

# Quantification of the Contribution of Environmental and Genetic Modifiers to Cystic Fibrosis Lung Function

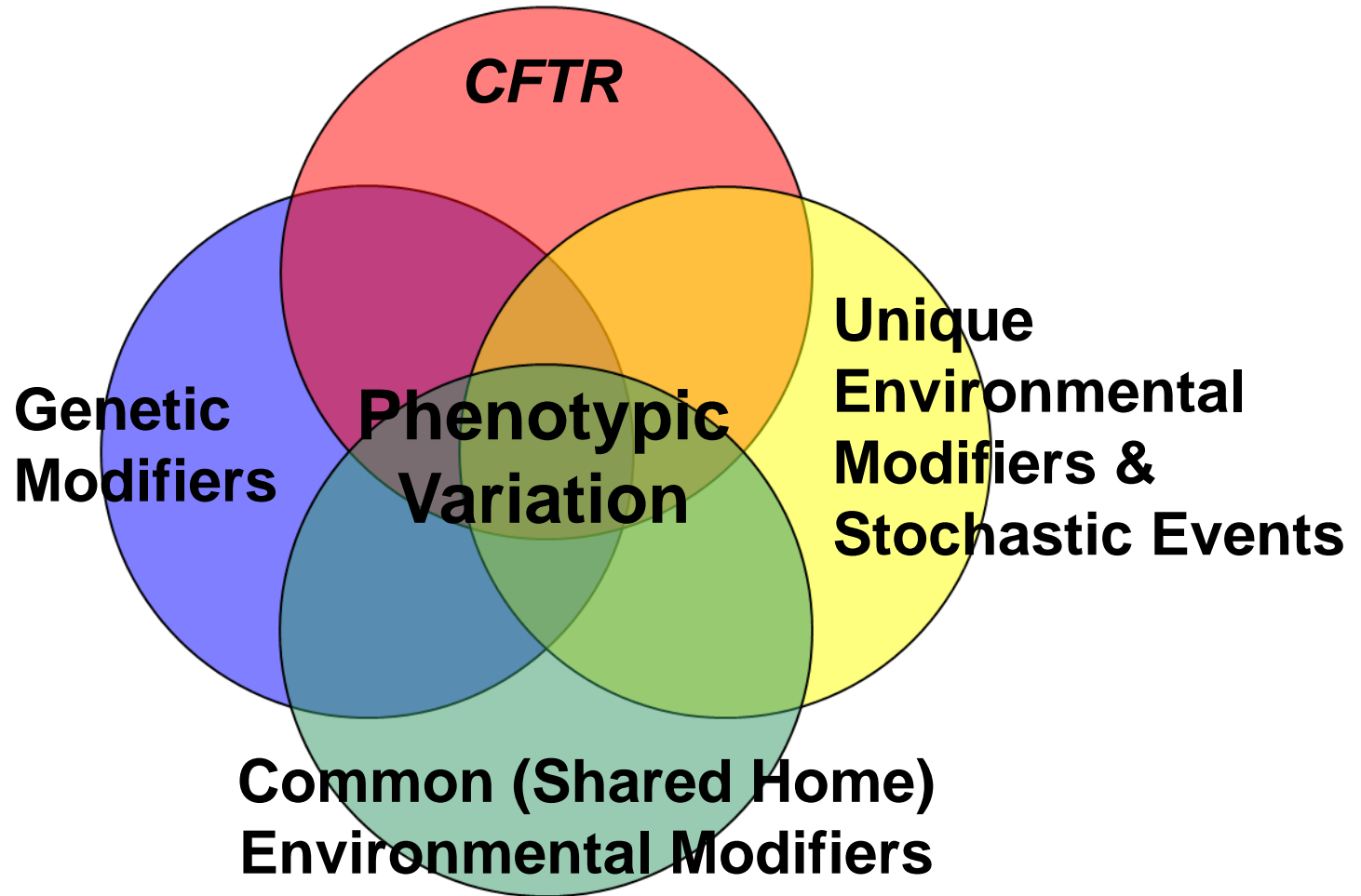
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M E D I C I N E

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# Sources of Variation in Cystic Fibrosis Lung Disease



