

Characterization of tumor-infiltrating lymphocytes in TCGA cancers

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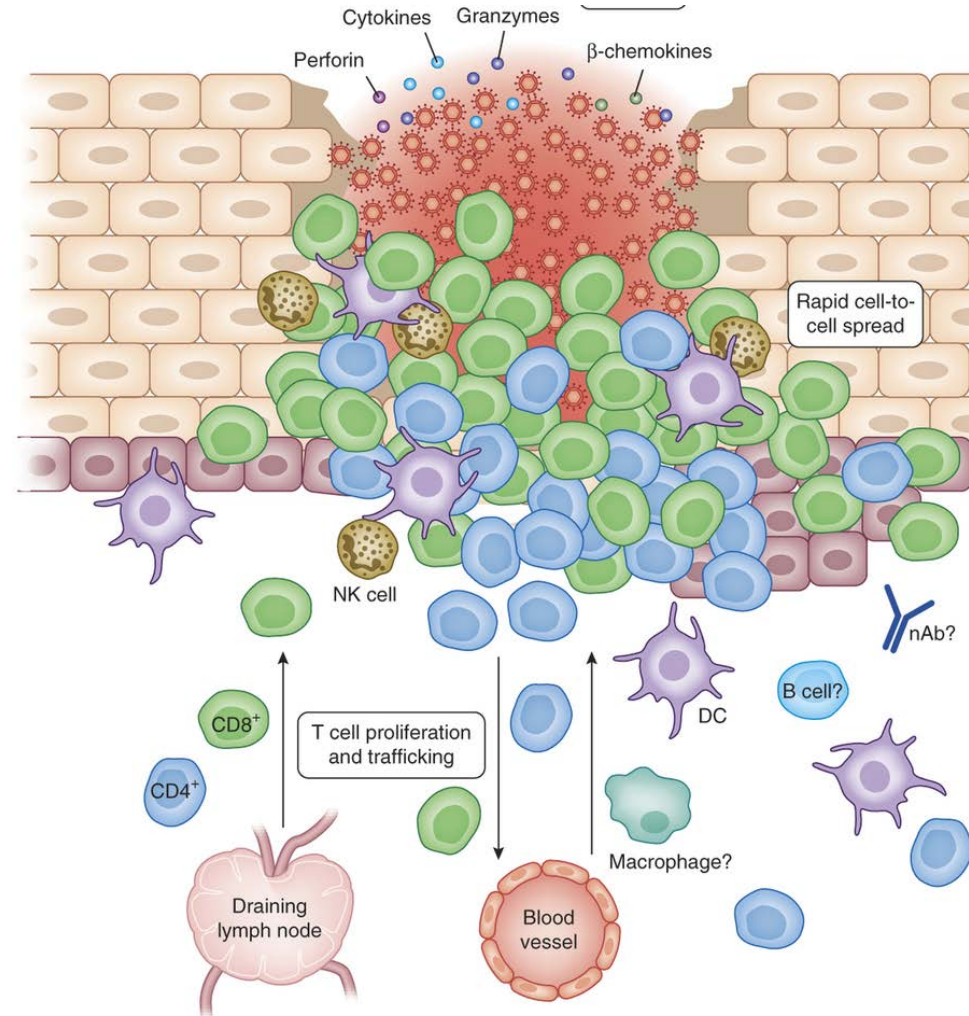
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Tumor-host immune interaction affects tumor development, progression, prognosis



Genomic profiling of TILs in human cancers

Molecular and Genetic Properties of Tumors Associated with Local Immune Cytolytic Activity

Michael S. Rooney,^{1,2} Sachet A. Shukla,^{1,3} Catherine J. Wu,^{1,3,4} Gad Getz,^{1,5} and Nir Hacohen^{1,4,6,*}

Quantified the immune cytolytic activity based on expression of two cytolytic effectors, GZMA and PRF1 across 18 tumor types.

(Rooney et al. Cell 160, 48–61, January 15, 2015)

Spatiotemporal Dynamics of Intratumoral Immune Cells Reveal the Immune Landscape in Human Cancer

Gabriela Bindea,^{1,2,3,11} Bernhard Mlecnik,^{1,2,3,11} Marie Tosolini,^{1,2,3} Amos Kirilovsky,^{1,2,3} Maximilian Waldner,^{1,2,3,4} Anna C. Obenauf,⁵ Helen Angell,^{1,2,3} Tessa Fredriksen,^{1,2,3} Lucie Lafontaine,^{1,2,3} Anne Berger,⁶ Patrick Bruneval,⁷ Wolf Herman Fridman,^{2,3,9} Christoph Becker,⁴ Franck Pagès,^{1,2,3,8} Michael R. Speicher,⁵ Zlatko Trajanoski,¹⁰ and Jérôme Galon^{1,2,3,6,*}

Characterized the immune landscape in 107 CRC patients by analyzing 28 immune cell types infiltrating tumors. (Bindea, et al. Immunity 39, 782–795, October 17, 2013)

Characterization of the immunophenotypes and antigenomes of colorectal cancers reveals distinct tumor escape mechanisms and novel targets for immunotherapy

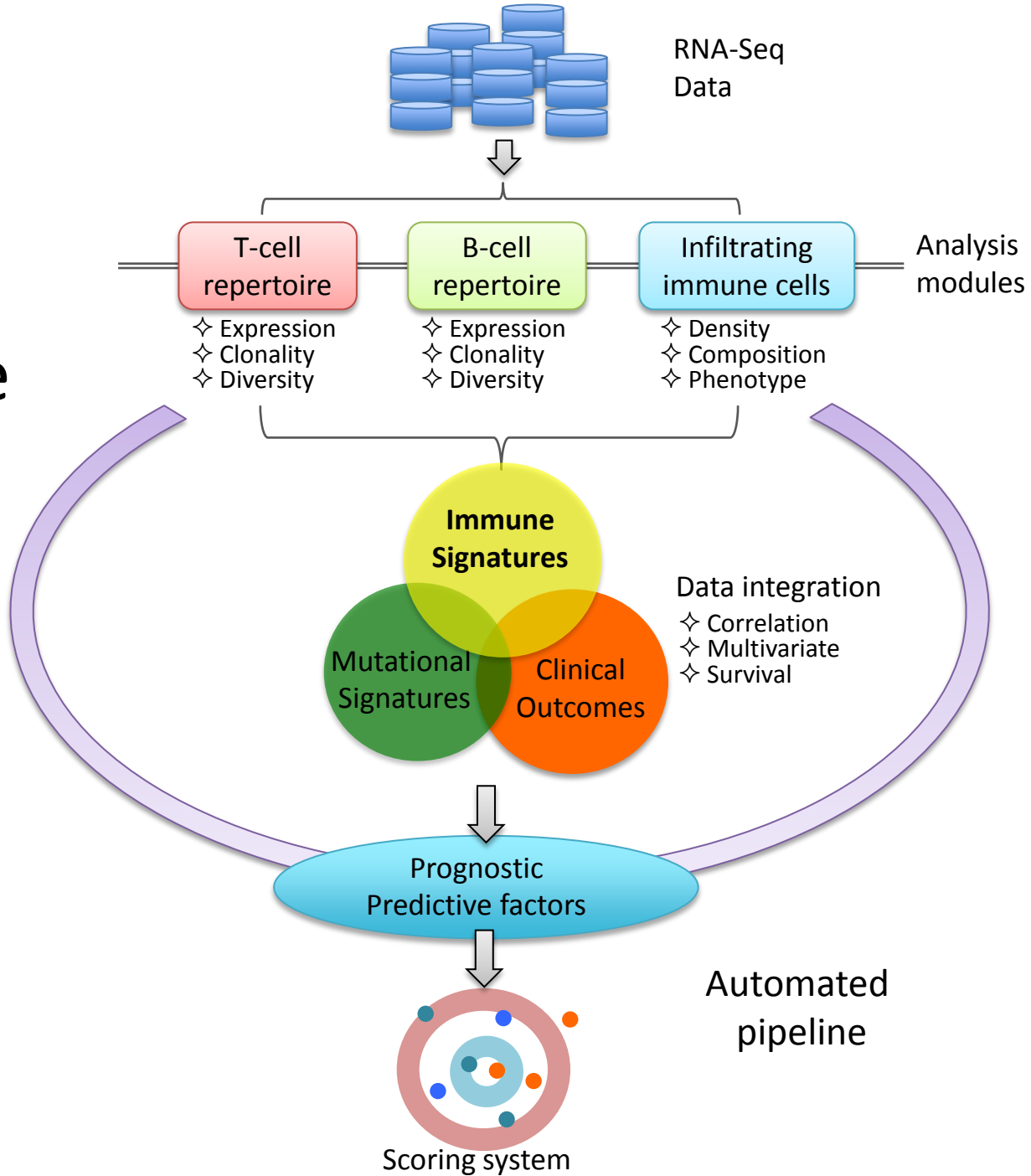
Mihaela Angelova^{1†}, Pornpimol Charoentong^{1†}, Hubert Hackl^{1†}, Maria L Fischer¹, Rene Snajder¹, Anne M Krogsdam¹, Maximilian J Waldner², Gabriela Bindea^{3,4}, Bernhard Mlecnik^{3,4}, Jerome Galon^{3,4} and Zlatko Trajanoski^{1*}

Poster #69

By Yasin Şenbabaoğlu profiled infiltration levels in 19 tumor types by mRNA-based T cell infiltration scores.

