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Burkitt Lymphoma Genome Sequencing Project:

Introduction

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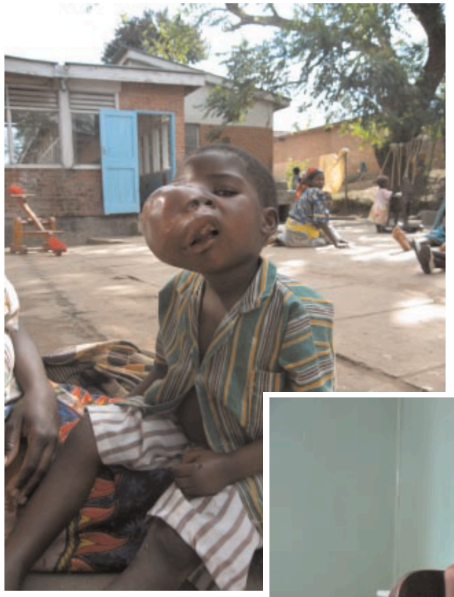
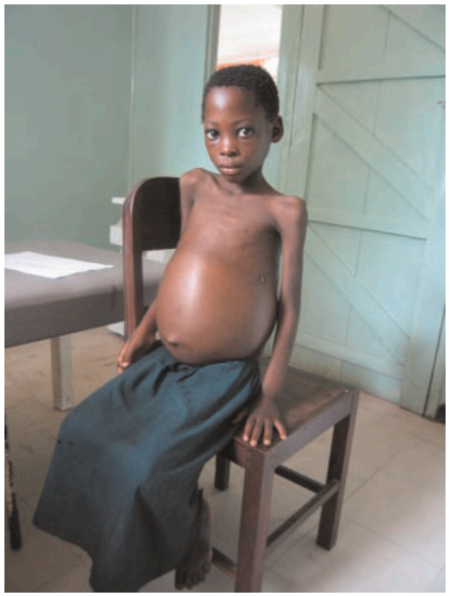
What is Burkitt lymphoma (BL)?





Aggressive B-cell non-Hodgkin lymphoma

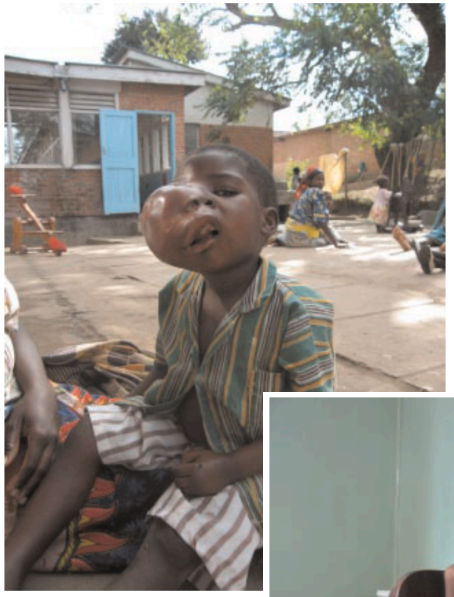
Most common in children located in malaria-endemic regions

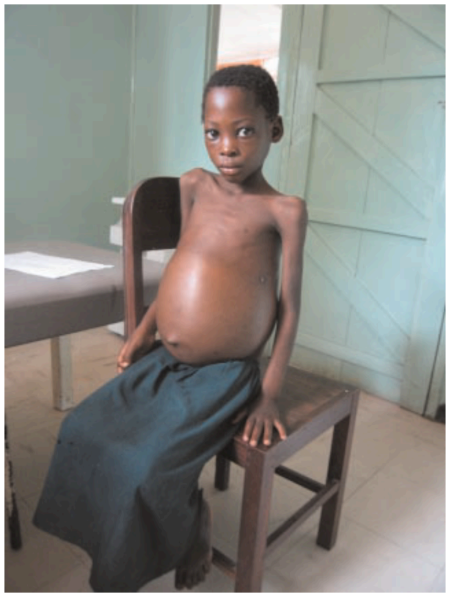
<u>Three clinical variants</u>:

1) Endemic BL
2) Sporadic BL
3) Immunodeficiency-related BL

Image source Ribeiro and Sandlund, 2008

Challenges in treating endemic BL





Late stage at presentation

Limitations in the ability to support intensive chemotherapeutic regimens

<u>More relevant to sporadic BL</u>:

- Less effective in adult and elderly patients
- Treatment-resistant disease

Image source Ribeiro and Sandlund, 2008

Mutational landscape in sporadic BL

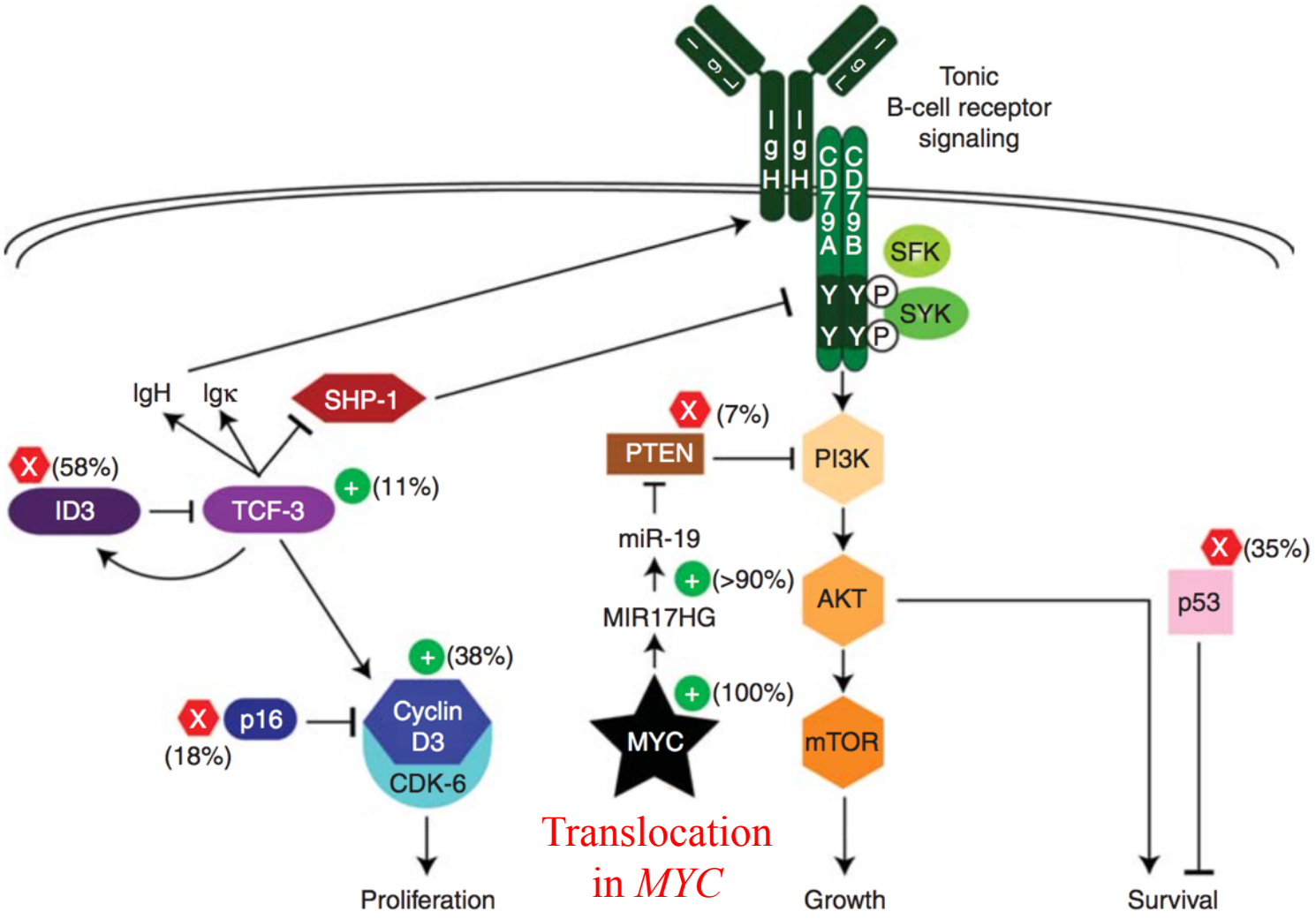


Image source Schmitz *et al.*, 2015

Recent genomic studies on endemic BL

In 2015: 20 samples with RNA-seq (Abate *et al.*)

In 2017: 28 samples with RNA-seq (Kaymaz *et al.*)

Limitations of these studies:

- Difficulty detecting true somatic variants
- Inability to compare gene expression with other RNA-seq dataset (due to batch effects)
- Limited sample sizes

Introducing the Burkitt Lymphoma Genome Sequencing Project (BLGSP)

An integrative molecular characterization of a large comprehensive BL cohort including an unprecedented representation of endemic cases

We aim to sequence 160 BL tumor-normal pairs

- 50% will be endemic (mostly paediatric)
- 38% will be sporadic (paediatric and adult)
- 12% will be from HIV+ patients

Multi-dimensional data

Whole genome sequencing (WGS)

- 80X for tumours and 40X for normals

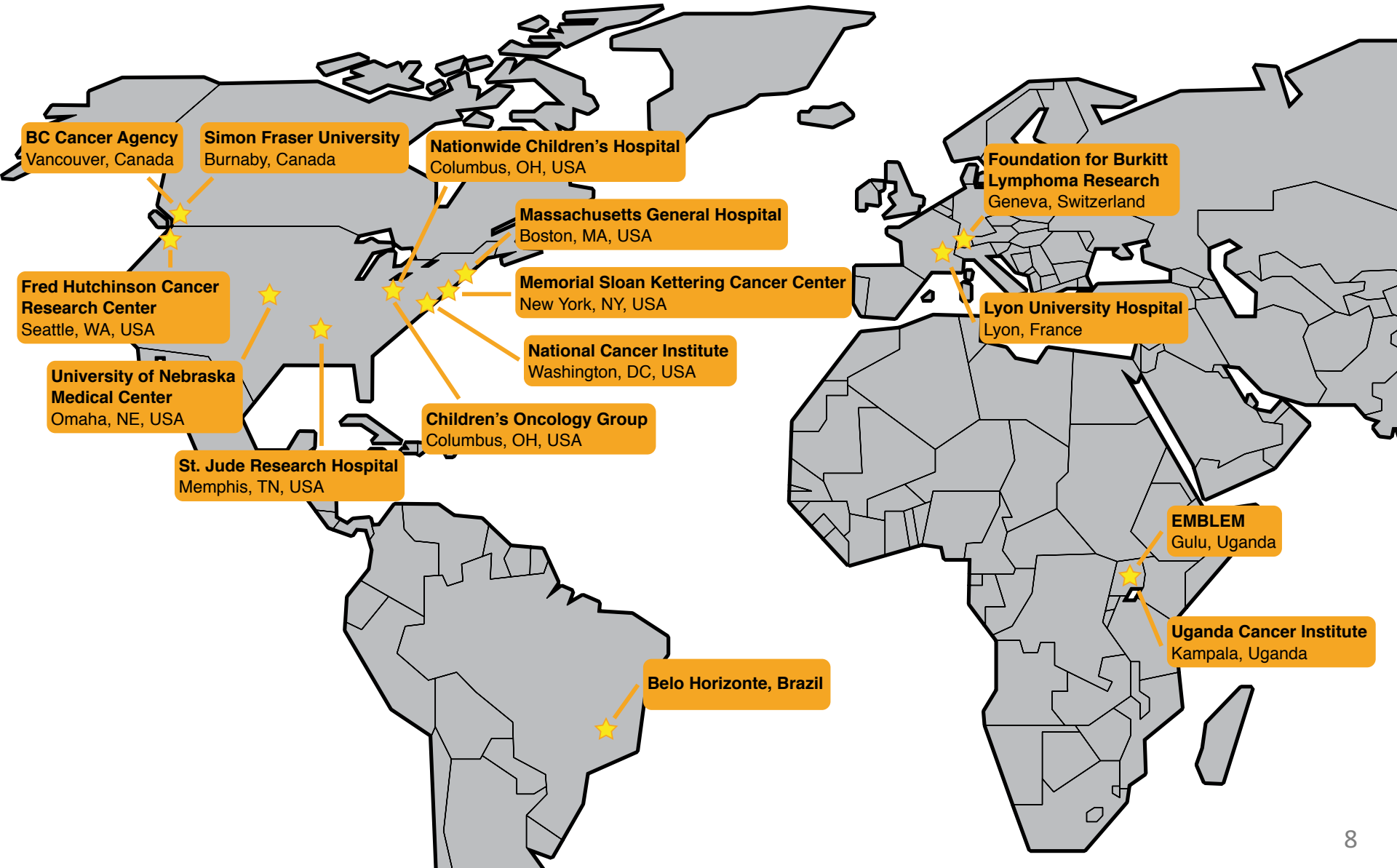
Ribo-depleted RNA sequencing (RNA-seq)

