Bioinformatics

CS300

Chapter 1:
Using Bioinformatics to study genetic disorders

Fall 2019

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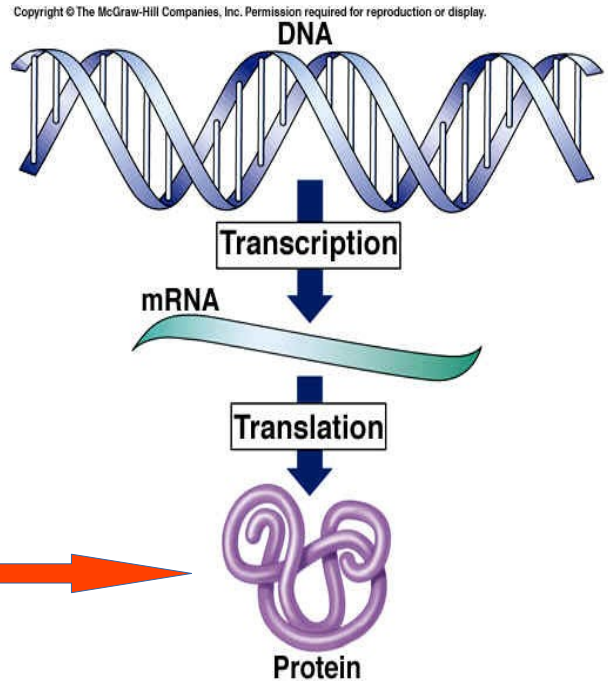
Genetic Disorder

- A disorder/disease with a genetic component
- Single gene disorders
- Mutation(s) in the sequence of a single gene
- Alters or eliminates protein product
- Caused by one or more abnormalities in the genome
  - substitutions
  - insertions
  - deletions
  - rearrangements

Mutations and Their Potential Effects

NonSense Mutation: a mutation in which a sense codon that corresponds to one of the twenty amino acids specified by the genetic code is changed to a chain-terminating codon.

Mutation is Here at DNA



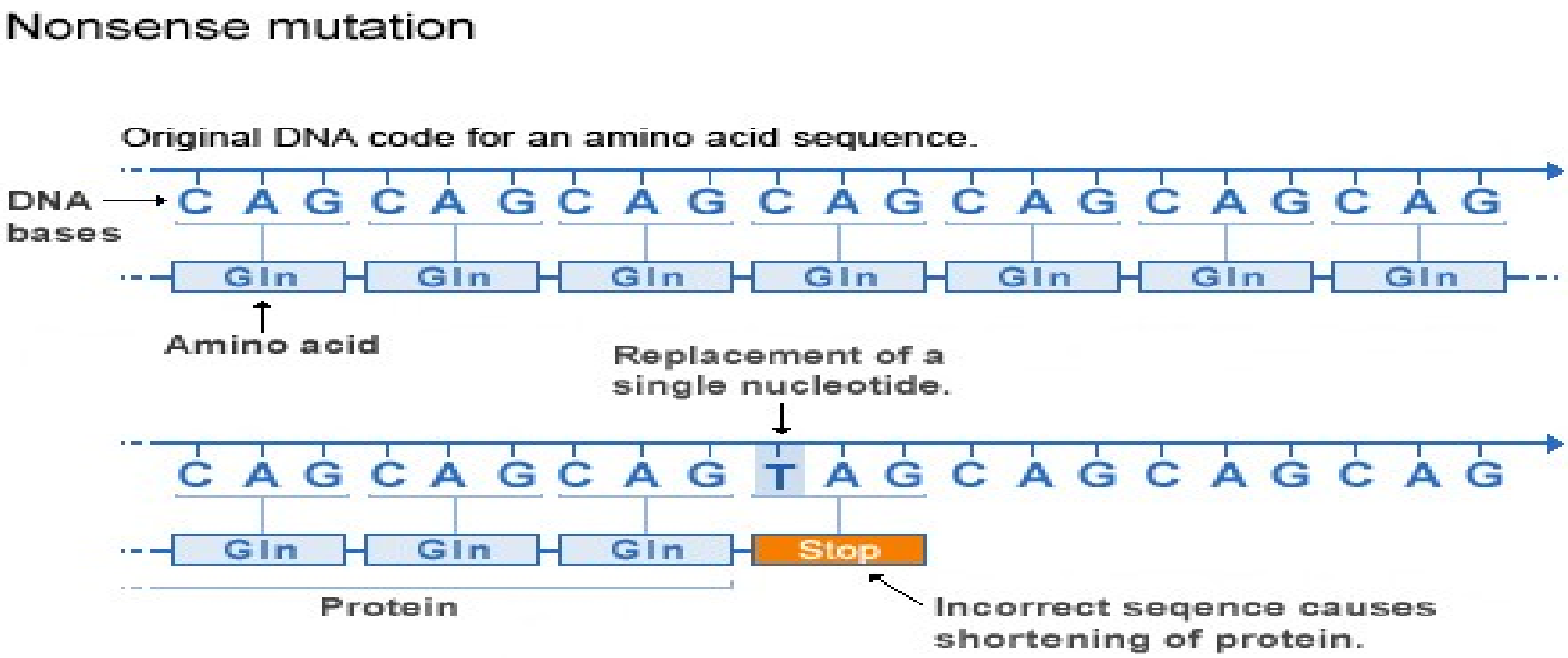
Mutation is noted here at protein

Mutations and Their Potential Effects

- Missense substitutions
- Nonsense substitutions
- Insertions/Deletions

Mutations that Alter Protein Products and

Mutations that Eliminate Protein Products



BioPython Programming

- `# install biopython`
- `python3 -m pip install biopython # global install`
- `python3 -m pip install biopython –user # local install`

```
import Bio # from python3 shell
print(Bio.__version__) # 1.74
```

General Website:
https://biopython.org/

Getting Started:
https://biopython.org/wiki/Getting_Started

Two Cool Programs To Write!!

ALLEGHENY COLLEGE

sequenceCompare.py

```
        Sequence Comparison tool:
        Usage: ./sequenceCompare.py

Note: The entered sequences must be the same length!!
Enter sequence :atcg
Enter sequence :attt

         SeqA_str : atcg
         SeqB_str : attt

        Sequences are different at position : 2
         SeqA_str[i] base is : c
         SeqB_str[i] base is : t

        Sequences are different at position : 3
         SeqA_str[i] base is : g
         SeqB_str[i] base is : t
```

Compare sequences to find their differences!

