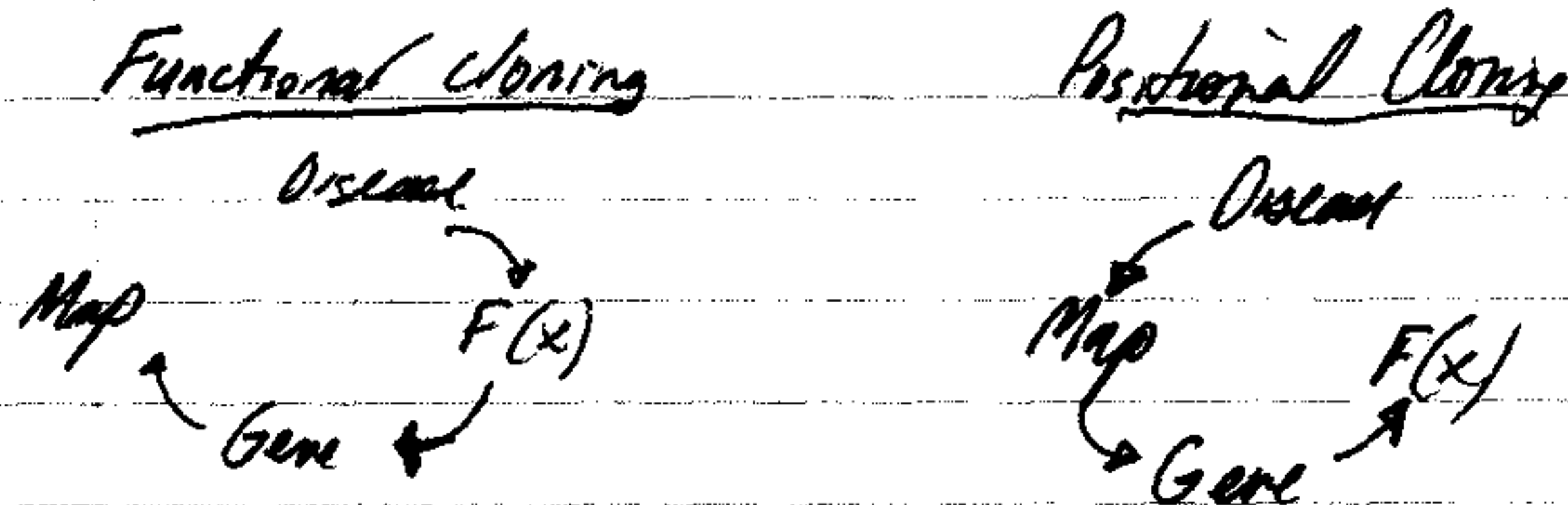


David Cox - Genome Evolution & Human Genetic Diseases

Human Genome Variation \rightarrow Human Genetic Disease



correlation of genetic vs. phenotype variation

4 Basic Principles of ~~comparative~~ Genetic Medicine

① Human Genome is 3×10^9 bp

② 99.9% identical in all humans

③ Classify disease by genetic diff. in affected indiv.

④ Design therapies for groups of indiv. who have a common genetic etiology

\rightarrow very similar to with infectious diseases

Evolution

Neo-Darwinists view of Molecular Evolution

① positive selection rather than mutation play the major role in molecular evolution.

② almost no mutant genes are selectively neutral

③ random drift NOT important

Neutral Theory

- most intraspecific variation DUE to drift/mutation
- weaker f(x) constraints → higher % of variation
- favorable mutations too rare to play major role

