

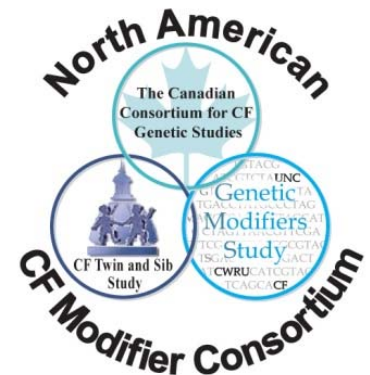
A haplotype in the *MSRA* gene appears to confer decreased risk of meconium ileus (MI) in CF

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North American CF Modifier Consortium:

- CF Twin and Sibling Study, Johns Hopkins University, Baltimore, MD
- Genetic Modifiers Study, University of North Carolina, Chapel Hill, NC and Case Western Reserve University, Cleveland, OH

Canadian Consortium for CF Genetic Studies, Toronto, ON



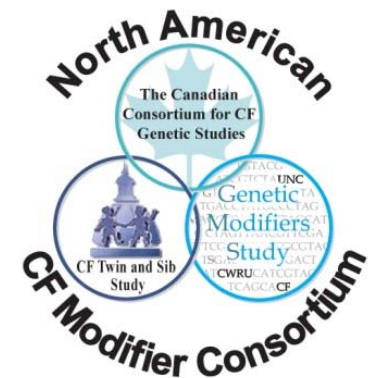
Meconium Ileus (MI)

- Intestinal obstruction in distal ileum
- Occurs in 15-20% of CF neonates
- Genetic
 - Sib recurrence ~25%
 - Heritability ~1
- Modifier gene studies
 - Chr19q13; Zielenski, et al, *Nat. Genet.* 1999
 - 4q35.1, **8p23.1** and 11q25; Blackman, et al, *Gastroenterology.* 2006
 - *ADIPOR2* (Chr12), *SLC4A4* (Chr4); Dorfman, et al, *Hum. Genet.* 2009

