

Genomic and Precision Medicine

Week 2: Applying Genomics to Medicine



Jeanette McCarthy, MD
Robert Nussbaum, MD



University of California
San Francisco

advancing health worldwide™

The Lecture

- **MODULE 1:** Background... Mendelian inheritance of disease
- **MODULE 2:** Genetic testing for Mendelian diseases
- **MODULE 3:** Newborn screening
- **MODULE 4:** Carrier testing

Mendelian Inheritance: Significance

- Mendelian disorders (in the aggregate) are present in ~2-3% of all newborns, although disease may not be manifest for years to decades, if ever!

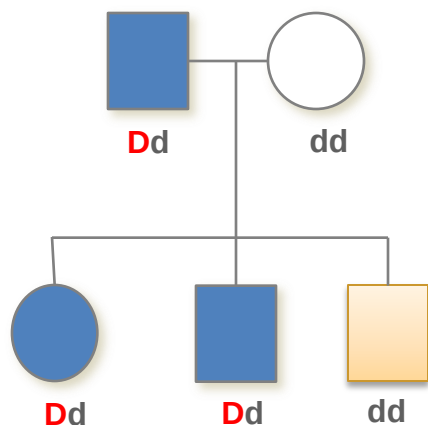
Online Mendelian Inheritance in Man

	Autosomal	X Linked	Y Linked	Mitochondrial	Totals
Genes	13,781	672	48	35	14,536
Disease with genetic basis known	3,758	283	4	28	4,073
Disease with genetic basis unknown	1,569	134	5	0	1,708
Disease suspected of being Mendelian	1,744	115	2	0	1,861
Totals	20,952	1,206	59	65	22,282

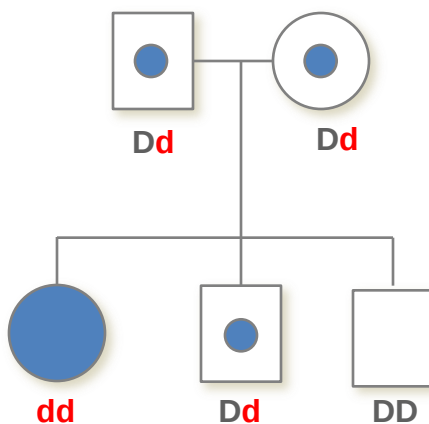


Characteristics of a “Typical” Mendelian Disorder

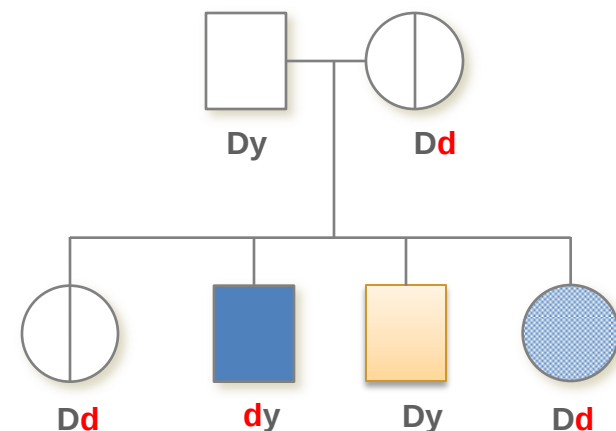
Autosomal Dominant



Autosomal Recessive



X-linked



  Affected male, female

  Unaffected male, female

 Affected female, XL, less severe than male

 Carrier, unaffected but may manifest disease

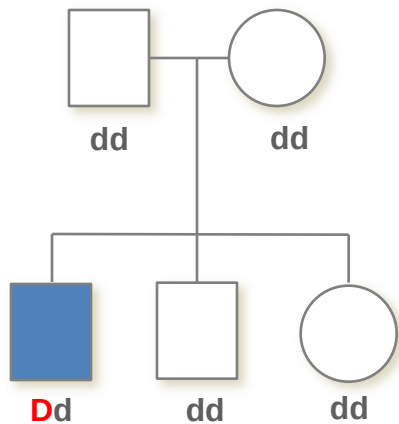
 Carrier, unaffected and will remain so

“Simple” Mendelian Disorders are not so simple

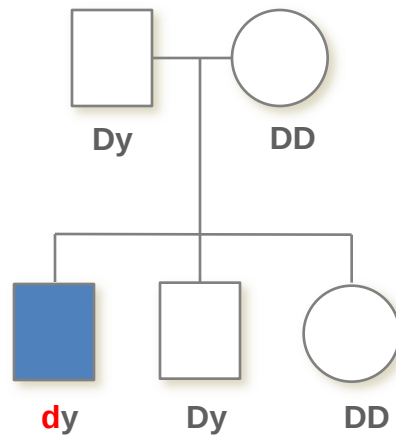
- New Mutation
- Mosaicism – The exception to every cell having the same DNA
- Decreased Penetrance – Disease genotype without phenotype
- Disease in Carriers of Recessive Disorders – Not always “silent”

Situations that Obscure Mendelian Inheritance

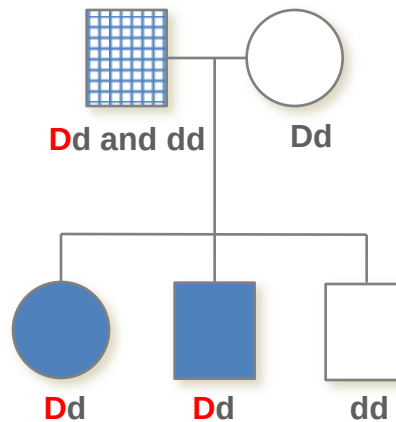
**New Mutation
AD**



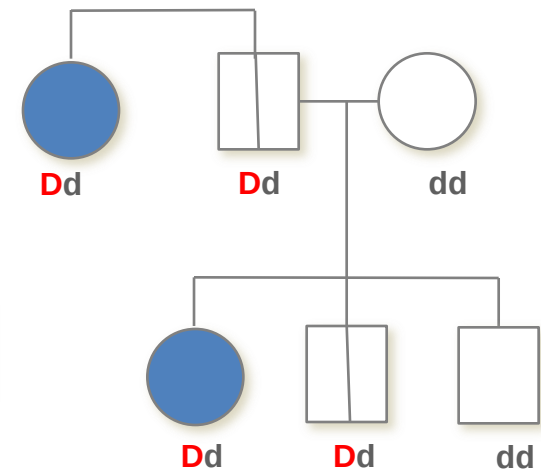
**New Mutation
XL**



**Mosaicism
Autosomal**



Reduced Penetrance



Increased Disease Risk in Carriers of Autosomal Recessive Disorders

- Gaucher Disease: 4-5-fold lifetime risk for Parkinson Disease
- Ataxia Telangectasia: 2-6-fold increased lifetime risk for breast cancer in females
- Cystic fibrosis: Increased risk for chronic sinusitis, bronchiectasis and pancreatitis
- Sickle cell trait: Splenic infarction with altitude, hypoxia or exercise, life-threatening rhabdomyolysis with exercise, renal medullary carcinoma in young adults