Characterized the immune phenotypes and Antigenomes of 598 CRC tumors.
Angelova et al. Genome Biology (2015) 16:64

Our automated analysis pipeline



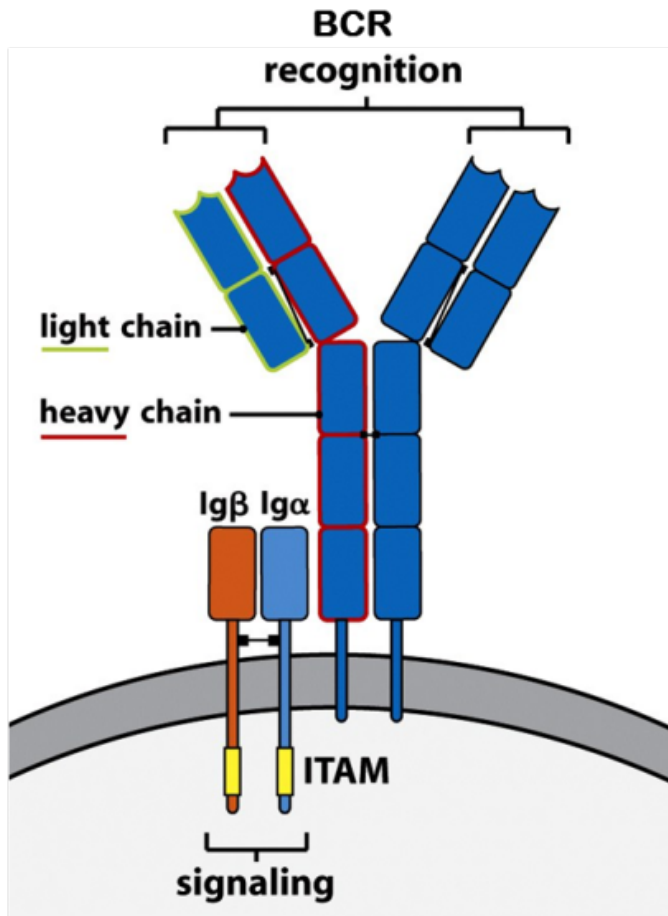
Goals

Use T-cell receptor (TCR) and B-cell receptor (BCR) gene expression to characterize TILs.

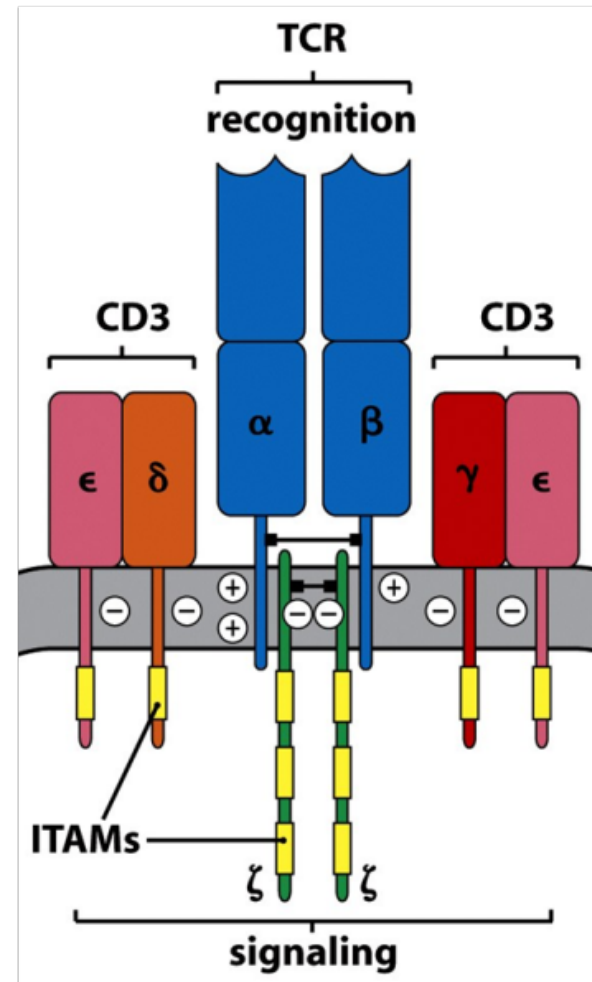
TCGA colon adenocarcinoma

TCGA testicular germ cell tumors

Structure of B cell and T cell antigen receptors

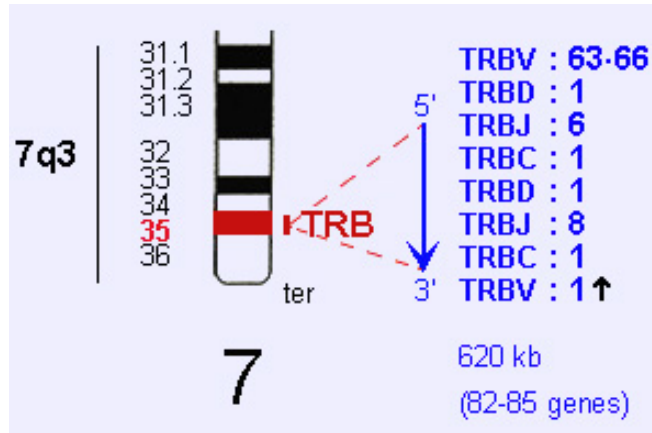


<http://www.shaltech.com/about-lymphoma/>

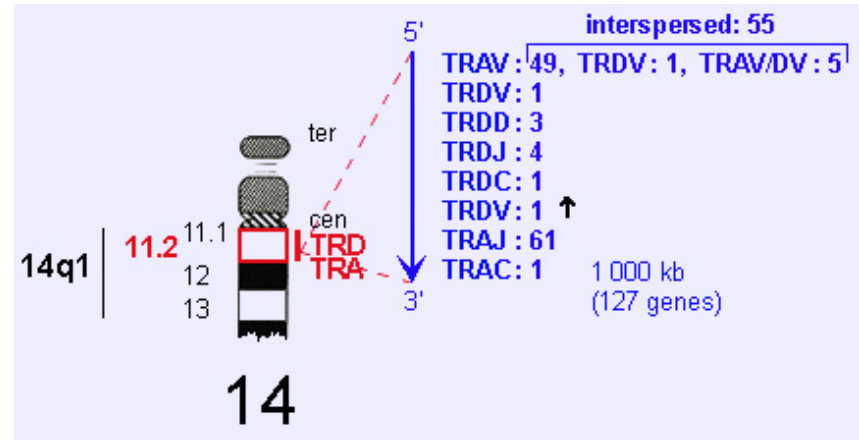


TCR and BCR gene loci, orientation and structure

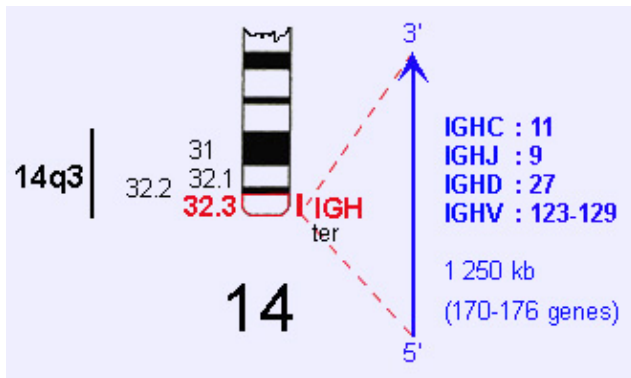
TCR-beta



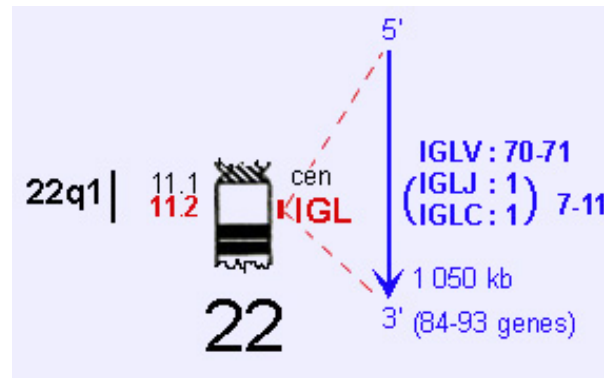
TCR-alpha



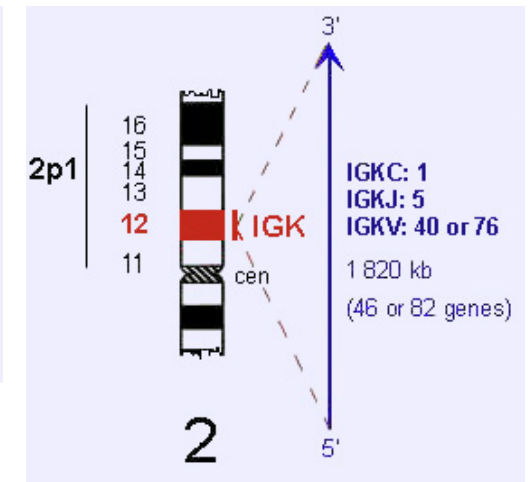
BCR, heavy chain



BCR, Light chain (lambda)