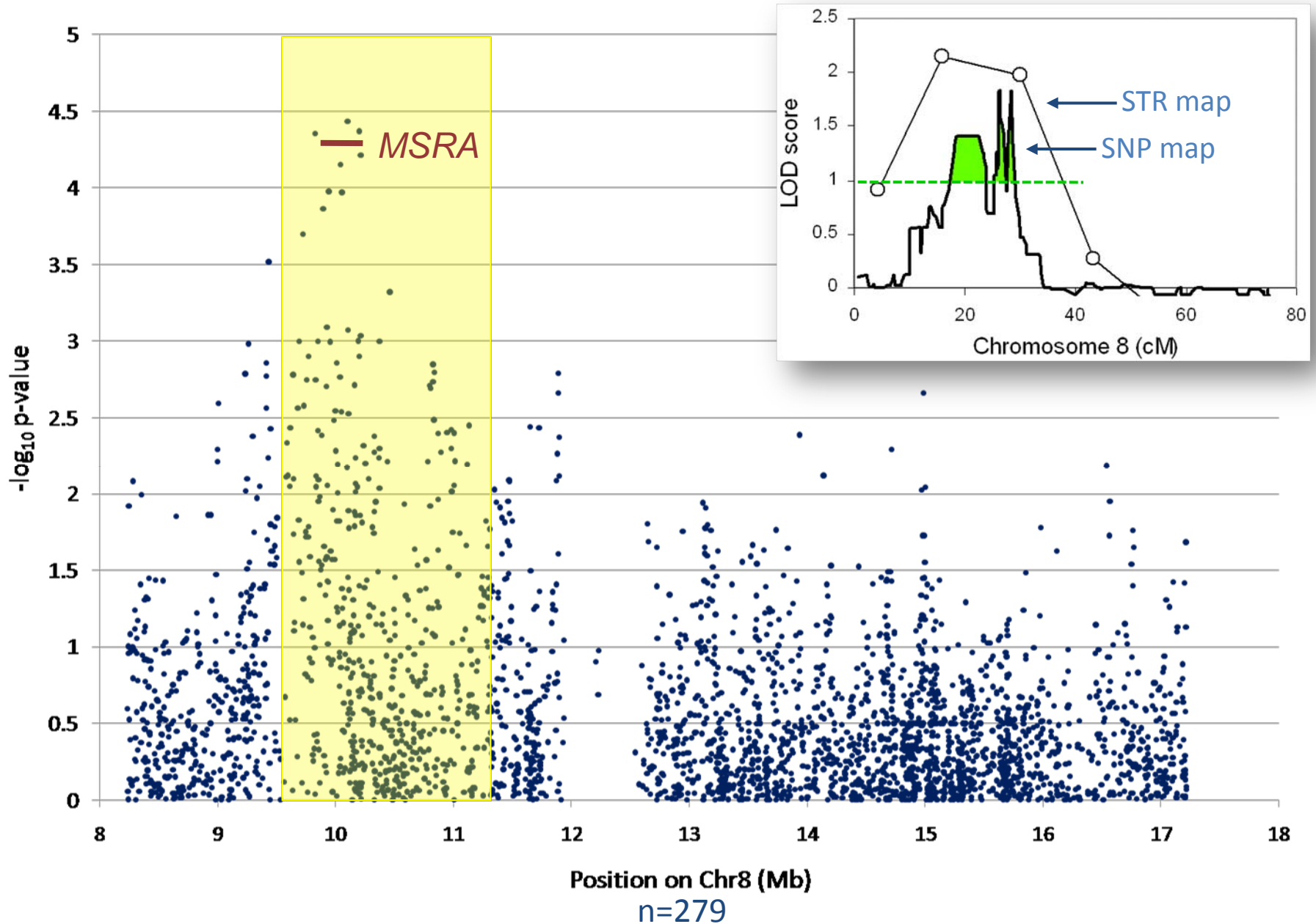
Study Populations

	Primary	Replication	
MI Status	CF Twin and Sibling Study (Hopkins)	Genetic Modifiers Study (UNC/CWRU)	Canadian Consortium for CF Genetic Studies
	Mean current age/Percent female		
No MI (controls)	n=109 16.7 years / 50.5%	n=166 31.0 years / 37.3%	n=1164 26.3 years / 45.7%
MI + (cases)	n=170 16.3 years / 50.6%	n=165 26.2 years / 41.8%	n=220 23.1 years / 49.1%