- On average, 200 million reads per sample

miRNA sequencing (miRNA-seq)

Patient outcome and other clinical metadata

BLGSP Consortium: Over a dozen institutions



BLGSP discovery cohort (so far)

Characteristic	Discovery (n = 109)	ICGC MALY * (n = 17)
Age		
Pediatric	101	17
Adult	4	0
Not submitted yet	4	0
Clinical Variant		
Endemic	77	0
Sporadic	17	17
HIV-associated	6	0
Unknown	5	0
Not submitted yet	4	0

* Some analyses are supplemented by 17 ICGC sporadic BLs

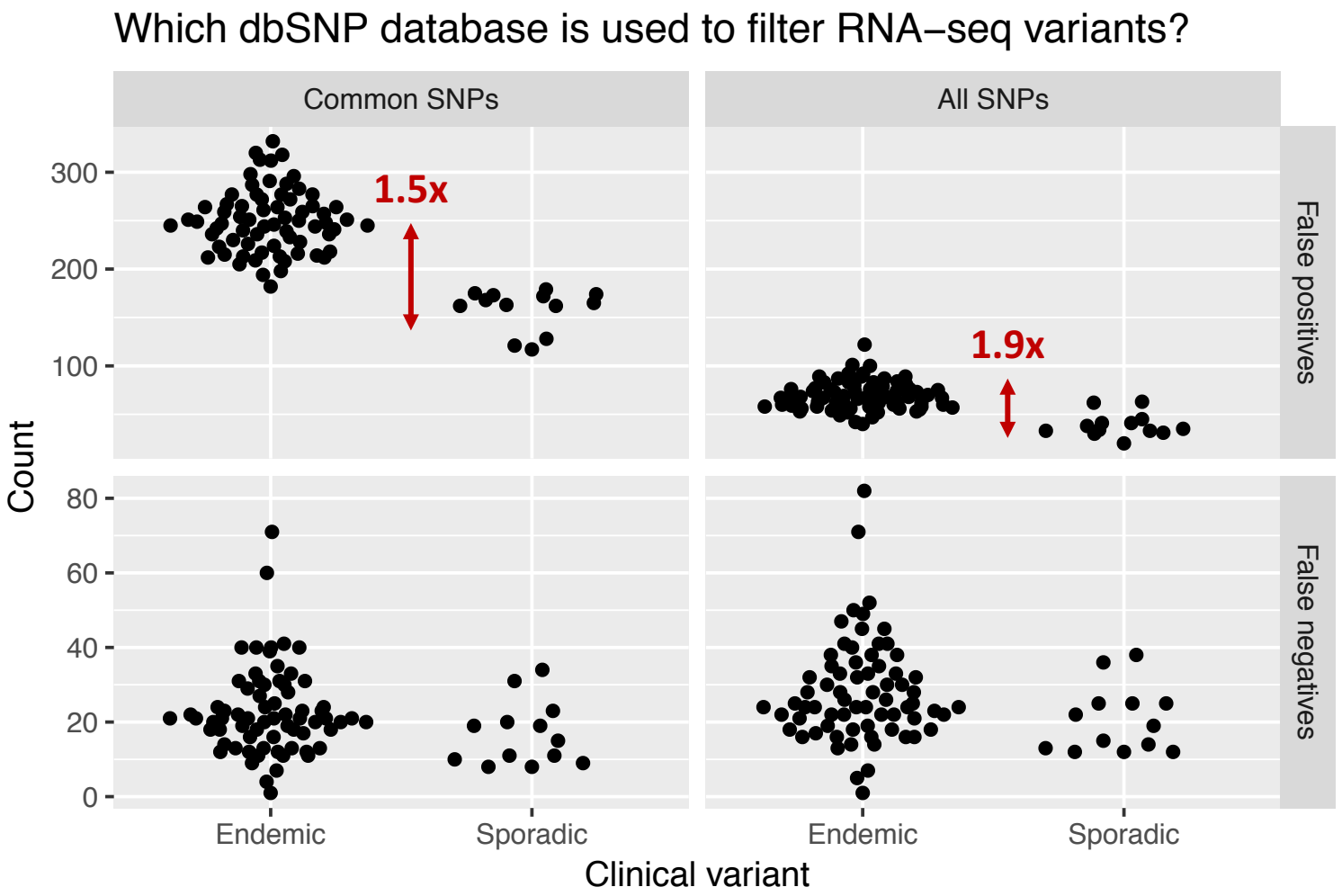
Importance of sequencing germline DNA, especially for African cases

Identifying somatic variants in RNA-seq data requires the removal of germline variation and RNA editing events