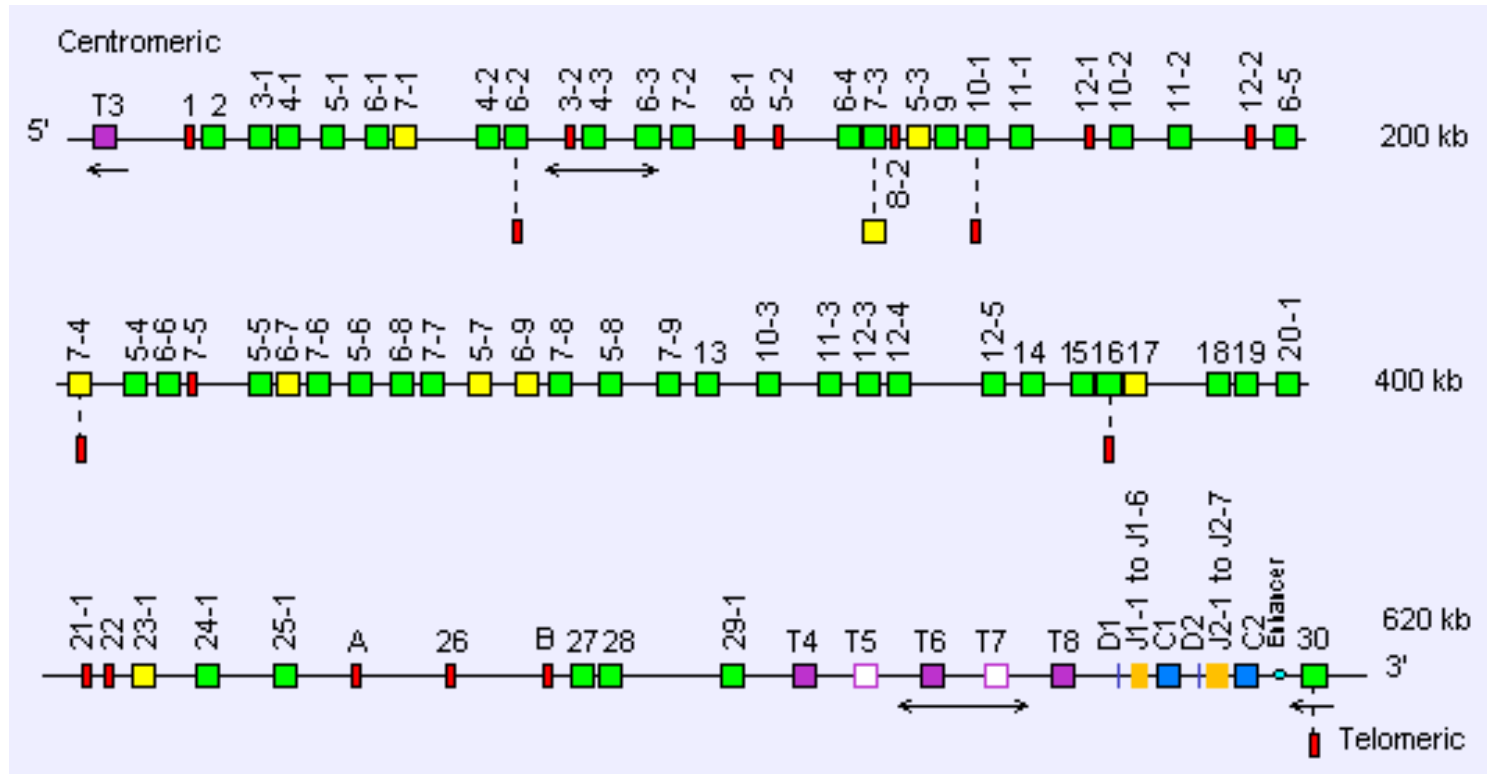


BCR, Light chain (kappa)



TCR-beta gene structure

<http://atlasgeneticsoncology.org/Genes/TCRBID24>



V-Gene: Green box: Functional; Yellow box: Open reading frame; Red: Pseudogene.

D-GENE: Blue: Functional.

J-GENE: orange: Functional .

C-GENE: Blue: Functional.

Purple: GENES NOT RELATED, Functional;

Purple open box: gene not related, Pseudogene.

