# MENDELIAN VS. COMPLEX / LINKAGE VS. ASSOCIATION

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• So, power is absolutely critical











### **MENDELIAN TRAITS**

- Monogenic model of inheritance
- Mutant alleles
  - **Highly penetrant** (linkage analysis)
  - Rare in general population
- Small impact on public health but large impact on biology
- Examples
  - Cystic fibrosis, phenylketonuria, hemophilia, ...
  - Monogenic forms of common disorders -- MODY (diabetes), early-onset Alzheimer's disease...



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- Testing deviation from random co-segregation between the phenotype and markers



#### LINKAGE CAN EFFECTIVELY IDENTIFY THE ALLELES OF LARGE EFFECTS



# **COMPLEX TRAITS**

- Complex model of inheritance multiple genetic and environmental factors and their interactions
- Medium and low effect alleles (linkage will not work -- sampling via proband does not guarantee presence of mutation)
- Examples: common diseases such as hypertension, breast cancer, diabetes; quantitative traits such as height, weight, blood pressure, lipid levels

Cases (patients)

Controls (healthy) 

Cases (patients)



Cases (patients)



Cases (patients)



# ASSOCIATION ANALYSIS (QUANTITATIVE TRAIT)

	Dat	ta		
ID	Trait	Genotype		₽.
1	8.3	AA		
2	8.5	AB	Trat	σ, .
3	9.1	AB		00 -
Ν	10.0	BB		



	Summary table		
	AA	AB	BB
Ν	222	230	48
Mean	8.01	8.96	10.01
SD	0.39	0.37	0.33

<u>Null hypothesis</u>: group means are the same ANOVA, Z-test, T-test Regression analysis

# LINKAGE VS. ASSOCIATION

- Association is a method to identify an allele
- Linkage is a method to identify a region
- Many differences between methods

	Linkage	Association
Most powerful design	Families with extreme phenotype	Case/control
Variants captured	Any of strong effect	Common (chip design)
Model usually captured	Loci with (rare) variants of strong effect	A common variant (usually small to moderate effect)
5,000 markers	Great!	Useless
1,000,000 markers	Reduce to 5,000	Great!
GW sig. threshold	15.2	29.72









# OUTLINE

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**Stats:** association, significance, multiple testing

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# Wed GWAS stories

**Stats:** association, significance, multiple testing