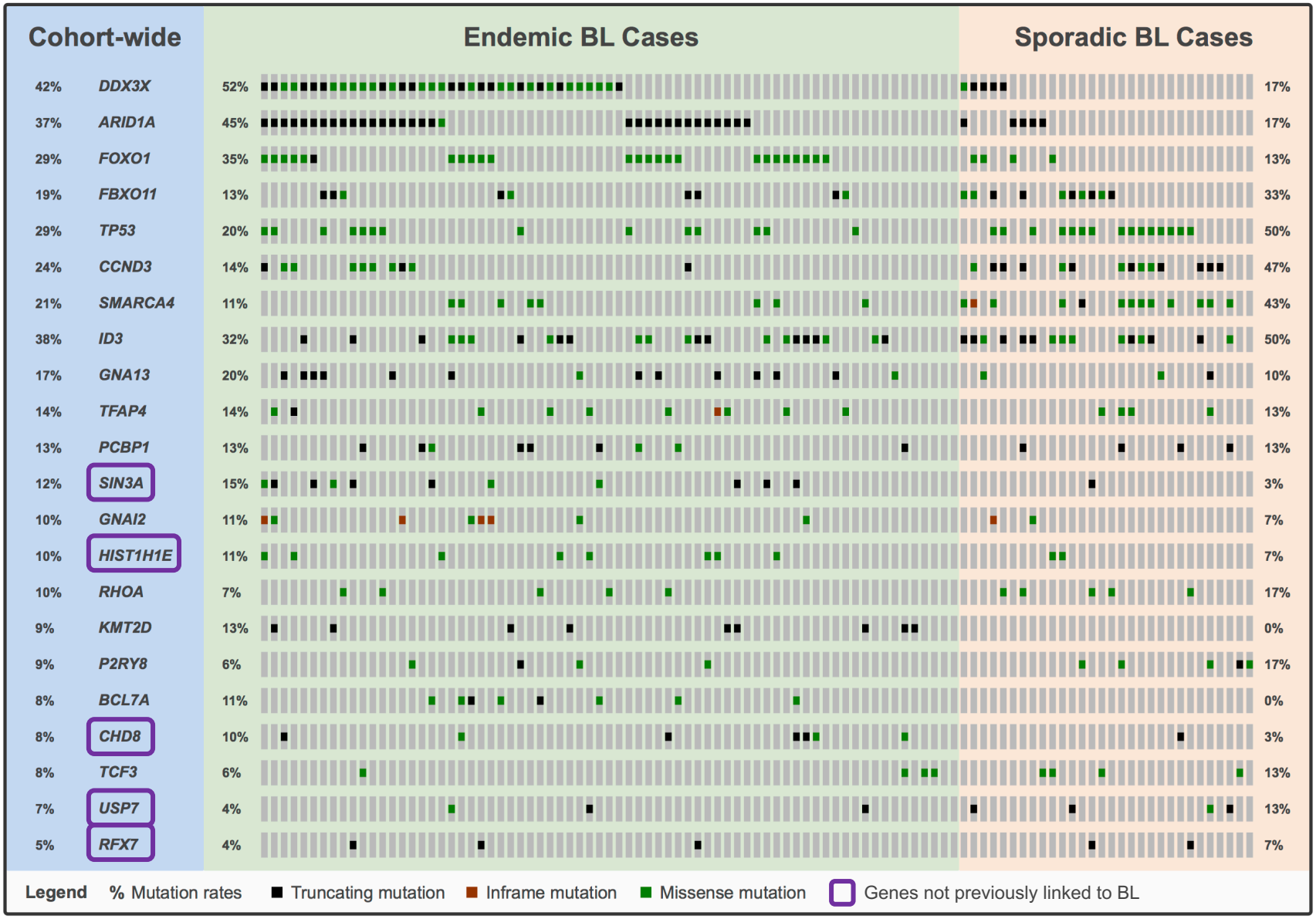
Removing germline variation is especially difficult with African cases:

- Current knowledge of germline variation (dbSNP) is biased towards non-African populations
- The African population harbours the highest genetic diversity in the world

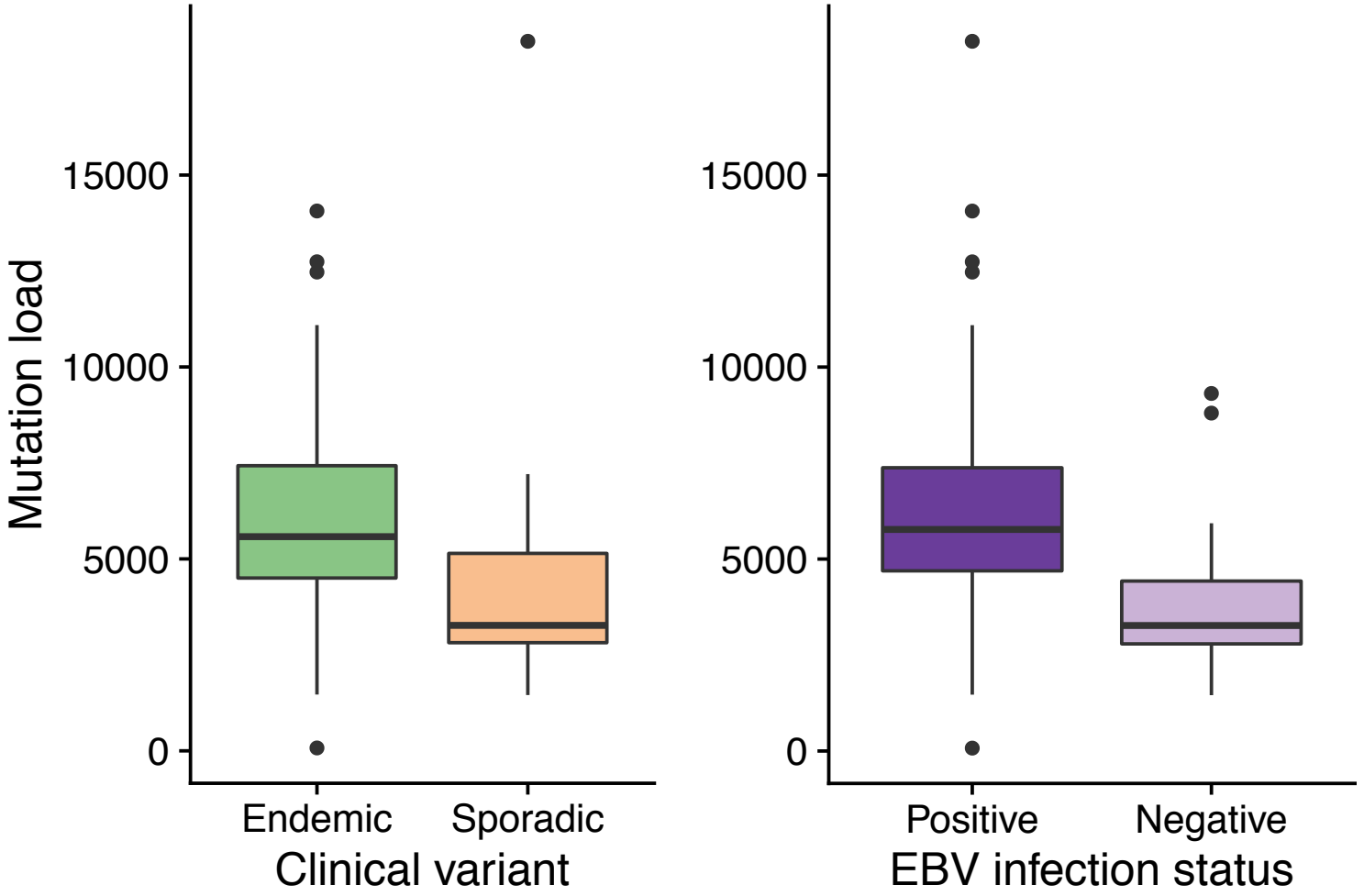
Case in point: Higher false positive rate for nonsynonymous mutations in endemic cases



