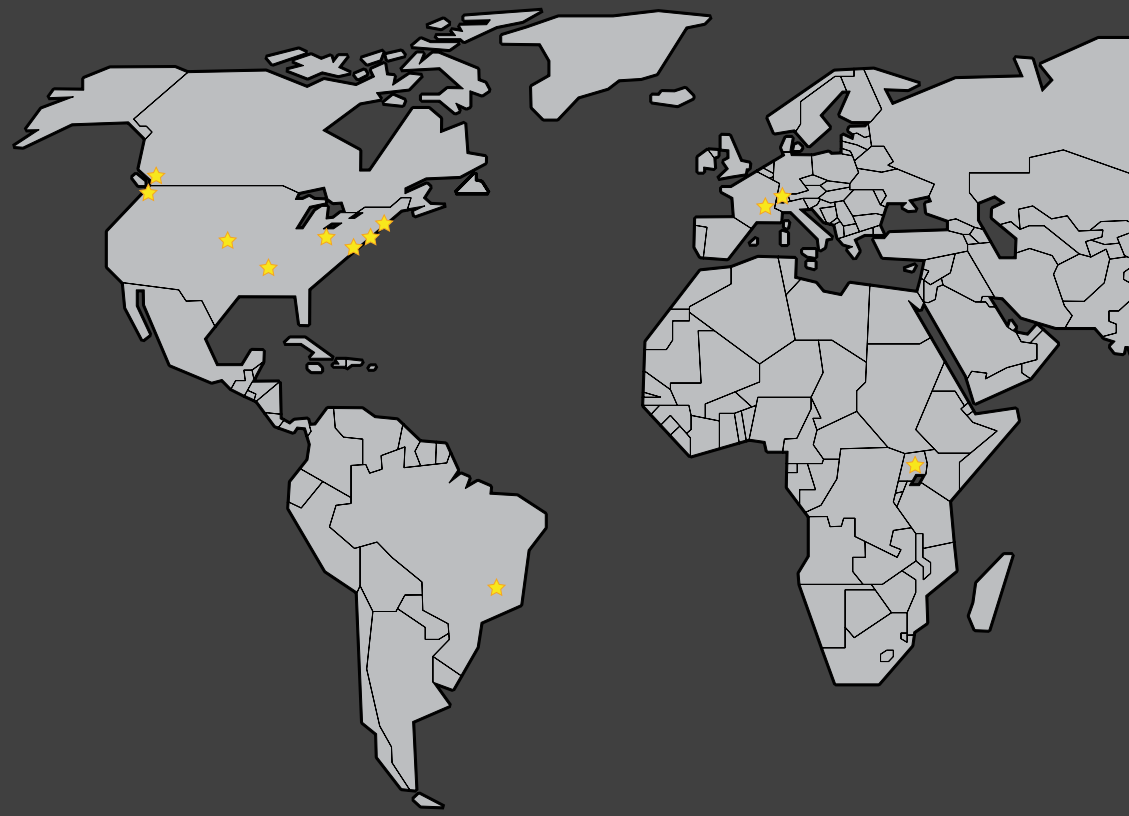
Burkitt Lymphoma Genome Sequencing Project:

Integrative Genomic and Transcriptomic Characterization of Burkitt Lymphoma



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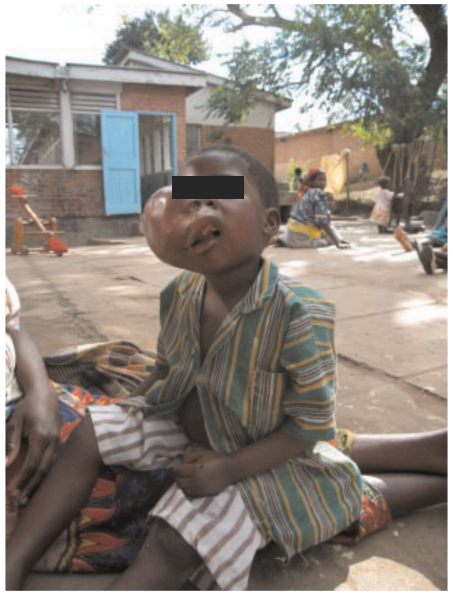
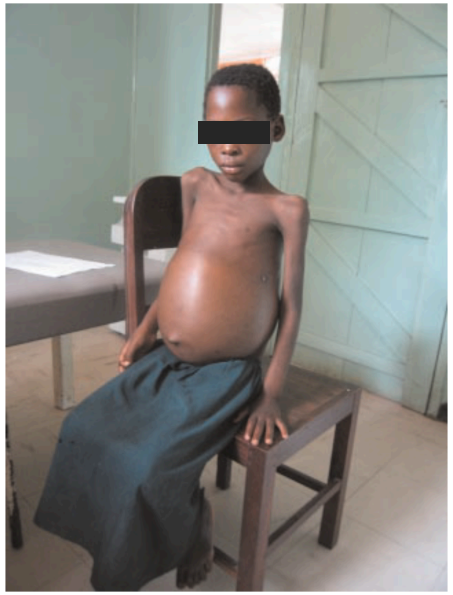
Burkitt lymphoma (BL) is an aggressive B-cell non-Hodgkin lymphoma



IG-*MYC* translocation is a genetic hallmark

Three clinical variants:

1) Sporadic BL: North America, Europe
2) Endemic BL: Africa, South America (malaria-endemic)
3) Immunodeficiency-related BL: global, mostly HIV+



Rare in sporadic, most common in children located in malaria-endemic regions such as equatorial Africa

Figure source: Ribeiro & Sandlund. *Pediatr Blood Cancer*. 2008;50(6):1125-6.