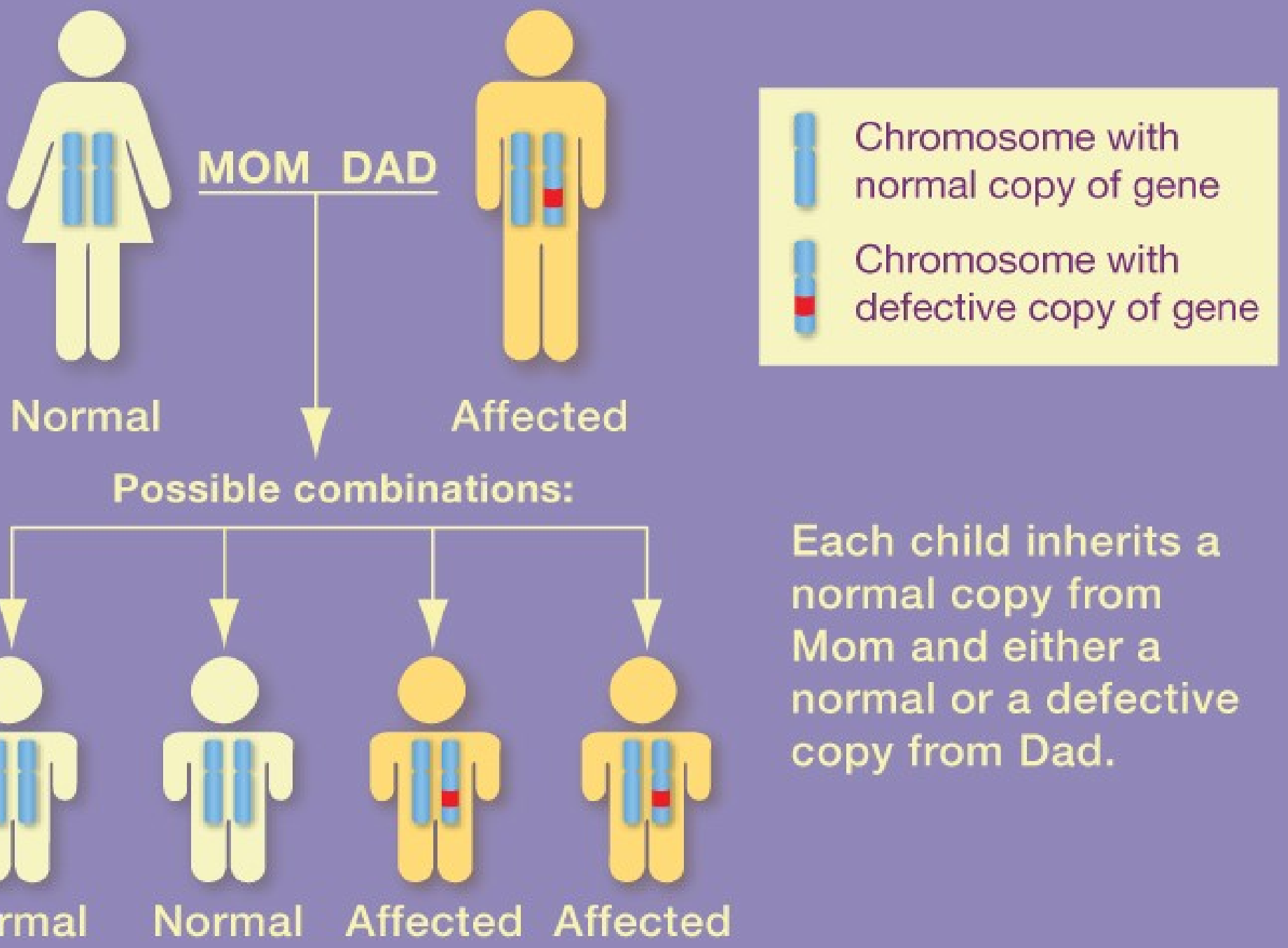
smallTranslator.py

```
Original seqDNA     : atgcccgctttcccccccccc Length : 21
DNA to RNA          : augcccgcuuucccccccccc
RNA to DNA          : atgcccgctttcccccccccc
PROT from RNA       : MPAFPPP
```

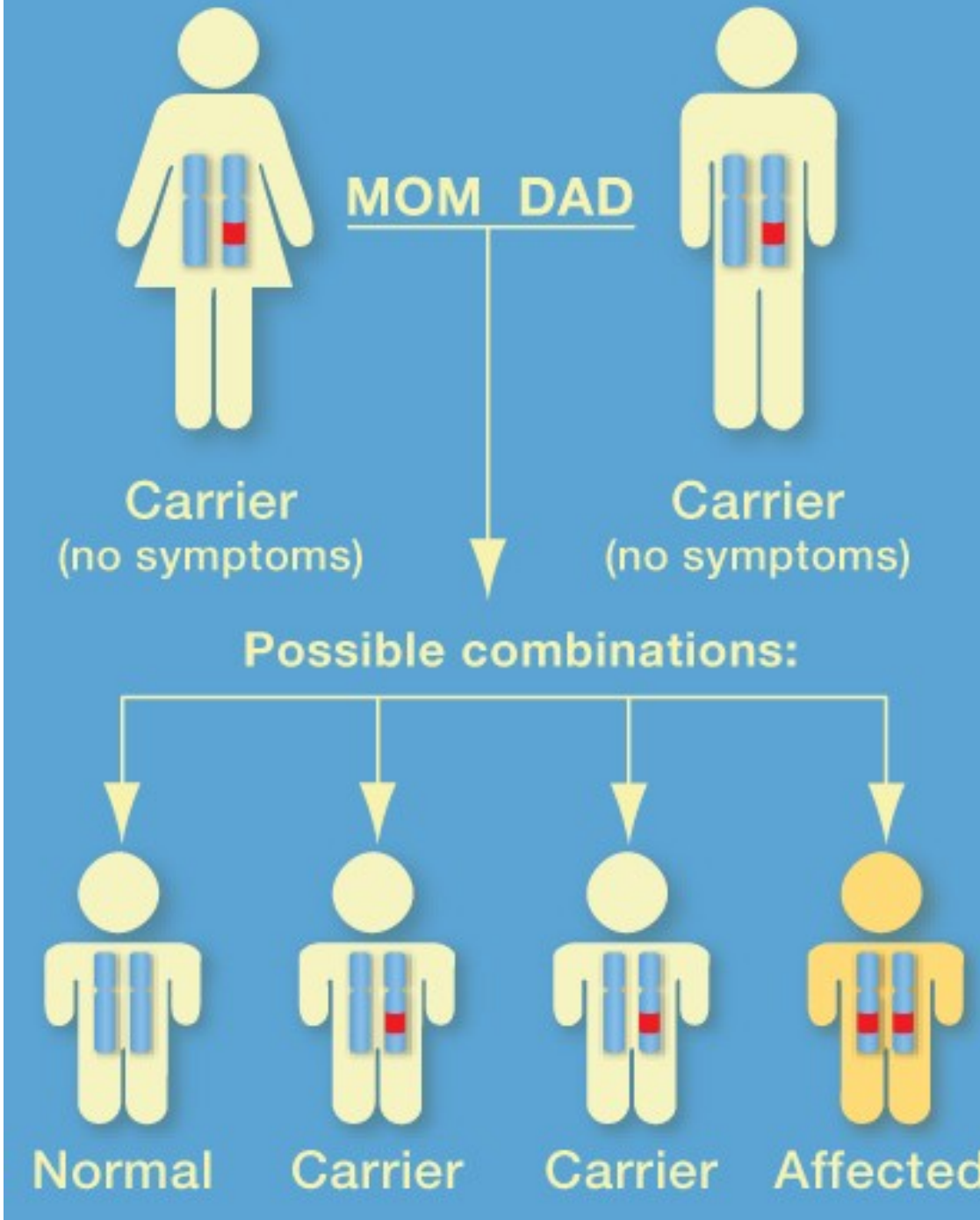
Derive protein sequences from DNA code!

Where Do Some of These Mutations Come From?

