

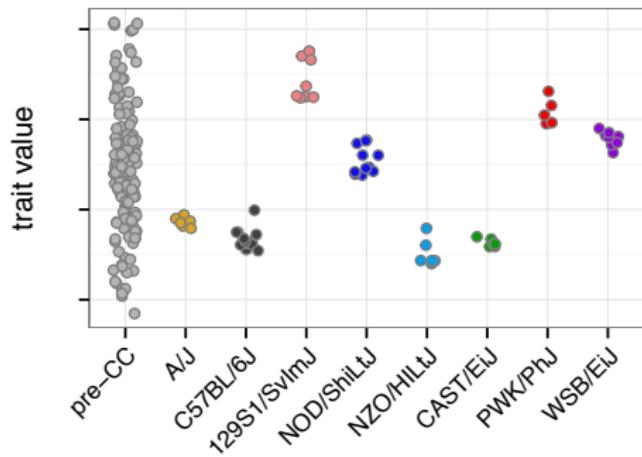
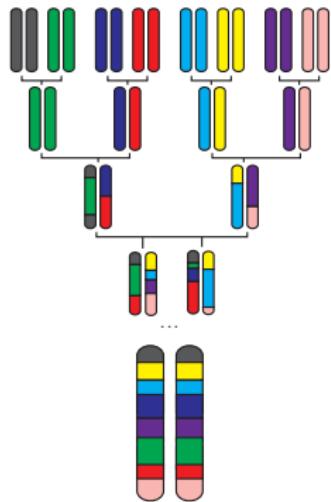
A new model for inflammatory bowel disease arising from the Collaborative Cross

Andrew P Morgan

Complex Traits Community 13th annual meeting
Humboldt-Universität zu Berlin
Berlin, Germany

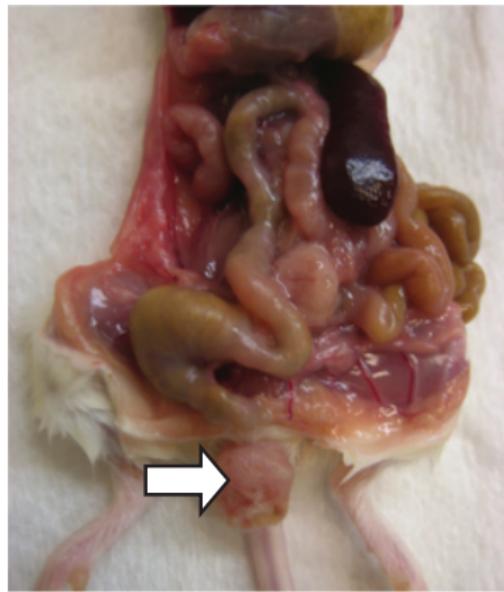
20 May 2014

The promise of the CC



Kelada et al. G3 2012; 2(2):157-165.