Current challenges with treating Burkitt lymphoma

Endemic BL

- Late stage at presentation
- Poor response to therapy
- Treatment-related toxicity

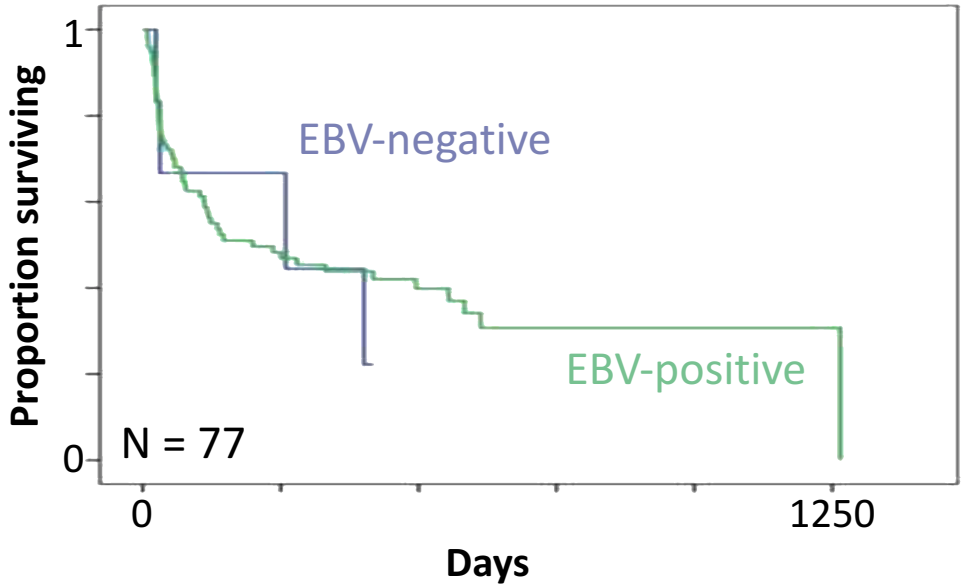


Figure source: Buckle *et al. Int J Cancer*. 2016;139(6):1231-40.

Sporadic BL

- Therapy is less effective in adult and elderly patients

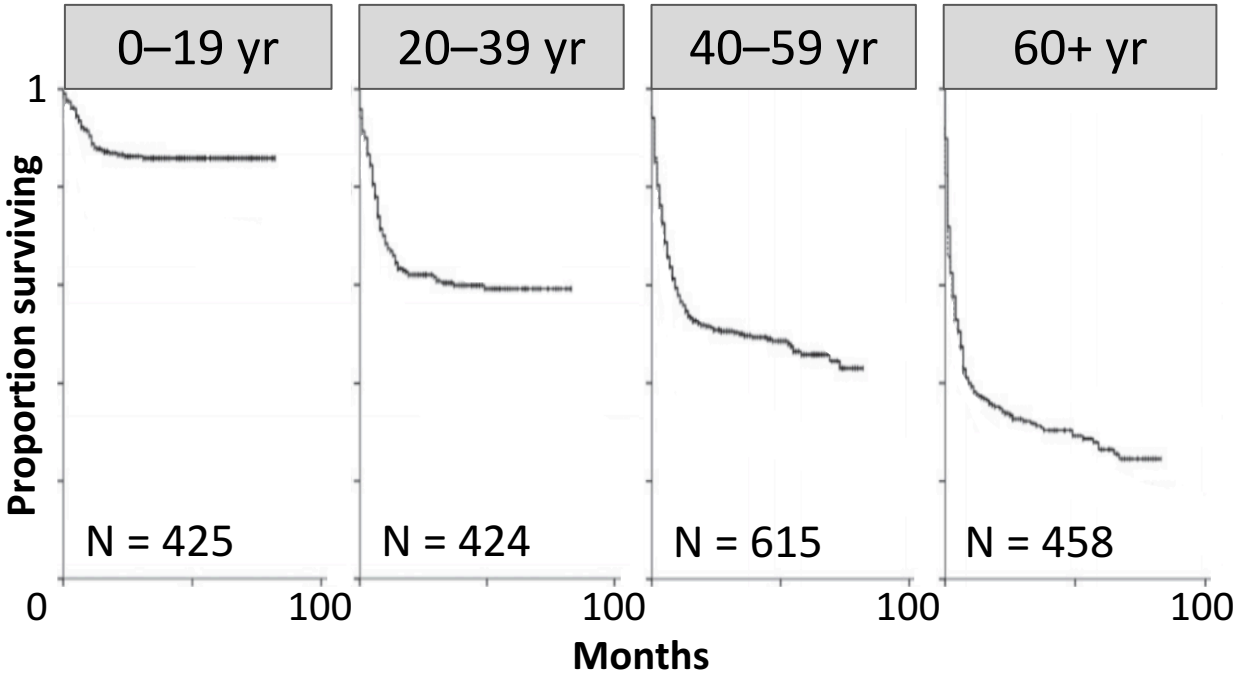


Figure source: Costa *et al. Blood*. 2013;121(24):4861-6.

Building a tremendous genomic resource for BL research

Variable	BLGSP (N = 95)	ICGC (N = 17)	Total (N = 112)
Sex			
Male	65	16	81
Female	30	1	31
Age Group			
Pediatric (0–20 yr)	92	17	109
Adult (21+ yr)	3	0	3
Clinical Variant			
Endemic	71	0	71
Sporadic	20	17	37
HIV-positive	4	0	4

Whole genome sequencing

- 80X tumors (ICGC at 40X)
- 40X matched normals

Ribo-depleted RNA sequencing

- 200 million reads per library

microRNA sequencing

Clinical metadata

References: Kretzmer *et al*. *Nat Genet*. 2015;47(11):1316-25. / Hezaveh *et al*. *Haematologica*. 2016;101(11):1380-9.