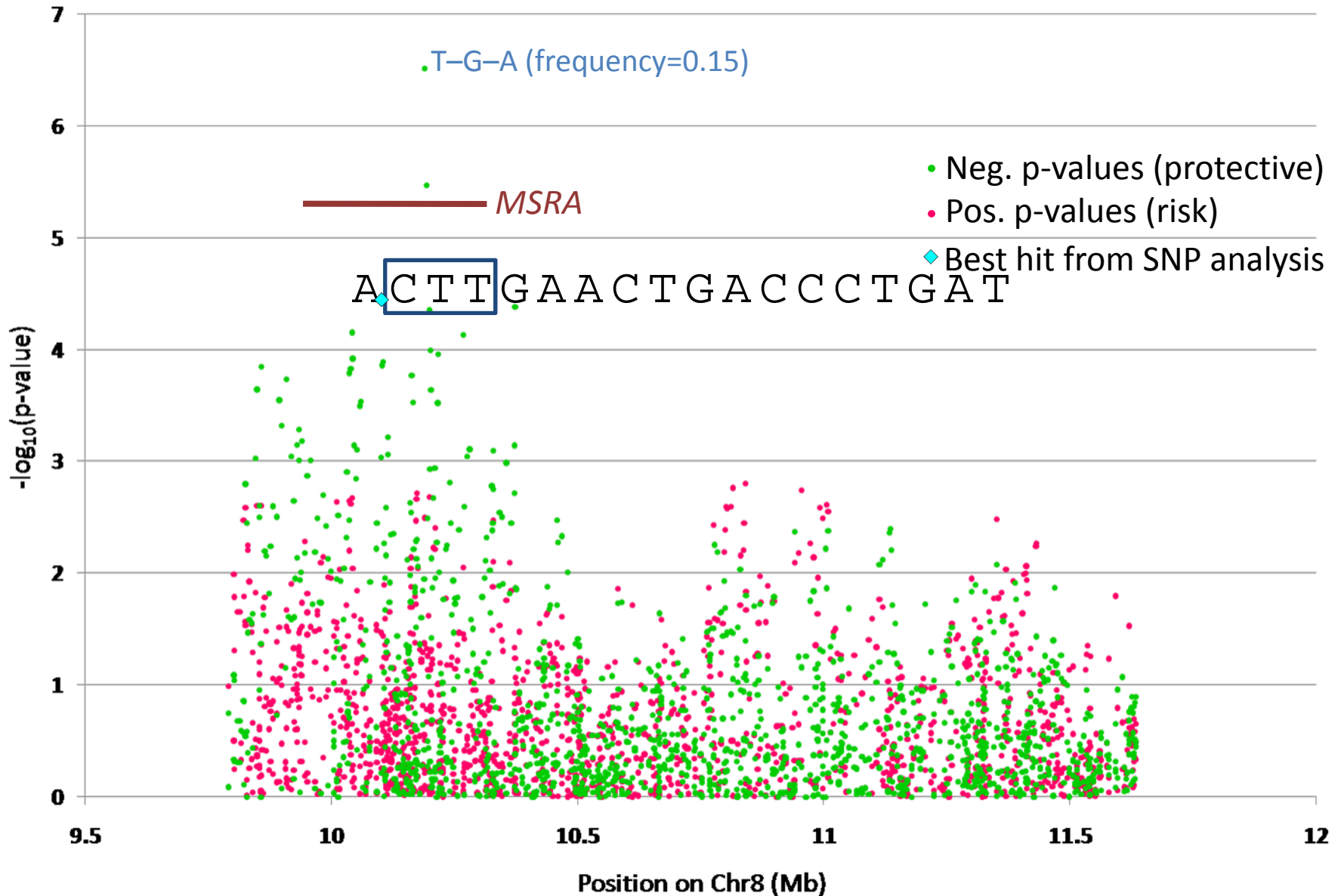
- All pancreatic insufficient (PI)
- Caucasian samples only in replication studies
- All samples genotyped for WGA using the Illumina 610 Quad SNP array



Association of SNPs under chr8p23.1 linkage peak in MI families



Haplotype analysis in *MSRA* region



CF Twin & Sibling study

(137 families with ≥ 1 sib with MI)

MI status	Number of T-G-A haplotypes			Total
	0	1	2	
No MI	62 (57.9)	38 (35.5)	7 (6.5)	107 (100)
MI +	126 (76.4)	37 (22.4)	2 (1.2)	165 (100)
Total	188	75	9	n=272

Fisher p=0.001

OR for 1 haplotype = 2.2 (95% CI: 1.5-3.2)

OR for 2 haplotypes = 4.8

p<0.0001, n=286

Replication Study: UNC

(validated subjects only, all Caucasian)

MI status	Number of T-G-A haplotypes			Total
	0	1	2	
No MI	107 (70.4)	35 (23.0)	10 (6.6)	152 (100)
MI +	112 (73.2)	40 (26.1)	1 (0.7)	153 (100)
Total	219 (71.8)	75 (24.6)	11 (3.6)	305

Fisher p=0.016

Replication Study: Canada

(Caucasians only, including 113 sibs)

MI status	Number of T-G-A haplotypes			Total
	0	1	2	
No MI	789 (82.7)	305 (86.9)	27 (90.0)	1,121 (84.0)
MI +	165 (17.3)	46 (13.1)	3 (10.0)	214 (100) (16.0)
Total	954 (71.5)	351 (26.3)	30 (2.3)	n=1,335

Fisher p=0.15

OR for 1 haplotype = 1.4 (95% CI: 1.0-1.9)