V(D)J recombination

Germline configuration



D to J recombination



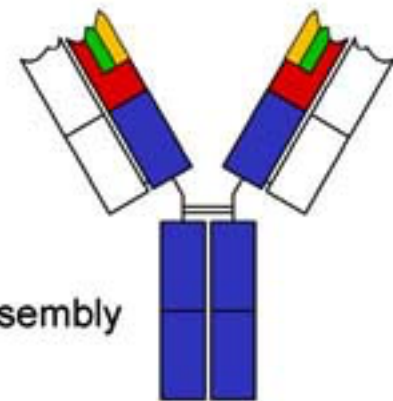
V to DJ recombination



transcription, splicing

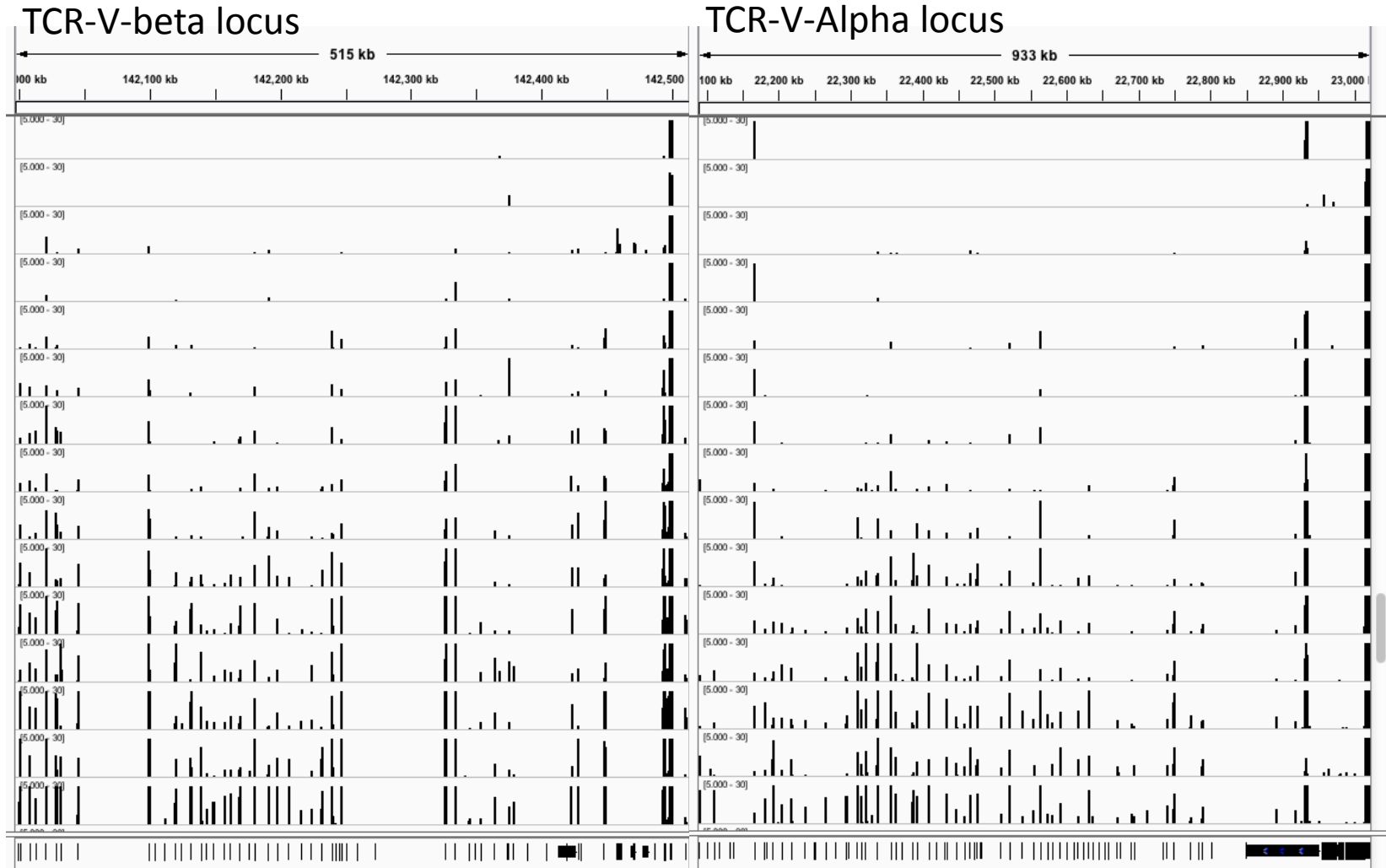


translation, assembly



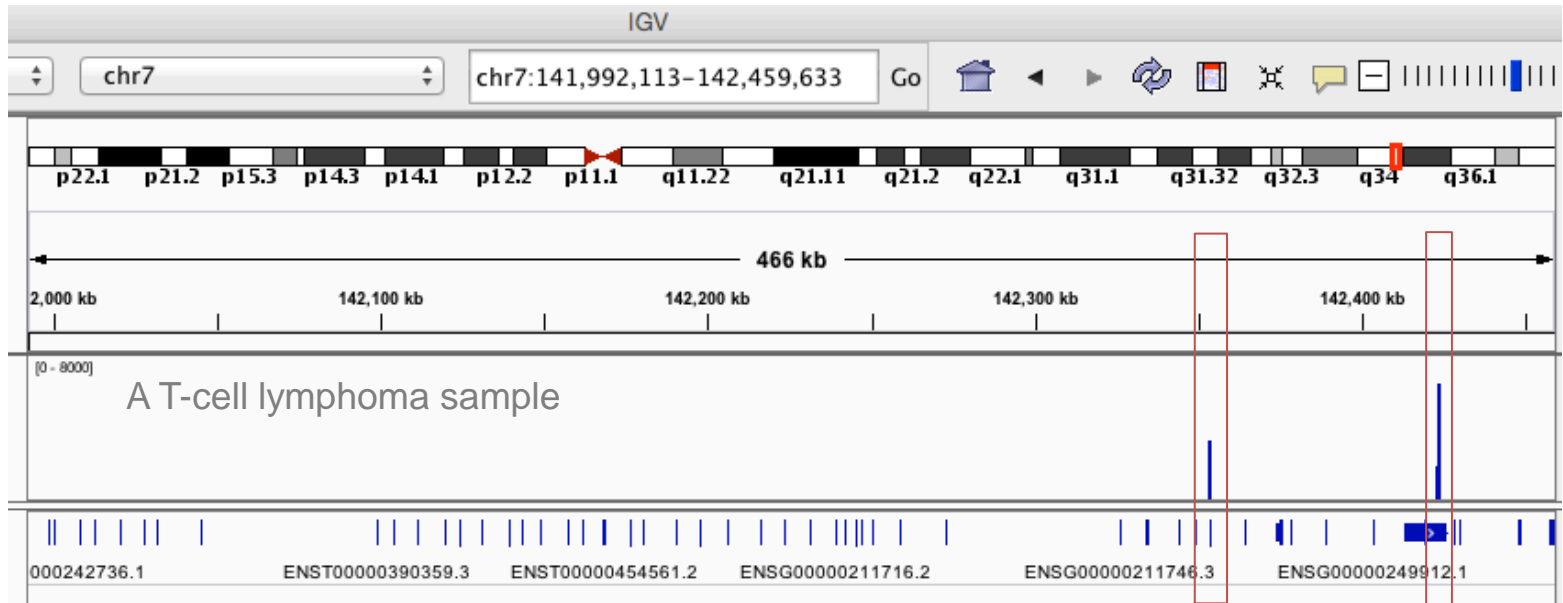
(adapted from Janeway 2001)

Diversity of TCR/BCR expression



CRC, representative cases

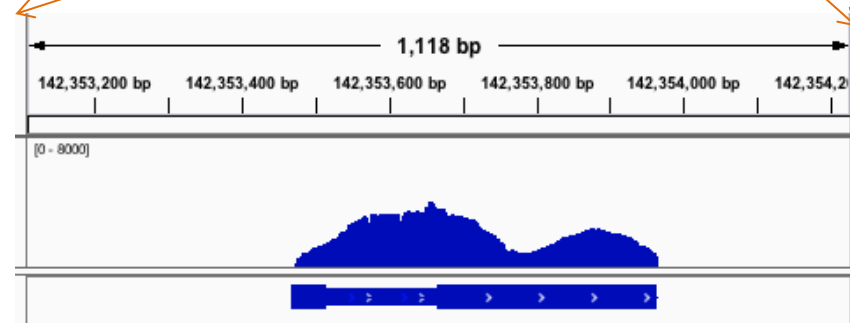
Quantify TCR/BCR expression using RNA-seq data



Biclonal
TCR-Vb

TRBV27

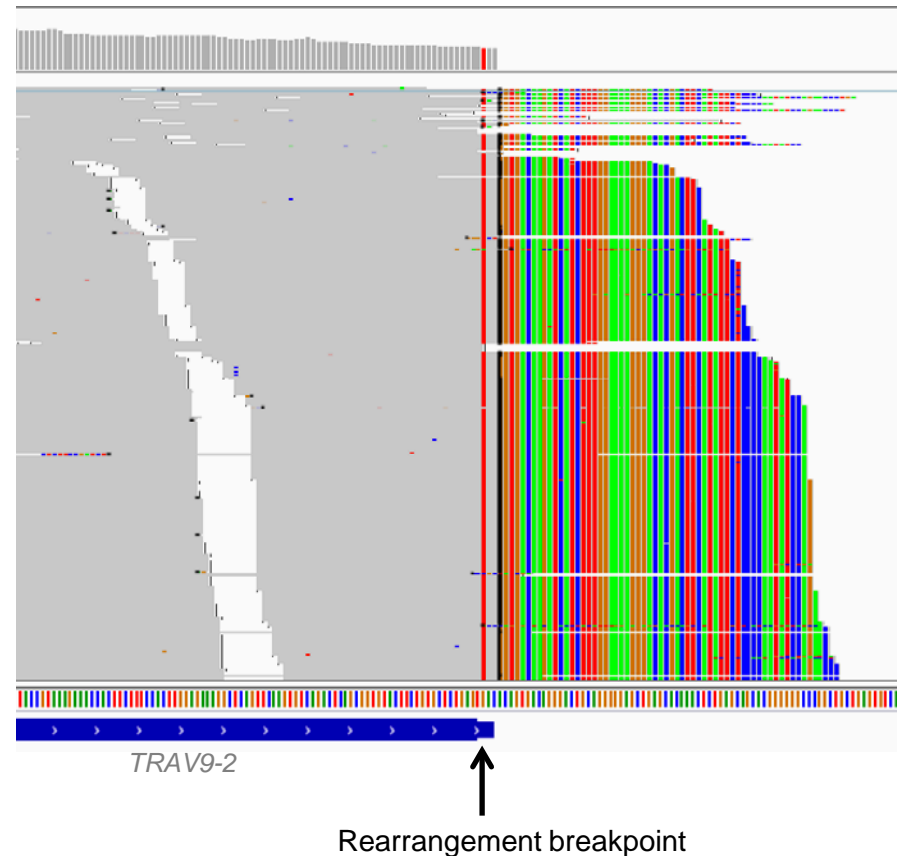
Count the sequencing reads on each gene segment and normalized it with sequencing depth and gene length.