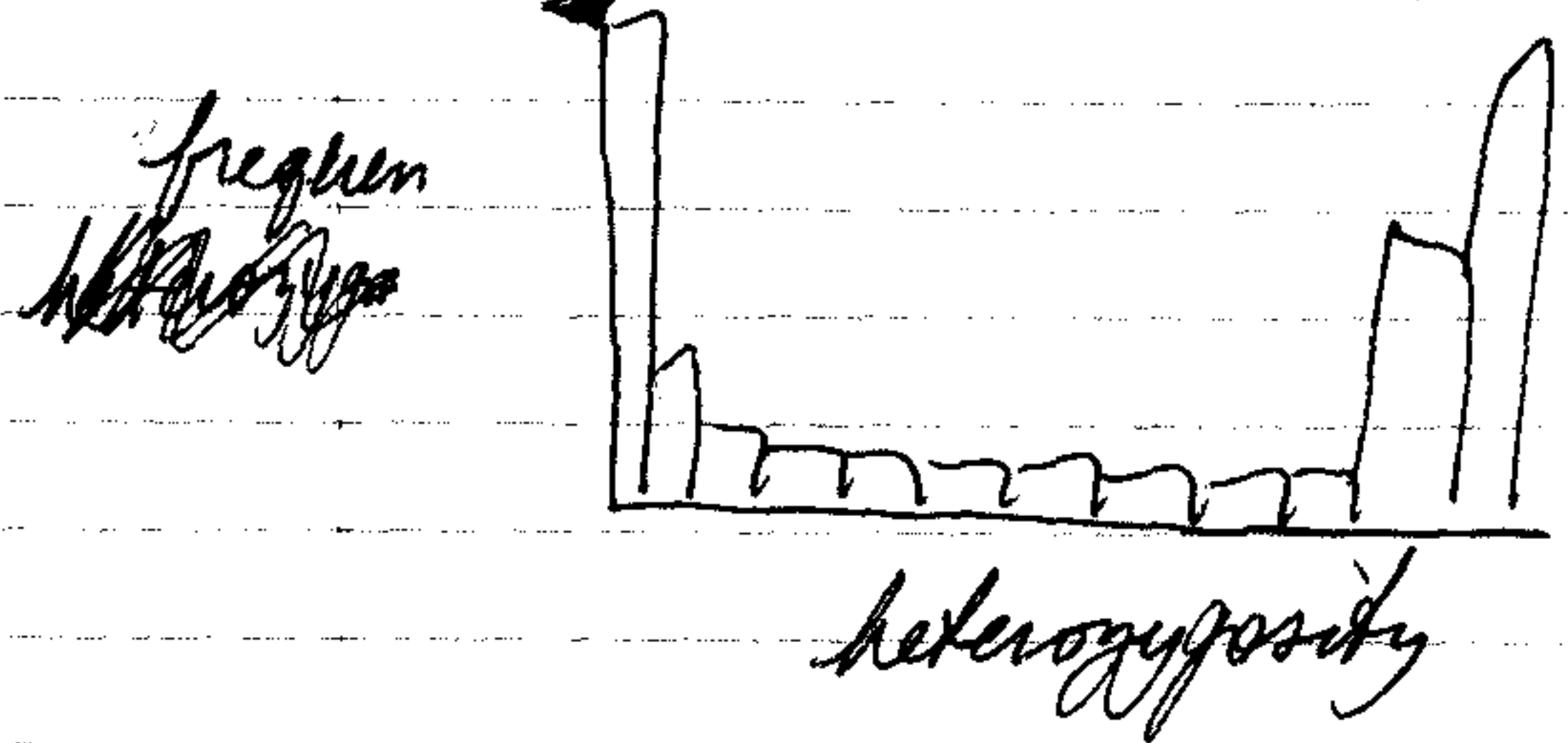
Supporting Evidence

dist. of

- pseudogenes have higher subs. rate than homologs
- synonymous subst. → non-syn.
- average heterozyg. fits predictions
- polymorphic alleles fits predictions

but many more rare alleles than neutral theory predicts

→ suggests that these are deleterious (e.g. human genetic disease)



Argues that stabilizing selection is the most common.
 Argues that directional selection occurs only w/ environmental changes

