$ of 0.15 *(0.153)*.

V5–51-D_-_-J6-IGHA1 is a is a 2 episode, 5 initial and final SEB gene that begins with a mesotropic SEB. *V5–51-D_-_-J6-IGHA1* is 2 M (5) gene with a final *esebssiwaagoT*$_Q$ of 0.13 *(0.134)*.

V5–51-D_-_-J6-IGHG4 is a is a 2 episode, 5 initial and final SEB gene that begins with a mesotropic SEB. *V5–51-D_-_-J6-IGHG4* is a 2 M (5) gene with a final *esebssiwaagoT*$_Q$ of 0.18 *(0.184)*.

V5–51-D_-_-J6-IGHE is a 2 episode, 5 initial and 6* final SEB gene that begins with an anisotropic SEB. *V5–51-D_-_-J6-IGHE* has one instance of anisotropy converted-to-mesotropy. *V5–51-D_-_-J6-IGHE* is 2 A [5(+ 1): 6*] ACM* gene with a final *esebssiwaagoT*$_Q$ of 0.15 *(0.152)*.

V5–51-D_-_-J6-IGHA2 is a 2 episode, 5 initial and final SEB gene that begins with a mesotropic SEB. *V5–51-D_-_-J_-J6-IGHA2* has one instance of indirect stIsotropy for anisotropy. *V5–51-D_-_-J6-IGHA2* s a 2 M (5)

Table 8 Chromosome 14 (–) strand chromatin Ig heavy chain locus recombination sequence for both alleles after *IGHV3–23-IGHD_-_-IGHJ6*

Gene *with respect to*, or n/a	Gene (no. of transcribed gene bases, or n/a)	Total no. of transcribed bases at gene locus, or n/a (episode category)[a, g3, g4g2, e]	Initial no. of sub-episode blocks (converted final no. of sub-episode blocks, or n/a)	2-digit *esebssiwaagoT*$_Q$ (*and 3-digit*) *esebssiwaagoT*$_Q$	*esebssiwaagoT*$_Q$ match (yes, no)[b]	Match recombination gene for further recombination, location upstream & downstream of, or n/a
n//a	***V3–23-D_-_ -J6*** (n/a)	n/a (3)	7 (n/a)	0.29 *(0.285)*	no	n/a
V3–23-D_-_-IGHJ6	*MIR4537* (70)	70 (3)	7 (n/a)	0.27 *(0.272)*	yes	iCSR with intergene bases of MIR4507/MIR4538 (Allele 1)
V3–23-D_-_-IGHJ6	*MIR4507/MIR4538* (119)	119 (3)	7 (n/a)	0.28 *(0.277)*	yes	iCSR with intergene bases of MIR4537 (Allele 1)
V3–23-D_-_-IGHJ6	*MIR4539* (60)	60 (3)	7 (5)	0.23 *(0.232)*	no	no
V3–23-D_-_-IGHJ6	*IGHD* (8914)	8914 (3)	7 (8)	0.22 *(0.218)*	no	initial allelic exclusion (Allele 2)
n/a	***V3–23-D_-_ -J6-IGHM*** (n/a)	n/a (3)	7 (n/a)	**0.28 *(0.277)***	yes	upstream of IGHG1 & IGHA2 to upstream of IGHM CSRs
V3–23-D_-_ -J6-IGHM	*IGHG3* (5492)	20,987[g3] (2)	5 (n/a)	0.21 *(0.214)*	no	no
V3–23-D_-_ -J6-IGHM	*IGHG1* (6729)	6729 (3)	7 (n/a)	0.27 *(0.271)*	yes	primary CSR
V3–23-D_-_ -J6-IGHM	*IGHA1* (1548)	1548 (3)	7 (n/a)	0.23 *(0.232)*	no	no
V3–23-D_-_ -J6-IGHM	*IGHG4/ IGHG2* (1726; 1739)	30,527[g4g2] (2)	5 (n/a)	0.22 *(0222)*	no	no
V3–23-D_-_ -J6-IGHM	*IGHE* (1788)	7667[e] (3)	7 (9)	0.19 *(0.190)*	no	no
V3–23-D_-_ -J6-IGHM	*IGHA2* (1508)	1508 (3)	7 (n/a)	0.26 *(0.258)*	yes	primary CSR
—	**no *V3–23-D_-_ -J6-IGHG3***	—	—	—	—	—
no *V3–23-D_-_ -J6-IGHG3*	*IGHG1* (6729)	6729 (3)	7 (-)	n/a	n/a	secondary CSR not applicable (n/a)
no *V3–23-D_-_ -J6-IGHG3*	*IGHA1* (1548)	1548 (3)	7 (-)	n/a	n/a	secondary CSR not applicable (n/a)
no *V3–23-D_-_ -J6-IGHG3*	*IGHG4/ IGHG2* (1726; 1739)	30,527[g4g2] (2)	5 (-)	n/a	n/a	secondary CSR not applicable (n/a)
no *V3–23-D_-_ -J6-IGHG3*	*IGHE* (1788)	7667 (3)	7 (–)	n/a	n/a	secondary CSR not applicable (n/a)
no *V3–23-D_-_ -J6-IGHG3*	*IGHA2* (1508)	1508 (3)	7 (–)	n/a	n/a	secondary CSR not applicable (n/a)
n/a	***V3–23-D_-_ -J6-IGHG1*** (n/a)	n/a (2)	5 (n/a)	**0.26 *(0.256)***[&]	yes	only upstream of IGHA1 to upstream of IGHG1 CSR
V3–23-D_-_ -J6-IGHG1	*IGHA1* (1548)	1548 (3)	7 (n/a)	0.26 *(0.263)*	yes	secondary CSR
V3–23-D_-_ -J6-IGHG1	*IGHG4/ IGHG2* (1726; 1739)	30,527 (2)	5 (n/a)	0.31 *(0.305)*	no	no
V3–23-D_-_ -J6-IGHG1	*IGHE* (1788)	7667 (3)	7 (9)	0.14 *(0.142)*	no	no
V3–23-D_-_ -J6-IGHG1	*IGHA2* (1508)	1508 (3)	7 (n/a)	0.22 *(0.223)*	no	no
n/a	***V3–23-D_-_ -J6-IGHA1*** (n/a)	n/a (3)	7 (n/a)	**0.17 *(0.171)***	yes	upstream of IGHE & IGHA2 to upstream of IGHA1 CSRs
V3–23-D_-_ -J6-IGHA1	*IGHG4/ IGHG2* (1726; 1739)	30,527 (2)	5 (n/a)	0.20 *(0.204)*	no	no
V3–23-D_-_ -J6-IGHA1	*IGHE* (1788)	7667 (3)	7 (n/a)	0.17 *(0.167)*	yes	tertiary CSR
V3–23-D_-_ -J6-IGHA1	*IGHA2* (1508)	1508 (3)	7 (n/a)	0.18 *(0.179)*	yes	tertiary CSR

Table 8 Chromosome 14 (–) strand chromatin Ig heavy chain locus recombination sequence for both alleles after *IGHV3–23-IGHD_-_-IGHJ6 (Continued)*

Gene *with respect to*, or n/a	Gene (no. of transcribed gene bases, or n/a)	Total no. of transcribed bases at gene locus, or n/a (episode category)[a, g3, g4g2, e]	Initial no. of sub-episode blocks (converted final no. of sub-episode blocks, or n/a)	2-digit *esebssiwaagoT$_Q$* (*and 3-digit*) *esebssiwaagoT$_Q$*	*esebssiwaagoT$_Q$* match (yes, no)[b]	Match recombination gene for further recombination, location upstream & downstream of, or n/a
—	**no *V3–23-D_-_ -J6-IGHG4***	—	—	—	—	—
no *V3–23-D_-_ -J6-IGHG4*	IGHE (1788)	7667 (3)	7 (–)	n/a	n/a	quaternary CSR not applicable (n/a)
no *V3–23-D_-_ -J6-IGHG4*	IGHA2 (1508)	1508 (3)	7 (–)	n/a	n/a	quaternary CSR not applicable (n/a)
n/a	***V3–23-D_-_ -J6-IGHE*** (n/a)	n/a (3)	7 (n/a)	**0.21 *(0.205)***	yes	upstream of IGHA2 to upstream of IGHE CSR
V3–23-D_-_ -J6-IGHE	*IGHA2* (1508)	1508 (3)	7 (n/a)	0.18 *(0.183)*	yes	quaternary CSR (final)
n/a	***V3–23-D_-_ -J6-IGHA2*** (n/a)	n/a (3)	7 (n/a)	**0.21 *(0.208)***	n/a	n/a

[a] > 11,864 ≤ 265,005 total transcribed bases, Episode category 2 gene; Episode category 3 gene bases, ≤ 11,864 total transcribed bases, Episode category 3 gene [b] *esebssiwaagoT$_Q$* match if gene *esebssiwaagoT$_Q$* ± 0.015 units [g3)] *GC14M105753/IGHG3* [g4g2)] *lnc-JAG2–1/IGHG4/IGHG2/ENSG00000253364* [e)] *ENSG00000227468/IGHE/ENSG00000254140*

Table 9 Chromosome 14 (–) strand chromatin Ig heavy chain locus recombination sequence for both alleles after *IGHV5–51-IGHD_-_-IGHJ6*

Gene *with respect to*, or n/a	Gene (no. of transcribed gene bases, or n/a)	Total no. of transcribed bases at gene locus, or n/a (episode category)[a, g3, g4g2, e]	Initial no. of sub-episode blocks (converted final no. of sub-episode blocks, or n/a)	2-digit *esebssiwaagoT$_Q$* (*and 3-digit*) *esebssiwaagoT$_Q$*	*esebssiwaagoT$_Q$* match (yes, no)[b,c]	Match recombination gene for further recombination, location upstream & downstream of, or n/a
n//a	***V5–51- D_-_-J6*** (n/a)	n/a (2)	5 (n/a)	0.23 *(0.233)*	no	n/a
V5–51- D_-_-J6	*MIR4537* (70)	70 (3)	7 (n/a)	0.15 *(0.152)*	yes	iCSR with intergene bases of MIR4507/ MIR4538 (Allele 1)
V5–51- D_-_-J6	*MIR4507/MIR4538* (119)	119 (3)	7 (n/a)	0.15 *(0.155)*	yes	iCSR with intergene bases of MIR4537 (Allele 1)
V5–51- D_-_-J6	*MIR4539* (60)	60 (3)	7 (n/a)	0.16 *(0.159)*	no	n/a
V5–51- D_-_-J6	*IGHD* (8914)	8914 (3)	7 (9)	0.17 *(0.169)*	yes	initial allelic exclusion (Allele 2)
n/a	***V5–51-D_-_-J6-IGHM*** (n/a)	n/a (2)	5 (n/a)	**0.16 *(0.165)***	yes	upstream of IGHG1, IGHA1, IGHG4/IGHG2, IGHE & IGHA2 to upstream of IGHM CSRs
V5–51-D_-_ -J6-IGHM	*IGHG3* (5492)	20,987[g3] (2)	5 (n/a)	0.22 *(0.215)*	no	n/a
V5–51-D_-_ -J6-IGHM	*IGHG1* (6729)	6729 (3)	7 (n/a)	0.16 *(0.160)*	yes	primary CSR
V5–51-D_-_ -J6-IGHM	*IGHA1* (1548)	1548 (3)	7 (n/a)	0.18 *(0.180)*	yes	primary CSR
V5–51-D_-_ -J6-IGHM	*IGHG4/ IGHG2* (1726; 1739)	30,527[g4g2] (2)	5 (n/a)	0.19 *(0.189)*	yes	primary CSR
V5–51-D_-_ -J6-IGHM	*IGHE* (1788)	7667[e] (3)	7 (n/a)	0.13 *(0.130)*	no	n/a
V5–51-D_-_ -J6-IGHM	*IGHA2* (1508)	1508 (3)	7 (n/a)	0.18 *(0.175)*	yes	primary CSR (final)
—	**no *V5–51-D_-_ -J6-IGHG3***	—	—	—	—	—
no *V5–51-D_-_ -J6-IGHG3*	*IGHG1* (6729)	6729 (3)	7 (-)	n/a	n/a	secondary CSR not applicable (n/a)
no *V5–51-D_-_ -J6-IGHG3*	*IGHA1* (1548)	1548 (3)	7 (-)	n/a	n/a	secondary CSR not applicable (n/a)
no *V5–51-D_-_ -J6-IGHG3*	*IGHG4/ IGHG2* (1726; 1739)	30,527[g4g2] (2)	5 (-)	n/a	n/a	secondary CSR not applicable (n/a)
no *V5–51-D_-_ -J6-IGHG3*	*IGHE* (1788)	7667 (3)	7 (–)	n/a	n/a	secondary CSR not applicable (n/a)
no *V5–51-D_-_ -J6-IGHG3*	*IGHA2* (1508)	1508 (3)	7 (–)	n/a	n/a	secondary CSR not applicable (n/a)
n/a	***V5–51-D_-_ -J6-IGHG1*** (n/a)	n/a (2)	5 (n/a)	**0.15 *(0.153)***	yes	upstream of IGHA1, IGHG4, IGHE & IGHA2 to upstream of IGHG1 CSRs
V5–51-D_-_ -J6-IGHG1	*IGHA1* (1548)	1548 (3)	7 (n/a)	0.17 *(0.166)*	yes	secondary CSR
V5–51-D_-_ -J6-IGHG1	*IGHG4/ IGHG2 (1726; 1739)*	30,527 (2)	5 (7)	0.14 *(0.137)*	yes	secondary CSR
V5–51-D_-_ -J6-IGHG1	*IGHE* (1788)	7667 (3)	7 (n/a)	0.14 *(0.145)*	yes	secondary CSR
V5–51-D_-_ -J6-IGHG1	*IGHA2* (1508)	1508 (3)	7 (n/a)	0.16 *(0.157)*	yes	secondary CSR (final)
n/a	***V5–51-D_-_ -J6-IGHA1*** (n/a)	n/a (2)	5 (n/a)	**0.13 *(0.134)***	yes	upstream of IGHG4, IGHE & IGHA2 to upstream of IGHA1 CSRs
V5–51-D_-_ -J6-IGHA1	*IGHG4/ IGHG2 (1726; 1739)*	30,527 (2)	5 (n/a)	0.11 *(0.106)*	yes	tertiary CSR
V5–51-D_-_ -J6-IGHA1	*IGHE* (1788)	7667 (3)	7 (n/a)	0.15 *(0.153)*	yes	tertiary CSR
V5–51-D_-_ -J6-IGHA1	*IGHA2* (1508)	1508 (3)	7 (n/a)	0.16 *(0.163)*	yes	tertiary CSR (final)

