Mapping host-pathogen genetic interactions in diverse mice

Aim: ID causative variants underlying immunity to tuberculosis

-many disease states/outcomes!

-failure human GWAS (clinical trait? bacterial strain? prior vaccination status?) and traditional “clinical trait” QTL mapping in mice

-ie bacterial burden is multigenic

-INSTEAD – using bacterial genetics to understand disease state/immunity

-leveraging bacterial mutants as “simpler” traits

*** How to look at the specific interactions (H-H, H-P, P-P)

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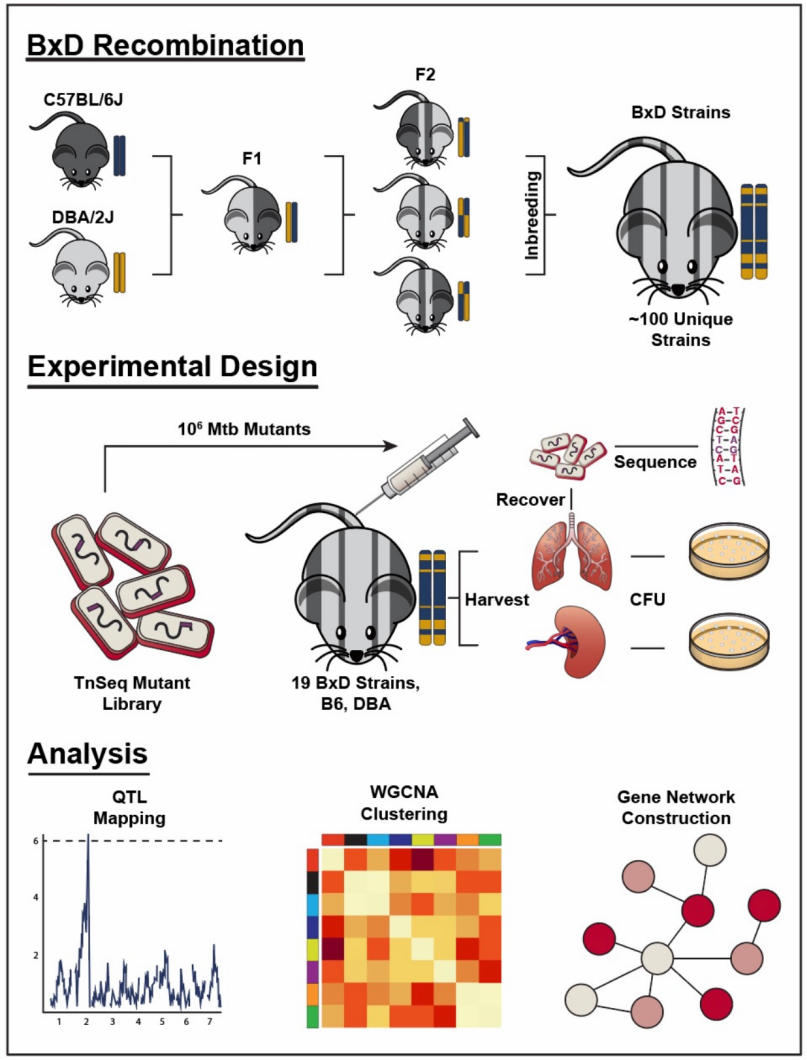
Rachel Meade

Erin Curtis



BXD – 19 strains + parents (n-2-5)