So - Goals of Human Genome Project

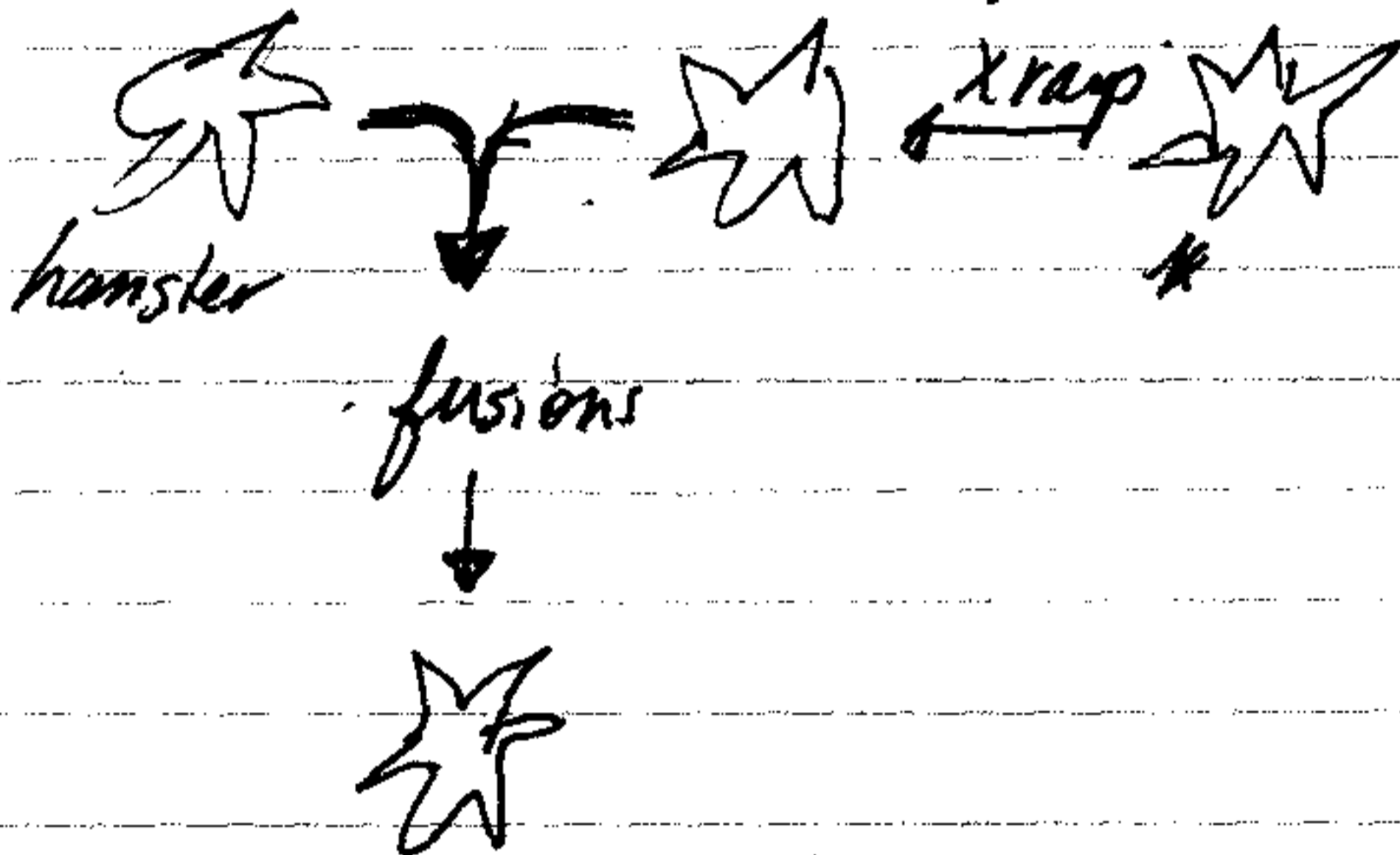
Physically isolate & order pieces

ID all human genes & position

Compare structure w/ other organisms

New technologies to sequence rapidly & cheaply

Whole Genome Radiation Hybrid Mapping



- hamster + $\frac{1}{3}$ of human genome in 5×10^6 bp pieces
- can map w/ cosegregation
- use likelihood methods to assign orders