Table 9 Chromosome 14 (−) strand chromatin Ig heavy chain locus recombination sequence for both alleles after *IGHV5–51-IGHD_-_-IGHJ6 (Continued)*

Gene *with respect to*, or n/a	Gene (no. of transcribed gene bases, or n/a)	Total no. of transcribed bases at gene locus, or n/a (episode category)[a, g3, g4g2, e]	Initial no. of sub-episode blocks (converted final no. of sub-episode blocks, or n/a)	2-digit *esebssiwaagoT$_Q$* (*and 3-digit*) *esebssiwaagoT$_Q$*	*esebssiwaagoT$_Q$* match (yes, no)[b,c]	Match recombination gene for further recombination, location upstream & downstream of, or n/a
n/a	***V5–51-D_-_ -J6-IGHG4*** (n/a)	n/a (2)	5 (n/a)	**0.18 *(0.184)***	no	no
V5–51-D_-_ -J6-IGHG4	*IGHE* (1788)	7667 (3)	7 (n/a)	0.15 *(0.146)*	no	no quaternary CSR with *V5–51-DJ6-IGHG4*
V5–51-D_-_ -J6-IGHG4	*IGHA2* (1508)	1508 (3)	7 (n/a)	0.15 *(0.153)*	no	no quaternary CSR with *V5–51-DJ6-IGHG4*
n/a	***V5–51-D_-_ -J6-IGHE*** (n/a)	n/a (2)	5 (6)	**0.15 *(0.152)***	yes	upstream of IGHA2 to upstream of IGHE CSR
V5–51-D_-_ -J6-IGHE	*IGHA2* (1508)	1508 (3)	7 (n/a)	0.13 *(0.129)*	yes	quaternary CSR (final)
n/a	***V5–51-D_-_ -J6-IGHA2*** (n/a)	n/a (2)	5 (n/a)	**0.15 *(0.148)***	n/a	n/a

[a] *GC14M107956/lnc-AL901608.1–17* (106,574,548–106,598,011): IGHV5–51 gene locus transcribed bases = 19,270 [*IGHV5–51* (Ig heavy variable 5–51) bases (106,578,742–106,579,236)/remaining *lnc-AL901608.1–17* [*IGHVIII-51–1* (pseudogene)/*IGHVII-51–2* (pseudogene)/*IGHV3–52* (pseudogene)/*IGHV3–53* bases (106,579,237–106,598,011)]. [b] > 11,864 ≤ 265, 005 total transcribed bases, Episode category 2 gene; Episode category 3 gene bases, ≤ 11,864 total transcribed bases, Episode category 3 gene. [c] esebssiwaagoT_Q match if gene *esebssiwaagoT$_Q$* ± 0.015 units [g3)] *GC14M105753/IGHG3* [g4g2)] *lnc-JAG2–1/IGHG4/IGHG2/ENSG00000253364* [e] *ENSG00000227468/IGHE/ENSG00000254140*

stIMfA gene with a final *esebssiwaagoT*$_Q$ of 0.15 *(0.148)* (Table 9, Additional file 10: Table S10).

See Table 9 and Additional file 10: Table S10 for *with respect to V5–51-D_-_-J6-IGHM*, *with respect to V5–51-D_-_-J6-IGHG1*, *with respect to V5–51-D_-_-J6-IGHA1*, *with respect to V5–51-D_-_-J6-IGHG4*, *with respect to V5–51-D_-_-J6-IGHE*, and *with respect to V5–51-D_-_-J6-IGHA2* genes.

Discussion

The intracellular pressure required to establish a horizontal reading frame for recombination of joining and diversity genes in native germline arrangement is the basis for predictable gene rearrangement

Variability-to-diversity-to-joining gene recombination is close to perfect when it completes in the pressuromodulated state in vivo [18]. As true allelic exclusion of the non-classical pathway in every case is due to failure of Allele 2 (IGHD) homologous recombination and not a failure of VDJ, Allele 1 (IGHM) accounts for 50% of VDJs while Allele 2 (IGHD) accounts for the other 50% of VDJs in vivo. The frequencies of diversity (D), joining (J) and variability (V) gene distribution is known, that of *IGHJ6* is 40% (*esebssiwaagoT*$_Q$: 0.097), that of *IGHJ5* is 10% (*esebssiwaagoT*$_Q$: 0.235), that of *IGHJ4* is 32% (*esebssiwaagoT*$_Q$: 0.110), that of *IGHJ3* is ~ 8.5% (*esebssiwaagoT*$_Q$: 0.112), that of *IGHJ2* is ~ 1.5% (*esebssiwaagoT*$_Q$: 0.114) and *IGHJ1* accounts for ~ 8.5% (*esebssiwaagoT*$_Q$: 0.116).

Allele 1 (IGHM) gene recombination begins first, when B-cell intracellular pressure is in the supra-pressuromodulated gene expression range [4]. Only *IGHJ5* that expresses at an *esebssiwaagoT*$_Q$ of 0.235 units can be the 1st step candidate gene for Allele 1, which only leaves 1 other step for Allele 1 J ↔ D recombination. Thus, *IGHJ5* is a 1-step J_ gene and recipient of 10% of Allele 1 one-step D_-_ genes 10% of the time, while it is a 2-step stepping stone J_ gene for Allele 1 non-functional (nf) gene *IGHD1–20 (nf)* (*esebssiwaagoT*$_Q$: 0.406) the rest of the time, making *IGHJ6* the recipient gene for 40% of the D_-_ genes involved in the 2-step of Allele 1 two-step.

Allele 2 (IGHD) gene recombination follows that of Allele 1, when B-cell intracellular pressure is in the infra-pressuromodulated range, *IGHJ1* through *IGHJ4* all express in the 0.110 to 0.116 *esebssiwaagoT*$_Q$ units range; of these, the first J_ gene *IGHJ1* and the third one *IGHJ3* are each present at a frequency of ~ 8.5% and are Allele 2 1-step J_ genes. *IGHJ2* is present at a frequency of ~ 1.5% and is also an Allele 2 1-step J_ gene. As *IGHJ2* is present at the lowest frequency, this implies that it is the 2-step stepping stone J_ gene for Allele 2 non-functional genes *IGHD4–11 (nf)* (*esebssiwaagoT*$_Q$: 0.293) and *IGHD5–18 (nf)* (*esebssiwaagoT*$_Q$: 0.254) the rest of the time, making *IGHJ2* the recipient of 32% of Allele 2 two-step D_-_ genes.

Germline functional diversity genes in their native configuration and destined to participate in 2-step Allele 1 (IGHM) recombination have *esebssiwaagoT*$_Q$s in the 0.342 to 0.295 units range, which is approximately 40% of D_-_ genes, while those germline functional diversity genes that participate in 1-step Allele 1 recombination have *esebssiwaagoT*$_Q$s in the 0.294 to 0.286 units range, which is the remaining 10% of D_-_ genes.

Germline functional diversity genes in their native configuration and destined to participate in 2-step Allele 2 (IGHD) recombination have *esebssiwaagoT*$_Q$s in the 0.276 to 0.233 units range, which is approximately 32% of D _-_ genes, while those germline functional diversity genes that participate in 1-step Allele 2 recombination have *esebssiwaagoT*$_Q$ in the 0.218 to 0.172 units range, which is the remaining 18% of D_-_ genes.

Germline non-functional diversity gene *IGHD7–27* that does not participate in D to J recombination has an *esebssiwaagoT*$_Q$ of 0.165.

Therefore, the intracellular pressure required to establish a horizontal reading frame for efficient RAG1 and RAG2 recombinase activity [4] is the basis for predictable B-cell joining and diversity gene recombination in the pressuromodulated state in vivo, of which the gene *esebssiwaagoT*$_Q$ is the measure as it is a property of the gene.

The 2-step and 1-step D to J recombination processes are mutually exclusive

The 2-step Allele 1 (IGHM) gene recombination process involves a more primed CD4R+ CD40LG T-cell-mediated CD40R B-cell CM polarization pressuromodulation effect as an uphill intracellular pressure of 0.41 *esebssiwaagoT*$_Q$ units is required for *IGHJ5* (*esebssiwaagoT*$_Q$: 0.235) to *IGHD1–20 (nf)* (*esebssiwaagoT*$_Q$: 0.406) gene recombination (*J5* ⟶ *D1–20 (nf)*).

The 1-step Allele 1 recombination process involves a less primed CD4R+ CD40LG T-cell-mediated CD40R B-cell CM polarization pressuromodulation effect when an intracellular pressure of 0.36 units is achieved, which is sufficient for *PRDM1* expression at 0.36 units and B-cell cyclic pressure oscillation, however Allele 1 two-step does not take place. Instead, 1-step Allele 1 recombination takes place as an intracellular pressure of 0.30 *esebssiwaagoT*$_Q$ units is achieved when *IGHJ5* (*esebssiwaagoT*$_Q$: 0.235) to *IGHD2–1* (*esebssiwaagoT*$_Q$: 0.296) recombination takes place (*J5* ⟶ *D2–1)*. The 2-step Allele 1 (IGHD) gene recombination process can also take place as it requires a maximum intracellular pressure of 0.293 *esebssiwaagoT*$_Q$ units to engage *IGHD4–11 (nf)* for recombination with *IGHJ2* (*esebssiwaagoT*$_Q$: 0.114) (*D4–11(nf)* ⟶ *J2*).

Therefore, when the Allele 1 (IGHM) recombination process is a 2-step process [J → D (D → J)], then the

Allele 2 (IGHD) recombination process is a 1-step process (D → J); and when the Allele 1 (IGHM) recombination process is a 1-step process (J → D), then the Allele 2 (IGHD) recombination process is a 2-step process [D → J (D → J)].