OR for 2 haplotypes = 1.9

p=0.04, n=1383

MSRA

- Methionine sulfoxide reductase A
 - Highly conserved, globally expressed
 - Enzymatically reduces methionine sulfoxide to methionine
 - Repairs oxidative damage to proteins to restore biological activity
- Recently implicated in central obesity & fat distribution
(Lindgren CM, et al. *PLoS Genet.* Epub 2009 Jun 26)
 - 5' variant associated with waist circumference
- Pigs fed soy protein diet have ↑ MSRA protein and ↑ oxidative stress responsiveness compared to casein diet
(Schwerin M, et al. *FASEB* Aug 2002)
- Link between nutrient absorption/digestion & MI?

Summary

- A haplotype in *MSRA* is protective against MI in CF
 - Replicated in two independent populations
 - Odds ratio = 2.2 – 4.8 in MI *families*
 - 1.4 – 1.9 in general CF population
- Causal variant
- Potential implications
 - Amelioration of the MI phenotype in mouse and pig models
 - Protective modifier facilitates development of therapeutics
 - CF modifier genes may be risk factors in general population
 - E.g. TCF7L2

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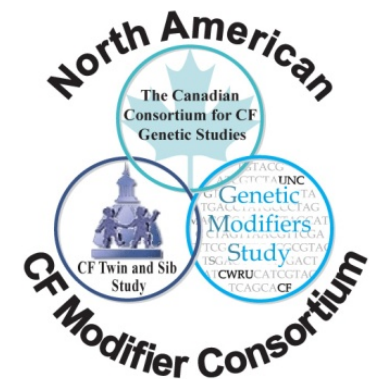
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CF Twin and Sib Study

"Investigating the factors that modulate the severity of Cystic Fibrosis by studying affected twins and sibline pairs..."

Albany Medical College Albany, NY
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Children's Hospital of Buffalo, NY
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Eastern Maine Medical Center Bangor ME
Emory University CF Center Atlanta, GA
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Hospital of the University of Pennsylvania Philadelphia, PA
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Lutheran Hospital Fort Wayne, IN
Marshfield Clinics Marshfield, WI
Massachusetts General Hospital Boston, MA
Medical College of Georgia Augusta, GA
Medical University of South Carolina Charleston, SC
Memphis Lung Physicians South Haven, MS
Methodist Children's Hospital San Antonio, TX
Miami Children's Hospital, Miami FL
Michigan State University Lansing, MI
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Pediatric Diagnostic Center Ventura, CA
Pediatric Pulmonary Associates Columbia, SC
Phoenix Children's Hospital Phoenix, AZ
Portsmouth Naval Medical Center Portsmouth, VA
The Prince Charles Hospital Brisbane, Australia
Providence Medical Center Anchorage, AK
Providence Medical Center Spokane WA
Rainbow Babies and Children's Hospital Cleveland OH
Riley Children's Hospital Indianapolis IN
Royal Hospital for Sick Children Yorkhill, Scotland
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Saint Luke's CF Clinic Boise, ID
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Saint Vincent's Hospital Green Bay, WI
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Joel Ledbetter, MD Karen Saronosky



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Toledo Children's Hospital Toledo, OH
Tufts New England Medical Center
Tulsa CF Center Tulsa, OK
University of Alabama CF Center Birmingham, AL
University of Arizona Tucson AZ
University of California at San Francisco CA
University of Chicago Chicago, IL
University of Florida Pediatric CF Center Gainesville, FL
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University of Iowa Hospitals and Clinics Iowa City, IA
University of Kentucky Lexington, KY
University of Massachusetts Medical Center Worcester, MA
University of Michigan Ann Arbor, MI
University of Minnesota Minneapolis, MN
University of Mississippi Medical Center Jackson, MS
University of Nebraska Omaha, NE
University of New Mexico Health Sciences Center Albuquerque, NM
University of North Carolina at Chapel Hill Chapel Hill, NC
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M E D I C I N E



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