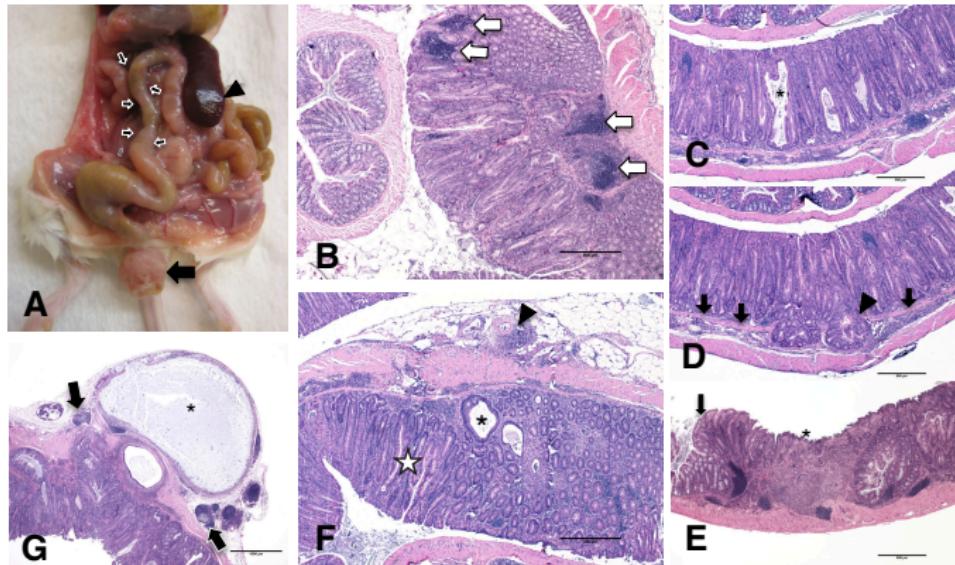
Initial observation in line OR3252



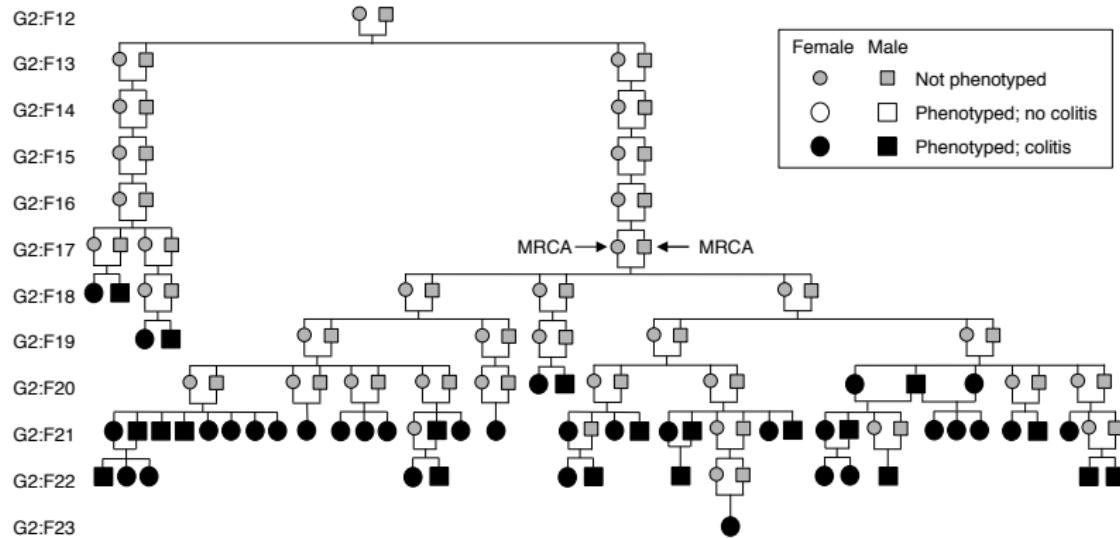
The colitis phenotype in CC011/Unc

No gut pathogens

The colitis phenotype in CC011/Unc

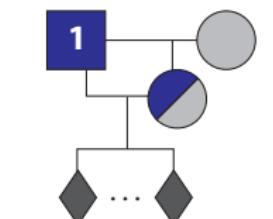


Evidence for genetic basis: pedigree