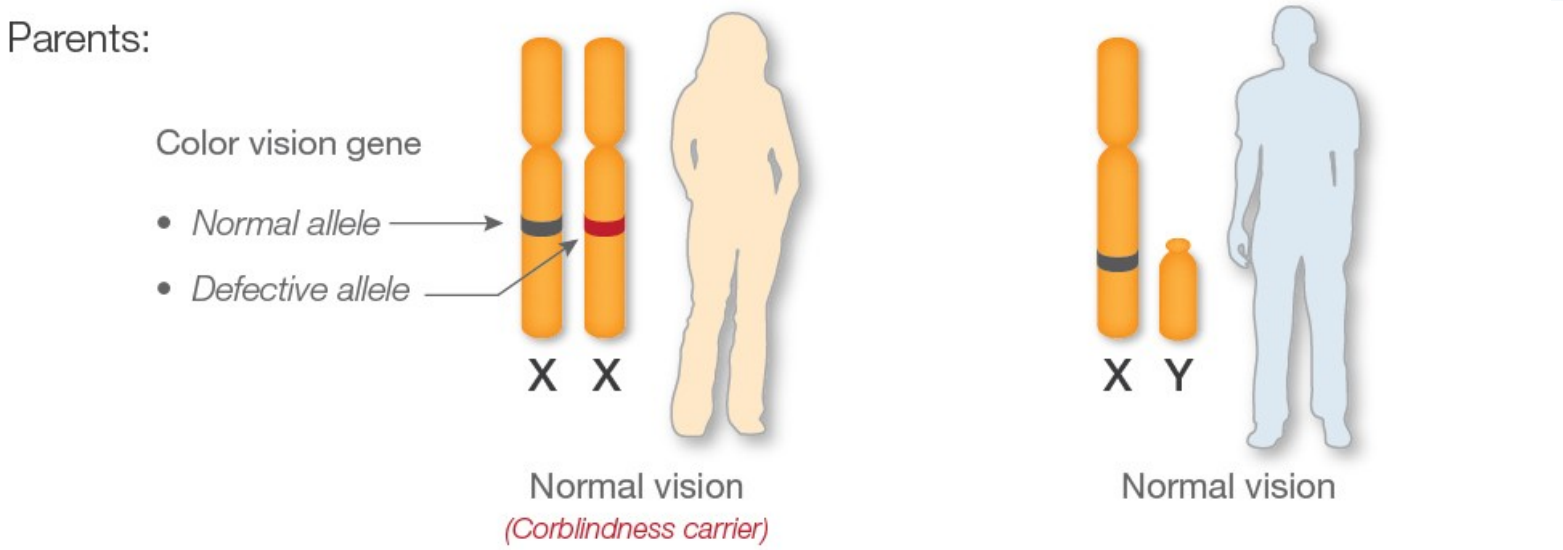
Autosomal Dominanant Inheritance

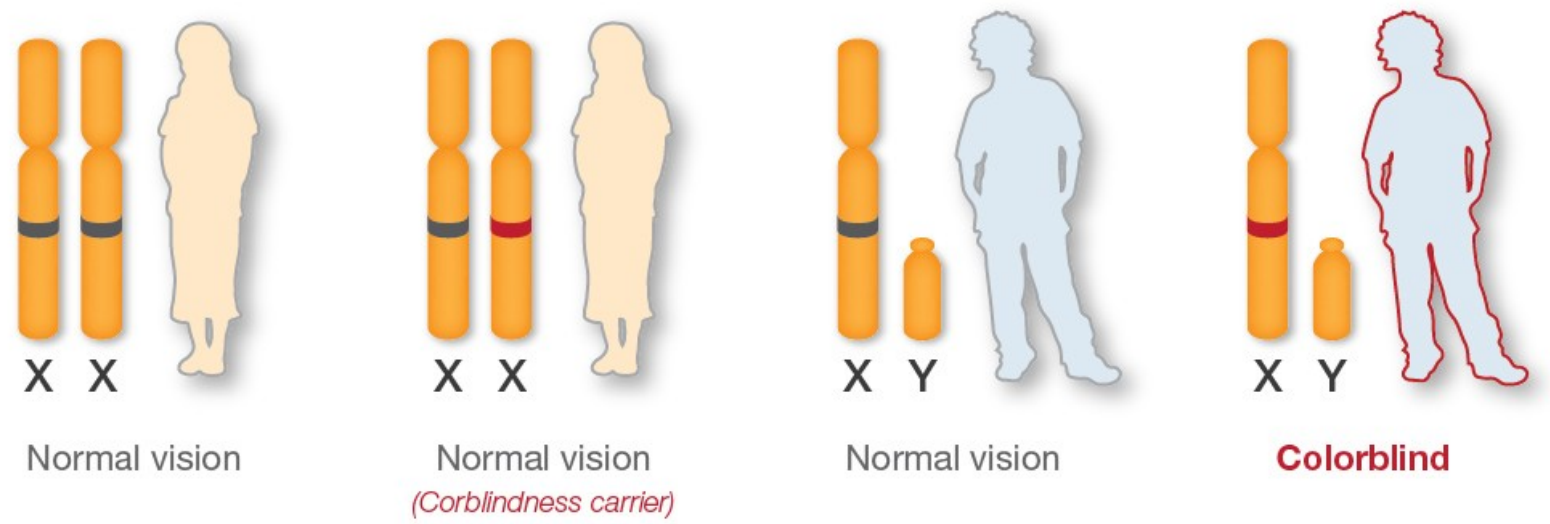


Autosomal Recessive Inheritance



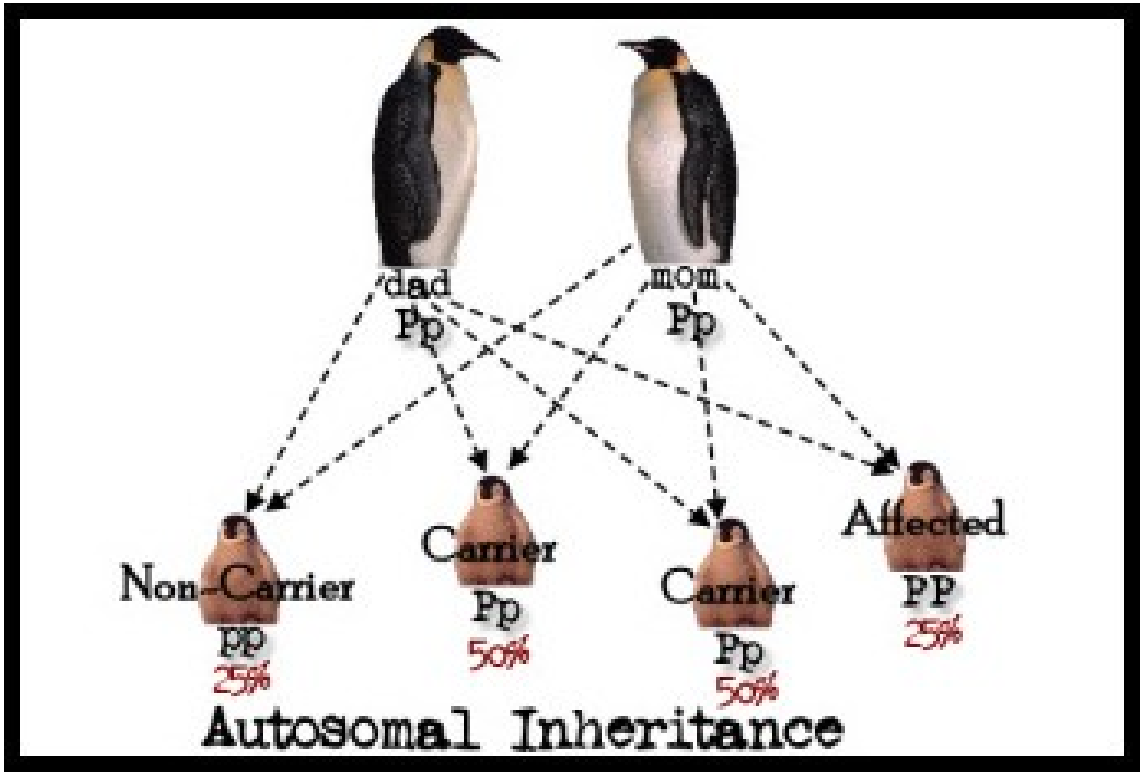
X-Linked Inharitance





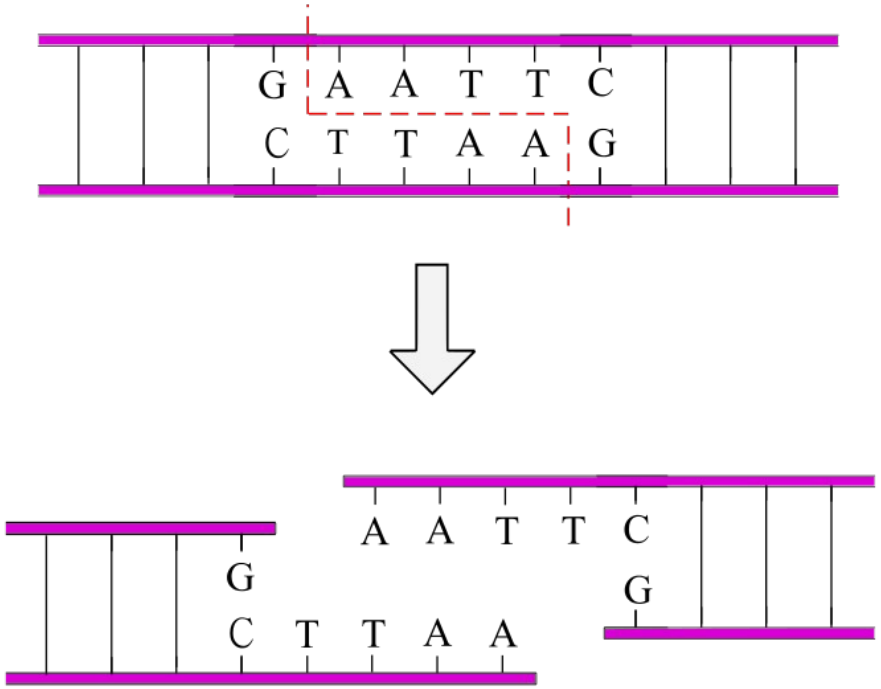
Single Gene Disorders

- Inheritance patterns are relatively simple
- Chances of inheritance in the text generation can be predicted by studying patterns in past generations.



