A. Chakravarty — Case Western

Complex Diseases

- defining "complex" is important

Most genetic diseases are due to multiple gene effects

Mendelian Disorders

- mutations are rare + of recent origin (individual mutations)
- mutational diversity high
- mutation necessary + sufficient for disease

Complex Disorders

- multiple genes
- susc. alleles have low penetrance
- susc. alleles have high pop. freq.
- environ, stochastic, + somatic/epigenetic factors important

Genetic Risk

$\lambda_R = \frac{\text{incidence among relatives}}{\text{population incidence}}$ = measurement of familial effects

$\lambda_R \cong 1000$ for mendelian (single gene $\therefore = 1000$)

$\lambda_R \geq 10$ for complex

$\lambda_{gene} = 2$ for complex

Complex Trait Genes in Humans

- none ID by positional cloning
- recurrence risk is low
- genes have small allelic effects

Best Successes
- testing SPECIFIC genes (eg HLA)
- mendelian subphenotypes (BRCA1, 2)
- studies in genetic isolates

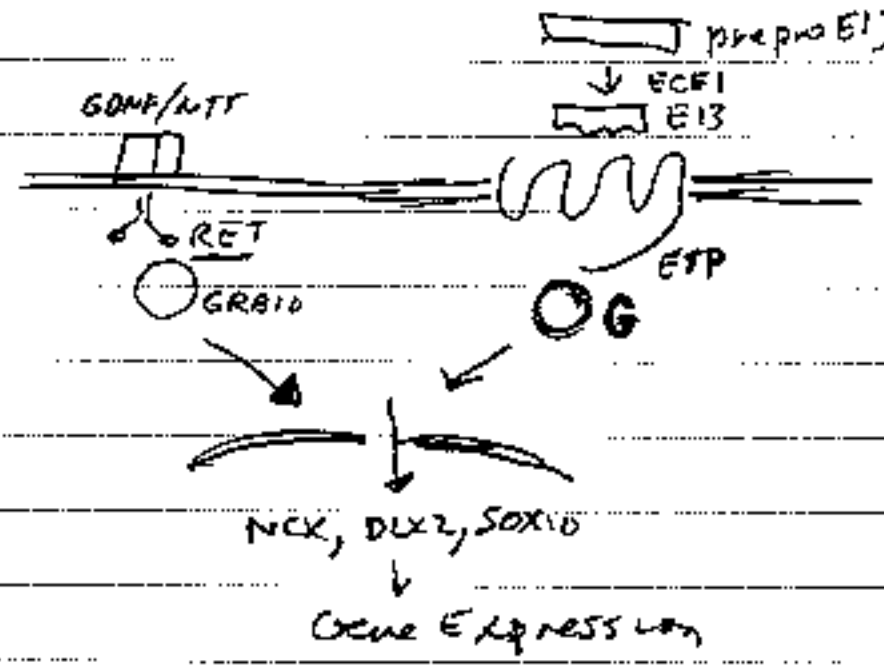
Hirschprung Disease HSCR

- ganglion cells do not innervate part of colon

Incidence: 1/5000 live births
Heritability: 100%
No consistent inheritance pattern
Sibling risk = 4% ($\lambda_s = 200$)
Variability in segment length
Sex ratio 4♂ : 1♀
Risk varies w/ length + gender

could this be some imprinting

Discordance of MZ twins suggests environmental factors



RET = receptor ≈ 70% of human mutations

- in mouse – no ♂/♀ difference
- in humans – mutations only found in heterozygotes

In humans
- presence of RET mutations had low penetrance
- so ... maybe other genes

LOD Scores
- most families show linkage to RET
- found another peak on Chr 9 (near FD locus)
(9q31)

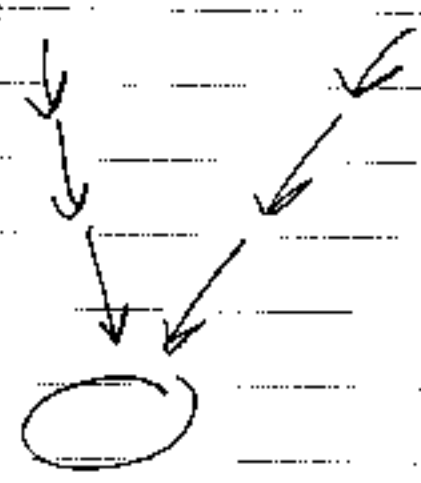
Segregation of RET + Chr 9q31

Family	RET haplo shown	RET mutation	9q31 haplo shown
+	+	standard	-
+	+	standard	-
+	+	unusual	+
+	+	more found	+
-	-	"	+

} NOT ALL RET MUTATIONS HAVE SAME PATTERS

Multiple Genes found → then what

Combined the alleles should better explain inheritance



If you have two pathways

Variation in BP candidates

Density (θ)

	African	US whites
Coding	2200 bp	1900
Synonymous	1250	900
Non-syn.	2900	3100
Noncoding	1401	1550
Total	1700	1700

θ = nuc. diversity
= avg. het.

5' UTR } more highly conserved than coding/intron
3' UTR }

Coding + intron Sim. in degree of polymorphism

SNP

- rarer = younger (assume) } will that differ for
- younger = less different than others