The above deductions are supported by the literature as D_-_ gene, *IGHD4–17*, must be the Allele 1 (IGHM) Step 2b of 2 recombination gene in which case the D_-_ gene, *IGHD1–26*, must be the Allele 2 (IGHD) Step 1 of 1 recombination gene [20].

Allele 1 (IGHM) 2-step recombination involves germline *IGHJ5* and *IGHD1–20 (nf)* recombination (step 1), *IGHD_-_* and *IGHJ6* gene *with respect to D1–20 (nf)-J5* recombination (step 2a) that results in *IGHD_-_-IGHJ6* (step 2b) and then *IGHV_-_* to *IGHD_-_-IGHJ6* recombination that results in *V_-_-DJ6*

Step 1 of the Allele 1 two-step recombination process begins after *PRDM1* expression at 0.36 $esebssiwaagoT_Q$ units, when B-cell intracellular pressure decreases to just below the *CD40* gene expression intracellular pressure of 0.26 $esebssiwaagoT_Q$ units to around 0.24 units and RAG2 engages the upstream handle of *IGHJ5* at an $esebssiwaagoT_Q$ of 0.235 units. At around 0.24 units there is an increase in cell pressure back to around 0.26 units as the *PRDM1* effect wanes, when the 1st maximum polarization period begins with increasing cell pressure to 0.41 units when RAG2 engages the downstream handle of *IGHD1–20 (nf)*, which results in *IGHD1–20 (nf)-IGHJ5* (Fig. 1).

The step 2a of the process is downhill and begins after RAG2 engages *IGHD3–10 with respect to D1–20 (nf)-J5*, which is the upper limit D_-_ gene *with respect to D1–20 (nf)-J5* with an $esebssiwaagoT_Q$ of 0.402 units. Then, cell pressure decreases back down into the *PRDM1* maximum expression range at 0.36 units, and thereafter, at a sufficient enough rate through the *CD40* expression cell pressure of 0.26 units into peri-nadir at 0.15 plus minus 0.05 units, which defines four fifths of one limb of 1st fully refractory period. In the downhill limb of the fully refractory period, RAG1 engages *IGHD4–17 with respect to D1–20 (nf)-J5* at 0.15 *(0.150)* units, which is lower limit for D_-_ genes *with respect to D1–20 (nf)-J5*. The step 2a stage completes after RAG1 association with *IGHJ6 with respect to D1–20-J5* at 0.101 units of the period nadir, when the two free ends of DNA come together to result in *IGHD_-_-IGHJ6* (step 2b) (Fig. 1).

The *IGHD_-_-IGHJ6* recombined gene $esebssiwaagoT_Q$ range is 0.13 *(0.133)* to 0.30 *(0.297)* units and the *IGHV_-_* gene $esebssiwaagoT_Q$ range *with respect to IGHD_-_-IGHJ6* is an unestablished lower limit to 0.41 *(0.415)* units. The VDJ step of the process completes between the 1st fully refractory pre-nadir period and the uphill limb of 2nd maximum polarization period. The lower limit of the *IGHV_* gene $esebssiwaagoT_Q$ range is unestablished as more variability genes need to be sampled (Fig. 1).

Allele 1 recombination is a 2-step process when a more primed CD4R+ T-cell is involved and the greater magnitude of the B-cell polarization pressuromodulation effect. This implies that during a more robust pressuromodulation effect:

(1) there is deceleration during the 2-step Allele 1 step 1 downhill limb around an intracellular pressure of 0.25 $esebssiwaagoT_Q$ units because it is a function of *PRDM1* expression that results in full expression of *CD40* at 0.26 units, after which there is maximum B-cell polarization and acceleration in the opposite direction with an uphill increase in cell pressure back to 0.41 units, then down into the *PRDM1* expression pressure of 0.36 units;

and (2) there is acceleration during the step 2a downhill limb through the *CD40* expression intracellular pressure into the fully refractory period because it is a function of preceding maximum *CD40* expression followed by *PRDM1* expression in series that then results in non-expression of *CD40* at 0.26 units, after which there is maintained acceleration downhill into the peri-nadir due to the PRDM1 *C-MYC* gene antagonism effect.

Allele 2 (IGHD) 1-step recombination step involves germline *IGHD_-_* and *IGHJ1, IGHJ2 or IGHJ3* recombination that results in *IGHD_-_-IGHJ1 -J2* or *-J3* (step1) and then *IGHV_-_* to *IGHD_-_-J1-J4, IGHD_-_-J2-J4* or *IGHD_-_-J3-J4* recombination that results in *V_-_-DJ6*

Step 1 of the Allele 2 one-step recombination process begins during the downhill limb of the 1st refractory period in between 0.22 *(0.218)* and 0.17 *(0.172)* $esebssiwaagoT_Q$ units at which the *IGHD_-_* genes are substrates for RAG. Step 1 completes to the point of *IGHD_-_-IGHJ1*, *–J2* or *-J3* during peri-nadir before the uphill limb in between 0.12 *(0.116)* and 0.11 *(0.112)* units at which the 1-step *IGHJ_* genes, *IGHJ1* (~ 8.5%), *IGHJ2* (~ 1.5%) or *IGHJ3* (~ 8.5%) are substrates for the same (Fig. 2).

The step 1 *IGHD_-_-IGHJ1*, *–J2* or *-J3* recombined gene $esebssiwaagoT_Q$ range is *0.11 (0.114)* to *0.35 (0.347)* units and the *IGHV_-_* gene *with respect to IGHD_-_-IGHJ12*, *–J* and *-J3* $esebssiwaagoT_Q$ range is an unestablished lower limit to 0.41 (*0.415*) units. The VDJ step of the Allele 2 one-step process completes during the uphill limb of the 1st fully refractory period into the 2nd maximum polarization period (Fig. 2).

The Allele 2 recombination process is a 1-step process during the more primed CD4R+ T-cell-mediated polarization effect and follows Allele 2 two-step after *CD40* non-expression as Allele 1 one-step begins during the downhill limb of the 1st fully refractory period.

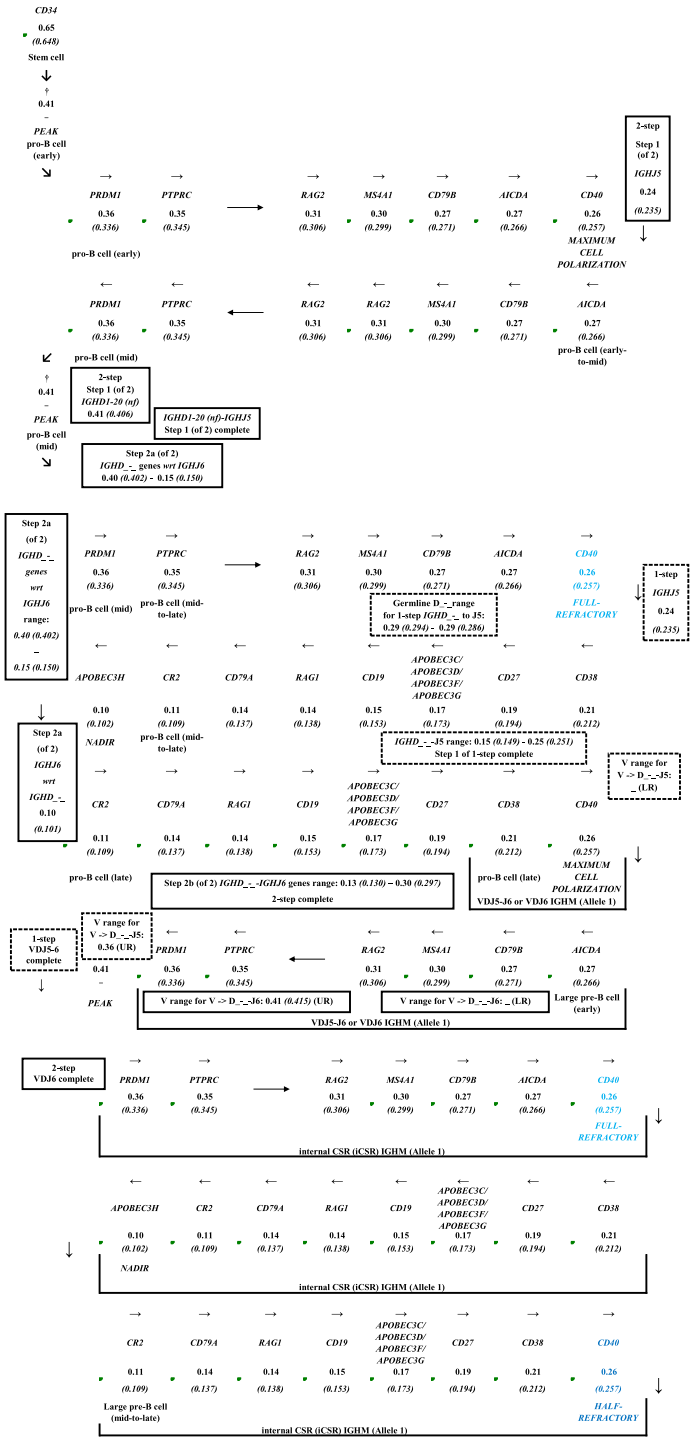

Fig. 1 Allele 1 (IGHM) 2-step and 1-step Ig heavy chain locus gene rearrangement recombination steps superimposed on the pressuromodulation map of B-cell differentiation stages. The Allele 1 two-step recombination steps are *IGHD1–20 (nf)* and *IGHJ5* recombination (step 1 of 2), *IGHD_-_* genes *with respect to D1–20(nf)-J5* (step 2a of 2) and *IGHJ6 with respect to D1–20(nf)-J5* (step 2a of 2) recombination that results that results in *IGHD_-_-IGHJ6* (step 2b of 2) through the final *IGHV_-_* and *IGHD_-_-IGHJ6* recombination that results in *V_-_-DJ6*. The Allele 1 one-step recombination step is *IGHD_-_* and *IGHJ5* recombination that results in *IGHD_-_-IGHJ5* (step 1 of 1) through the final *IGHV_-_* and *IGHD_-_-J5* recombination that results in *V_-_-DJ6*. Note: Allele 1 locus rearrangement recombination steps complete to the point of the CM IgM+ B-cell before Allele 2 VDJ completes. †, upper *esebssiwaagoT*$_O$ units range, 0.41–0.36. Black, *CD40* at maximum cell polarization potential. Dark blue, *CD40* at half-refractory. Light blue, *CD40* at full-refractory. Text boxes with complete borders, 2-step. Text boxes with dashed borders, 1-step. Large rectangular box with complete borders, extra-nodal secretory antibody phase