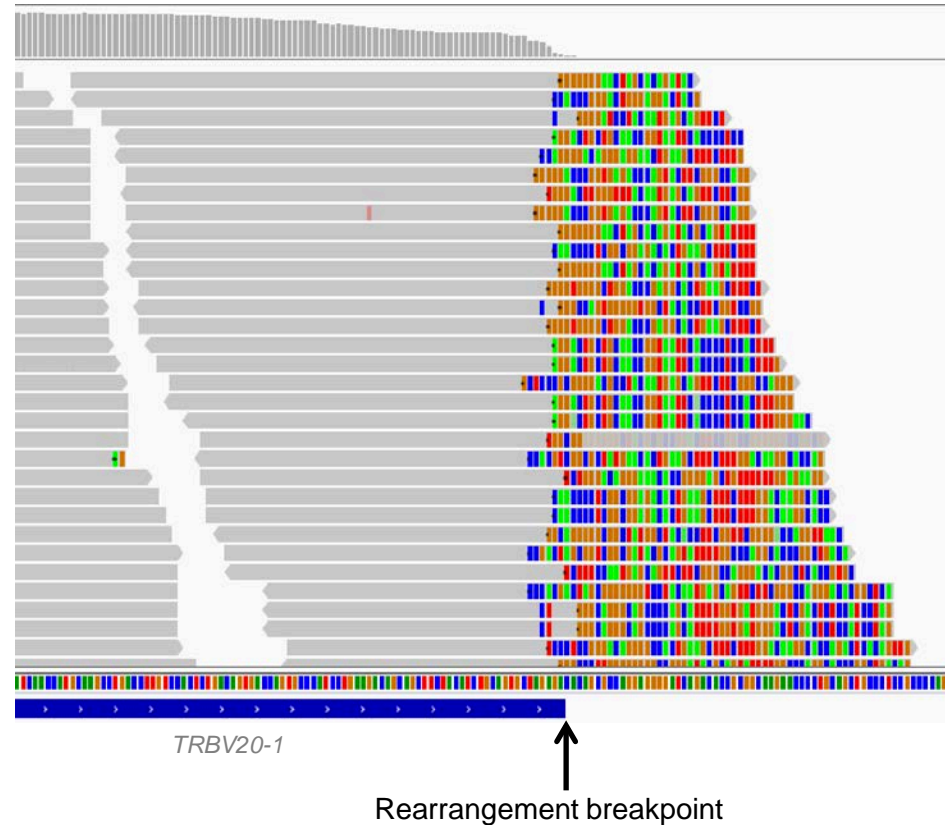
TRBV23-1

Examining TCR/BCR clonality by analyzing the soft-clipped sequencing reads

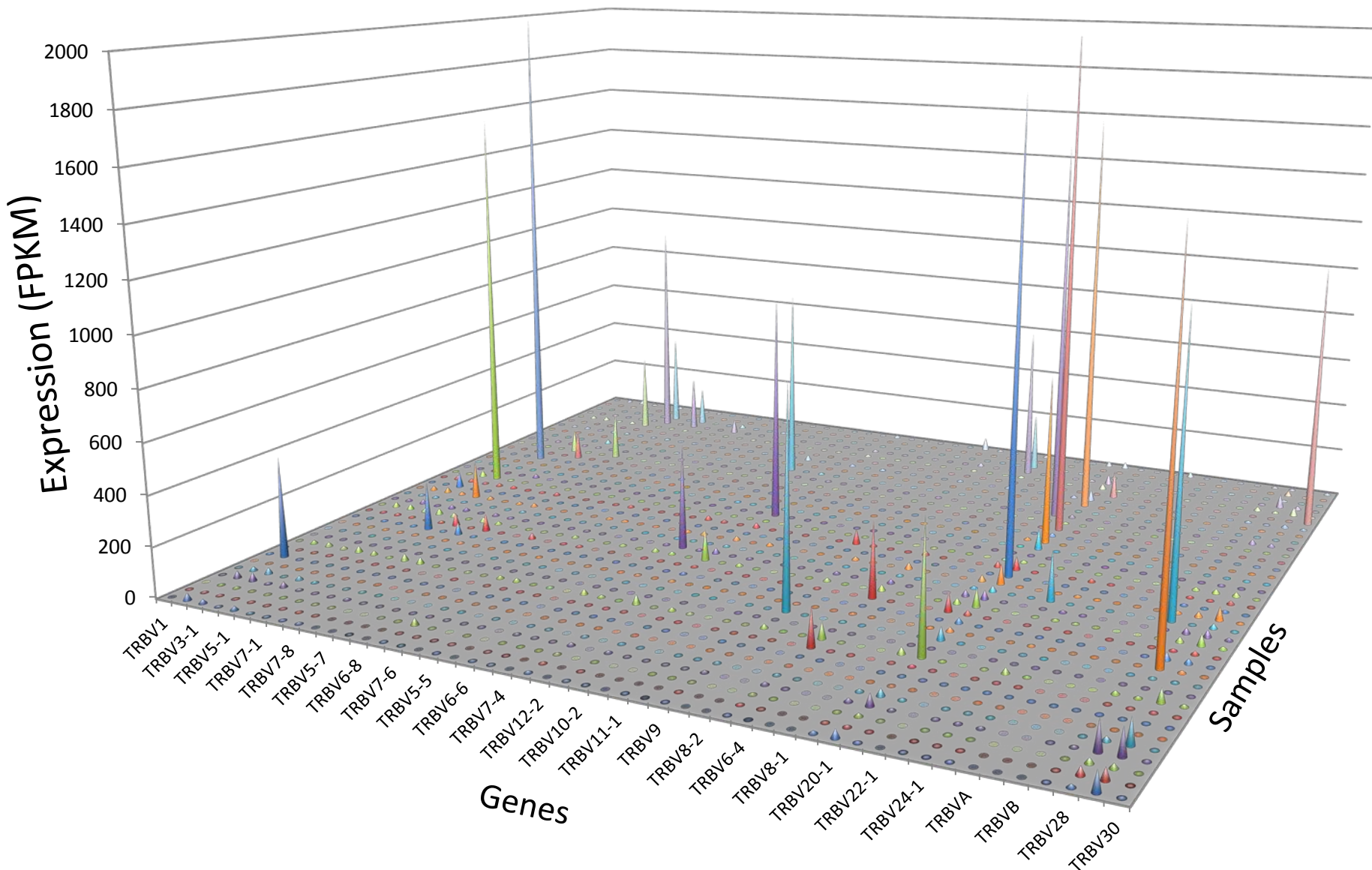
Monoclonal signature



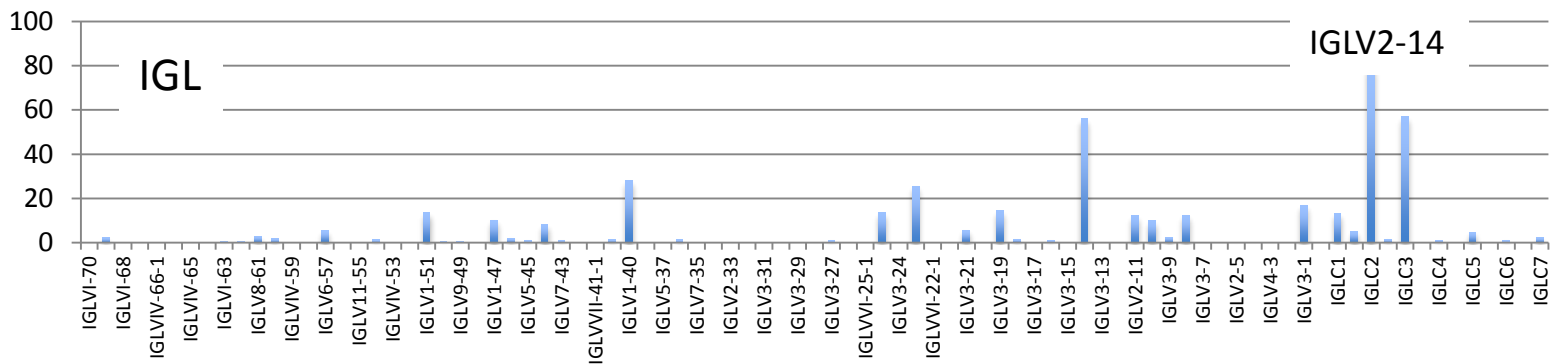
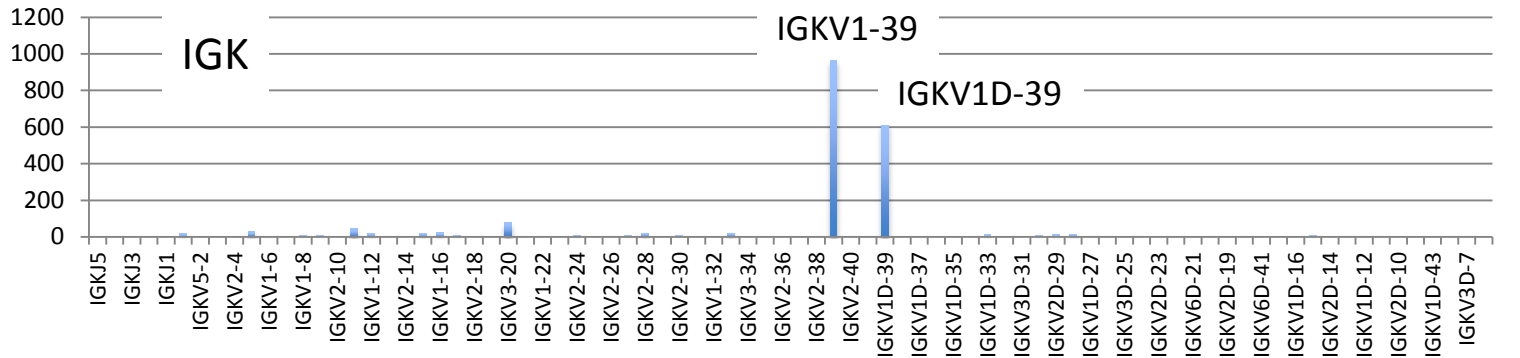
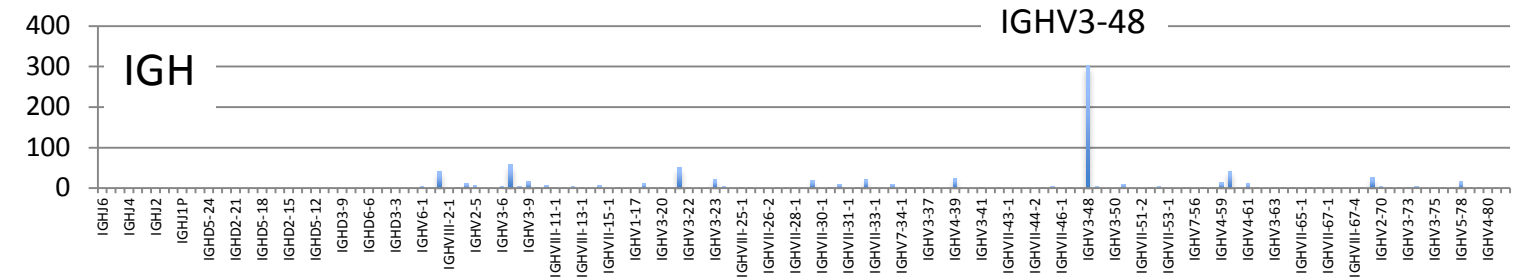
Polyclonal signature