Significantly mutated genes (SMGs) in BL



Endemic or EBV-positive cases have a higher mutation burden



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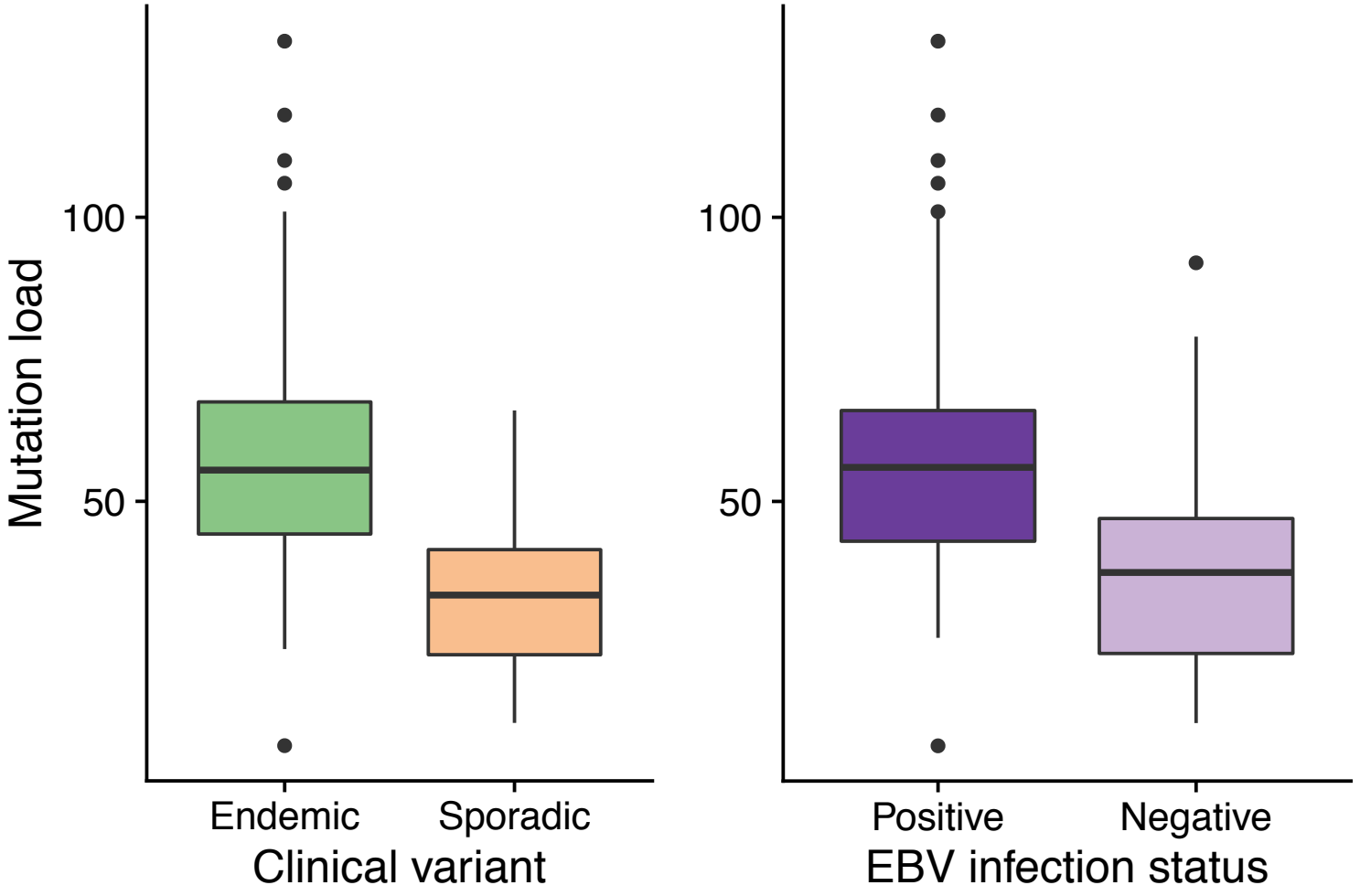