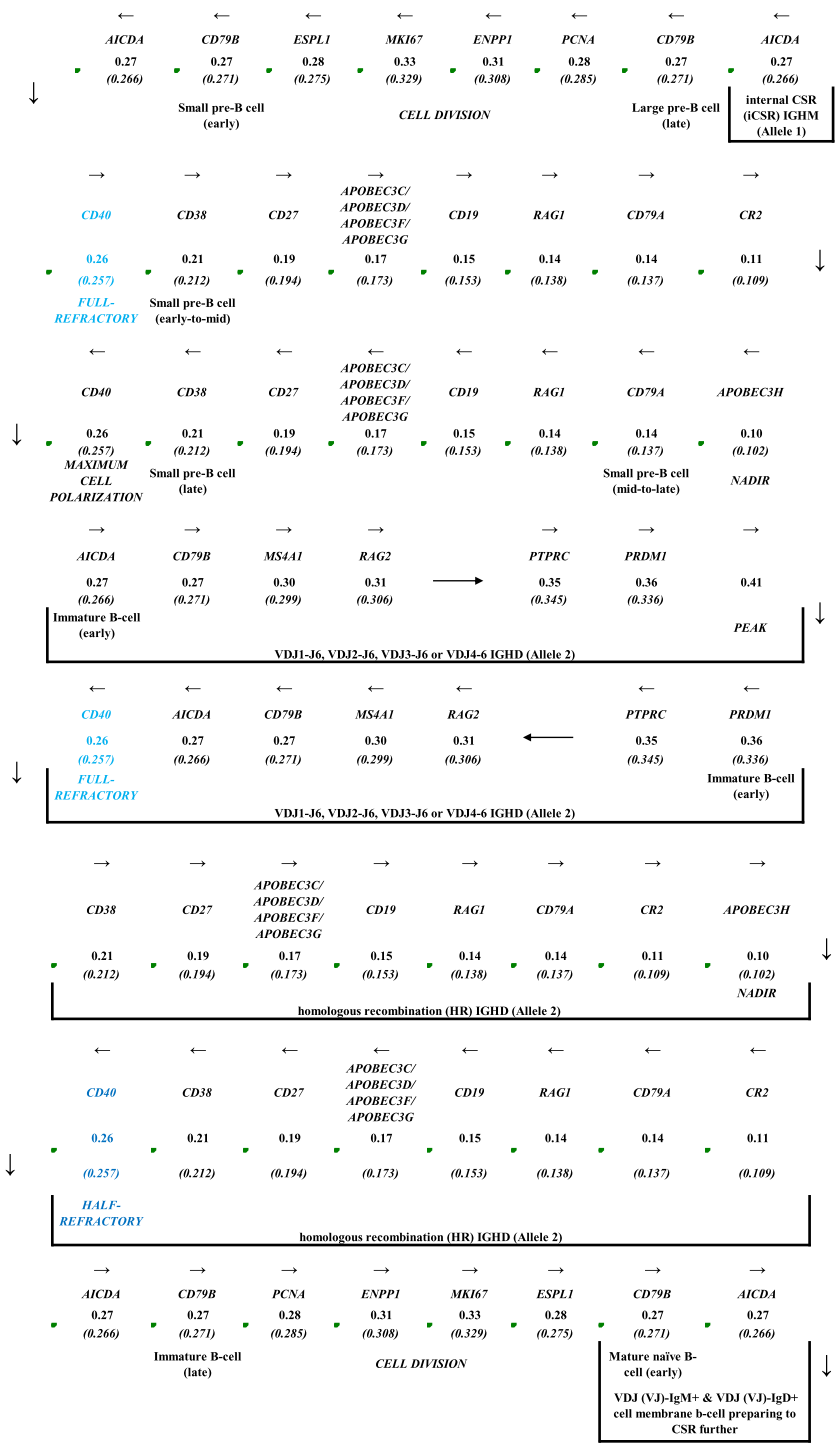

Fig. 1 Allele 1 (IGHM) 2-step and 1-step Ig heavy chain locus gene rearrangement recombination steps superimposed on the pressuromodulation map of B-cell differentiation stages. The Allele 1 two-step recombination steps are *IGHD1–20 (nf)* and *IGHJ5* recombination (step 1 of 2), *IGHD_-_* genes *with respect to D1–20(nf)-J5* (step 2a of 2) and *IGHJ6 with respect to D1–20(nf)-J5* (step 2a of 2) recombination that results that results in *IGHD_-_-IGHJ6* (step 2b of 2) through the final *IGHV_-_* and *IGHD_-_-IGHJ6* recombination that results in *V_-_-DJ6*. The Allele 1 one-step recombination step is *IGHD_-_* and *IGHJ5* recombination that results in *IGHD_-_-IGHJ5* (step 1 of 1) through the final *IGHV_-_* and *IGHD_-_-J5* recombination that results in *V_-_-DJ6*. Note: Allele 1 locus rearrangement recombination steps complete to the point of the CM IgM+ B-cell before Allele 2 VDJ completes. †, upper $esebssiwaagoT_O$ units range, 0.41–0.36. Black, *CD40* at maximum cell polarization potential. Dark blue, *CD40* at half-refractory. Light blue, *CD40* at full-refractory. Text boxes with complete borders, 2-step. Text boxes with dashed borders, 1-step. Large rectangular box with complete borders, extra-nodal secretory antibody phase

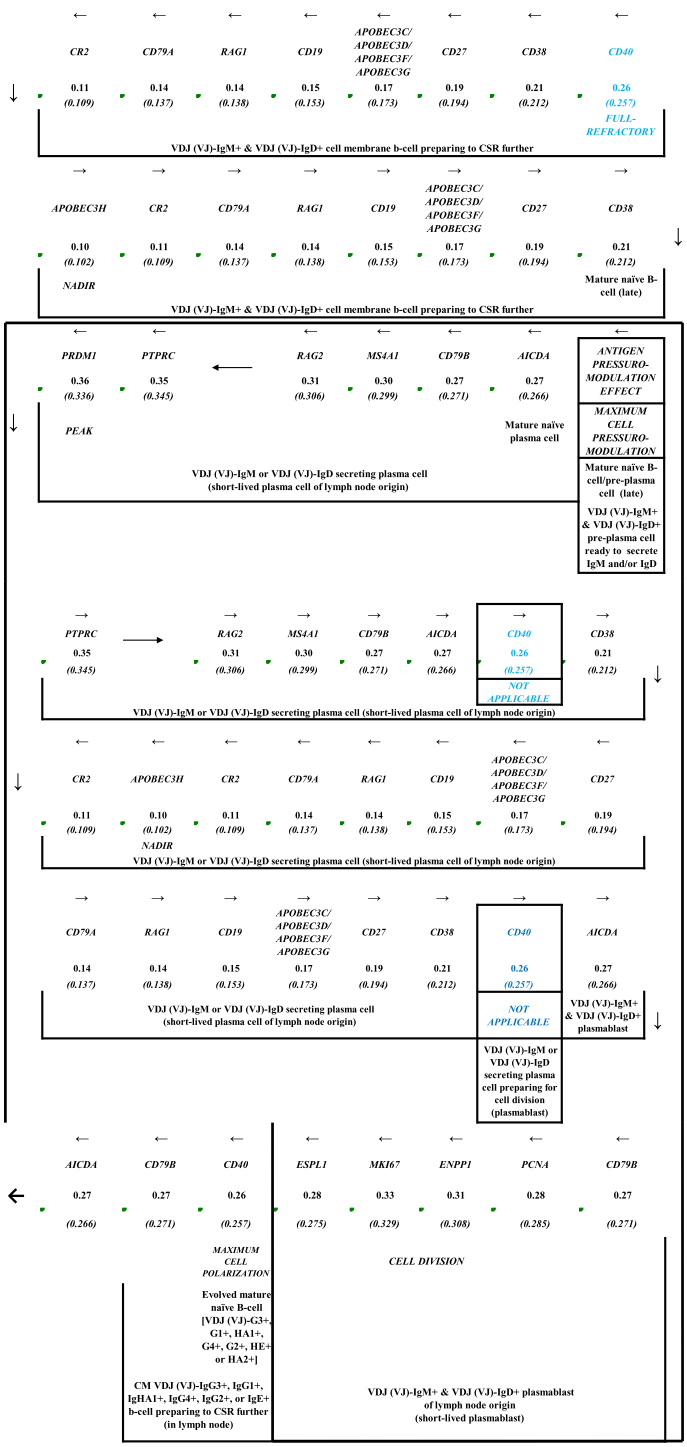

Fig. 1 Allele 1 (IGHM) 2-step and 1-step Ig heavy chain locus gene rearrangement recombination steps superimposed on the pressuromodulation map of B-cell differentiation stages. The Allele 1 two-step recombination steps are *IGHD1–20 (nf)* and *IGHJ5* recombination (step 1 of 2), *IGHD_-_* genes *with respect to D1–20(nf)-J5* (step 2a of 2) and *IGHJ6 with respect to D1–20(nf)-J5* (step 2a of 2) recombination that results that results in *IGHD_-_-IGHJ6* (step 2b of 2) through the final *IGHV_-_* and *IGHD_-_-IGHJ6* recombination that results in *V_-_-DJ6*. The Allele 1 one-step recombination step is *IGHD_-_* and *IGHJ5* recombination that results in *IGHD_-_-IGHJ5* (step 1 of 1) through the final *IGHV_-_* and *IGHD_-_-J5* recombination that results in *V_-_-DJ6*. Note: Allele 1 locus rearrangement recombination steps complete to the point of the CM IgM+ B-cell before Allele 2 VDJ completes. †, upper *esebssiwaagoT*$_O$ units range, 0.41–0.36. Black, *CD40* at maximum cell polarization potential. Dark blue, *CD40* at half-refractory. Light blue, *CD40* at full-refractory. Text boxes with complete borders, 2-step. Text boxes with dashed borders, 1-step. Large rectangular box with complete borders, extra-nodal secretory antibody phase

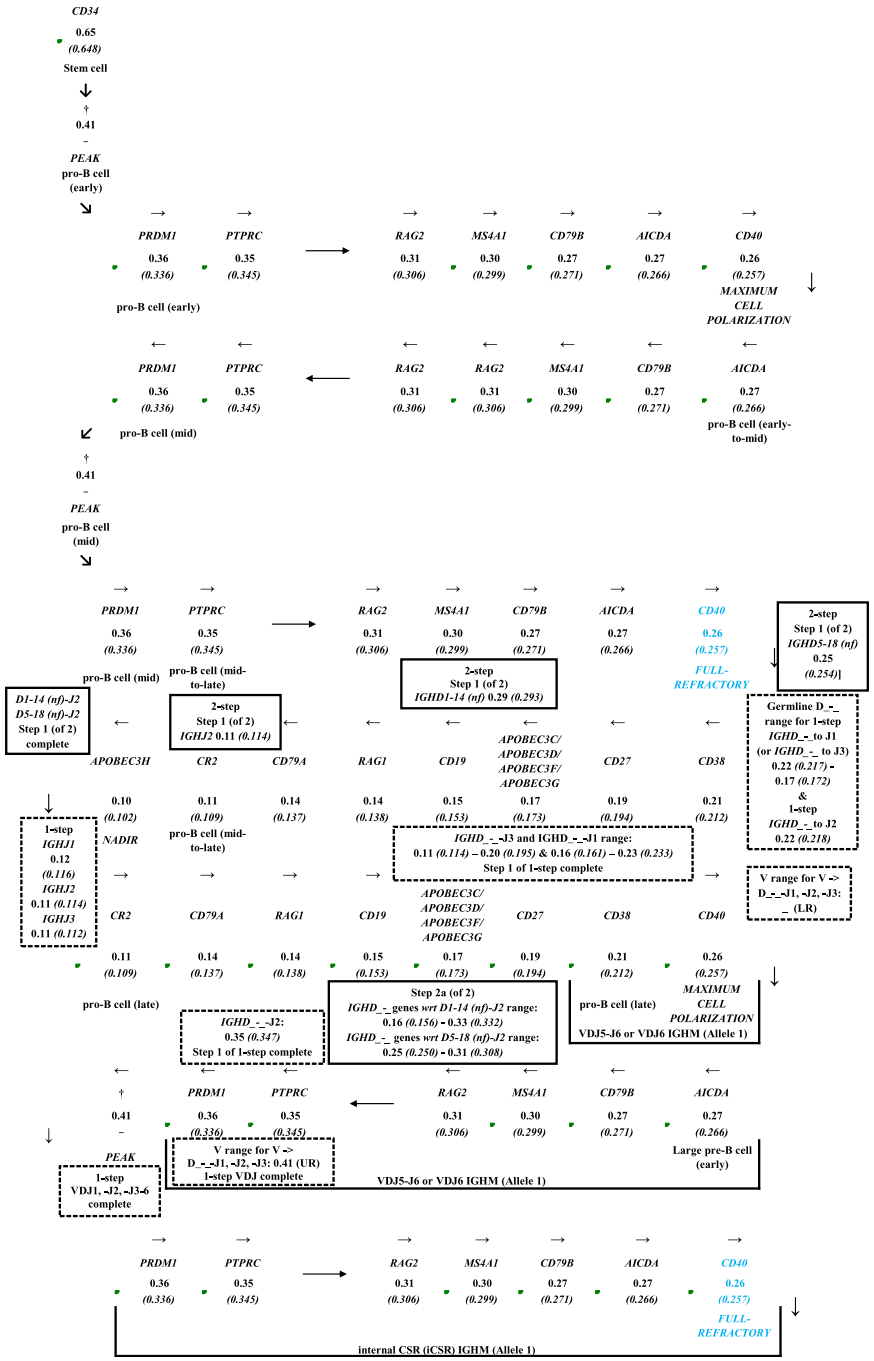

Fig. 2 Allele 2 (IGHD) 1-step and 2-step Ig heavy chain locus gene rearrangement recombination steps superimposed on the pressuromodulation map of B-cell differentiation stages. The Allele 2 one-step recombination step is *IGHD_-_* and *IGHJ1, IGHJ2 or IGHJ3* recombination that results in *IGHD_-_-IGHJ1 -J2 or -J3* (step 1 of 1) through the final *IGHV_-_* and *IGHD_-_-IGHJ1, IGHD_-_-IGHJ2* or *IGHD_-_-IGHJ3* recombination that results in *V_-_-DJ6*. The Allele 2 two-step recombination steps are *IGHD1–14 (nf)* or *IGHD5–18 (nf)* and *IGHJ2* recombination (step 1 of 2), the *IGHD_-_* genes *with respect to D1–14 (nf)-J2 or D5–18 (nf)-J2* (step 2a of 2) and the *IGHJ4 with respect to D1–14 (nf)-J2 or D5–18 (nf)-J2* (step 2a of 2) recombination that results in *IGHD_-_-IGHJ4* (step 2b of 2) through the final *IGHV_-_* and *IGHD_-_-IGHJ4* recombination that results in *V_-_-DJ6*. Note: Allele 2 Ig locus rearrangement recombination follows that of Allele 1 and always completes to the point of VDJ rearrangement in the marrow. In the classical pathway, homologous recombination or initial allelic exclusion followed by delayed Allele 2 iCSR (i.e. CM IgM+ IgD+) are the rule in the lymph node. In the non-classical pathway, Allele 2 locus recombination completes to the point of VDJ rearrangement (i.e CM IgM+ only). †, upper $esebssiwaagoT_O$ units range, 0.41–0.36. Black, *CD40* at maximum cell polarization potential. Dark blue, *CD40* at half-refractory. Light blue, *CD40* at full-refractory. Text boxes with complete borders, 2-step. Text boxes with dashed borders, 1-step. Large rectangular box with complete borders, extra-nodal secretory antibody phase