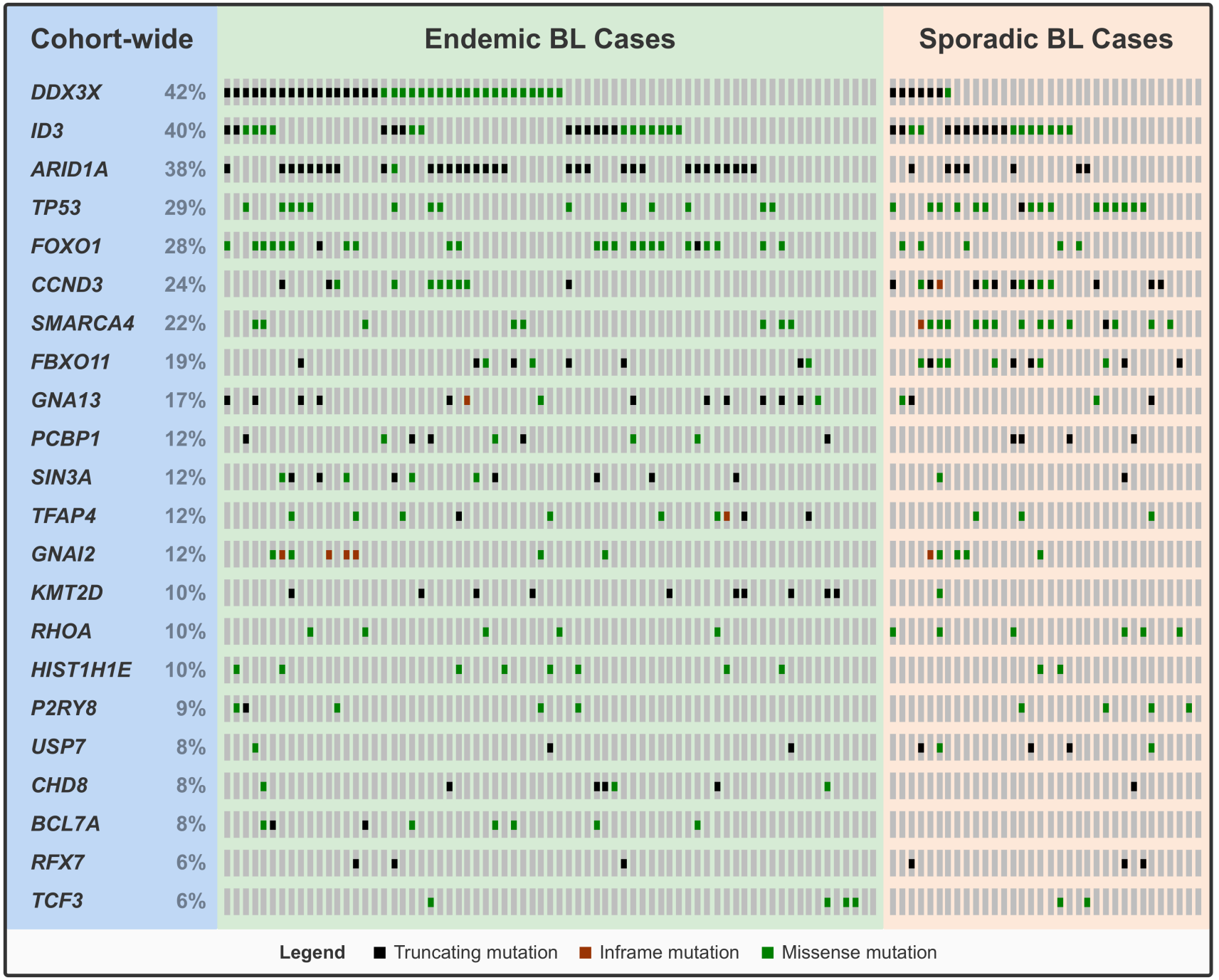
Refining the mutational landscape in BL

Novel BL genes:

SIN3A, CHD8, USP7, RFX7, HIST1H1E

Subtype-specific mutations:

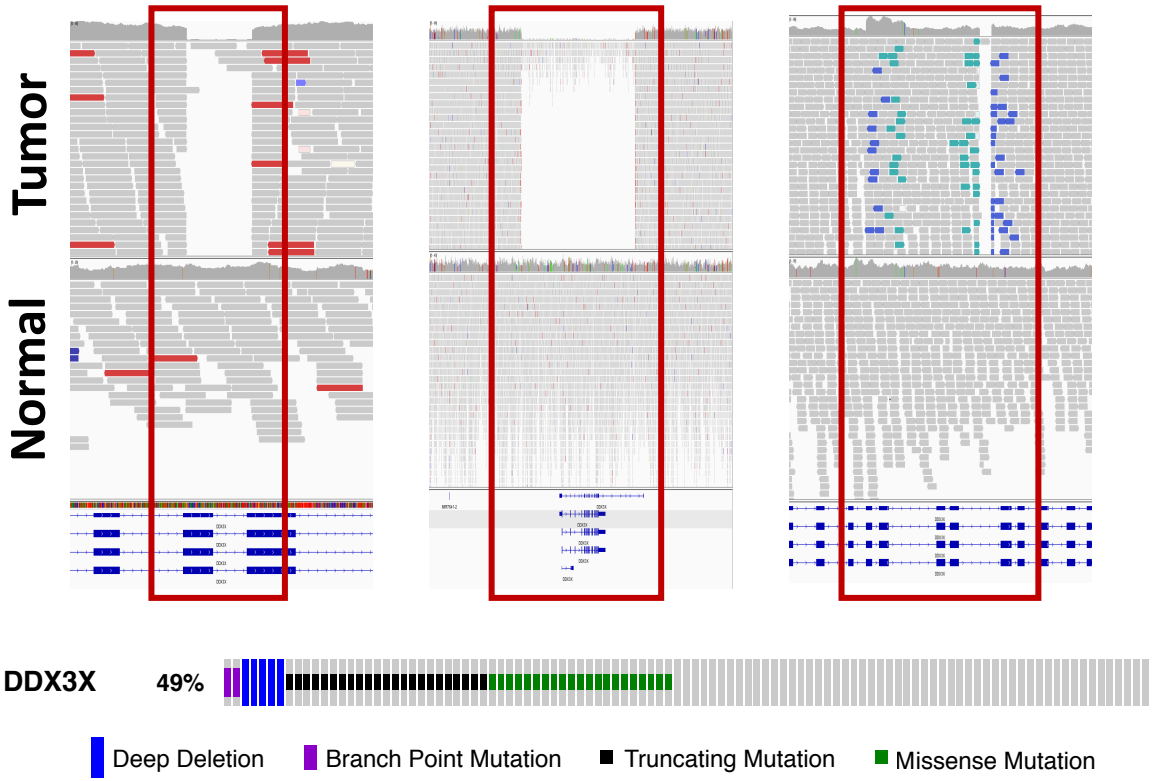
More differences based on EBV status than clinical variant