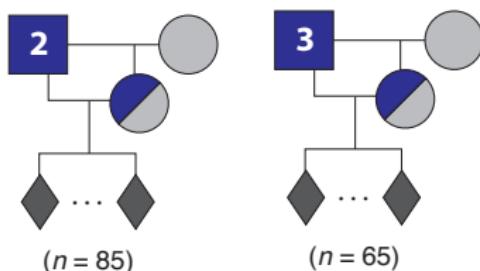


Evidence for genetic basis: backcross

CC011/Unc C57BL/6J



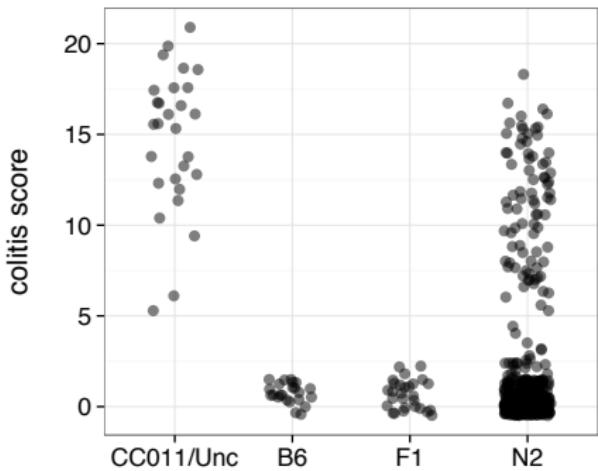
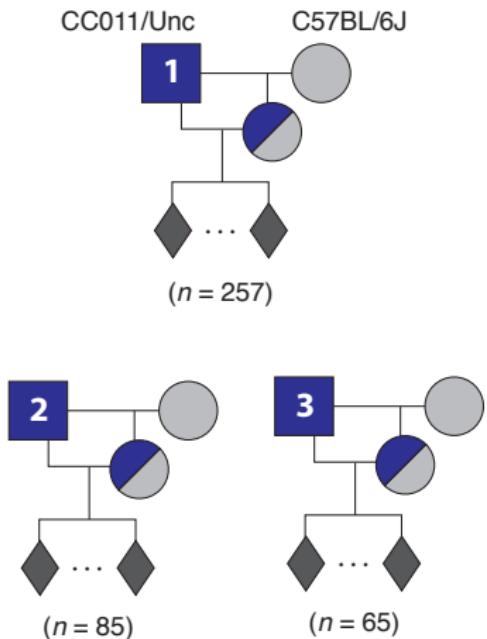
(n = 257)



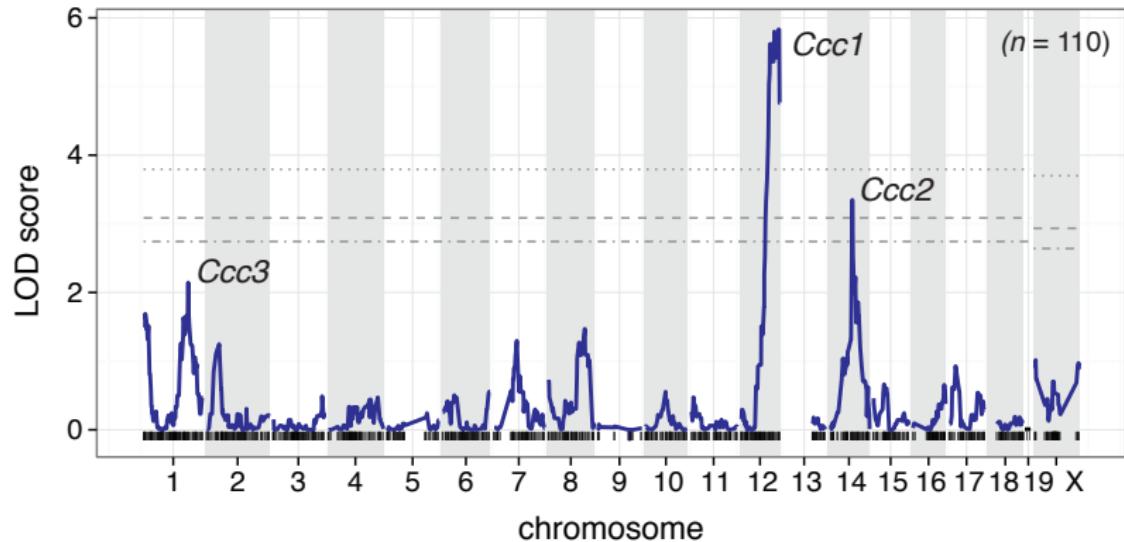
(n = 85)

(n = 65)