Infected with 100,000 Mtb mutants

1 month – sac

plate organ

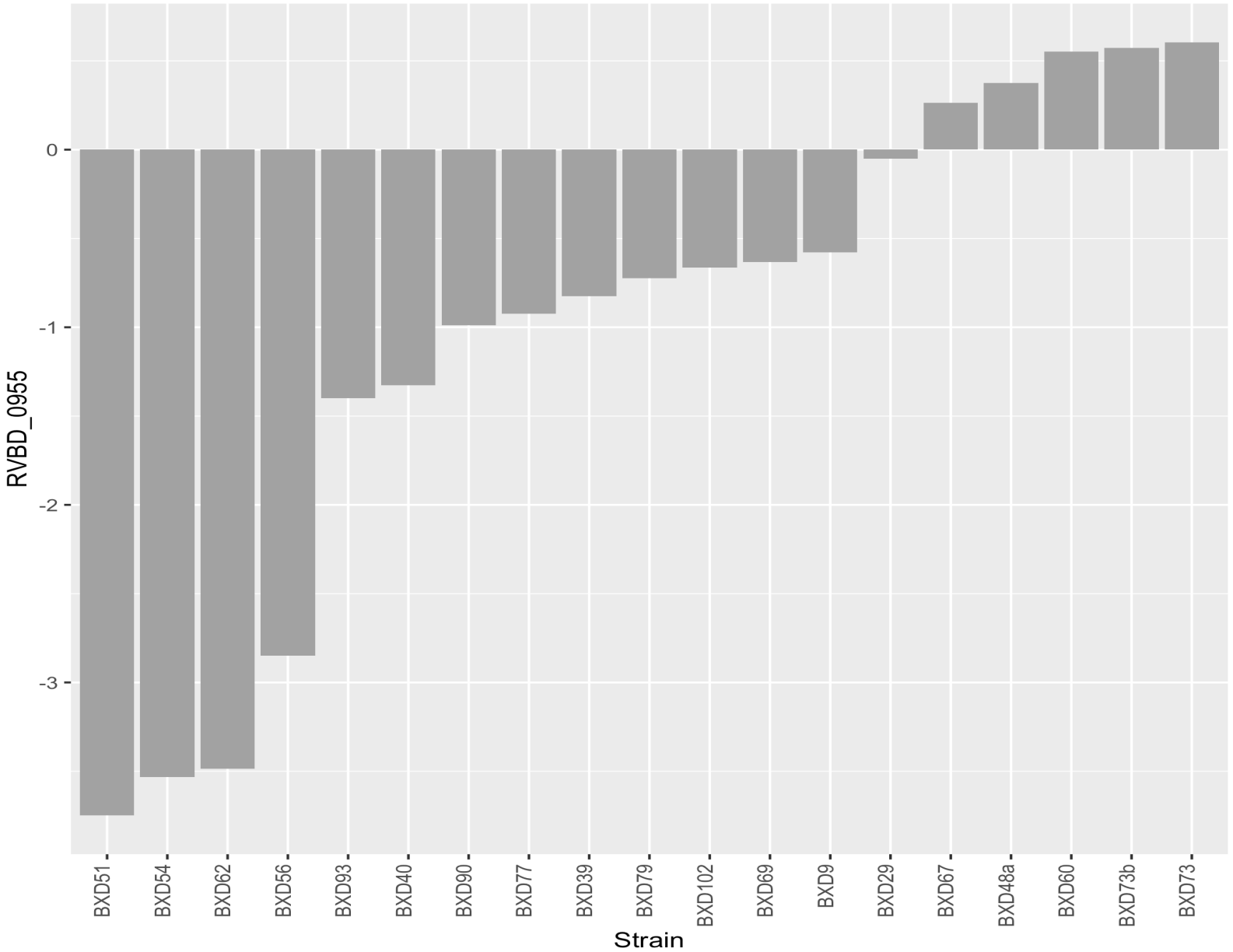
-get viable bacteria (CFU)
-plate for mutant recovery

sequence mutants (TnSeq)

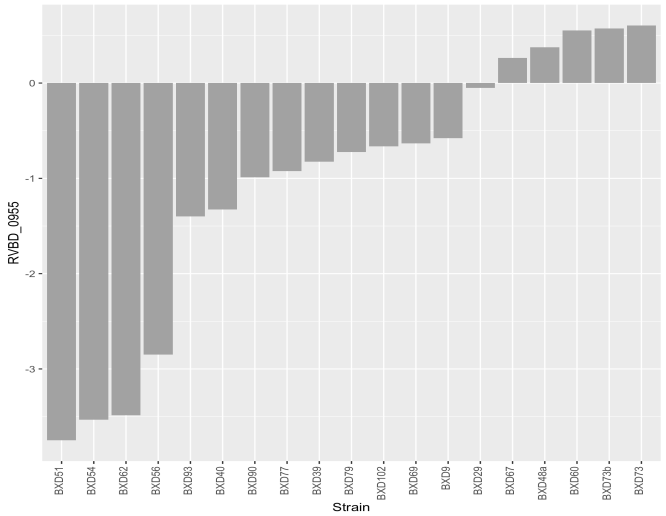
-counts of mutants across mouse genotypes
-compare to input library (all mutants)