Novel structural and non-coding mutations in *DDX3X*

Deletions and inversions (N = 5)

Predicted to disrupt open reading frame and truncate protein



Branch point mutations (N = 2)

Aberrant transcript splicing observed in RNA-seq data

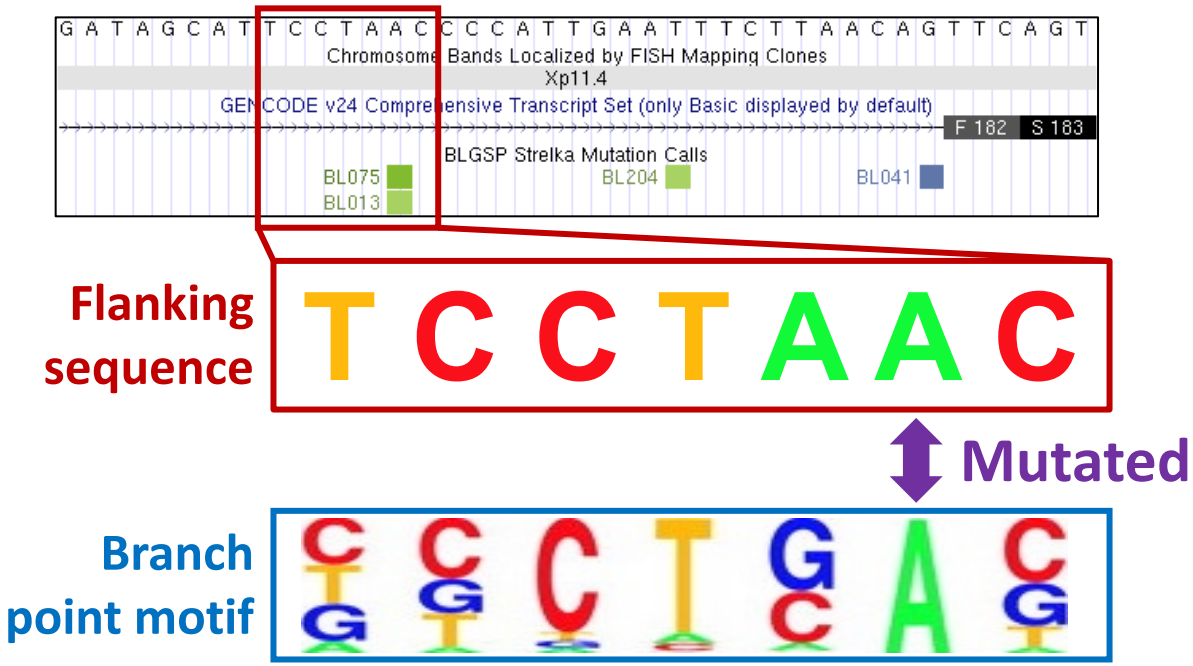
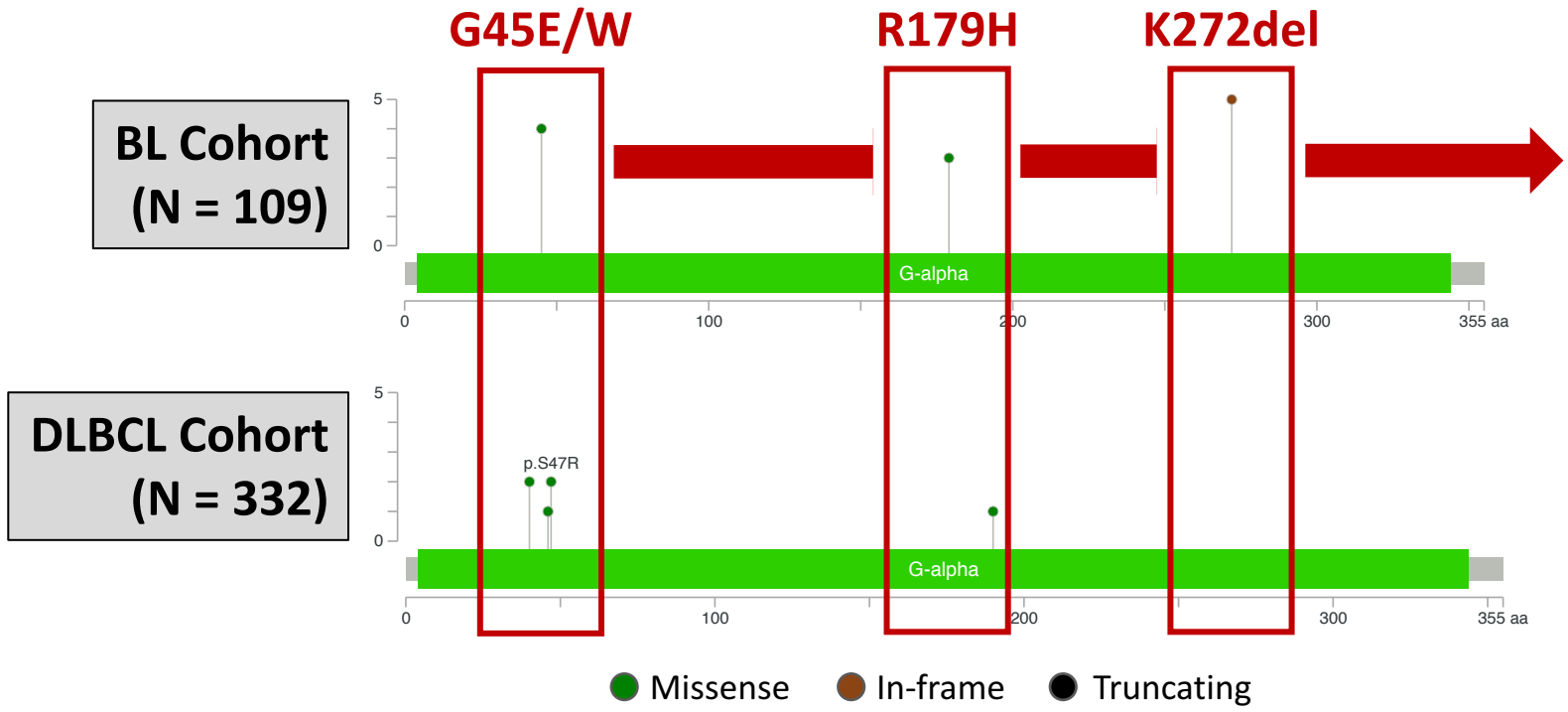


Figure source: Lim and Burge. *Proc Natl Acad Sci U S A.* 2001;98(20):11193-8.