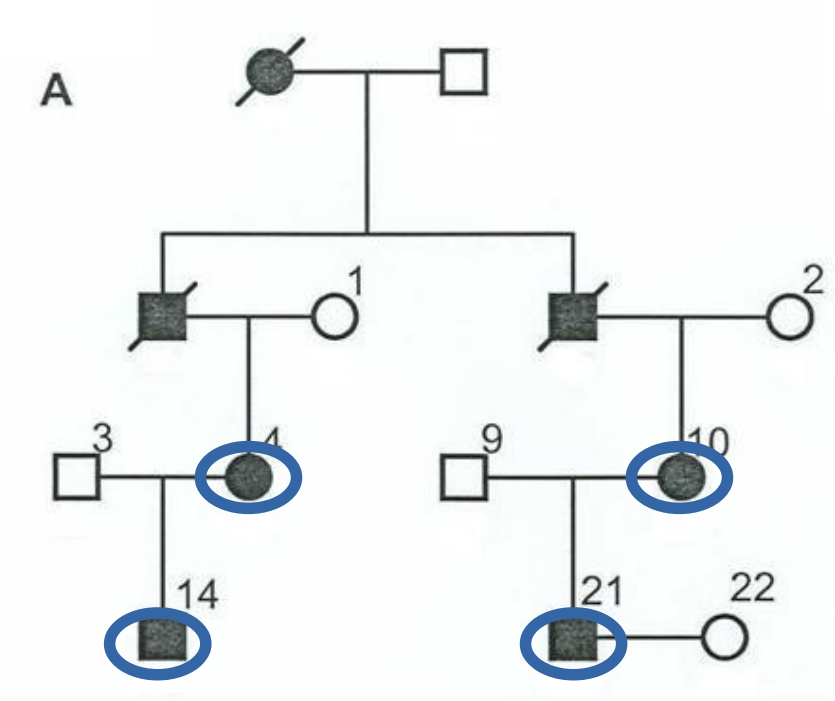
Single Gene Disorders

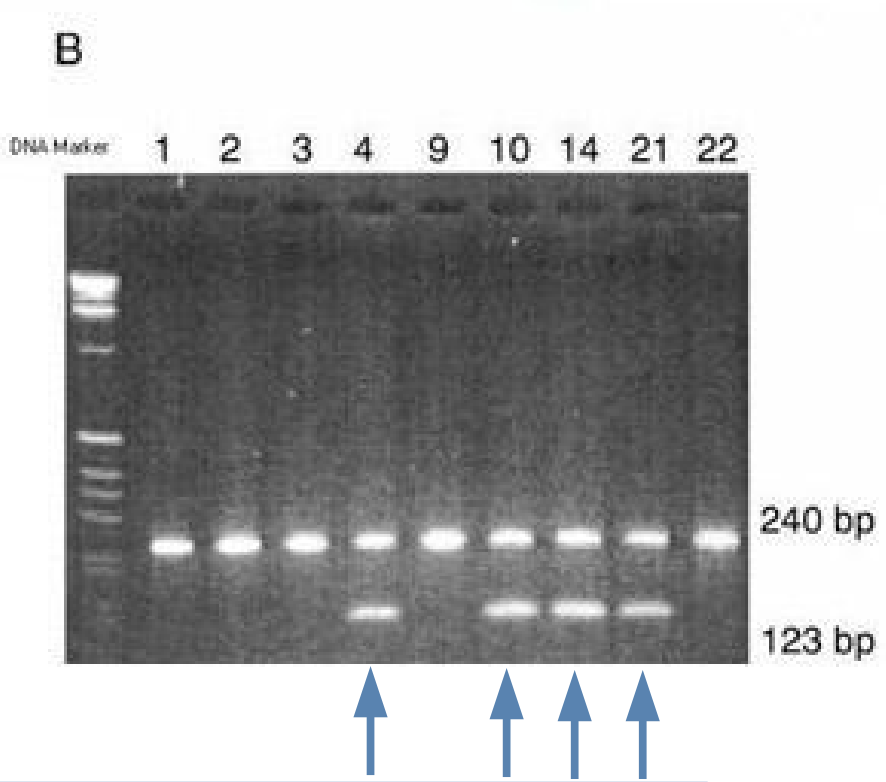
- Most genes identified in the 1980s-1990s
  - Pre-Bioinformatics: biological wet-lab work
- Restriction enzymes to cut sequences
- Cut DNA at specific sequence
  - 100s of different patterns
  - Disorder-breading sequences could be studied