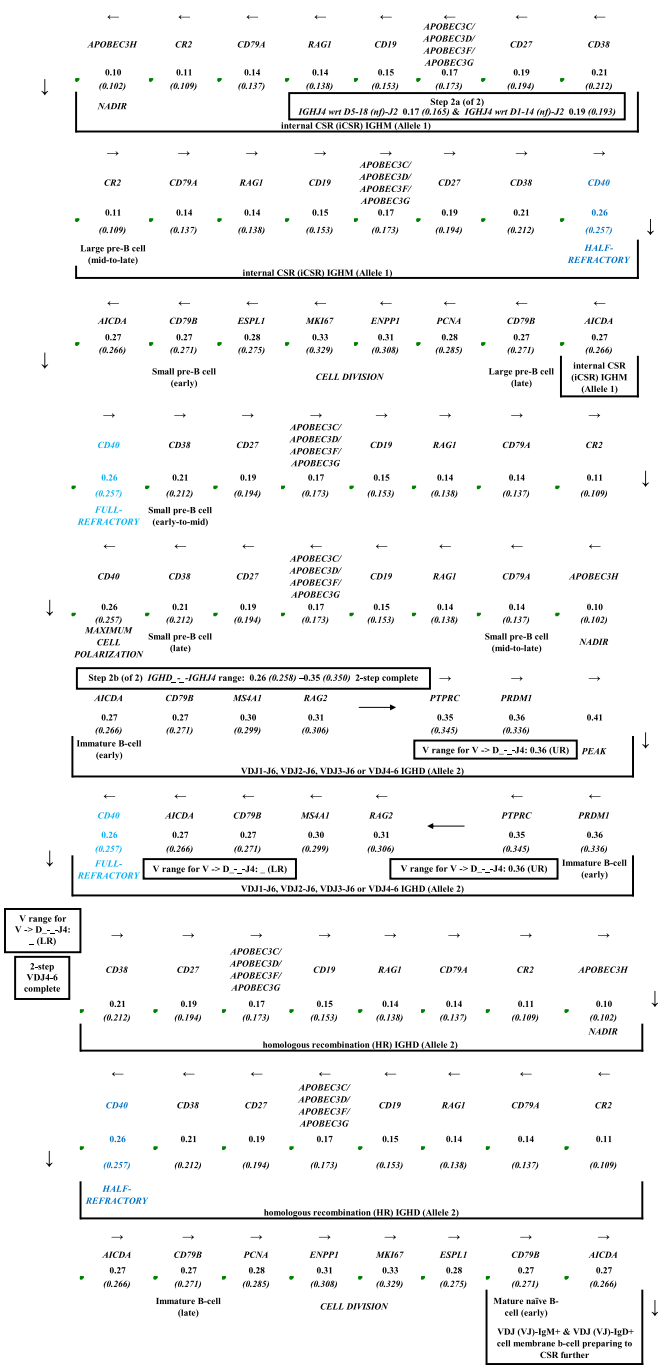

Fig. 2 Allele 2 (IGHD) 1-step and 2-step Ig heavy chain locus gene rearrangement recombination steps superimposed on the pressuromodulation map of B-cell differentiation stages. The Allele 2 one-step recombination step is *IGHD_-_* and *IGHJ1, IGHJ2 or IGHJ3* recombination that results in *IGHD_-_-IGHJ1 -J2 or -J3* (step 1 of 1) through the final *IGHV_-_* and *IGHD_-_-IGHJ1, IGHD_-_-IGHJ2* or *IGHD_-_-IGHJ3* recombination that results in *V_-_-DJ6*. The Allele 2 two-step recombination steps are *IGHD1–14 (nf)* or *IGHD5–18 (nf)* and *IGHJ2* recombination (step 1 of 2), the *IGHD_-_* genes *with respect to D1–14 (nf)-J2 or D5–18 (nf)-J2* (step 2a of 2) and the *IGHJ4 with respect to D1–14 (nf)-J2 or D5–18 (nf)-J2* (step 2a of 2) recombination that results in *IGHD_-_-IGHJ4* (step 2b of 2) through the final *IGHV_-_* and *IGHD_-_-IGHJ4* recombination that results in *V_-_-DJ6*. Note: Allele 2 Ig locus rearrangement recombination follows that of Allele 1 and always completes to the point of VDJ rearrangement in the marrow. In the classical pathway, homologous recombination or initial allelic exclusion followed by delayed Allele 2 iCSR (i.e. CM IgM+ IgD+) are the rule in the lymph node. In the non-classical pathway, Allele 2 locus recombination completes to the point of VDJ rearrangement (i.e CM IgM+ only). †, upper $esebssiwaagoT_Q$ units range, 0.41–0.36. Black, *CD40* at maximum cell polarization potential. Dark blue, *CD40* at half-refractory. Light blue, *CD40* at full-refractory. Text boxes with complete borders, 2-step. Text boxes with dashed borders, 1-step. Large rectangular box with complete borders, extra-nodal secretory antibody phase

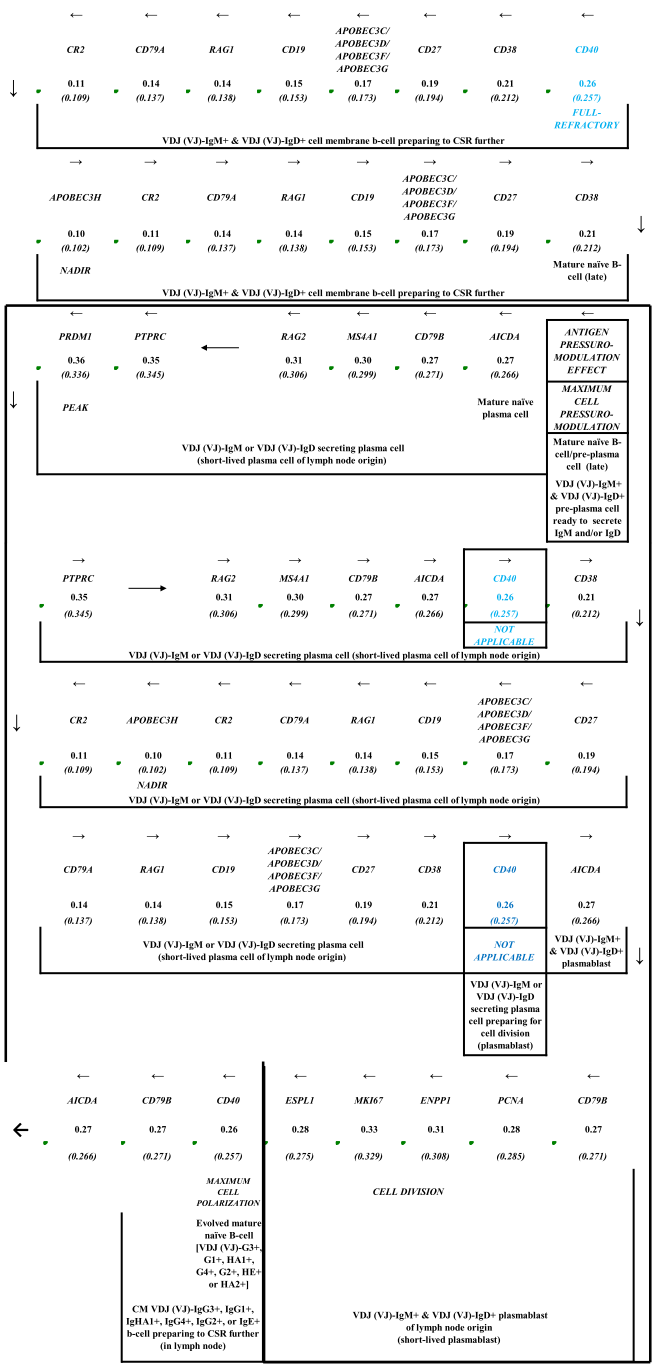

Fig. 2 Allele 2 (IGHD) 1-step and 2-step Ig heavy chain locus gene rearrangement recombination steps superimposed on the pressuromodulation map of B-cell differentiation stages. The Allele 2 one-step recombination step is *IGHD_-_* and *IGHJ1, IGHJ2 or IGHJ3* recombination that results in *IGHD_-_-IGHJ1 -J2 or -J3* (step 1 of 1) through the final *IGHV_-_* and *IGHD_-_-IGHJ1*, *IGHD_-_-IGHJ2* or *IGHD_-_-IGHJ3* recombination that results in *V_-_-DJ6*. The Allele 2 two-step recombination steps are *IGHD1–14 (nf)* or *IGHD5–18 (nf)* and *IGHJ2* recombination (step 1 of 2), the *IGHD_-_* genes *with respect to D1–14 (nf)-J2 or D5–18 (nf)-J2* (step 2a of 2) and the *IGHJ4 with respect to D1–14 (nf)-J2 or D5–18 (nf)-J2* (step 2a of 2) recombination that results in *IGHD_-_-IGHJ4* (step 2b of 2) through the final *IGHV_-_* and *IGHD_-_-IGHJ4* recombination that results in *V_-_-DJ6*. Note: Allele 2 Ig locus rearrangement recombination follows that of Allele 1 and always completes to the point of VDJ rearrangement in the marrow. In the classical pathway, homologous recombination or initial allelic exclusion followed by delayed Allele 2 iCSR (i.e. CM IgM+ IgD+) are the rule in the lymph node. In the non-classical pathway, Allele 2 locus recombination completes to the point of VDJ rearrangement (i.e CM IgM+ only). †, upper $esebssiwaagoT_Q$ units range, 0.41–0.36. Black, *CD40* at maximum cell polarization potential. Dark blue, *CD40* at half-refractory. Light blue, *CD40* at full-refractory. Text boxes with complete borders, 2-step. Text boxes with dashed borders, 1-step. Large rectangular box with complete borders, extra-nodal secretory antibody phase

Allele 2 (IGHD) 2-step recombination involves germline *IGHJ2* and *IGHD4–11 (nf)* or *IGHD5–18 (nf)* recombination (step 1), *IGHD_-_* and *IGHJ4 with respect to D4–11(nf)-J2* and *D5–18(nf)-J2* gene recombination (step 2a) that results in *IGHD_-_-IGHJ4* (step 2b) and then *IGHV_-_* to *IGHD_-_-IGHJ4* recombination that results in *V_-_-DJ6*

Step 1 of the Allele 2 two-step recombination process begins during the second downhill limb at an intracellular pressure of 0.29 *esebssiwaagoT*$_Q$ units with RAG association with either *IGHD4–11 (nf)* (*esebssiwaagoT*$_Q$: 0.293) or *IGHD5–18 (nf)* (*esebssiwaagoT*$_Q$: 0.254) followed by *IGHJ2* association at 0.114 units during the 1st peri-nadir, which results in *IGHD4–11 (nf)-IGHJ2* or in *IGHD5–18 (nf)*-IGHJ2 (Fig. 2).