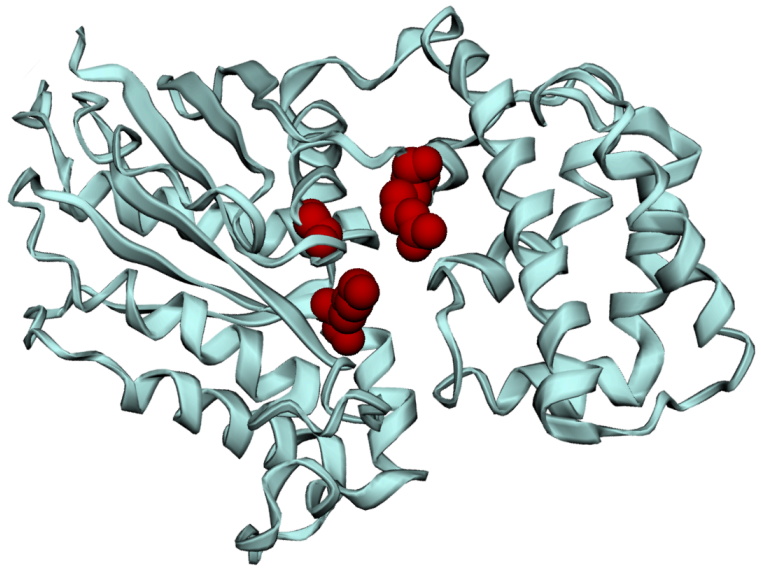
Potentially activating mutation hotspots in *GNAI2*

Mutated residues cluster in protein structure around GDP binding site

R179H is orthologous to gain-of-function R201H mutations in *GNAS*



Mutated residues in $G\alpha_{i2}$ protein



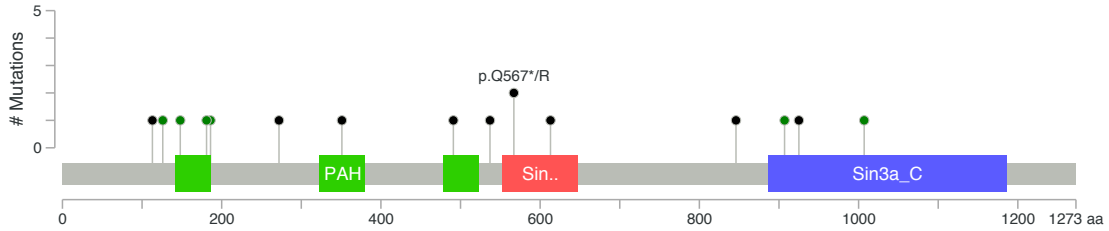
References: Kretzmer *et al. Nat Genet*. 2015;47(11):1316-25. / Landis *et al. Nature*. 1989;340(6236):692-6.

Novel genes carry out functions relevant to BL biology

Mutations in *SIN3A* (N = 16)

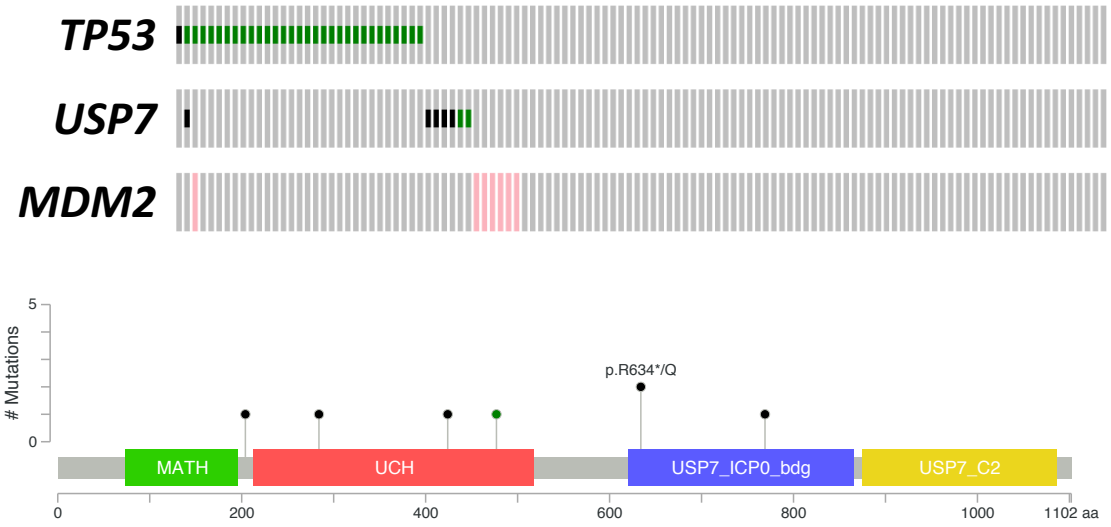
Known antagonist of Myc activity

Induces histone acetylation of Myc responsive genes



Mutations in *USP7* (N = 7)

Encodes a deubiquitinase that counteracts Mdm2-mediated degradation of p53



Missense In-frame Truncating Copy number gain

Non-coding mutations form clusters in the genome

One cluster overlaps a validated *PAX5* enhancer

Similar mutations found in:

- Chronic lymphocytic leukemia (CLL)
- Other B-cell lymphomas

PAX5 plays an important role in B-cell differentiation

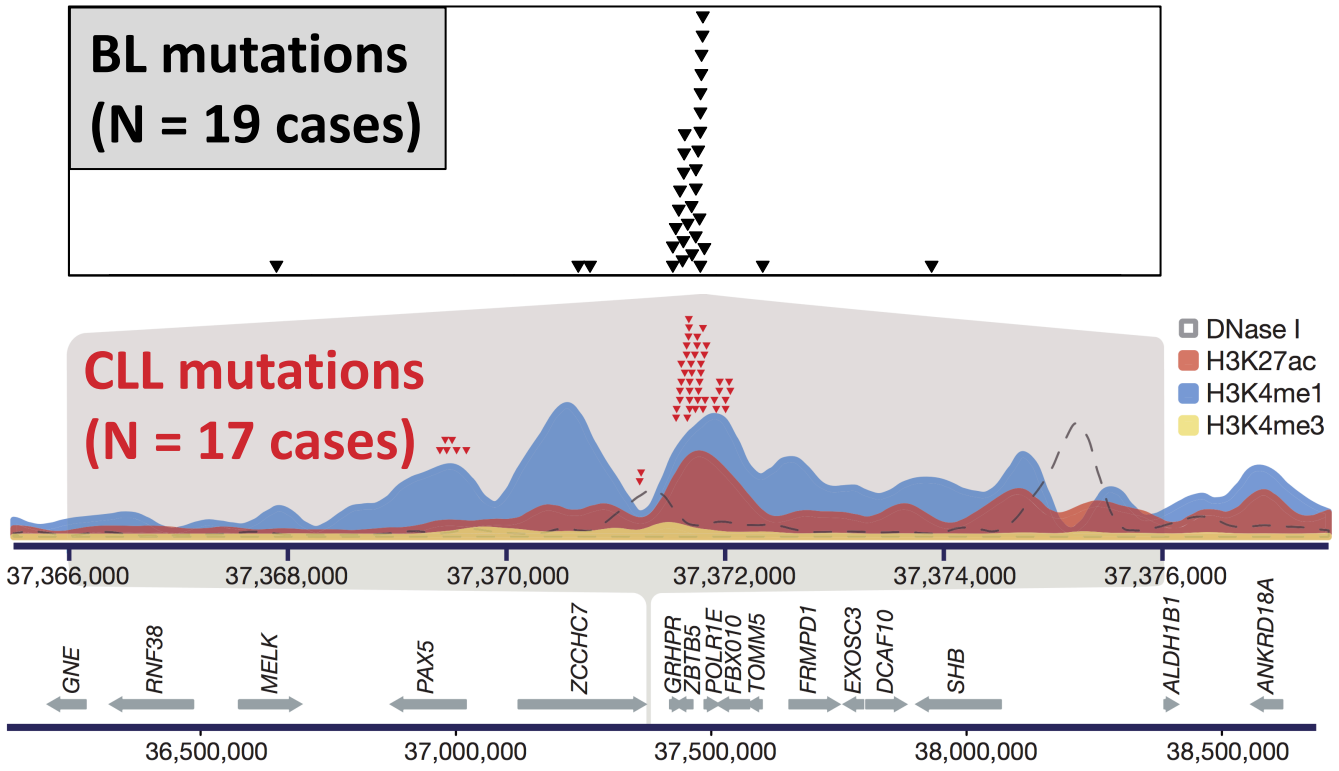
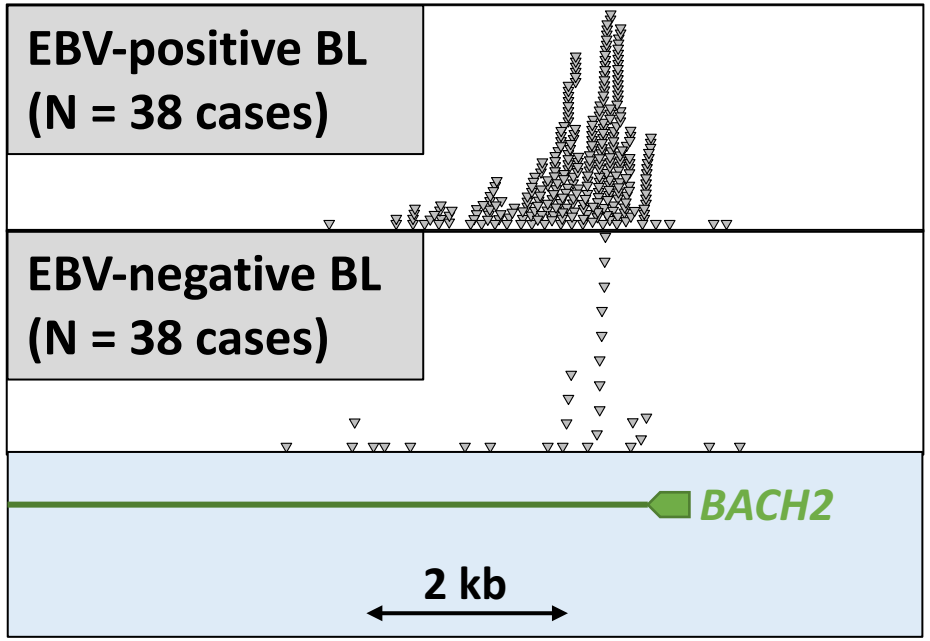
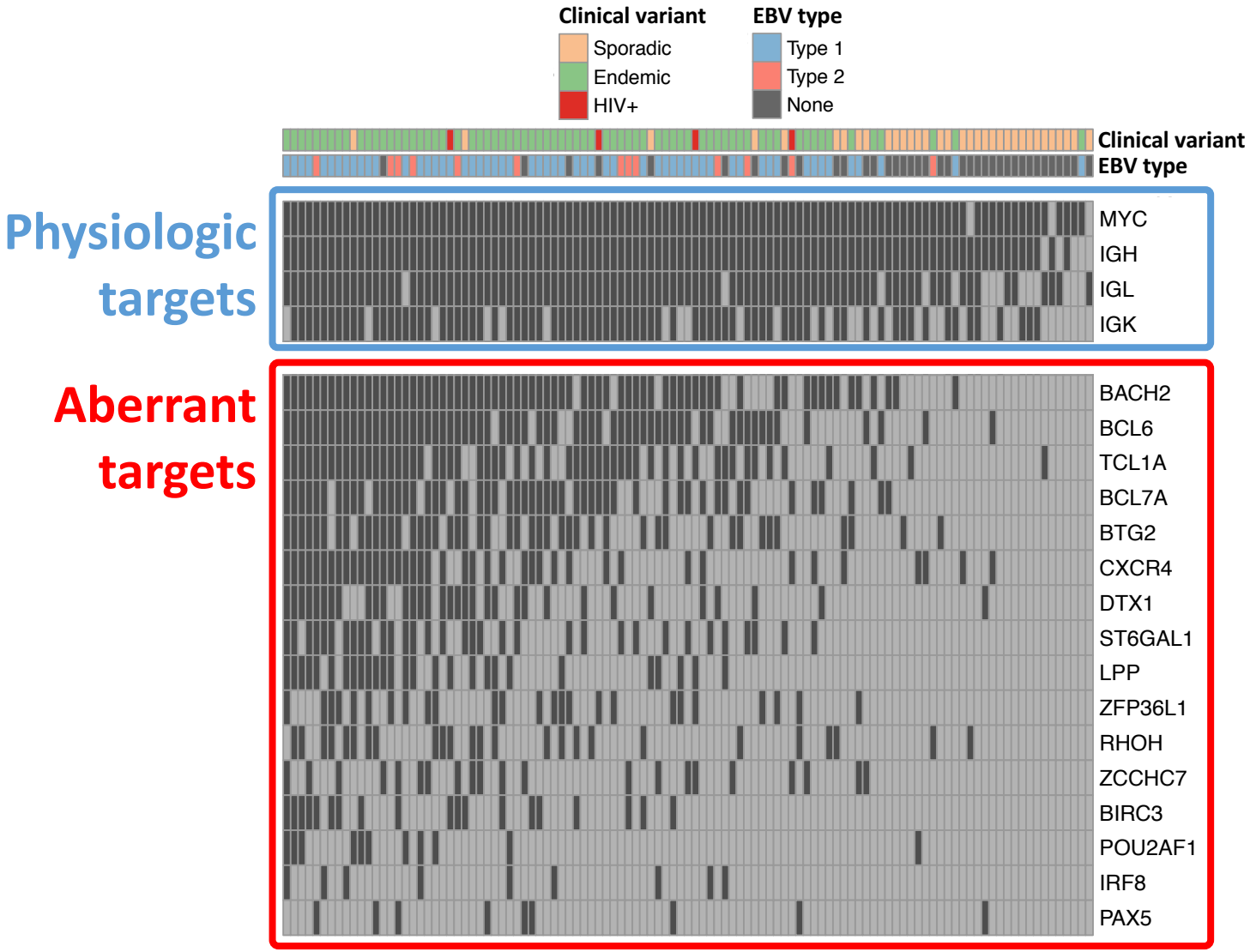