Single Gene Disorders

Pedigree analysis + Restriction Digest Analysis

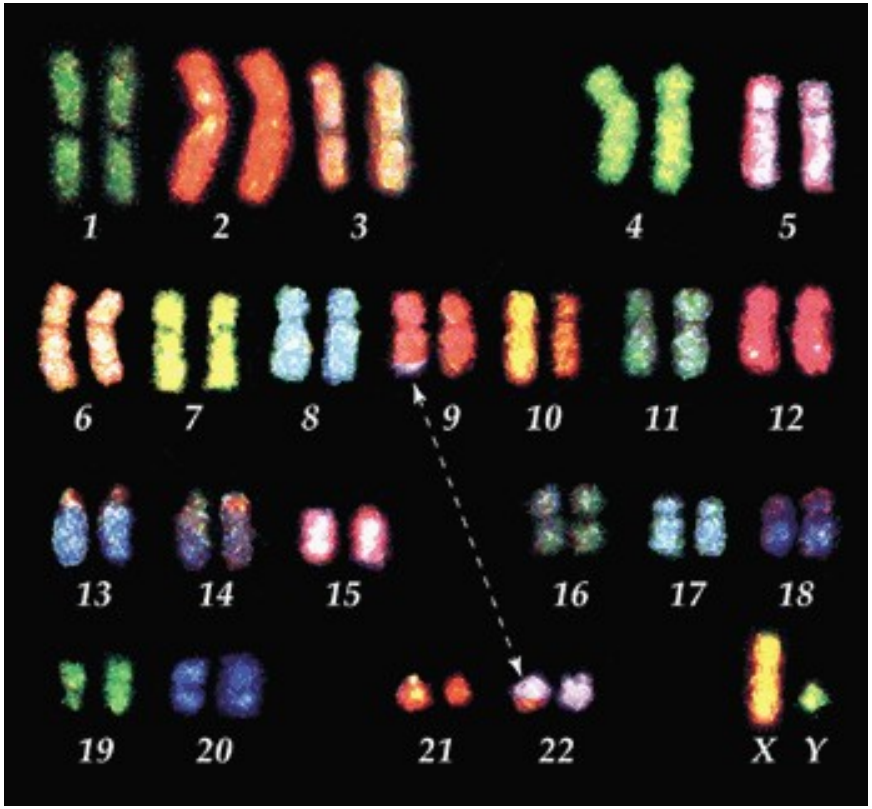


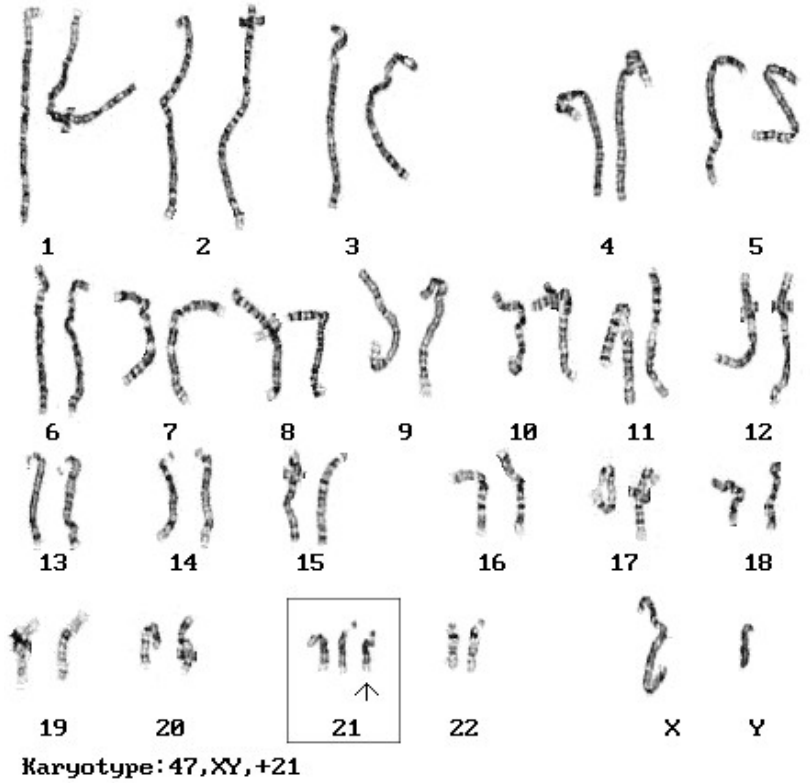


Double bands indicate a carrier of a gene allele

Cytogenetics

- The field of biology concerned with mapping genes to specific locations on chromosomes