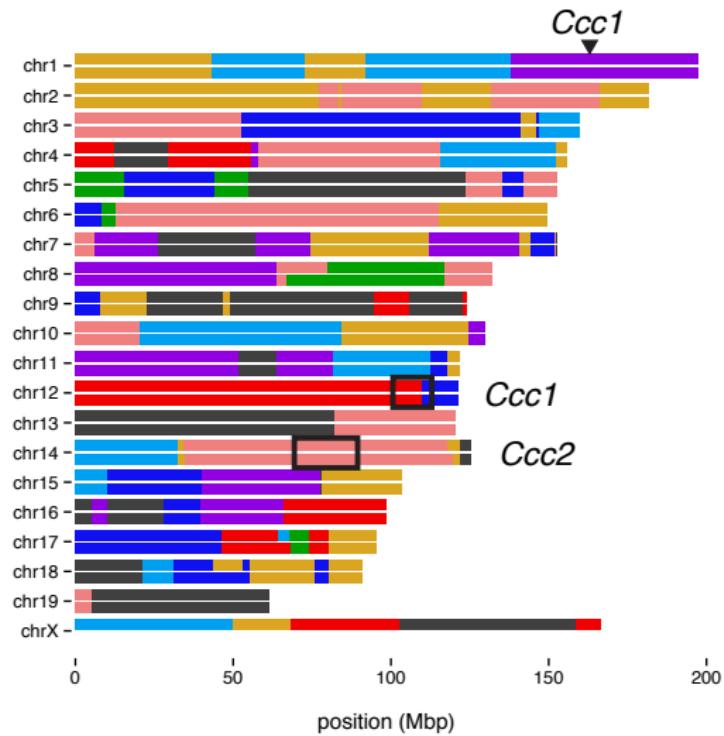
Evidence for genetic basis: backcross



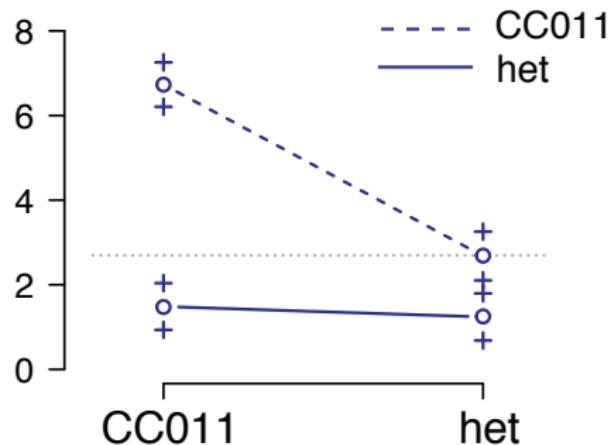
Novel colitis QTL in backcross to C57BL/6J



Novel colitis QTL in backcross to C57BL/6J



Cross-subspecies epistasis (in expected directions)

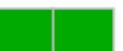


Ccc1 × Ccc3
(*musculus × domesticus*)