Figure source: Puente *et al. Nature*. 2015;526(7574):519-24.

Aberrant somatic hypermutation is a feature of endemic or EBV-positive BL

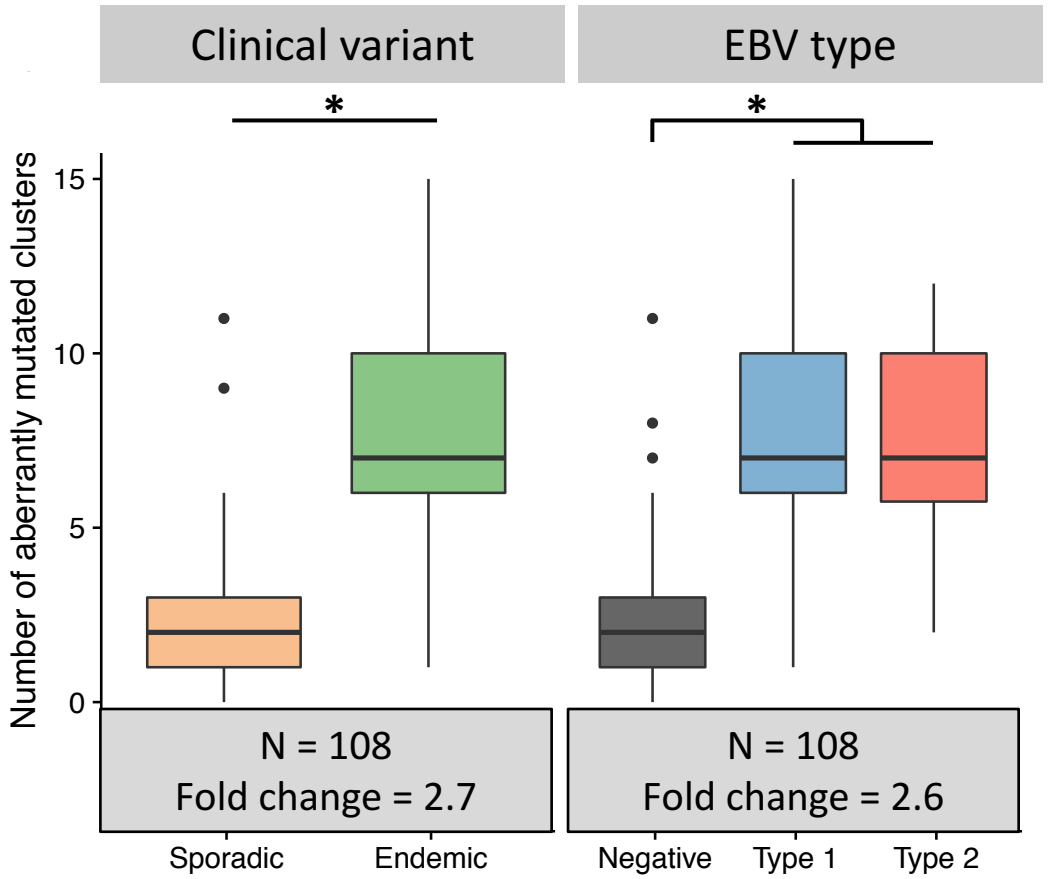
Many non-coding mutations can be linked to somatic hypermutation