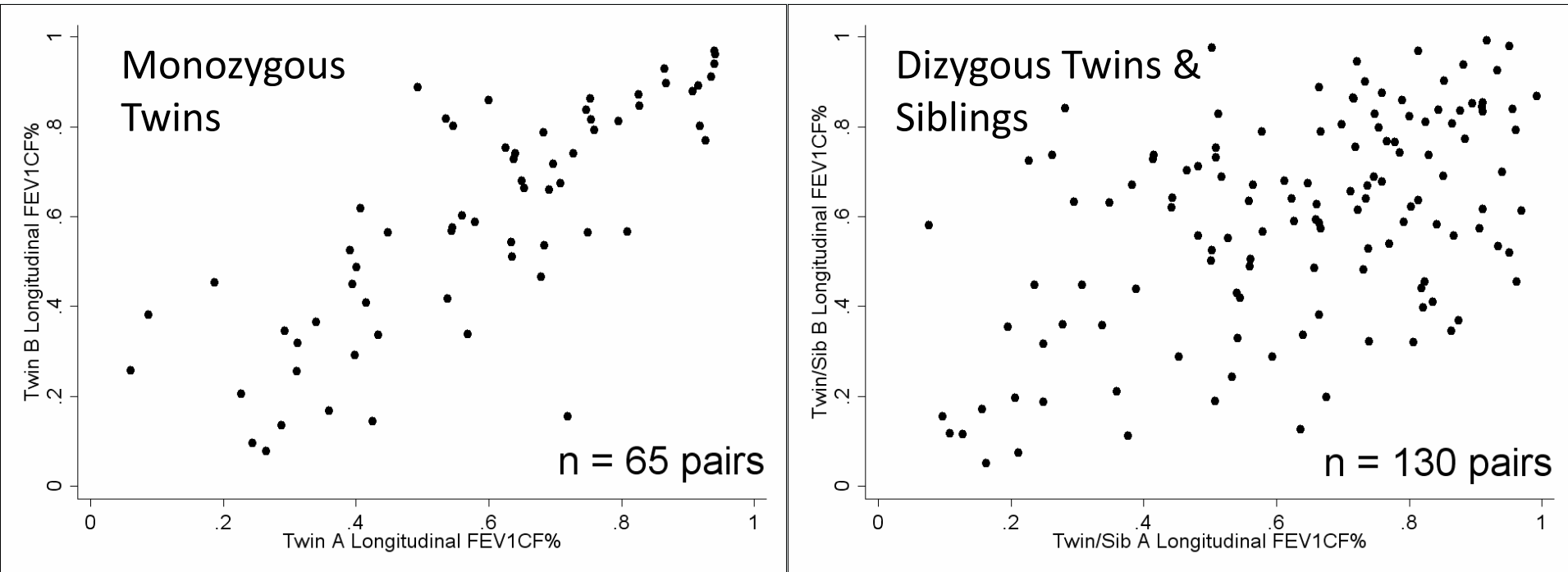
# Study Population: U.S. CF Twin-Sibling Study

(Based at Johns Hopkins University)

- Lung function measure
  - CF-specific FEV<sub>1</sub> percentile (Kulich *et al.* *AJRCCM* 2005)
  - Lung function was averaged over periods of time corresponding to living in selected locations

Comparison	Intra-pair	Intra-individual
Variation Measure	<b>Correlation:</b> Is there a genetic contribution? <b>Difference:</b> Estimating contribution of genes vs. environment	<b>Difference:</b> Confirming environment contribution estimates
Analysis Subset	67 pairs of MZ twins 11 pairs of same-sex DZ twins 125 pairs of same-sex sibs born within 3 yrs of each other	40 pairs of sibs ( <b>not</b> in intra-pair analyses)

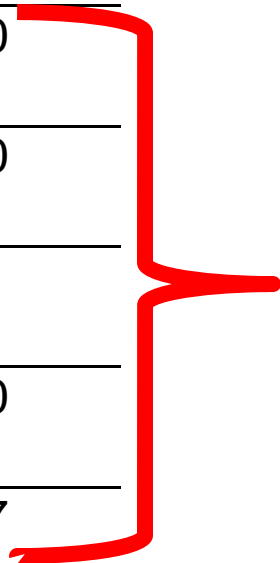
# Intra-pair Correlation: Monozygous twins resemble each other more closely than dizygous twins



- Heritability estimate for lung function is 0.57 suggesting a strong genetic contribution

# Intra-pair correlation: CF lung disease remains highly heritable over time

Age Group (yo)	MZ Lung Function r	DZ/Sib Lung Function r	Heritability Estimate (MZ DZ/Sib)	
6-10	0.6470 (60 pairs)	0.4729 (n = 131 pairs)	0.35	Decreased reproducibility at young ages
10-14	0.8756 (48 pairs)	0.5238 (n = 114 pairs)	0.70	
14-18	0.9120 (41 pairs)	0.6102 (n = 82 pairs)	0.60	High Heritability
18-22	0.8623 (34 pairs)	0.5056 (n = 49 pairs)	0.71	
22-26	0.8645 (23 pairs)	0.3476 (n = 28 pairs)	1.00	
26-30	0.7872 (13 pairs)	0.3540 (n = 13 pairs)	0.87	