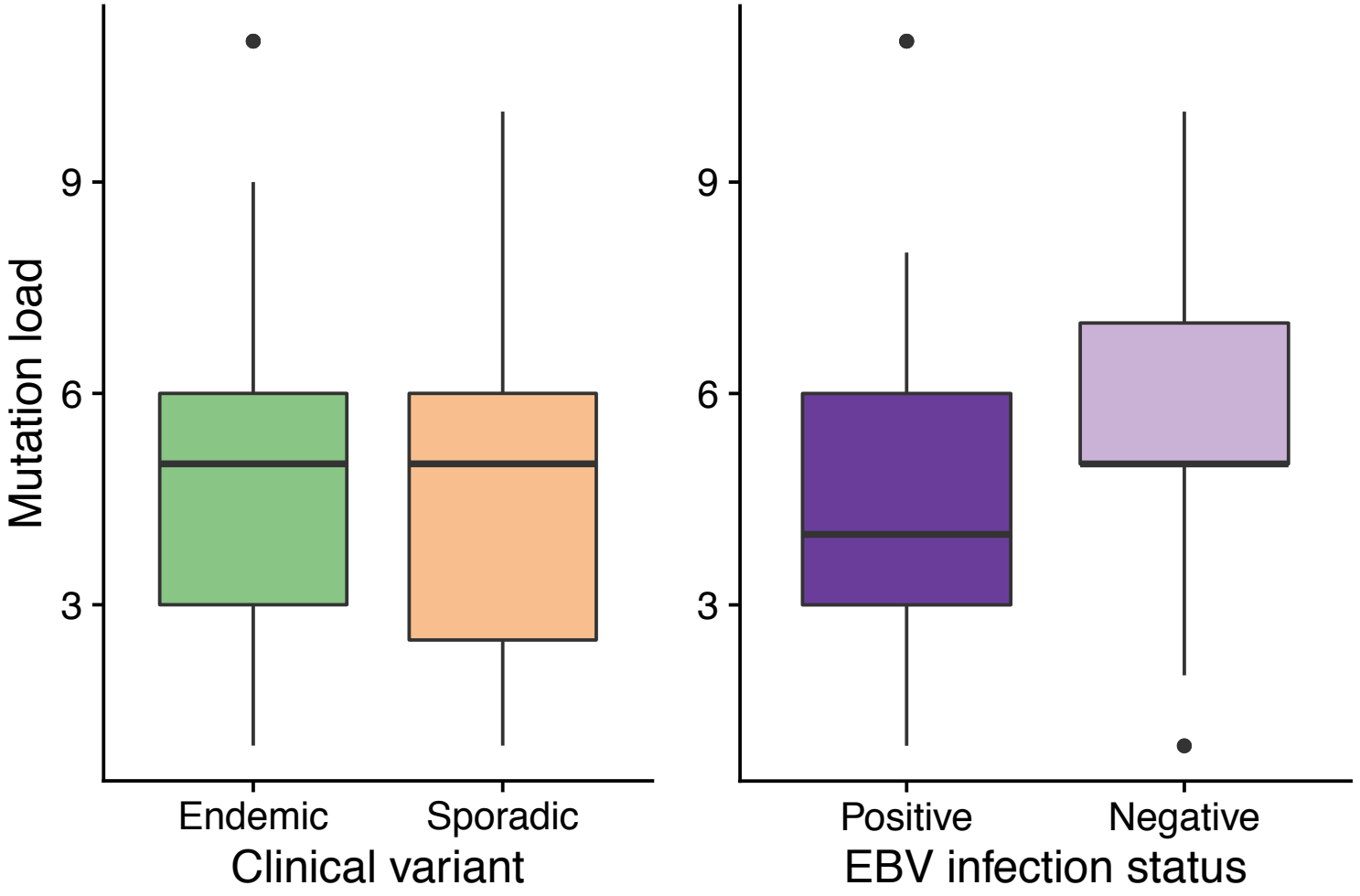
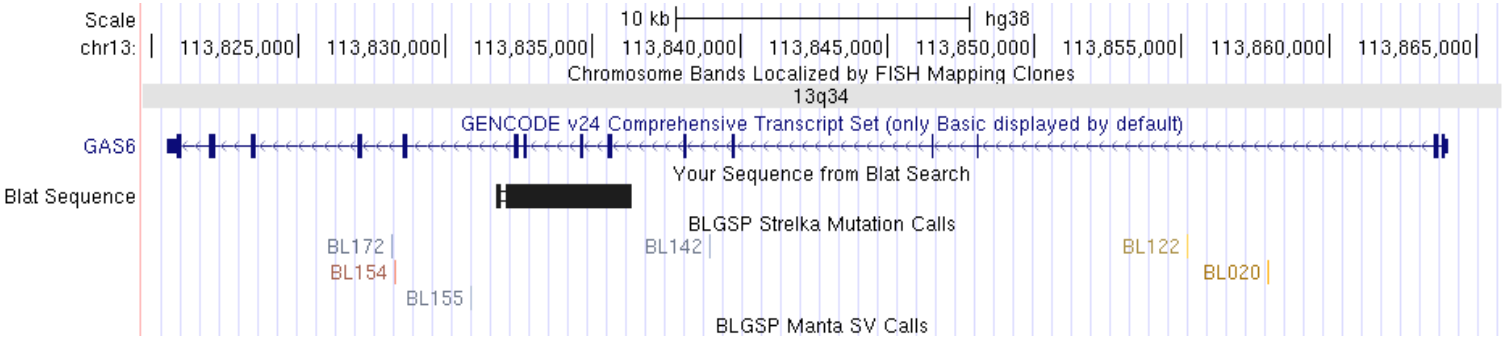


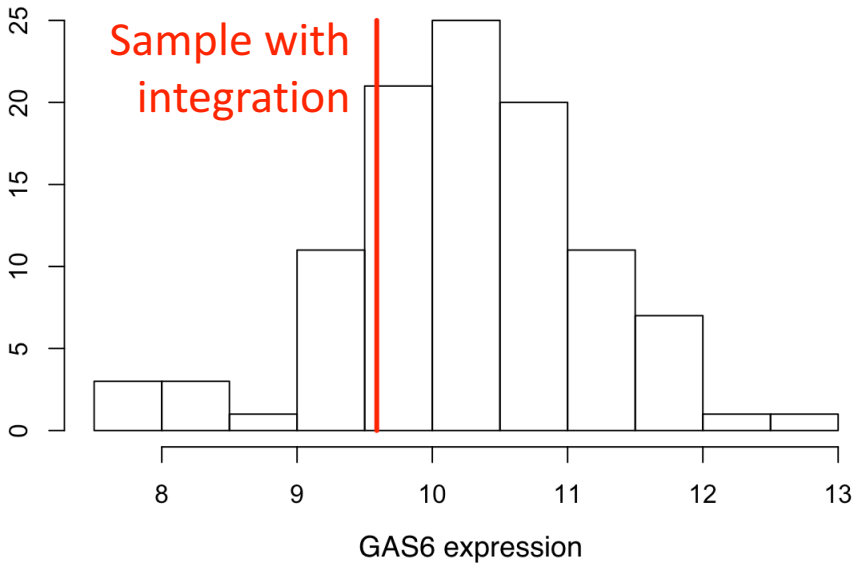
EBV-positive tumours harbour fewer nonsynonymous mutation in BL genes