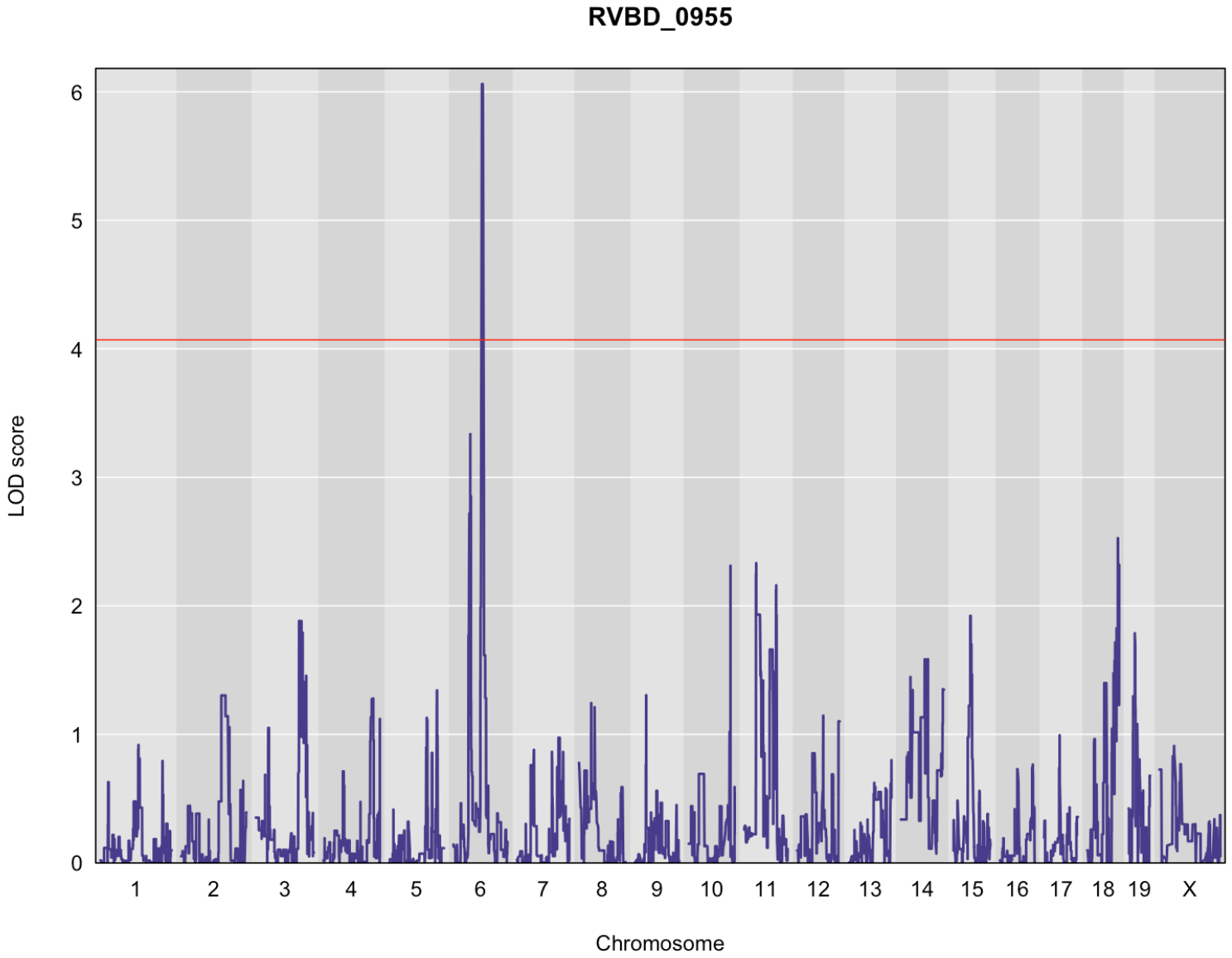
Overall – end up with counts for each mutant in each condition/host
-we compare to input library to look at ratio (ie abundance of mutant in the pool after selection in a mouse compared to input pool)

Differential growth of Mtb mutants across diverse hosts



Mapping Mtb mutant abundance in RI panels





eLife

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MICROBIOLOGY AND INFECTIOUS DISEASE

Persistent *Mycobacterium tuberculosis* infection in mice requires PerM for successful cell division

Ruojun Wang, Kaj Kreutzfeldt, Helene Botella, Julien Vaubourgeix, Dirk Schnappinger, Sabine Ehrt