**Correlation decreases with time suggesting accumulation of environmental exposures**

# Intra-pair difference regression quantifies contributions to variation

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2$$

Y = Absolute intra-pair difference

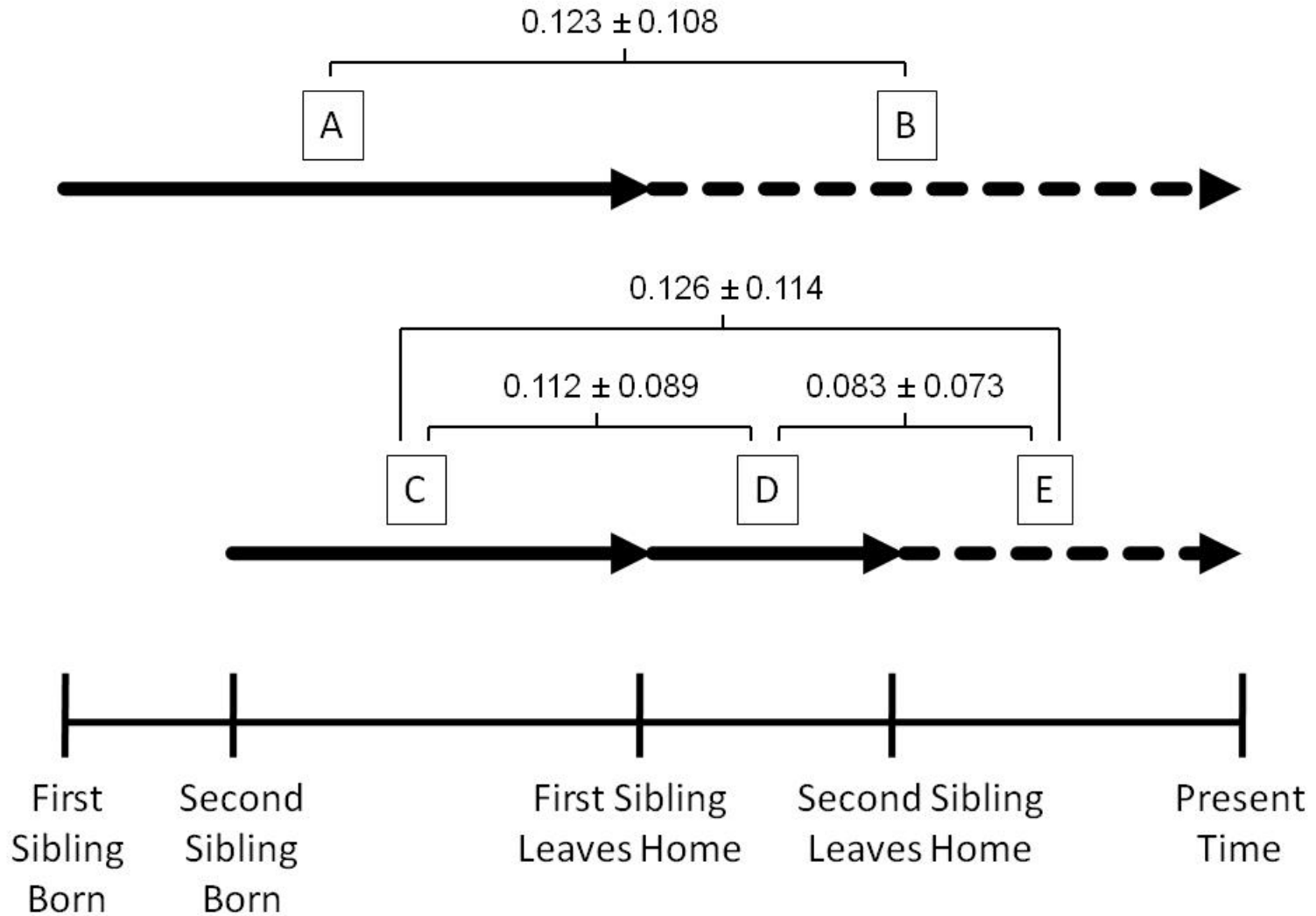
$X_1$  = [0 if living together, 1 if living apart]

$X_2$  = [0 if MZ twins, 1 if DZ twins/siblings]

Co-efficient	Contribution	Value (FEV <sub>1</sub> Percentile)	<i>p</i> value
$\beta_0$	Unique Environment	0.080	<0.001
$\beta_1$	Common Environment (Shared Home)	0.032	0.010
$\beta_2$	Genetic	0.112	<0.001