The step 2a of 2 of the process begins in the peri-nadir at 0.16 *(0.156) esebssiwaagoT*$_Q$ units and continues units into the uphill limb of the 2nd three-fourths maximum polarization period when intracellular pressure increases to 0.33 *(0.332)* units, which is the cell pressure range for *IGHD_-_* genes *with respect to D1–14 (nf)-J2* and *D5–18 (nf)-J2*. Then, *IGHD_-_ with respect to D1–14 (nf)-J2* or *D5–18 (nf)-J2*, and *IGHJ4 with respect to D1–14 (nf)-J2* or *IGHJ4 with respect to D5–18 (nf)-J2* gene recombination follows in the 3rd three-fourths full-refractory period when the B-cell pressure is in the 0.19 *(0.193)* to 0.17 *(0.165) esebssiwaagoT*$_Q$ units range, and ends in *IGHD_-_-IGHJ4* when step 2b is complete. There is no *IGHD_-_* to *IGHJ4* gene recombination during the first 3/8^{ths} refractory period in between the 2nd three-fourths maximum polarization period and the 3rd three-fourths full-refractory period, when cell division takes place (Fig. 2).

The 2-step Allele 2 VDJ step begins with the 3rd three-fourths maximum polarization period in the *IGHD_-_-IGHJ4* recombined gene intracellular pressure range between 0.26 *(0.258)* and 0.35 *(0.350) esebssiwaagoT*$_Q$ units, and completes in the *IGHV_-_* gene *with respect to IGHD_-_-IGHJ4* cell pressure range between an unestablished lower limit and the *PRDM1* expression pressure of 0.36 units as the upper limit (Fig. 2) due to a less pressuromodulated B-cell.

Allele 2 recombination is a 2-step process when Allele 1 recombination is a 1-step process as a less primed CD4R+ T-cell is involved, which results in lesser grade pressuromodulation of the B-cell. This implies that during a less robust pressuromodulation effect: (1) there is ¾^{ths} of maximum polarization during the maximum polarization periods but sufficient enough for full *PRDM1* expression at 0.36 *esebssiwaagoT*$_Q$ units, and (2) there is ¾^{ths} of full refractoriness during the fully refractory periods during which there is only transient *CD40* expression comparable to non-expression.

Allele 1 (IGHM) 1-step recombination step involves germline *IGHD_-_* and *IGHJ5* recombination that results in *IGHD_-_-IGHJ5* (step1) and then *IGHV_-_* and *IGHD_-_-J5* recombination that results in *V_-_-DJ6*

The Allele 1 one-step recombination process begins during the downhill limb after the 1st three-fourths maximal polarization period in between 0.29 *(0.294)* and 0.29 *(0.286) esebssiwaagoT*$_Q$ units range when the genes destined for Allele 1 one-step are horizontal, and completes to the point of *IGHD_-_-IGHJ5* at 0.24 *(0.235) esebssiwaagoT*$_Q$ units just as the 1st refractory period begins at which the 1-step *IGHJ_* gene, *IGHJ5* expresses (Fig. 1).

The step 1 *IGHD_-_-IGHJ5* recombined gene B-cell pressure range is 0.15 *(0.149)* to 0.25 *(0.251)* and the *IGHV_-_* gene *with respect to IGHD_-_-IGHJ5 esebssiwaagoT*$_Q$ range is the unestablished lower limit to 0.36 *esebssiwaagoT*$_Q$ units. The 1-step Allele 1 VDJ begins in the peri-nadir and completes during the 2nd three-fourths maximum polarization period (Fig. 1).

The Allele 1 recombination process is a 1-step process during the less primed CD4R+ T-cell-mediated B-cell polarization effect. The Allele 1 one-step process can begin after the 1st three-fourths maximal polarization period during the downhill limb as the intracellular pressure decreases at a slower rate compared to the Allele 2 two-step process into the three-fourths refractory *CD40* expression period.

Variability gene *esebssiwaagoT*$_Q$s can be constant or variable

The variability genes that were sampled from 5′ to 3′ include, *IGHV4–61*, *IGHV4–59*, *IGHV5–51*, *IGHV3–48*, *IGHV4–28*, *IGHV3–23* and *IGHV1–3*. All of these except *IGHV1–3* have constant *esebssiwaagoT*$_Q$s *with respect to* germline *IGHD_-_* genes.

The *esebssiwaagoT*$_Q$ for *IGHV1–3* varies depending on the downstream location of *IGHD_-_-IGHJ6* in Allele 1 two-step or *IGHD_-_-IGHJ4*, *IGHJ5* and *IGHJ6* in series in Allele 2 two-step for example since the split integration includes the intergene distances downstream of these genes *with respect to IGHV1–3*.

IGHV_-_ to *IGHDJ_* recombination results in VDJ6 for both alleles

Variability gene to DJ_ gene recombination results in VDJ6 for both Allele 1 (IGHM) 1-step *D_-_-J5* genes and for Allele 2 (IGHD) 1-step *D_-_-J1*, *–J2*, *–J3* and 2-step *D_-_-J4* genes.

After *IGHV_-_* to *IGHD_-_-IGHJ1* for example, the *V_-_-D_-_-J1* becomes a *V_-_-D_-_-J1-J6* gene as the VDJ promoters offer sufficient transcription factor-bound anchoring stability for RNA polymerase to be able to transcribe the entire V-to-J6 complex. The VDJ promoters however do not offer enough stability for transcription further

downstream to immunoglobulin heavy chain M *(IGHM)*, which requires internal consensus sequence recognition (iCSR) excision of intervening bases around the *MIR* genes for *VDJ6-IGHM*. Analogously, homologous recombination displacement removal of intervening bases results in *VDJ6-IGHD*, which transcribes *in toto* as one gene.

This observation forms the basis for determining the gene *esebssiwaagoT*$_Q$ *with respect to* the correct VDJ, which is VDJ6.

CD4R+ T-cells are positively pressuromodulated

Antigen presenting cells (APC) scavenge endocytic antigens and re-present endocytic antigen fragments to the T-cell receptor (TCR) [21, 22] and other T-cell receptors [22]. Therefore, APC-mediated positive pressuromodulator antigen presentation to CD4R+ T-cells results in endocytic positive pressuromodulation of the CD4R+ T-cell.

More primed CD4R+ T-cells are subject to higher grades of positive pressuromodulation that results in maximal *CD40LG* expression and CD40LG R+ T-cell-mediated CD40R+ B-cell polarization effect that increases B-cell pressure to 0.41 *esebssiwaagoT*$_Q$ units (Allele 1 two-step/Allele 2 one-step), while less primed T-cells are subject to lower grades of positive pressuromodulation, which only increases B-cell pressure into the *PRDM1* expression range of 0.36 units (Allele 2 two-step/Allele 1 one-step).

Antigen presenting cell-dependent T-cell-mediated B-cell polarization is the primary mode of increasing B-cell pressure in the classical maturation pathway, where vaccines serve the purpose of boosting the response [23].

B-cells are subject to the effect of both positive and negative forms of antigen pressuromodulation

The effects of positive pressuromodulation out-weigh those of mixed or negative forms during B-cell maturation from the VDJ pro-B-cell stage to the consensus sequence recognition (CSR) isotype switching Evolved mature B-cell stage, as it is during oscillating positive pressuromodulation [4].

In the classical pathway the dominant form of pressuromodulation is T-cell-mediated B-cell polarization via CD40R, while in the non-classical pathway the dominant form is positive pressuromodulator antigen-mediated B-cell pressuromodulation such as toll-like receptor (TLR) [24]-mediated endocytic via high isoelectric point basic peptides such as profilin II [25] during acute infection for example.

The B-cell to plasma cell transformation takes place in the presence of an antigen load. The majority of antigens such as virus capsid peptide and microbe cell wall or membrane fragments [26] are positive pressuromodulators of cell surface receptors [1], which increase and maintain B-plasma cell pressure in the supra-pressuromodulated range (≥ 0.25 *esebssiwaagoT*$_Q$ units) [2]. A minority of antigens such as phospholipases and proteases [27] are negative pressuromodulators of cell membranes [1], which decrease and maintain B-plasma cell pressure in the infra-pressuromodulated range (< 0.25 *esebssiwaagoT*$_Q$ units) [2].

IGHV1–3 antibody heavy chain recombination sequence after *IGHV1–3-IGHD_-_-IGHJ6* is iCSR followed by further CSRs for allele 1 (IGHM) and homologous recombination for allele 2 (IGHD)

For Allele 1 (IGHM), there is internal CSR (iCSR) [11] between the switch sequence region intergene bases of *MIR4507 with respect to V1–3DJ6* (*esebssiwaagoT*$_Q$: 0.260) and the sequence intergene bases of *MIR4539 with respect to V1–3DJ6* (*esebssiwaagoT*$_Q$: 0.268), which is the closest *esebssiwaagoT*$_Q$ match between the candidate *MIR_* genes of the *IGHM* switch region. The resultant recombined gene is *V1–3-D_-_-J6-remaining MIR/MIRs-IGHM* with an *esebssiwaagoT*$_Q$ of 0.275 (Table 7), and the cell a CM IgM+ Mature naïve B-cell.

For Allele 2 (IGHD), there is homologous recombination displacement replacement of 442 intergene bases downstream of *IGHJ6* of *V1–3-D_-_-IGHJ6* (*esebssiwaagoT*$_Q$: 0.226) by 443 intergene bases upstream of *IGHD with respect to V1–3-D_-_-IGHJ6* (*esebssiwaagoT*$_Q$: 0.198) [14] due to an *esebssiwaagoT*$_Q$ match between the two genes, at minus 0.014 units for the former (*IGHD*) and plus 0.014 units for the latter (*V1–2-DJ6*), which meets the *esebssiwaagoT*$_Q$ match criterion of ±0.015 units with reference to the gene as it is the point of convergence. The resultant gene is *V1–3D_-_-J6-IGHD* with an *esebssiwaagoT*$_Q$ of 0.320 (Table 7).

For Allele 1 (IGHM), the downstream genes for further CSR to *V1–3DJ6-IGHM* (*esebssiwaagoT*$_Q$: 0.275) are *IGHG3* (*esebssiwaagoT*$_Q$: 0.271) and *IGHA2* (*esebssiwaagoT*$_Q$: 0.258), but not *IGHG1*, *IGHA1*, *IGHG4/IGHG2* and *IGHE*. The *esebssiwaagoT*$_Q$ match for *IGHG3 with respect to V1–3DJ-IGHM* is plus minus 0.002 units and that for *IGHA2* is plus minus 0.0085 units. The former will be a primary *IGHG3* switch-to-*IGHM* switch region CSR resulting in *V1–3DJ6-IGHG3* with an *esebssiwaagoT*$_Q$ of 0.306, and the latter will be a direct primary *IGHA2* switch-to-*IGHM* switch region CSR resulting in *V1–3DJ6-IGHA2* with an *esebssiwaagoT*$_Q$ of 0.258 (Table 7).

After primary CSR, the CD4R+ T-cell polarized 1st generation Evolved mature naïve nodal B-cell will express both *V1–3DJ6-IGHG3* (*esebssiwaagoT*$_Q$: 0.306) and *V1–3DJ6-IGHD* (*esebssiwaagoT*$_Q$: 0.320) simultaneously when the B-cell intracellular pressure oscillates to 0.313 *esebssiwaagoT*$_Q$ units as *V1–3DJ6-IGHG3* (+ 0.007) and *V1–3DJ6-IGHD* (– 0.007) are within 0.014 units of each other. Likewise, an antigen stimulated extra-nodal B-plasma cell will secrete both IgG3

and IgD (see Fig. 1 or Fig. 2 periphery/tissue nidus secretory phase).