Weill Cornell Medical College, United States; Weill Cornell Graduate School of Medical Sciences, Cornell University, United States

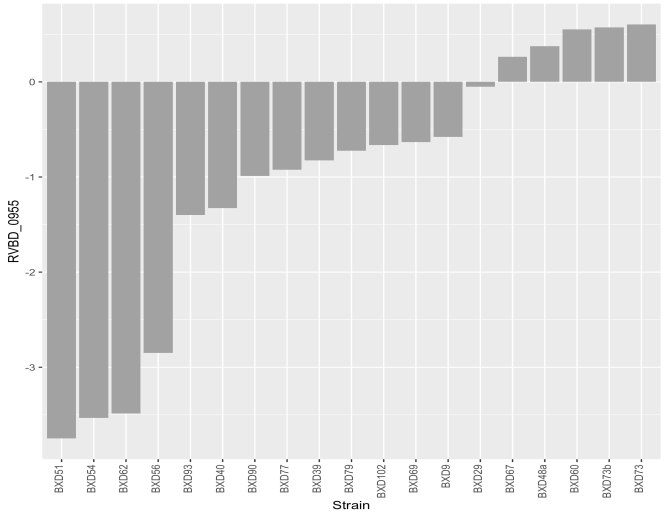
RESEARCH ARTICLE Nov 21, 2019

***0955 (PerM) is required for chronic infection in C57BL/6J mice but not acute!!!

**Using the BXD, we show that PerM is not required in chronic phase of some hosts

-different selective pressure for PerM across BXD

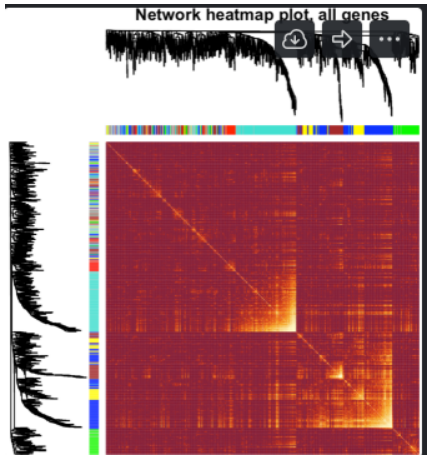
-what is different about immunity/host stress in those BXD?



mapping single mutant traits:

qtl	lodindex	lodcolumn	gene	chr	pos	lod	ci_lo	ci_hi	mycobrowser_class
1	911	RVBD_0959	-	15	50.05	6.38928202	49.925	50.69	conserved hypotheticals
2	60	RVBD_0955	-	6	40.51	6.06016634	40.51	41.238	cell wall & cell processes
3	203	RVBD_1512	epiA	15	12.91	6.04811567	12.43	13.0833333	intermediary metabolism and respiration
3	203	RVBD_1512	epiA	6	43.1966667	5.53913444	42.6766667	44.78	intermediary metabolism and respiration
4	7	RVBD_0066c	icd2	13	11.5936364	5.28110865	9.02142857	12.5618182	intermediary metabolism and respiration
5	20	RVBD_2115c	mpa	6	41.602	5.14222679	40.874	42.85	cell wall & cell processes
6	698	RVBD_0793	-	18	25.438	4.77507686	15.32	26.5325	intermediary metabolism and respiration
7	646	RVBD_2089c	pepE	10	47.3466667	4.73978559	44.698	48.705	intermediary metabolism and respiration
8	898	RVBD_0397A	-	6	45.16	4.67863924	44.91	47.365	conserved hypotheticals
9	288	RVBD_0242c	fabG4	15	47.5666667	4.65920426	45.0775	48.66	lipid metabolism
10	556	RVBD_1956	higA	2	80.095	4.65011327	78.082	80.29	virulence, detoxification, adaptation