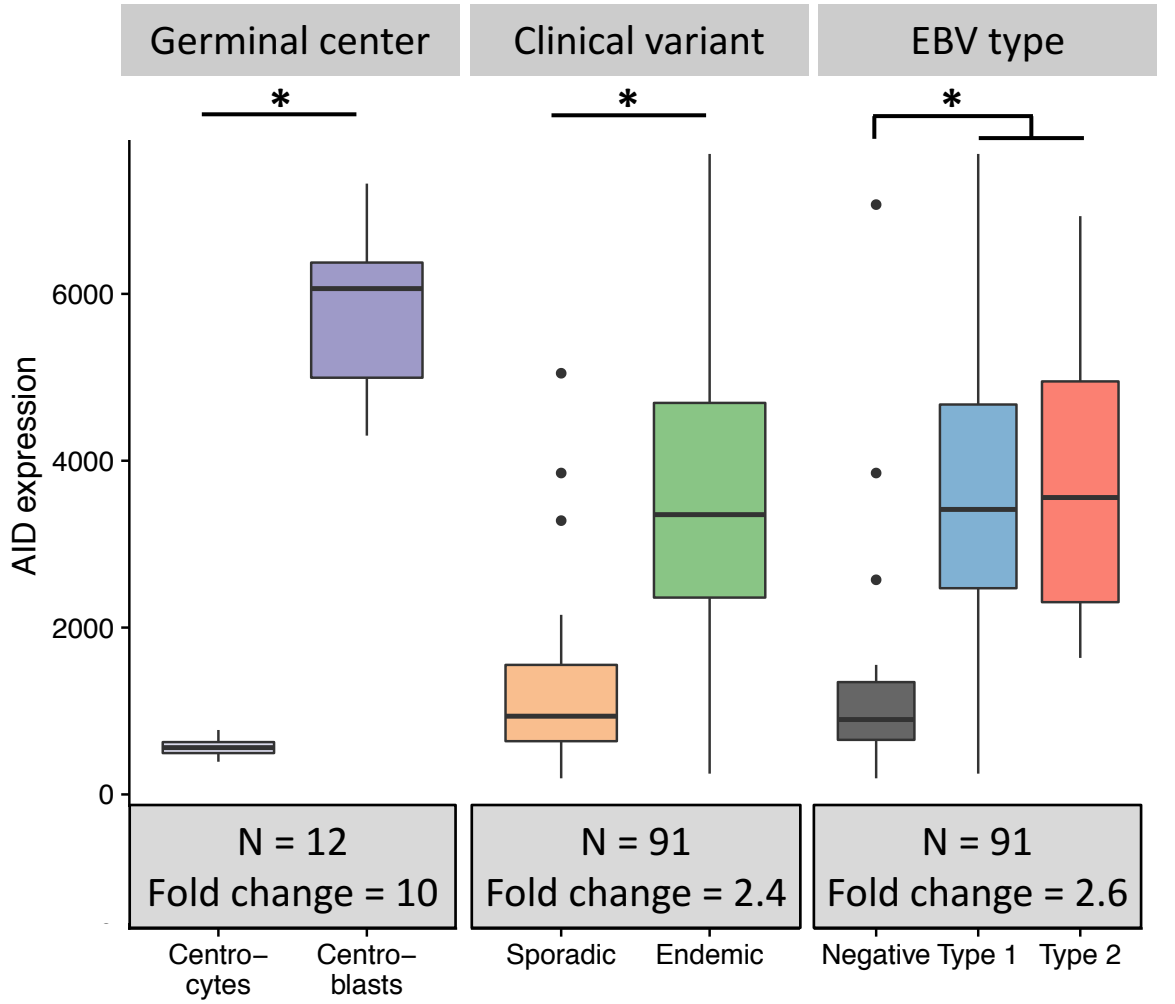


AID activity is significantly higher in EBV-positive tumors

Number of mutated clusters



AID mRNA expression



Results summary

Landscape of coding and non-coding mutations was refined for both established and novel genes associated with BL

Greater differences exist based on EBV status than geographic origin:

- Number of significantly differentially mutated genes
- Aberrant somatic hypermutation and AID expression

Possible therapeutic opportunities warrant further investigation:

- Potential activating hotspot mutations in *GNAI2*
- Mdm2 inhibitors for *USP7*-mutant, *TP53*-wildtype tumors

Acknowledgements

British Columbia Cancer Agency
Vancouver, Canada
Andy Mungall
Karen Novik
Marco A. Marra
Ryan D. Morin
Yussanne Ma

Foundation for Burkitt Lymphoma Research
Geneva, Switzerland
Jean Paul Martin
John D. Irvin
Marie-Reine Martin

George Washington University
Washington, DC
Fabio Leal
Jeffrey Bethony

Infectious Disease Research Institute
Seattle, WA
Corey Casper

Leidos Biomedical Research
Frederick, MD
Maureen Dyer

Massachusetts General Hospital
Boston, MA
Jeremy S. Abramson
Nancy Lee Harris

Memorial Sloan Kettering Cancer Center
New York, NY
Ariela Noy

National Cancer Institute
Bethesda, MD
Daniela S. Gerhard
Elaine S. Jaffe
Louis M. Staudt
Nicholas B. Griner
Patee Gesuwan
Roland Schmitz
Sam M. Mbulaiteye
Tanja M. Davidsen
Thomas Gross
Wyndham Wilson
Yiwen He

Nationwide Children's Hospital
Columbus, OH
Hilary Allen
Jay Bowen
Julie M. Gastier-Foster

St. Jude Children's Hospital
Memphis, TN
Charles G. Mullighan
John Kim Choi
John T. Sandlund
Thomas Alexander

Uganda Cancer Institute
Kampala, Uganda
Abraham Omoding
Constance Namirembe
Jackson Orem

University of Nebraska Medical Center
Omaha, NE
Timothy C. Greiner

The patients and their families

Thank you for your attention

Any questions?