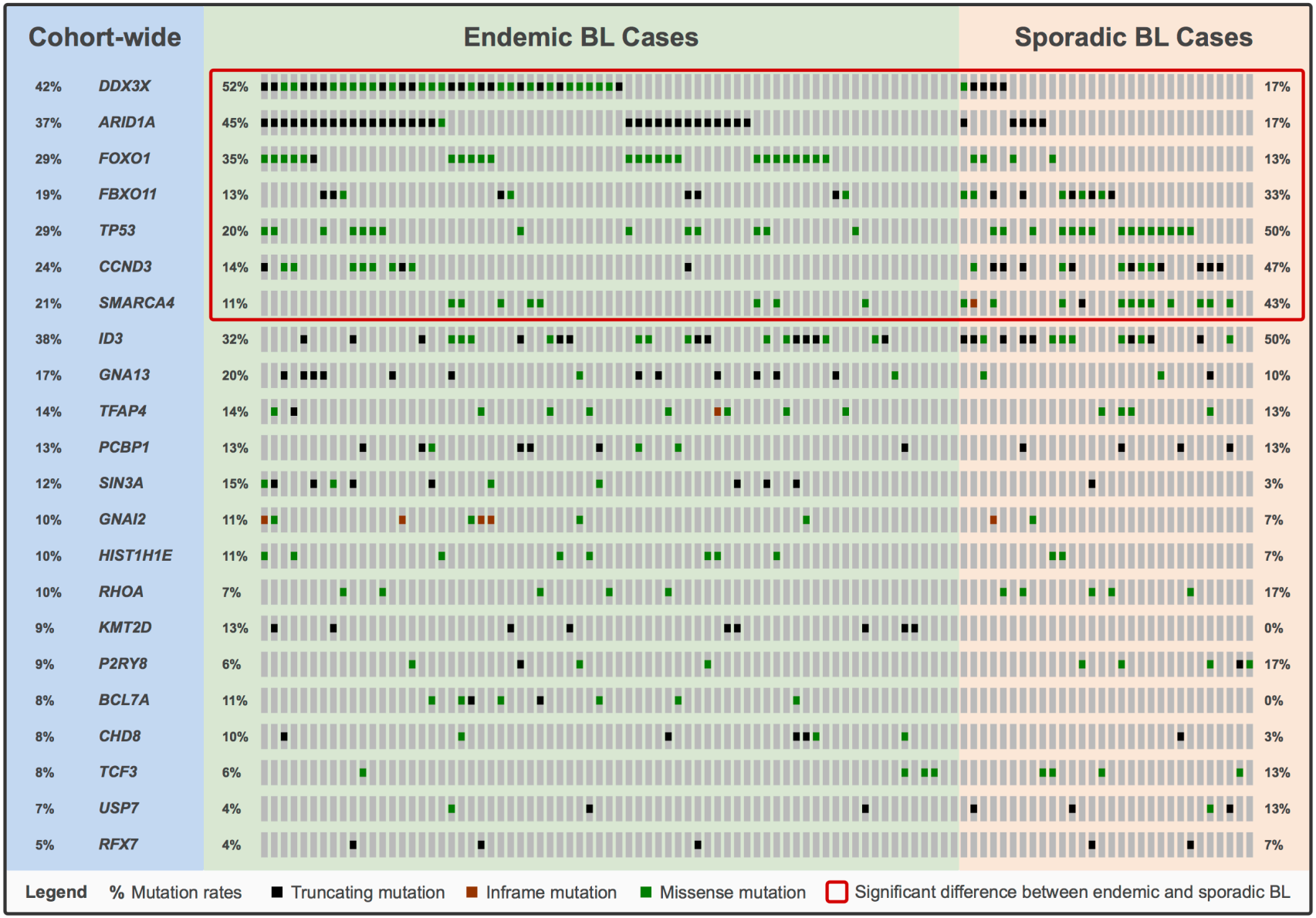
A single high-confidence EBV integration event has been identified so far