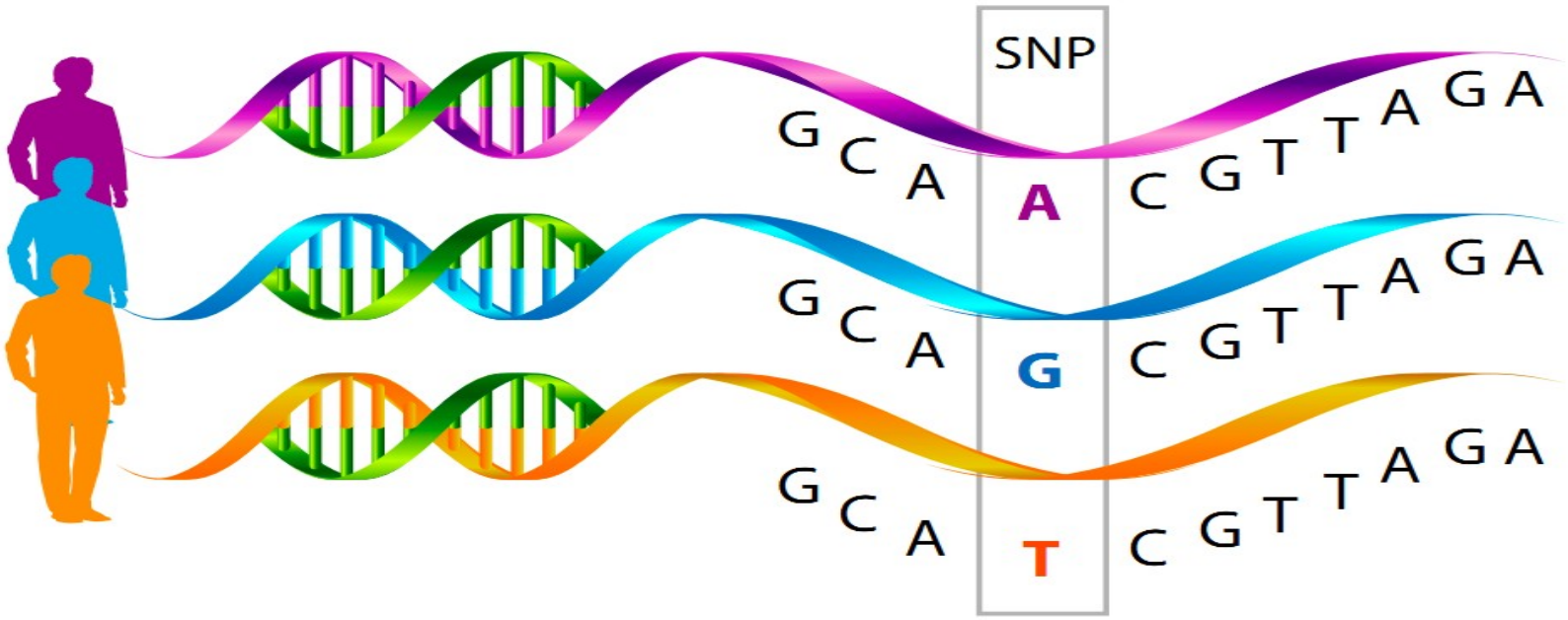


Genetic Disorder

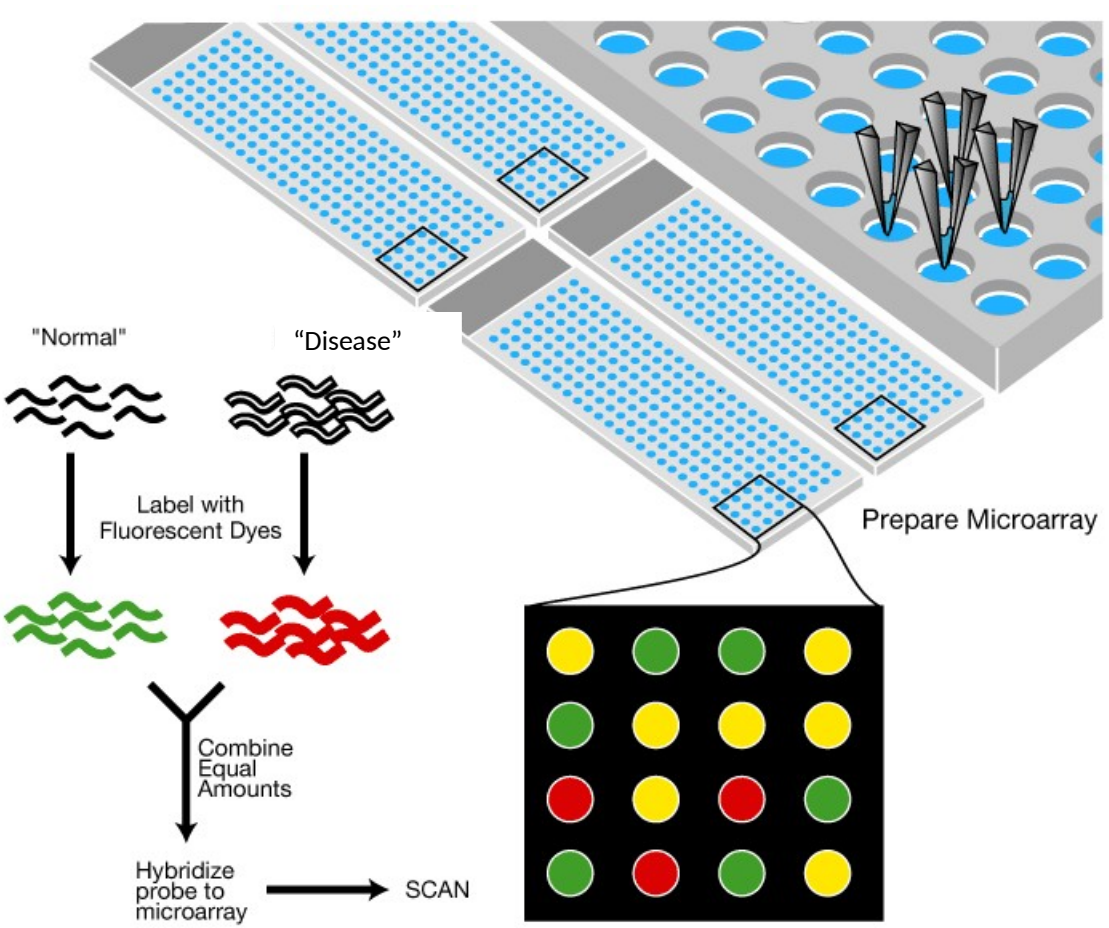
- A disease with a genetic component
- Caused by one or more abnormalities in the genome
- Complex or multifactorial disorders
  - Do not have a single genetic cause
  - Likely associated with the effects of multiple genes in combination with lifestyle and environmental factors
  - Do not have a clear cut pattern of inheritance

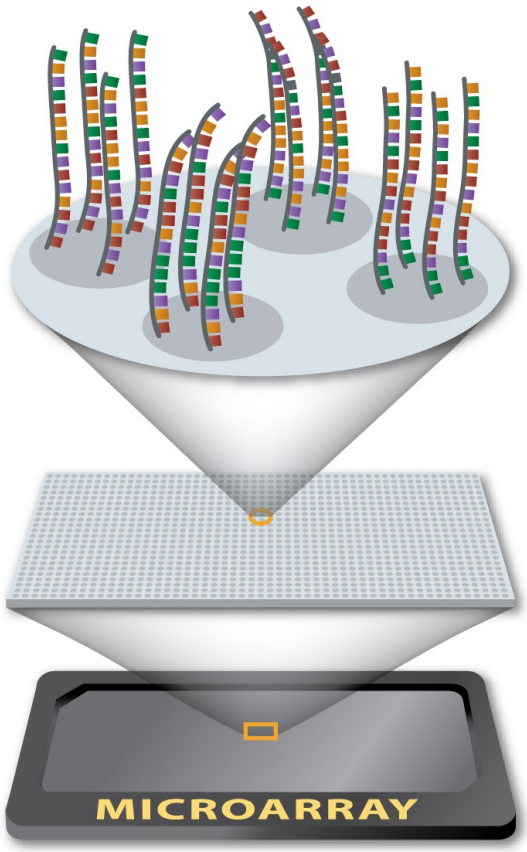
Genome-Wide Association Studies

- new technology/analysis - early 2000s
  - bioinformatics
- screen 1000s of genomes at once for **SNPs**
  - single nucleotide polymorphisms
  - Some SNPs may indicate disorders