The only secondary CSR for a CM IgG3+/IgD+ 1st generation Evolved mature naïve nodal B-cell is *IGHG4 with respect to V1–3DJ6-IGHG3* (*esebssiwaagoT*$_Q$: 0.325) at plus minus 0.0095 units, which will result in *V1–3DJ6-IGHG4* with an *esebssiwaagoT*$_Q$ of 0.237 (Table 7).

The further CSR for the CM IgG4+ 2nd generation nodal cell will be a tertiary CSR to *IGHA2 with respect to V1–3DJ6-IGHG4* (*esebssiwaagoT*$_Q$ of 0.226), where there is a match at plus minus 0.0055 units, which results in CM IgHA+ 3rd generation nodal cell. After both direct primary CSR between *IGHA2* and *V1–3DJ6-IGHM* and indirect tertiary CSR between *IGHA2* and *V1–3DJ6-IGHG4*, the resultant gene is the same, *V1–3DJ6*-IGHA2 expressed at 0.185 units, one expressed by a 1st generation cell and the other by a 3rd generation cell.

IGHV3–23 antibody heavy chain recombination sequence after *IGHV3–23-IGHD_-_-IGHJ_-J6* is iCSR followed by further CSRs for allele 1 (IGHM) and initial allelic exclusion for allele 2 (IGHD)

For Allele 1 (IGHM), there is internal CSR between the sequence intergene bases of *MIR4537 with respect to V3–23DJ6* (*esebssiwaagoT*$_Q$: 0.272) and the intergene bases of *MIR4539 with respect to V3–23DJ6* (*esebssiwaagoT*$_Q$: 0.277), which is the closest *esebssiwaagoT*$_Q$ match and results in *V3–23-D_-_-J6-remaining MIR/MIRs-IGHM* with an *esebssiwaagoT*$_Q$ of 0.277 (Table 8).

For Allele 2 (IGHD), homologous recombination does not take place between *IGHD* (*esebssiwaagoT*$_Q$: 0.208) and *V3–23-D_-_-J6* (*esebssiwaagoT*$_Q$: 0.285) as there is no *esebssiwaagoT*$_Q$ match (Table 8). Instead, delayed internal CSR will follow, which will result in Allele 2 *V3–23-D_-_-J6-remaining MIR/MIRs-IGHM* and in further CSRs analogous to Allele 1.

For both alleles, the primary CSR *esebssiwaagoT*$_Q$ match genes for *V3–23DJ6–IGHM* (*esebssiwaagoT*$_Q$: 0.277) are *IGHG1* (*esebssiwaagoT*$_Q$: 0.271) and *IGHA2* (*esebssiwaagoT*$_Q$: 0.258), respectively. A primary direct *IGHG1*-to-*IGHM* CSR at plus minus 0.003 units results in *V3–23DJ6-IGHG1* that expresses at an *esebssiwaagoT*$_Q$ of 0.256, and a primary direct *IGHA2*-to-*IGHM* CSR at plus minus 0.0095 units results in *V3–23DJ6-IGHA2* that expresses at an *esebssiwaagoT*$_Q$ of 0.208 (Table 8).

The CM IgG1+/IgG1+ 1st generation Evolved mature naïve B-cell secondary CSRs with *IGHA1 with respect to V3–23DJ6-IGHG1* with an *esebssiwaagoT*$_Q$ of 0.263 that is sufficiently horizontal at minus 0.0035 units in reference to *V3–23DJ6-IGHG1*, which is the only potential CSR for *V3–23DJ6-IGHG1* with a downstream gene and results in *V3-23DJ6-IGHA1* with an *esebssiwaagoT*$_Q$ of 0.171 (Table 8).

For the population of isotype switching B-cells, there are two potential tertiary CSRs for a CM IgA1+/IgA1+ 2nd generation-Evolved mature naïve B-cell with an *esebssiwaagoT*$_Q$ of 0.171 units, one with *IGHE with respect to V3–23DJ6-IGHA1* at 0.167 units (±0.002), and the other with *IGHA2 with respect to V3–23DJ6-IGHA1* at 0.179 units (±0.004). The further quaternary CSR for CM IgE+/IgE+ 3rd generation-Evolved mature naïve B-cell at 0.205 *esebssiwaagoT*$_Q$ units is with *IGHA2 with respect to V3–23DJ6-IGHE* at an *esebssiwaagoT*$_Q$ of 0.183 units (± 0.011) (Table 8).

The higher generation-Evolved mature naïve cells in reference to *V3–23DJ6-IGHM* are more somatically mutated B-cells to the point of B-cell to B-plasma cell transformation as they are the product of multiple CSRs [28], particularly when CSRing around the intracellular pressures at which the somatic hypermutation (SHM) cytidine deaminases (CDA) are maximally expressed and available [4].

IGHV5–51 antibody heavy chain recombination sequence after *IGHV5–51-IGHD_-_-IGHJ_-J6* is iCSR followed by further CSRs for allele 1 (IGHM) and initial allelic exclusion for allele 2 (IGHD)

For Allele 1 (IGHM), there is internal CSR between the sequence intergene bases of *MIR4537 with respect to V5–51DJ6* (*esebssiwaagoT*$_Q$: 0.152) and those of *MIR4507/MIR4538 with respect to V5–51DJ6* (*esebssiwaagoT*$_Q$: 0.155), which is the closest *esebssiwaagoT*$_Q$ match and results in *V5–51-D_-_-J6-remaining MIR/MIRs-IGHM* with an *esebssiwaagoT*$_Q$ of 0.165 (Table 9).

For Allele 2 (IGHD), homologous recombination does not take place between *IGHD* (*esebssiwaagoT*$_Q$: 0.169) and *V5–51-D_-_-J6* (*esebssiwaagoT*$_Q$: 0.233), internal CSR takes place on both alleles (Table 9).

There are four potential primary CSR *esebssiwaagoT*$_Q$ match genes for *V5–51DJ6-IGHM* (*esebssiwaagoT*$_Q$: 0.165), *IGHG1* that is horizontal at 0.160 units (±0.0025), *IGHA1* that is horizontal at 0.180 units (±0.0075), *IGHG4* that is horizontal at 0.189 units (±0.012), and *IGHA2* that is horizontal at 0.175 units (±0.005), where the choice of further CSR depends on the B-cell pressure as it oscillates with cyclic periodicity in context of the local *milieu*. Primary CSR with *V5–51DJ6–IGHM* will result in either *V5–51DJ6-IGHG1* (*esebssiwaagoT*$_Q$: 0.153), *V5–51DJ6-IGHA1* (*esebssiwaagoT*$_Q$: 0.134), *V5–51DJ6-IGHG4* (*esebssiwaagoT*$_Q$: 0.184) or *V5–51DJ6-IGHA2* (*esebssiwaagoT*$_Q$: 0.148), and in a 1st generation evolved B-cell (Table 9).

There are also four potential downstream secondary CSR *esebssiwaagoT*$_Q$ match genes for *V5–51DJ6-IGHG1* (*esebssiwaagoT*$_Q$: 0.153), *IGHA1* at 0.166 units (±0.0065), *IGHG4* at 0.137 units (±0.008), *IGHE* at 0.145 units (±0.004), and *IGHA2* at 0.157 units (±0.002). Secondary

CSR with *V5–51DJ6-IGHG1* will result in the recombined genes as before expressing at the their respective *esebssiwaagoT*$_Q$s, in either *V5–51DJ6-IGHA1*, *V5–51DJ6-IGHG4*, or *V5–51DJ6-IGHA2* and in addition, *V5–51DJ6-IGHE* that expresses at 0.152 units, and in a 2nd generation evolved B-cell (Table 9).

There are three potential downstream tertiary CSR *esebssiwaagoT*$_Q$ match genes for *V5–51DJ6-IGHA1* (*esebssiwaagoT*$_Q$: 0.134), *IGHG4* at 0.106 units (±0.014), *IGHE* at 0.153 units (±0.0095), and *IGHA2* at 0.163 units (±0.00145). Tertiary CSR with *V5–51DJ6-IGHA1* will result in the recombined genes as after the prior isotype switch, in either *V5–51DJ6-IGHG4*, *V5–51DJ6-IGHE* or *V5–51DJ6-IGHA2*, and in a 3rd generation evolved B-cell (Table 9). Thus, tertiary CSRed 3rd generation evolved B-cell plasma cells will express and secrete antibody that is somatically hypermutated, for example IgE that is the product of three sequential CSRs (*V5–51DJ6-IGHM* ⟶ *V5–51DJ6-IGHA1* ⟶ *V5–51DJ6-IGHG1* ⟶ *V5–51DJ6-IGHE*) [29].

There is no potential for a further quaternary CSR from *V5–51DJ6-IGHG4* (*esebssiwaagoT*$_Q$: 0.184), as there is no match with downstream genes, *IGHE* has an *esebssiwaagoT*$_Q$ of 0.146, while *IGHA2* has an *esebssiwaagoT*$_Q$ of 0.153, both being outside of the match range, *IGHE* at plus minus 0.019 units and *IGHA2* at plus minus 0.0155 units when neither DNA segment is horizontal enough for stable CSR by cytidine deaminases [4] (Table 9).

There is the potential for a quaternary CSR between *IGHA2 with respect to V5–51DJ6-IGHE* (*esebssiwaagoT*$_Q$: 0.129) and upstream *V5–51DJ6-IGHE* (*esebssiwaagoT*$_Q$: 0.152) as its plus minus 0.0115 units at the point of gene *esebssiwaagoT*$_Q$ convergence (Table 9),

During the secretory phase, B-plasma cells with recombined *V5–51* antibody heavy chain genes will express the *V5–51DJ6-IGH_* antibody gene in response to negative pressuromodulation antigens of the cell membrane such as lipases and proteases.

Clinical correlation with allergen-induced immunogenicity

Allergic disease states such as rhinitis, asthma and venom sensitivity are subsets of IgE-mediated Type I hypersensitivity, the former two caused by mucosal exposure to plant pollen (i.e. *Amb a* series) and arthropod excreta (*Der p*) for example [27, 30], and the latter one caused by intravascular exposure to hymenoptera venoms (bee, *Api m*; jacket, *Ves g*; wasp, *Pol a*) [31].

Pollen and mite excreta are contaminated with endotoxins such as bacterial lipopolysaccharide (LPS) [32] and fungal profilin II [24, 25] and proteases [33]; while, honey bee venom apitoxin contains gland melittin (*Api m* III) [34], mast cell degranulating peptide 401 [35] and enzymes hyaluronidase (*Api m* II), phospholipase A2 (*Api m* 1), acid phosphatase (*Api m* IV) and dipeptidyl peptidase 4 (*Api m* V) [31, 36, 37].

In the classical pathway, antigen presenting cells (APC) scavenge and endocytose agglomerated nanoparticulates such as pollen-coated with lipopolysaccharide [38, 39] and melittin peptide lysed-cell membrane complexes [34] and re-present previously encountered endocytic positive pressuromodulator antigen fragments to CD4R+ T-cells for subsequent T-cell–mediated B-cell polarization pressuromodulation; while, in the non-classical pathway, dissoluted monomeric forms of LPS and profilin II positively pressuromodulate B-cells via endocytosis [40], as does melittin [41] however in concentrated form it is cell lytic as it is a very basic peptide [42].

In atopic allergic disease, antigen-specific serum IgE antibody is present; it is a product of multiple sequential indirect CSRs at the intracellular pressures at which there is maximal expression of somatic hypermutation (SHM) enzymes [4], as is the case in atopic rhinitis [20, 43], asthma [44, 45] and venom sensitivity [46, 47].

In bee venom sensitization and asthma for example, over time there is a shift from somatically hypermutated specific IgE to specific IgG4 [45–47]. The IgG4 is less mutated than IgE which CSR equivalently, probably since the PRDM1-induced drop in B-cell pressure to between 0.10 and 0.12 units is transient during the peri-nadir when SHM enzyme APOBEC3H is expressed [4]. The basis for the shift from IgE to IgG4 is probably a shift in B-cell pressure from a higher pressure at around 0.144 *esebssiwaagoT*$_Q$ units required for CSR to *IGHE* to a lower pressure at around 0.124 *esebssiwaagoT*$_Q$ units required for CSR to *IGHG4* (i.e. *V5–51*), due to the exposure of local lymph node B-cells to similar concentrations of negative antigen pressuromodulator enzymes such as phospholipase A2 during each successive sting, but to decreasing concentrations of positive antigen pressuromodulators (i.e. LPS) due to increasing endocytic efficiency of scavenging cells.