n = 62 pairs; model overall *p* value: <0.0001

# Intra-individual differences: Following the same individual over time in an independent subject set



n = 40 pairs

# Intra-individual difference regression confirms environmental contribution

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2$$

Y = Absolute intra-individual difference

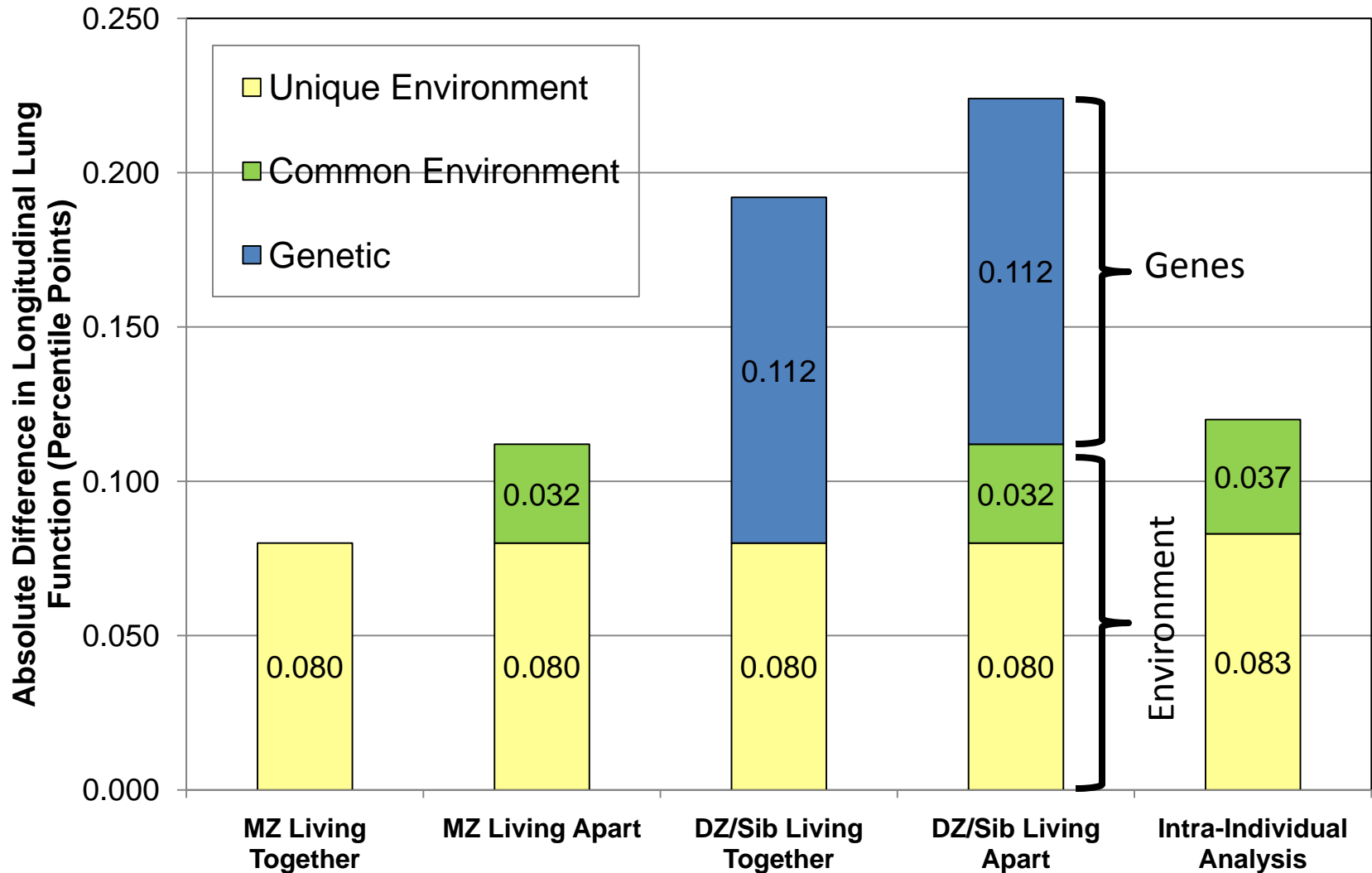
$X_1$  = [0 if no change, 1 if leaving sibling with CF]

$X_2$  = [0 if no change, 1 if leaving parents]

Co-efficient	Contribution	Model 1 FEV <sub>1</sub> Percentile ( <i>p</i> value)	Model 2 FEV <sub>1</sub> Percentile ( <i>p</i> value)
$\beta_0$	Unique Environment	0.070 (<0.001)	<b>0.083</b> (<0.001)
$\beta_1$	Common Environment (Shared Home: Sibling)	0.041 (0.006)	<b>0.037</b> (0.005)
$\beta_2$	Common Environment (Shared Home: Parents)	0.013 (0.310)	

n = 40 pairs; model 2 overall *p* value: 0.007

# Genetic and environmental factors contribute equally to variation in lung function



# Conclusions

- Heritability remains constant over time despite increasing environmental effects...genetic modifier studies may need to stratify by age
- Genetic and environmental contributions are roughly equal...emphasizing the need for both types of studies
- The unique environment contributes more to variation than does the common environment, but stochastic effects cannot be parsed out

# Acknowledgments

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