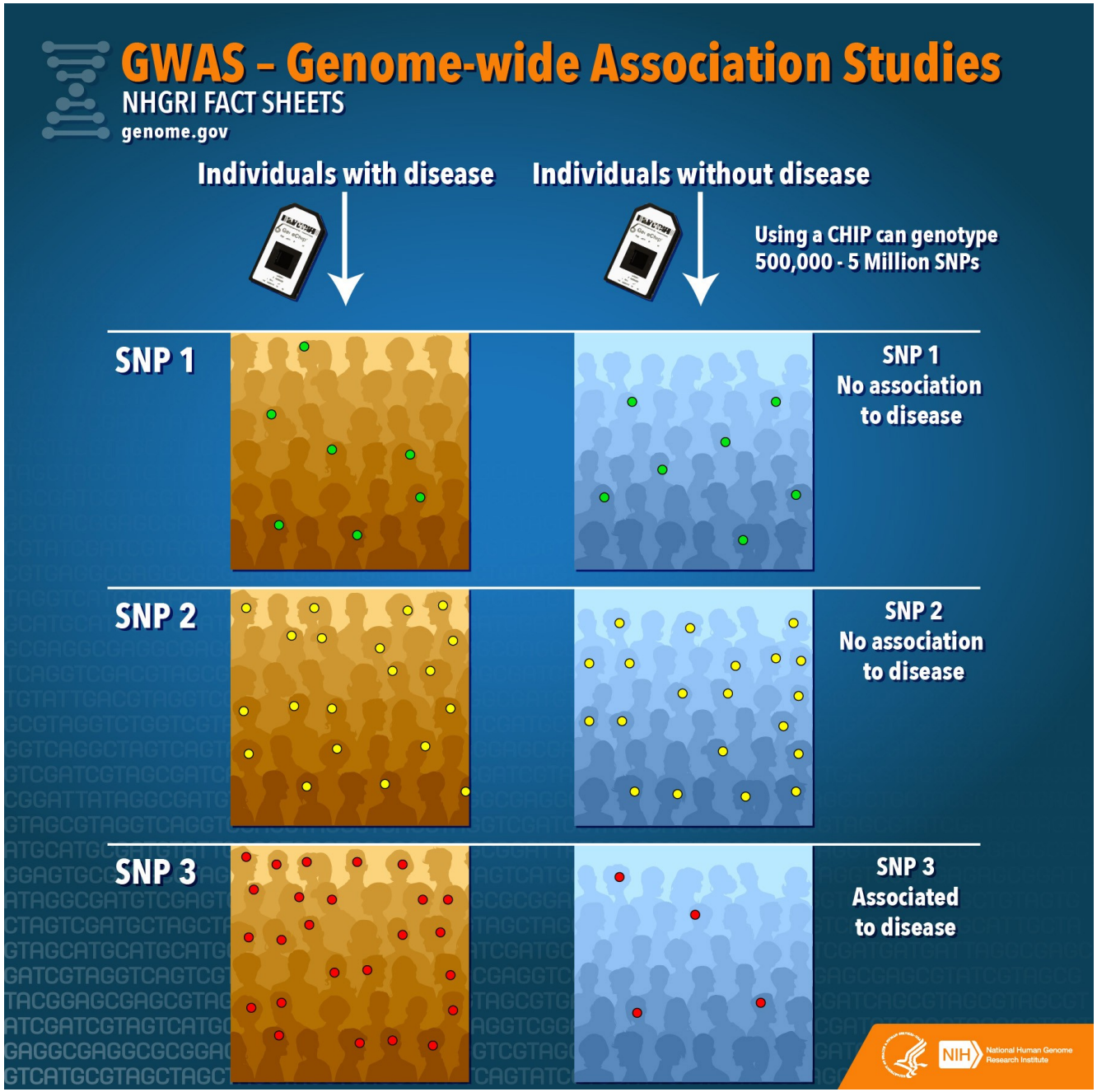


DNA Microarray

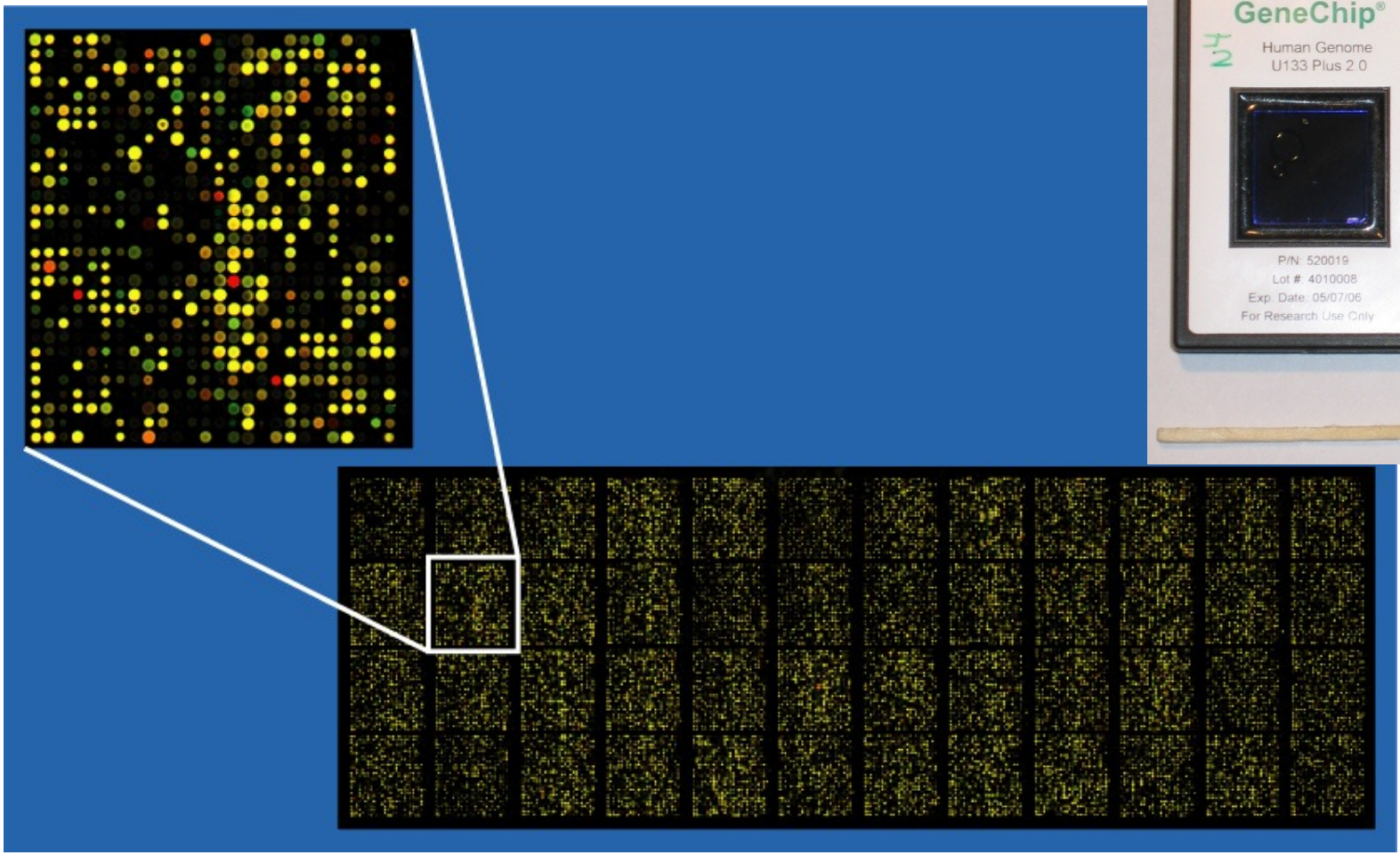




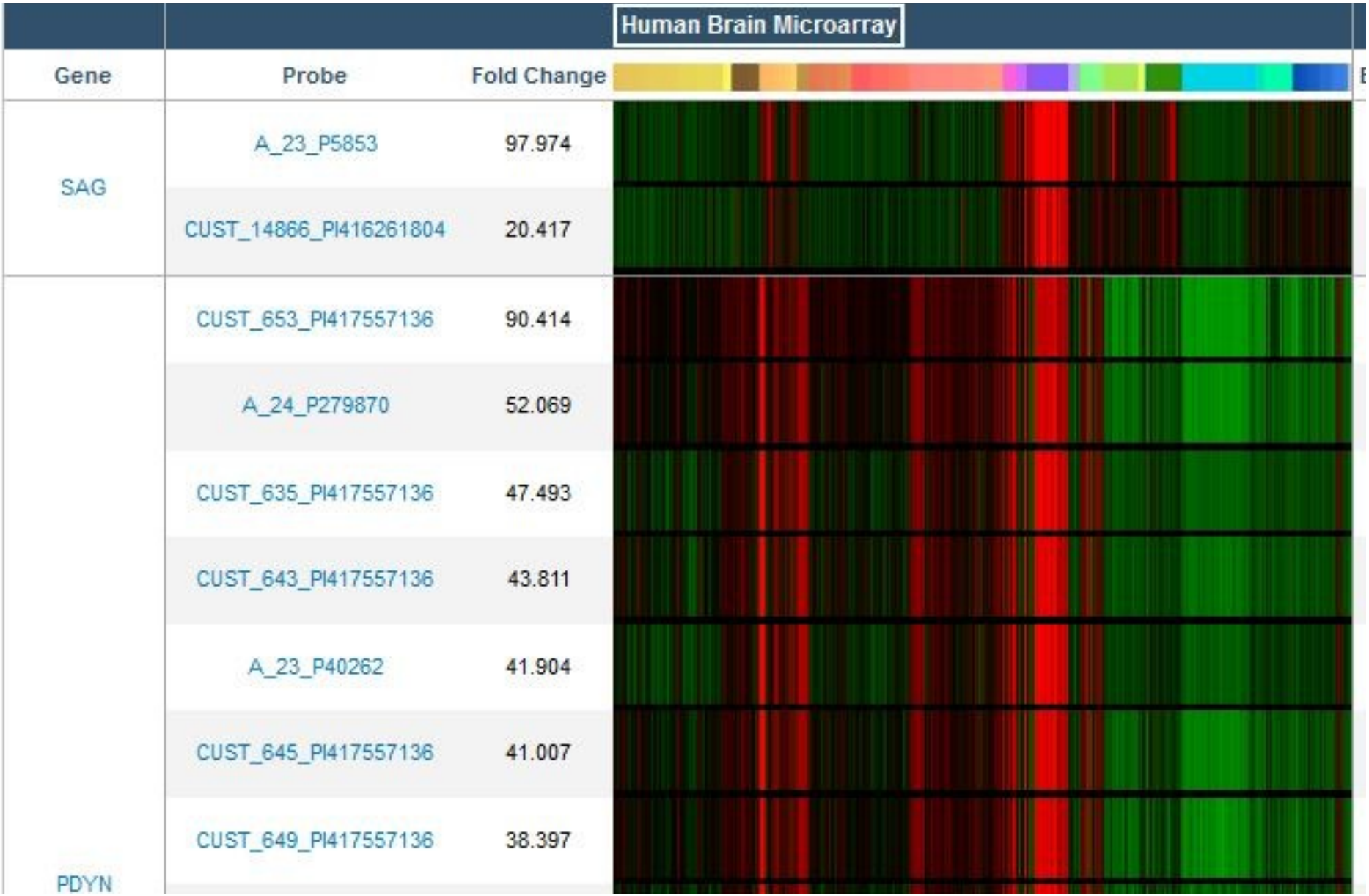
Testing for genes of a specific allele


GWAS – Genome-wide Association Studies
NHGRI FACT SHEETS
genome.gov
Individuals with disease
Individuals without disease
Using a CHIP can genotype
500,000 - 5 Million SNPs
SNP 1
SNP 1
No association
to disease
SNP 2
SNP 2
No association
to disease
SNP 3
SNP 3
Associated
to disease
NIH
National Human Genome
Research Institute

DNA Microarray



DNA Microarray



Gene	Probe	Fold Change
SAG	A_23_P5853	97.974
	CUST_14866_PI416261804	20.417
PDYN	CUST_653_PI417557136	90.414
	A_24_P279870	52.069
	CUST_635_PI417557136	47.493
	CUST_643_PI417557136	43.811
	A_23_P40262	41.904
	CUST_645_PI417557136	41.007
	CUST_649_PI417557136	38.397

Candidate SNPs that May Be Correlated with Disorders Using *Genome-Wide Association Studies* (*GWAS*)

Table 2. GWAS results for all SNPs with $p < 10^{-6}$ in the 23andMe cohort.

SNP	Chr	Position	Region	Alleles	MAF	Cohort	OR	p
rs34637584	12	39020469	*LRRK2*	G/A	0.002	23andMe	9.615 (6.43–14.37)	1.82×10^{-28}
						IPDGC	–	–
i4000416	1	153472258	*GBA*	T/C	0.005	23andMe	4.048 (3.08–5.32)	5.17×10^{-21}
						IPDGC	–	–
rs356220	4	90860363	*SNCA*	C/T	0.375	23andMe	1.285 (1.22–1.36)	2.29×10^{-19}