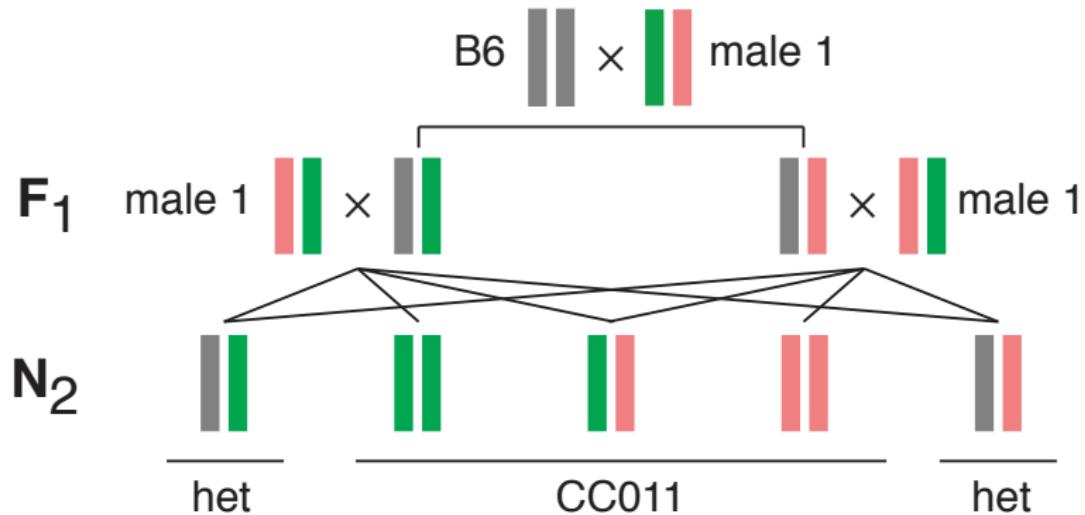
Unexplained genetic heterogeneity

locus	male 1 (n = 257)	male 2 (n = 85)	male 3 (n = 65)
<i>Ccc1</i>	✓		
<i>Ccc2</i>	✓		
<i>Ccc3</i>	✓	✓	✓

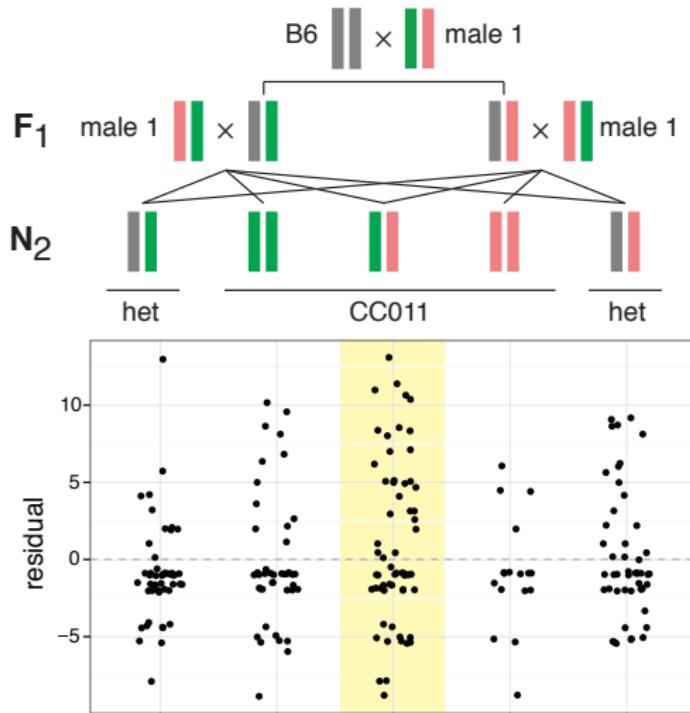
Unexplained genetic heterogeneity

locus	male 1 (n = 257)	male 2 (n = 85)	male 3 (n = 65)
<i>Ccc1</i>	✓		
<i>Ccc2</i>	✓		
<i>Ccc3</i>	✓	✓	✓
chr8			
chr12			
chr14			
chr17			
chr18			
	98.85%	98.60%	99.61%