TCR expression in T-cell lymphoma patients

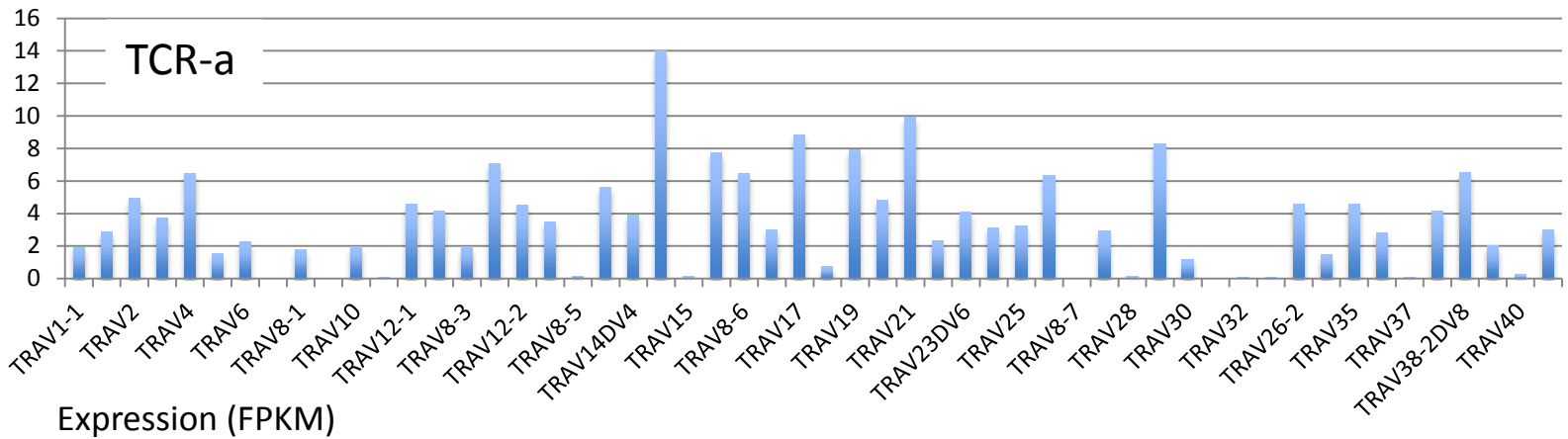
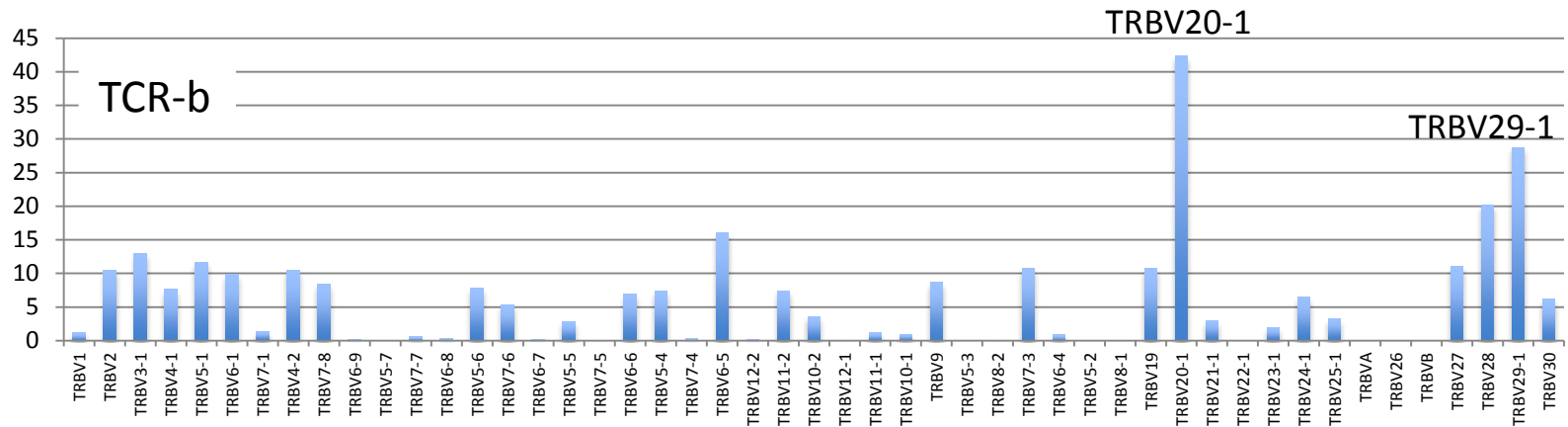


BCR expression in a B-cell lymphoma patient



Expression (FPKM)

TCR repertoire in this B-cell lymphoma patient



TCR expression In TCGA-CRC (n=63)