						IPDGC	–	–
rs12185268	17	41279463	*MAPT*	A/G	0.211	23andMe	0.769 (0.72–0.82)	2.72×10^{-14}
						IPDGC	–	–
rs10513789	3	184242767	*MCCC1/LAMP3*	T/G	0.201	23andMe	0.803 (0.75–0.86)	2.67×10^{-10}
						IPDGC	0.873 (0.83–0.92)	1.7×10^{-6}
rs6812193	4	77418010	*SCARB2*	C/T	0.365	23andMe	0.839 (0.79–0.89)	7.55×10^{-10}
						IPDGC	0.90 (0.86–0.94)	3.29×10^{-6}
rs6599389	4	929113	*GAK*	G/A	0.075	23andMe	1.311 (1.19–1.44)	3.87×10^{-8}
						IPDGC	–	–
rs11868035	17	17655826	*SREBF1/RAI1*	G/A	0.309	23andMe	0.851 (0.80–0.90)	5.61×10^{-8}
						IPDGC	0.95 (0.91–0.996)	0.033
rs823156	1	204031263	*SLC41A1*	A/G	0.183	23andMe	0.827 (0.77–0.89)	1.27×10^{-7}
						IPDGC	–	–
rs4130047	18	38932233	*RIT2/SYT4*	T/C	0.313	23andMe	1.161 (1.10–1.23)	2.44×10^{-7}
						IPDGC	1.077 (1.03–1.13)	0.0014
rs2823357	21	15836776	*USP25*	G/A	0.376	23andMe	1.149 (1.09–1.21)	6.32×10^{-7}
						IPDGC	0.971 (0.93–1.02)	0.187

Data for Research

- Typically Protein: **Uniprot**
  - http://www.uniprot.org/
- Search: Pink1 (protein)

- Typically DNA and Genes: **National Center for Biotechnology Informatics (NCBI)**
  - https://www.ncbi.nlm.nih.gov/
- Search: “orchid” in Nucleotide database
  - (https://www.ncbi.nlm.nih.gov/nuccore/NC_030915.1)

NCBI
National Center for Biotechnology Information