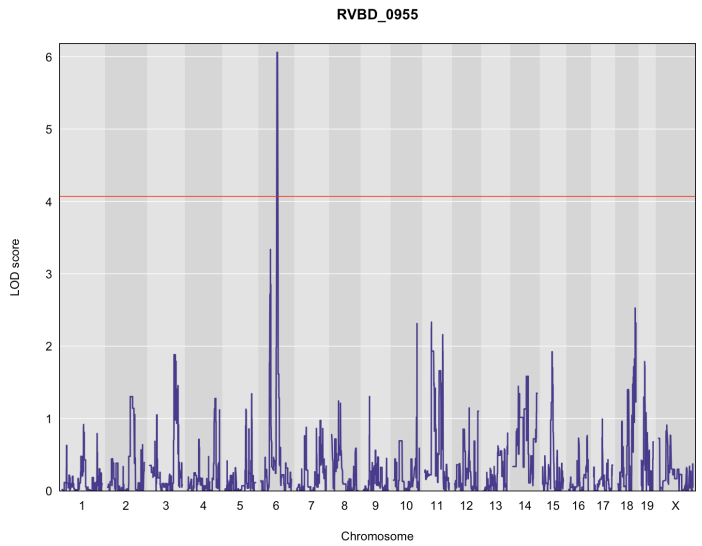
vs. mapping modules (ie. dimension reduction and map eigengenes > map bacterial pathways??)

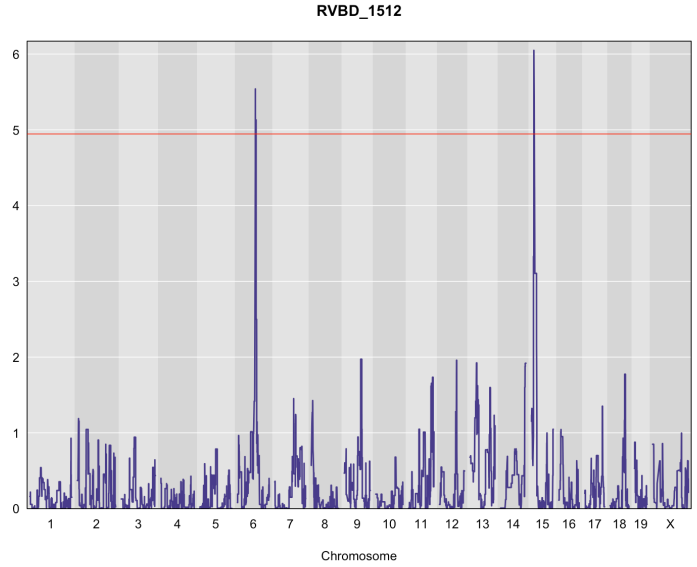


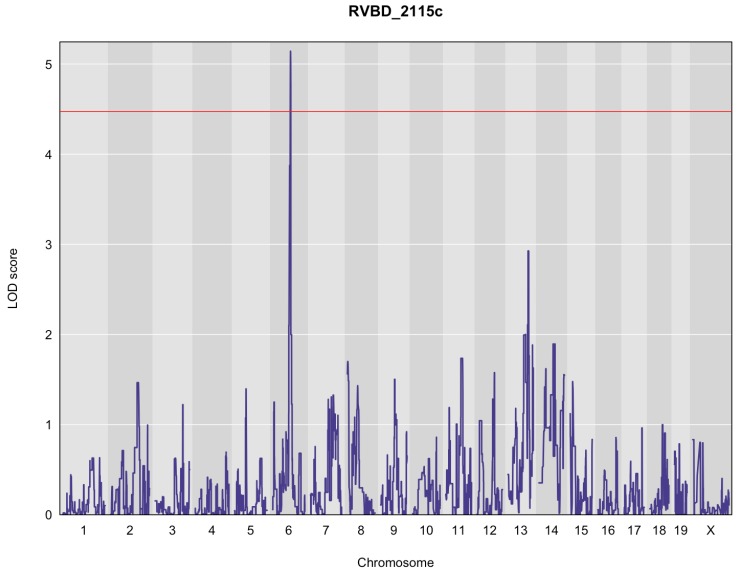
Host-pathogen hotspots?

ie. host regions where many mutants co-map

	match1.pheno	match1.gene	match1.chr	match1.pos	match1.lod	match1.ci_lo	match1.ci_hi	match2.pheno	match2.gene	match2.chr	match2.pos	match2.lod	match2.ci_lo	match2.ci_hi
1	RVBD_0959	-	15	50.05	6.38928202	49.925	50.69	RVBD_0242c	fabG4	15	47.56666667	4.659204257	45.0775	48.66
2	RVBD_0955	-	6	40.51	6.06016634	40.51	41.238	RVBD_1512	epiA	6	43.19666667	5.539134437	42.67666667	44.78
3	RVBD_0955	-	6	40.51	6.06016634	40.51	41.238	RVBD_2115c	mpa	6	41.602	5.142226788	40.874	42.85
4	RVBD_0955	-	6	40.51	6.06016634	40.51	41.238	RVBD_0397A	-	6	45.16	4.678639239	44.91	47.365
5	RVBD_1512	epiA	6	43.1966667	5.53913444	42.67666667	44.78	RVBD_2115c	mpa	6	41.602	5.142226788	40.874	42.85
6	RVBD_1512	epiA	6	43.1966667	5.53913444	42.67666667	44.78	RVBD_0397A	-	6	45.16	4.678639239	44.91	47.365
7	RVBD_2115c	mpa	6	41.602	5.14222679	40.874	42.85	RVBD_0397A	-	6	45.16	4.678639239	44.91	47.365