MS status

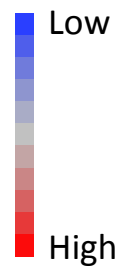
TCR-V-beta

TCR-V-alpha

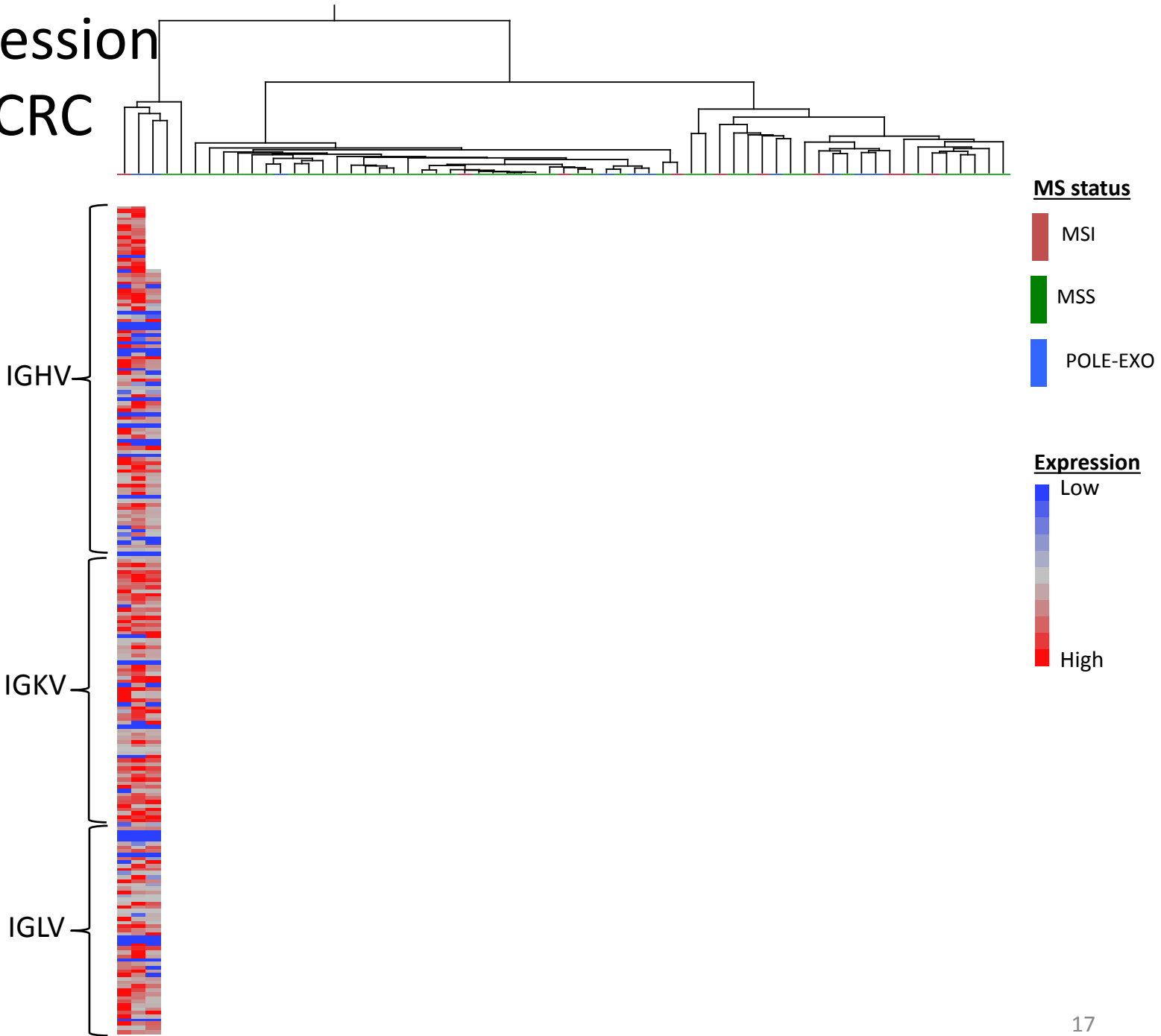
MS status



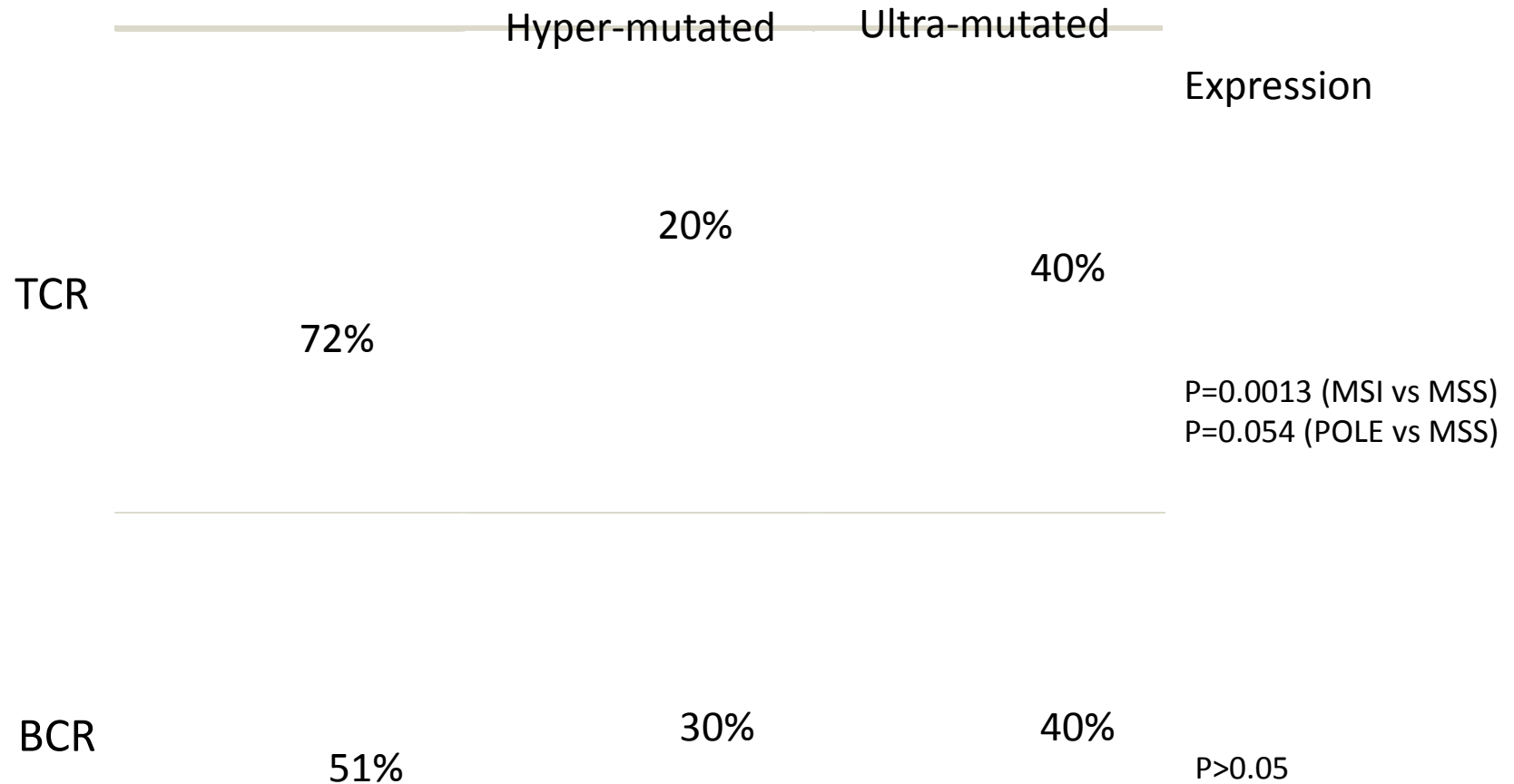
Expression



BCR expression In TCGA-CRC (n=63)



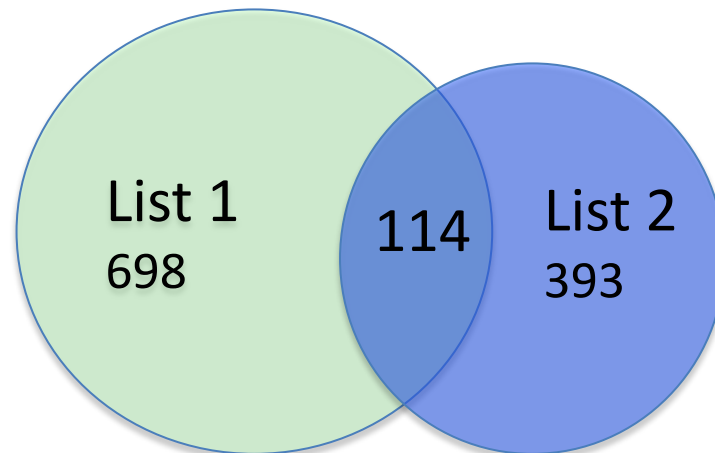
TCR expression in CRC is associated with MS status (n=63)



Characterization of TIL subpopulations using defined immune “metagenes”

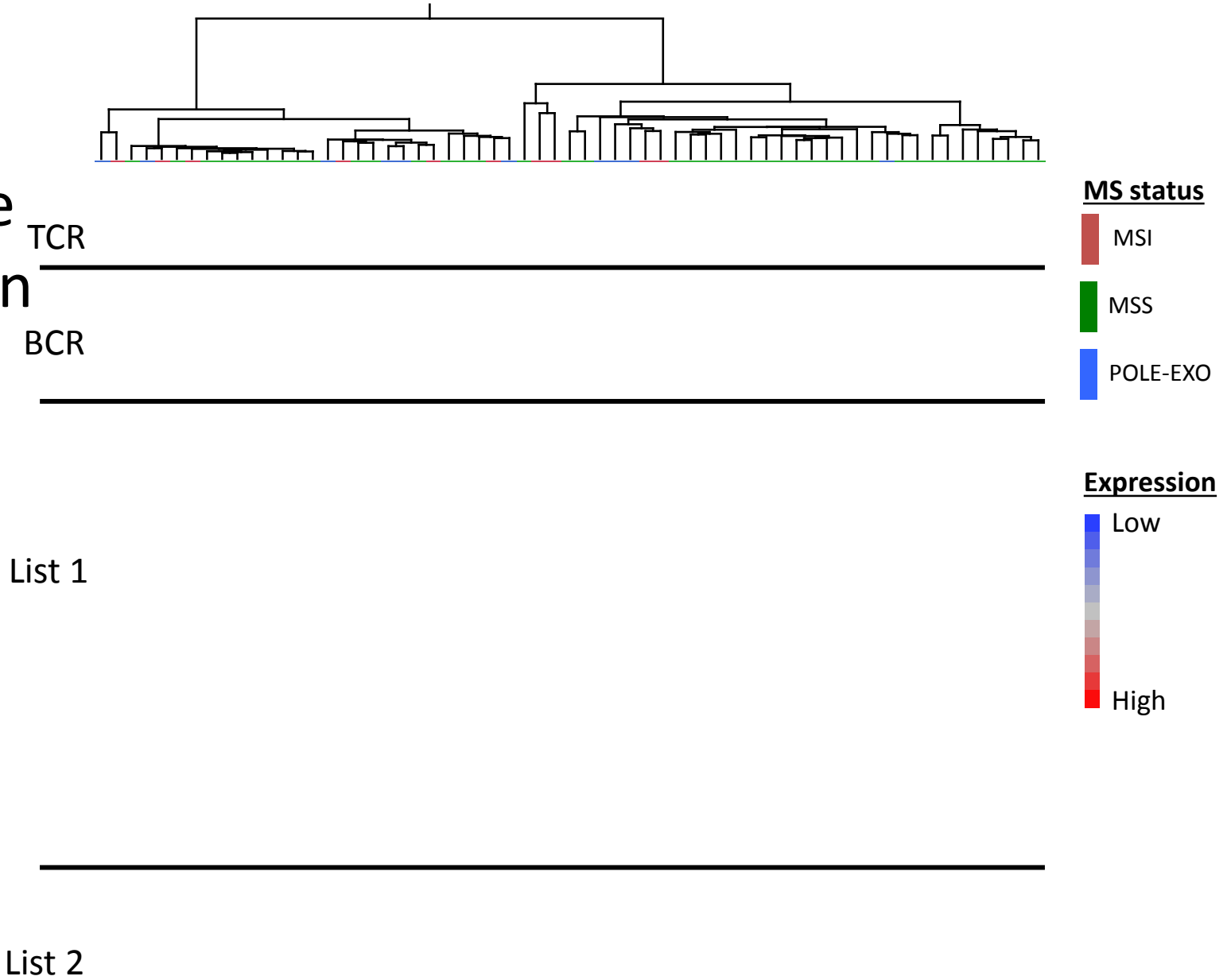
Gene list 1 (Angelova et al. *Genome Biology* (2015) 16:64):
812 genes for 28 immune cell subpopulations.

Gene list 2. (Bindea, et al. *Immunity* 39, 782–795, October 17, 2013)
507 genes for 25 immune cell subpopulations

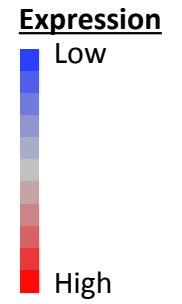
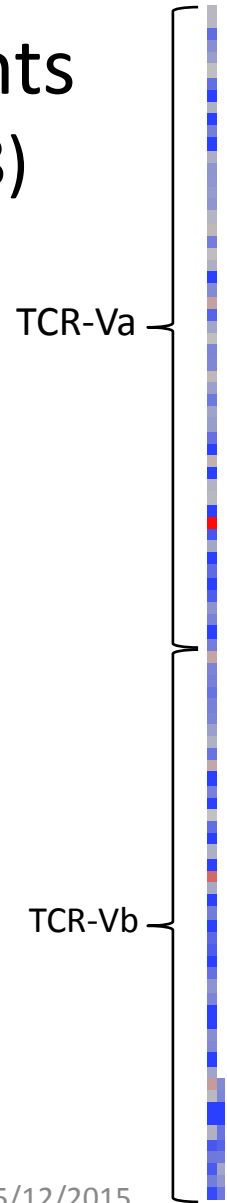


Overlapped: 114 genes for 24 cell types

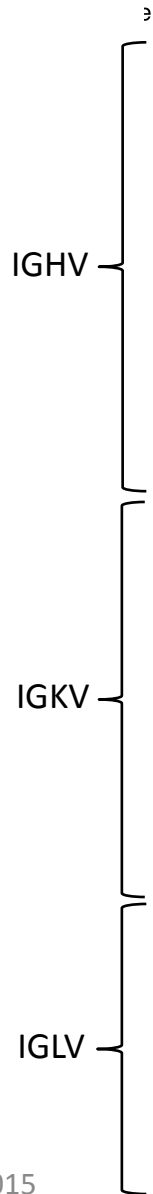
TCR/BCR, immune metagene Expression





TCR expression In TGCT patients (n=138)




BCR expression in TGCT patients (n=138)