Conclusions

In this study, the recently developed gene *esebssiwaagoT*$_Q$-based B-cell maturation stage gene overexpression pressuromodulation map [4] has been utilized as a template to stimulate B-cell immunoglobulin locus recombination events that take place in the pressuromodulated state in vivo. Germline joining-to-diversity gene rearrangements have been performed *with respect to* the germline followed by variability-to-diversityjoining gene recombinations through further consensus sequence recognition (CSR) isotype switching recombinations *with respect to* their recombined position.

Based on the findings of this study the following inferences can be made: (1) the *esebssiwaagoT*$_Q$ of a joining

(*J*_) and diversity (*D*_-_) gene in its native germline configuration is the basis for predictable subsequent gene rearrangement; (2) *D*_-_ to *J*_ gene recombination events are bi-allelic and mutually exclusive; (3) the entire process from beginning to end depends on the grade of the pressuromodulation effect, and as per the classical pathway it is an antigen presenting cell (APC)-dependent CD4R+ T-cell-mediated B-cell polarization process; (4) CD4R+ T-cells are positively pressuromodulated, while B-cells are subject to the effect of both positive and negative forms of antigen pressuromodulation; and (5) the B-cell to plasma cell transformation and the extra-nodal periphery/tissue nidus phase take place in the presence of antigen load and either positive or negative pressuromodulation of the cell to its recombined antibody gene expression intracellular pressure.

B-cell gene recombination rearrangement events can be predicted with a reasonable degree of certainty. It is envisioned that further *esebssiwaagoT*$_Q$-based study of the remaining B-cell variability gene recombinations isotype switching events will further our understanding of pressuromodulated basis for antigen selection including the evolutionary underpinnings of.

Additional files

Additional file 1: Table S1. Chromosome 14 Ig heavy chain locus mined location data. (PDF 375 kb)

Additional file 2: Table S2. Chromosome 14 (–) strand chromatin Ig heavy chain locus immunoglobulin gene *esebssiwaagoT*$_Q$s to final 2-digit (and 3-digit) *esebssiwaagoT*$_Q$ for germline genes in native 5′- > 3′ chronology before gene rearrangement[1(a)] Episodes beginning with an anisotropic (A) or mesotropic (M) SEB; [1(b)] non-contributory anisotropic sub-episode block (NCA); [1(c)] non-contributory single or multiple stabilizing isotropy points or reverse stabilizing isotropy point(s), NCstI; [1(d)] anisotropy converted-to-mesotropy, ACM; and [1(e)] indirect reverse stIsotropy and/or stIsotropy for anisotropy or for mesotropy, stMfA or stMfM. (DOC 51 kb)

Additional file 3: Table S3. Chromosome 14 (–) strand chromatin Ig heavy chain locus joining gene *esebssiwaagoT*$_Q$s to final 2-digit (and 3-digit) *esebssiwaagoT*$_Q$ for germline genes in native 5′- > 3′ chronology before gene rearrangement[1(a)] Episodes beginning with an anisotropic (A) or mesotropic (M) SEB; [1(b)] non-contributory anisotropic sub-episode block (NCA); [1(c)] non-contributory single or multiple stabilizing isotropy points or reverse stabilizing isotropy point(s), NCstI; [1(d)] anisotropy converted-to-mesotropy, ACM; and [1(e)] indirect reverse stIsotropy and/or stIsotropy for anisotropy or for mesotropy, stMfA or stMfM. (DOC 44 kb)

Additional file 4: Table S4. Chromosome 14 (–) strand chromatin Ig heavy chain locus diversity gene *esebssiwaagoT*$_Q$s to final 2-digit (and 3-digit) *esebssiwaagoT*$_Q$ for germline genes in native 5′- > 3′ chronology before gene rearrangement[1(a)] Episodes beginning with an anisotropic (A) or mesotropic (M) SEB; [1(b)] non-contributory anisotropic sub-episode block (NCA); [1(c)] non-contributory single or multiple stabilizing isotropy points or reverse stabilizing isotropy point(s), NCstI; [1(d)] anisotropy converted-to-mesotropy, ACM; and [1(e)] indirect reverse stIsotropy and/or stIsotropy for anisotropy or for mesotropy, stMfA or stMfM. *For *IGHD1–20*^{rf}, NCA of SEB no. 7 due to reverse anisotropy preceding original ending confirmation mesotropic SEB (no. 8) which sums into SEB no. 6 with inclusion of anisotropic SEB no. 9 as the ending SEB, which precedes the new ending confirmation mesotropic SEB (no. 10) (final SEB count is 7*) *For *IGHD1–1*, ACM of initial anisotropic ending confirmation SEB no. 8 due to 0.25-factor-adjusted reverse stIsotropy preceding SEB (no. 8), which sums into initial mesotropic SEB no. 7, and the new ending confirmation anisotropic SEB is no. 9 (final SEB count is 7*). (DOC 71 kb)

Additional file 5: Table S5. Chromosome 14 (–) strand chromatin Ig heavy chain locus diversity (D)-to-joining (J) recombination sequence *esebssiwaagoT*$_Q$s to final 2-digit (and 3-digit) *esebssiwaagoT*$_Q$ before VDJ for allele 1 (IGHM) [1(a)] Episodes beginning with an anisotropic (A) or mesotropic (M) SEB; [1(b)] non-contributory anisotropic sub-episode block (NCA); [1(c)] non-contributory single or multiple stabilizing isotropy points or reverse stabilizing isotropy point(s), NCstI; [1(d)] anisotropy converted-to-mesotropy, ACM; and [1(e)] indirect reverse stIsotropy and/or stIsotropy for anisotropy or for mesotropy, stMfA or stMfM. (DOC 66 kb)

Additional file 6: Table S6. Chromosome 14 (–) strand chromatin Ig heavy chain locus diversity (D)-to-joining (J) recombination sequence *esebssiwaagoT*$_Q$s to final 2-digit (and 3-digit) *esebssiwaagoT*$_Q$ before VDJ for allele 2 (IGHD)[1(a)] Episodes beginning with an anisotropic (A) or mesotropic (M) SEB; [1(b)] non-contributory anisotropic sub-episode block (NCA); [1(c)] non-contributory single or multiple stabilizing isotropy points or reverse stabilizing isotropy point(s), NCstI;[1(d)] anisotropy converted-to-mesotropy, ACM; and [1(e)] indirect reverse stIsotropy and/or stIsotropy for anisotropy or for mesotropy, stMfA or stMfM. (DOC 76 kb)

Additional file 7: Table S7. Chromosome 14 (–) strand chromatin Ig heavy chain locus variability gene *esebssiwaagoT*$_Q$s to final 2-digit (and 3-digit) *esebssiwaagoT*$_Q$ for germline genes in native 5′- > 3′ chronology[1(a)] Episodes beginning with an anisotropic (A) or mesotropic (M) SEB; [1(b)] non-contributory anisotropic sub-episode block (NCA); [1(c)] non-contributory single or multiple stabilizing isotropy points or reverse stabilizing isotropy point(s), NCstI; [1(d)] anisotropy converted-to-mesotropy, ACM; and [1(e)] indirect reverse stIsotropy and/or stIsotropy for anisotropy or for mesotropy, stMfA or stMfM. §*Inc-AL901608.1–10/IGHV1–3/IGHV4–4* gene locus *esebssiwaagoT*$_Q$ is *D*_-_ -*J*_ location dependent. (DOC 46 kb)

Additional file 8: Table S8. Chromosome 14 (–) strand chromatin Ig heavy chain locus gene recombination sequence *esebssiwaagoT*$_Q$s to final 2-digit (and 3-digit) *esebssiwaagoT*$_Q$ for both alleles after *IGHV1–3-IGHD*_-_-*IGHJ6*[1(a)] Episodes beginning with an anisotropic (A) or mesotropic (M) SEB; [1(b)] non-contributory anisotropic sub-episode block (NCA); [1(c)] non-contributory single or multiple stabilizing isotropy points or reverse stabilizing isotropy point(s), NCstI; [1(d)] anisotropy converted-to-mesotropy, ACM; and [1(e)] indirect reverse stIsotropy and/or stIsotropy for anisotropy or for mesotropy, stMfA or stMfM. For *IGHV1–3- IGHD*_-_-*IGHJ6*, *ACM within initial anisotropic SEB no. 4, which results in a final SEB count of 9 [7(+ 2):9], and then stIMfA of initial anisotropic ending confirmation SEB no. 8 (final SEB no. 10) due to 0.25-factor-adjusted reverse stIsotropy preceding SEB (no. 10), which sums into initial mesotropic SEB no. 9, and the new ending confirmation anisotropic SEB is no. 11 (final SEB count is 9*). For *V1–3-D*_-_ -*J*_-*J6-IGHG4*, *ACM of initial anisotropic ending confirmation SEB no. 5 due to 0.25-factor-adjusted reverse stIsotropy preceding SEB (no. 5), which sums into f mesotropic SEB no. 4, and the new ending confirmation anisotropic SEB is no. 7 (final SEB count is 5*). (DOC 74 kb)

Additional file 9: Table S9. Chromosome 14 (–) strand chromatin Ig heavy chain locus gene recombination sequence *esebssiwaagoT*$_Q$s to final 2-digit (and 3-digit) *esebssiwaagoT*$_Q$ for both alleles after *IGHV3–23-IGHD*_-_-*IGHJ6*[1(a)] Episodes beginning with an anisotropic (A) or mesotropic (M) SEB; [1(b)] non-contributory anisotropic sub-episode block (NCA); [1(c)] non-contributory single or multiple stabilizing isotropy points or reverse stabilizing isotropy point(s), NCstI; [1(d)] anisotropy converted-to-mesotropy, ACM; and [1(e)] indirect reverse stIsotropy and/or stIsotropy for anisotropy or for mesotropy, stMfA or stMfM. (DOC 74 kb)

Additional file 10: Table S10. Chromosome 14 (–) strand chromatin Ig heavy chain locus gene recombination sequence *esebssiwaagoT*$_Q$s to final 2-digit (and 3-digit) *esebssiwaagoT*$_Q$ for both alleles after *IGHV5–51-IGHD*_-_-*IGHJ6*[1(a)] Episodes beginning with an anisotropic (A) or mesotropic (M) SEB; [1(b)] non-contributory anisotropic sub-episode block (NCA); [1(c)] non-contributory single or multiple stabilizing isotropy points or reverse stabilizing isotropy point(s), NCstI; [1(d)] anisotropy converted-to-mesotropy, ACM; and [1(e)] indirect reverse stIsotropy and/or stIsotropy for anisotropy or for mesotropy, stMfA or stMfM. *ACM of initial SEB no. 5 due to 0.25-factor-adjusted reverse stIsotropy preceding SEB (no. 5), which sums into ending confirmation mesotropic SEB no. 6, and the new ending confirmation anisotropic SEB is no. 7 (final SEB count is 6*). (DOC 77 kb)

Abbreviations
ACM: Anisotropy converted-to-mesotropy; *esebssiwaagoT*$_Q$: Episodic sub-episode sums split-integrated weighted average-averaged gene overexpression tropy quotient; HR: Homologous recombination; iCSR: Internal consensus sequence recognition CSR; NCA: Non-contributory anisotropic sub-episode block; NCstI: Non-contributory single or multiple stabilizing isotropy points or reverse stabilizing isotropy point(s); *prpT*$_Q$: Paired point tropy quotient; SEB: Sub-episode block; SHM: Somatic hypermutation; stMfA: Indirect reverse stIsotropy and/or stIsotropy for anisotropy; stMfM: Indirect reverse stIsotropy and/or stIsotropy for mesotropy

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Availability of data and materials
The mined data utilized in this study is publicly available at the GeneCards database (https://www.genecards.org/) genomic neighborhood GeneLoc genome locator (https://genecards.weizmann.ac.il/) and the LNCipedia.org database (http://www.lncipedia.org/). All data analysed this study are included in the supplementary information files of this article.

Authors' contributions
HS conceptualized the research, developed the methodology, analyzed the data, and wrote the manuscript.

Ethics approval and consent to participate
Not applicable.

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Competing interests
The authors declare that they have no competing interests.

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