Next steps?

Q. ONLY 19 BXD strains!!!!!!

-gross clinical traits, need MANY strains to map QTL

-Are Tn mutants simpler traits (endophenotypes!) > dont need as many mouse strains?
-Did we just get lucky with BXD strains/recombinations?

Q. how to tease apart hotspots
-interactions > multi QTL model > CAPE for hotspots?
-CAPE on the mutants that map to chr6 and 15?

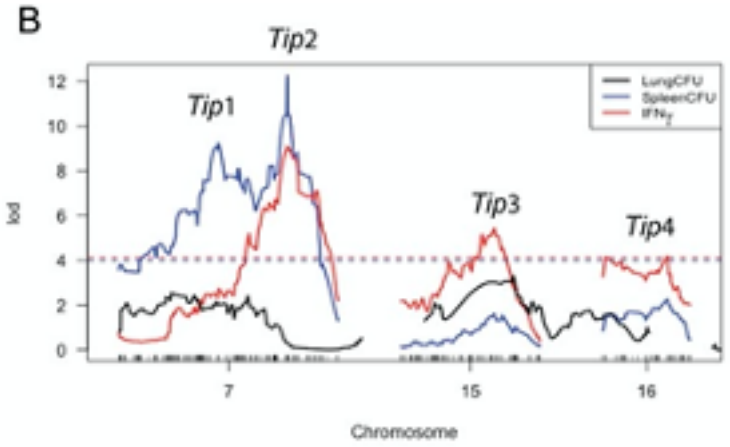
Q. Biological dissection of interaction – make single + combination mutants in extreme host backgrounds
-mice (macs?? immortalize and crispr host loci + Mtb mutants)

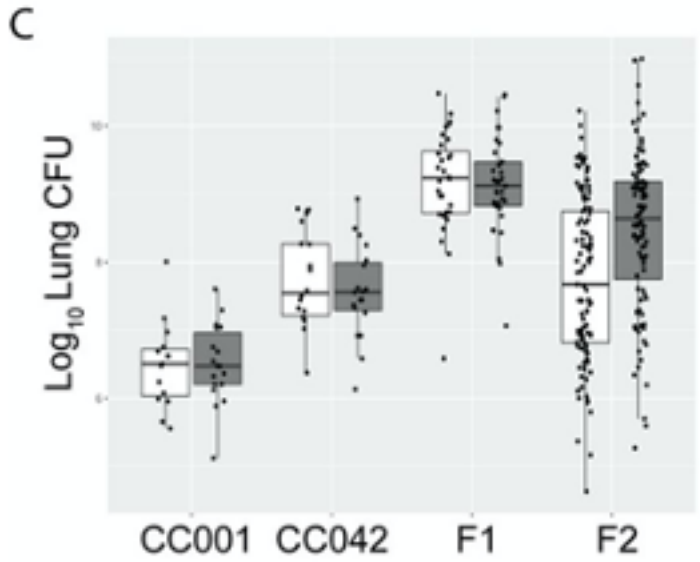
new data sets (would love your thoughts on future cool things to look at!)

-BXD: 19 + parents > TnSeq (abundance of 4000 Mtb mutants)

-CC: 55 + parents > TnSeq + 20 Clinical traits/cytokines
mapped clinical and hipQTL
CAPE + mouse/mac dissection

-CC001xCC042 F2: 170 F2 > 1 strain Mtb
mini-muga genotyped
4 QTL (Smith mBio 2019)
Q - interesting interactions
Q - underdominance





-CC030xCC029 F2: 200 F2 > TnSeq
genotyped on minimuga
phenotyped lung and spleen CFU
organs in freezer ready to plate for Tn libraries and Tnseq??