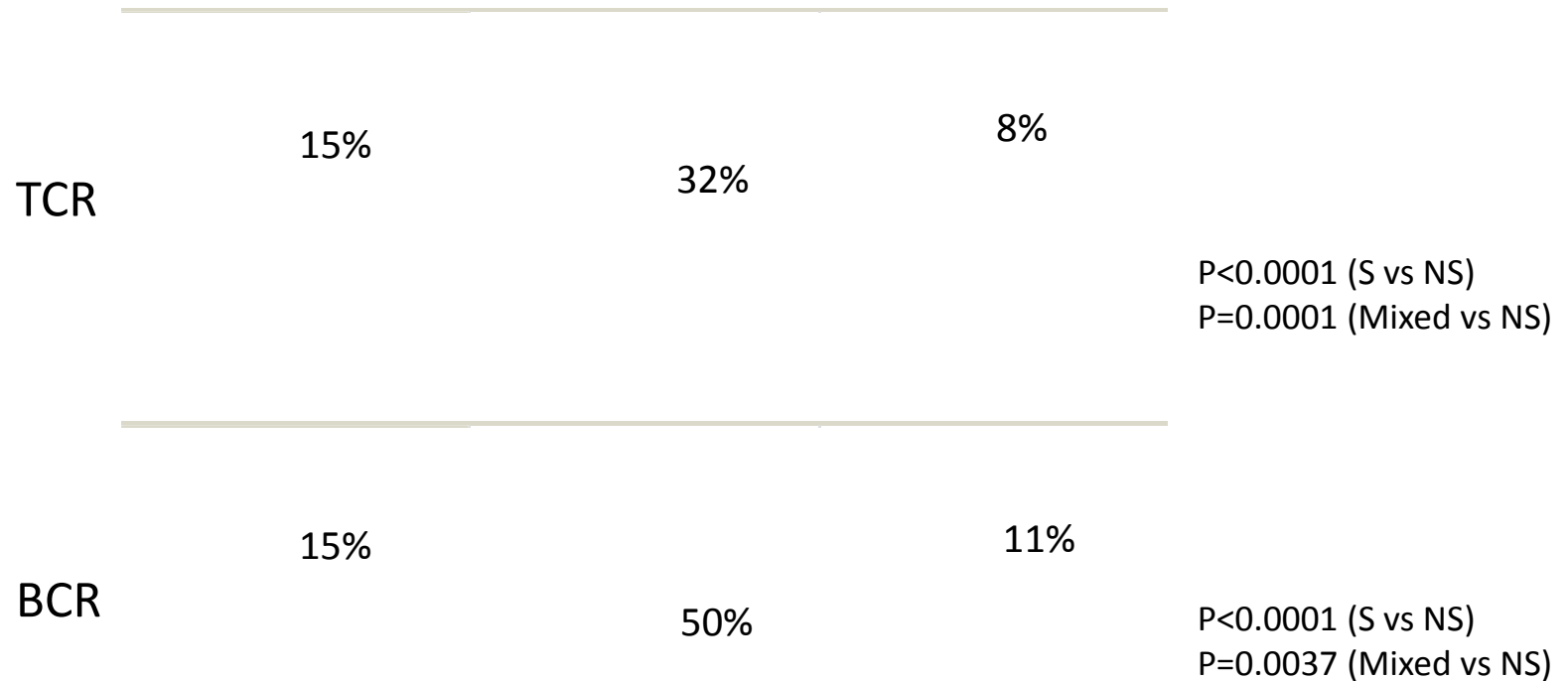
Histopathology

-  Seminoma
-  Non-Seminoma
-  Mixed (S+NS)

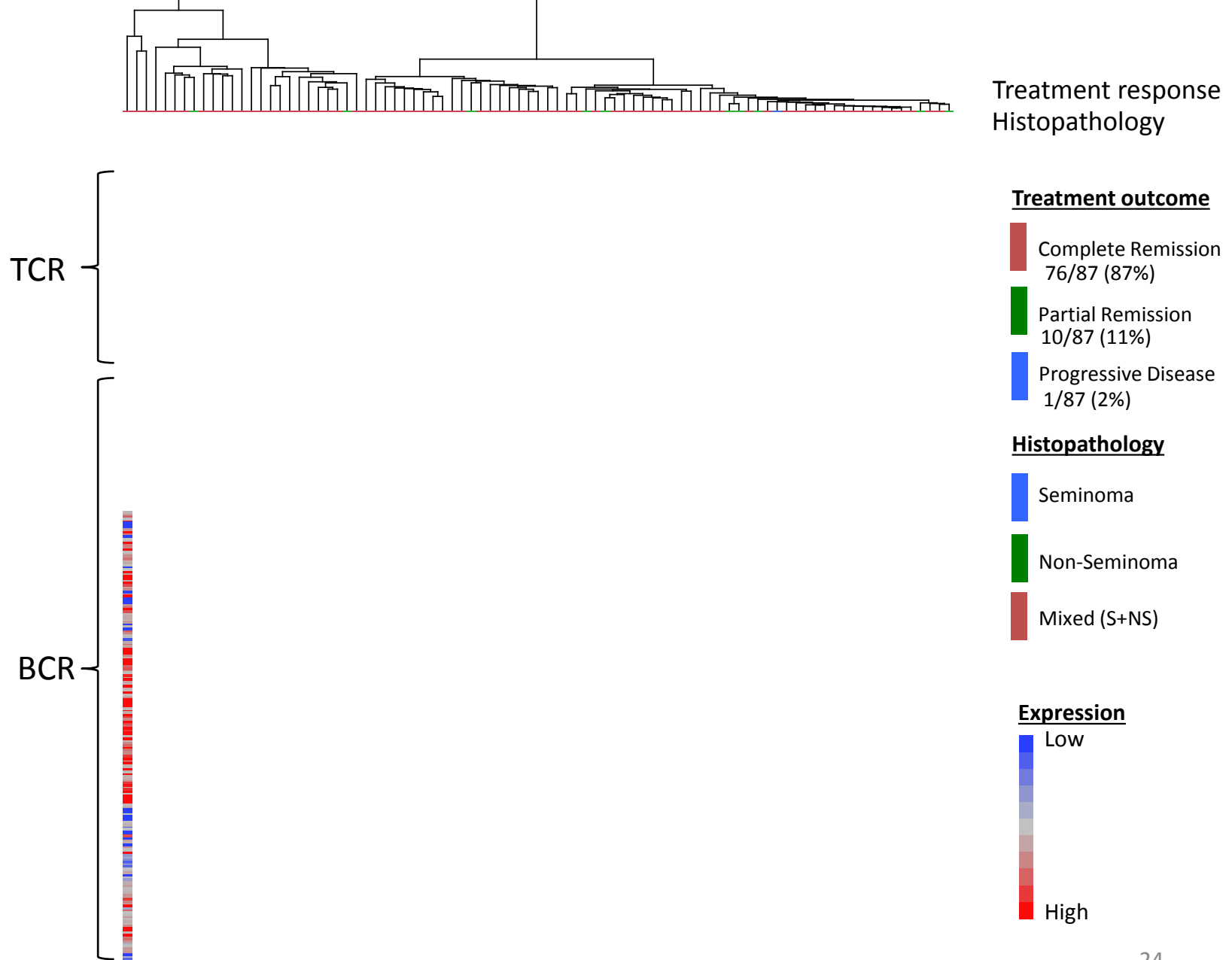
Expression

-  Low
-  High

TCR/BCR expression in TCGA-TGCT is associated with histopathological subtypes



TCR/BCR expression in TGCT and correlation with outcomes (n=87)



TCR expression in TCGA-TGCT is correlated with treatment outcomes

treatment_outcome_first_course

TCR

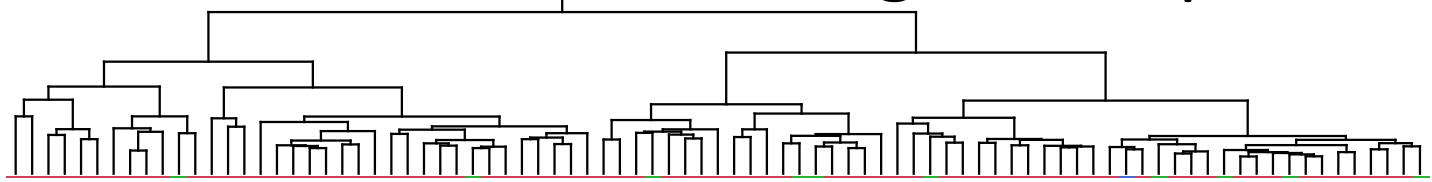
P=0.0113

treatment_outcome_first_course

BCR

P>0.05

TCR/BCR and immune "metagene" expression



Treatment response

Histopathology

TCR

BCR

List 1

List 2

Treatment outcome

Complete Remission
76/87 (87%)

Partial Remission
10/87 (11%)

Progressive Disease
1/87 (2%)

Histopathology

Seminoma

Non-Seminoma

Mixed (S+NS)

Expression

Low

High



Summary

- The presence and density of TILs can be estimated by analyzing the TCR/BCR gene expression using RNA-seq data;
- TCR/BCR expression profiles are associated with molecular phenotypes and treatment outcomes.

Future Directions

- To extend the analysis to TCGA pan-can project, get a comprehensive picture of immune signatures in major types of human cancers;
- To correlate the immune signatures with mutational signatures for more insights;

Acknowledgements

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Baylor
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The Cancer Genome Atlas

Linghua Wang, 5/12/2015



*Understanding genomics
to improve cancer care*