It affects the *GAS6* gene, but no striking expression pattern

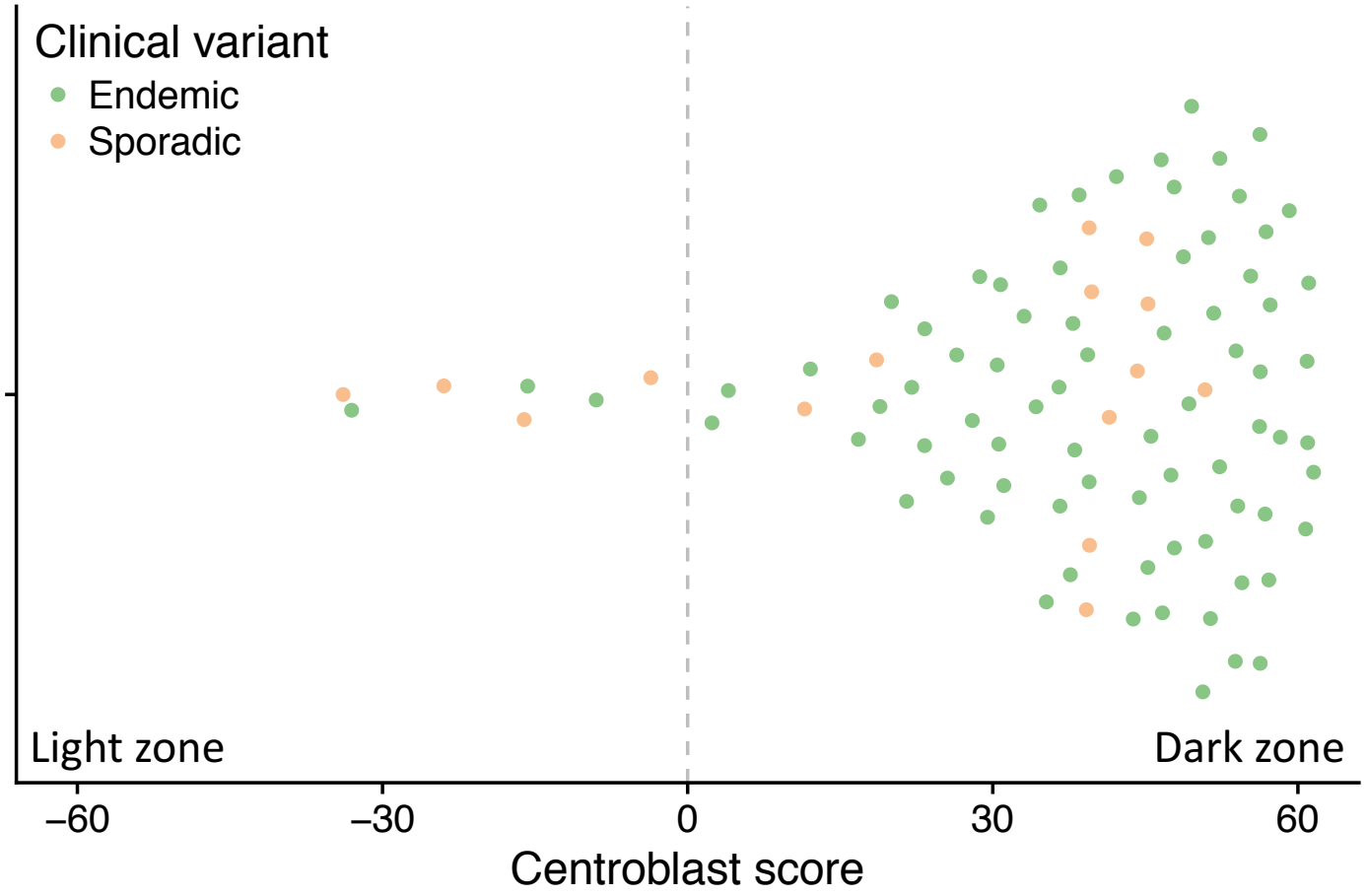




Differential mutation rates for several genes

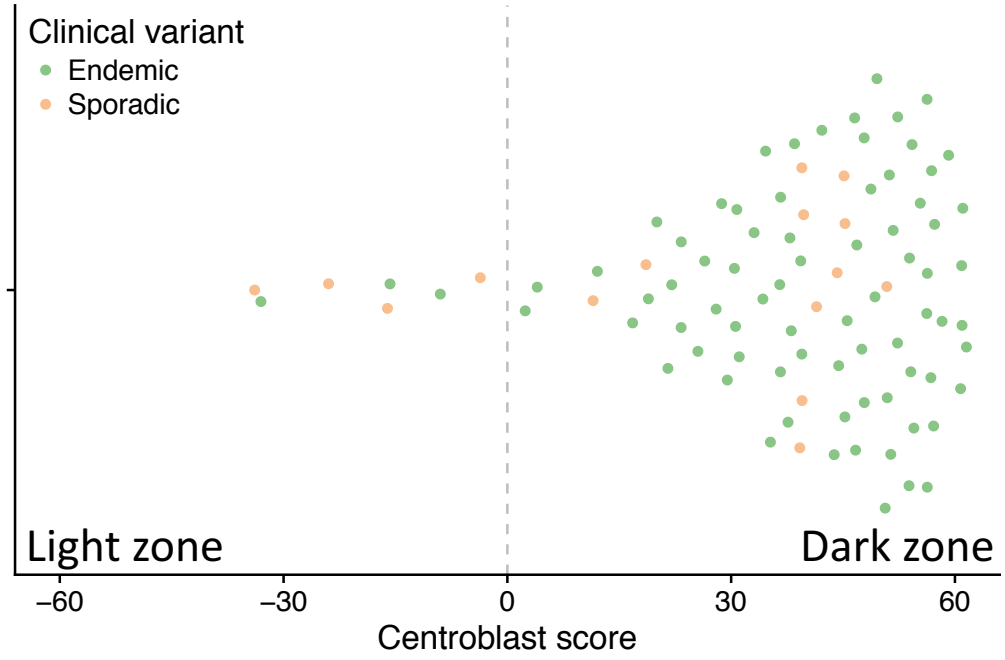


Most BL tumours resemble cells in the germinal center dark zone

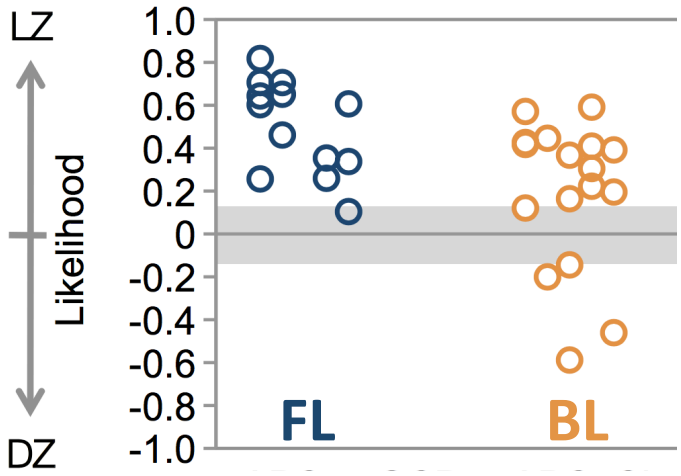


There's a need to reconcile seemingly contradictory results

BL tumours are more similar to dark zone cells



BL tumours are more similar to light zone cells



Source: Victora *et al.*, 2012

Summary

We identified high-confidence significantly mutated genes

- Including novel genes not previously linked to BL
- Some genes show differential mutation rates

EBV-positive tumours show attenuated selection for driver mutations in BL genes

EBV integration events are rare and likely passenger events

BL tumors resemble cells in the germinal center dark zone

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And the patients and their families

Merci pour votre attention!

Thank you for your attention!