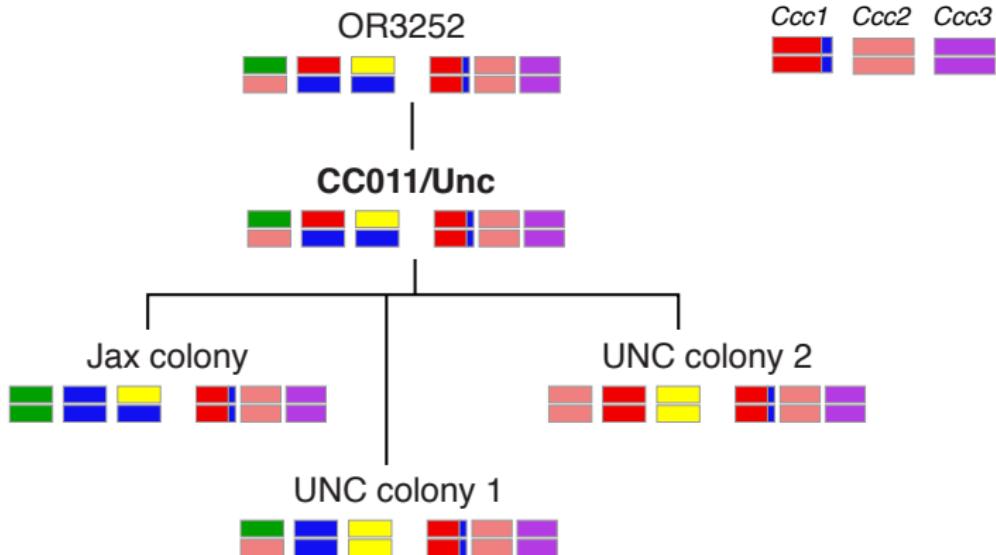
Non-additive genetic effects



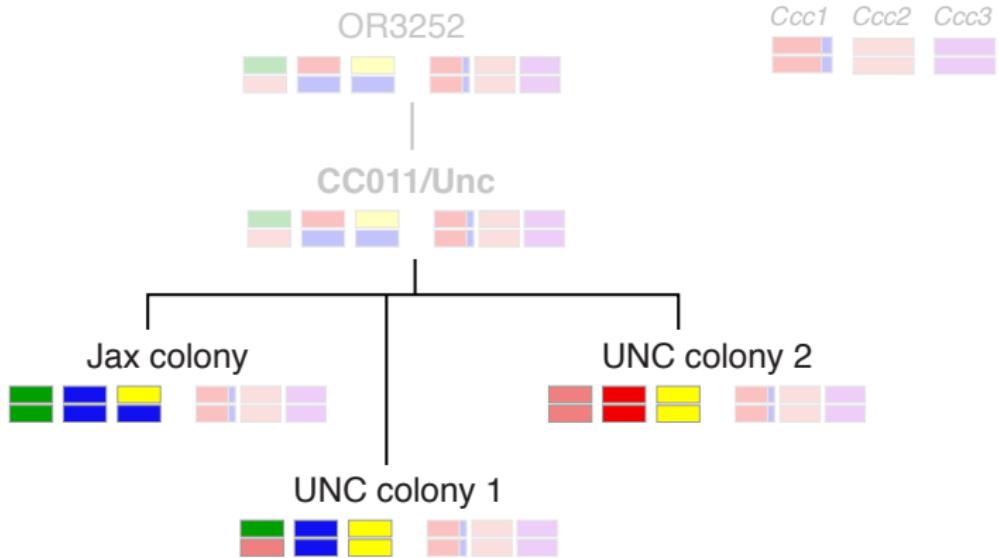
Non-additive genetic effects



“Mendelizing” a complex trait



“Mendelizing” a complex trait



Conclusions

CC011/Unc is a new model for **spontaneous** IBD without infections, chemicals or knock-outs.

- Wild-derived alleles in new combinations are important
- Cross-subspecies epistasis predominates
- Residual heterozygosity is blessing and curse

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Future directions

$$V(\text{trait}) = \sigma_{\text{genes}}^2 + \sigma_{\text{microbes}}^2 + \sigma_{\text{breeding}}^2 + \dots + \sigma_{\text{other}}^2$$

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Acknowledgments

Rogala AR, Morgan AP, Christensen AM, Gooch TJ, Bell TA, Miller DR, Godfrey VL, Pardo-Manuel de Villena F. *Mamm Genome* 2014; **25**(3): 95–108.

Veterinarians

Allison Rogala

Lexi Christensen
Virginia Godfrey

Collaborative Cross

Fernando Pardo-Manuel de Villena
Darla Miller
Tim Bell
Justin Gooch
Mouse crew

Funding

U01CA134240

U54AI081680

P50MH090338

P50HG006582

T32GM067553

AG-IA-0202-05 (Ellison Med Fdn)

Section 2

Supplementary material

Range of colitis severity

