

Genetic Disease Summary Table Draft 1/25/02

Independent Variables	Classes	Subclasses	Notes	Examples
Origin of mutation	Stably inherited		Must either be recessive or not affect reproductive fitness	<ul style="list-style-type: none"> Tay-Sachs disease Charcot-Marie-Tooth type X
	Spontaneous	<p>In gamete</p> <p>In somatic germ cell</p> <p>In somatic embryonic cell</p> <p>In somatic cell leading to unrestricted cell division</p>	<p>Caused by DNA replication and editing errors</p> <p>Includes triplet repeat expansions and imprinting errors</p> <p>Affects offspring of individual with mutation; may affect >1 child</p> <p>Leads to somatic mosaicism</p> <p>Leads to tumor formation (cancer/neoplasia)</p>	<ul style="list-style-type: none"> Achondroplasia Prader-Willi syndrome Angelman syndrome Duchenne muscular dystrophy McCune-Albright syndrome Breast cancer Lung cancer
Location of the defect	Autosomal chromosomes		<p>Few differentiators among the 22 autosomal chromosomes</p> <p>No gender bias</p>	<ul style="list-style-type: none"> Cystic fibrosis Canavan disease
	X chromosome		<p>Recessive disorders affect more men than women; dominant disorders affect more women than men</p>	<ul style="list-style-type: none"> Lesch-Nyhan syndrome X-linked hypophosphatemia
	Y chromosome		<p>Affect only males</p>	<ul style="list-style-type: none"> Mutations in azoospermia factor c
Physical nature of the defect	Mitochondrial DNA		<p>Inherited through maternal line</p> <p>Variable phenotypes due in part to heteroplasmy</p>	<ul style="list-style-type: none"> MERRF MELAS Kearns-Sayre syndrome
	Single-gene defects		<p>Most genetic disorders have been associated with multiple types of defects (point mutations, deletions, etc.)</p>	
	Point mutations		<p>Result in synonymous, missense, nonsense, and splice site mutations</p>	<ul style="list-style-type: none"> Achondroplasia
	Deletions		<p>Vary in size from one base pair to >1 gene</p> <p>Effect can be worse with frame shift</p>	<ul style="list-style-type: none"> Cri-du-chat syndrome
	Insertions		<p>Vary in size</p> <p>Effect can be worse with frame shift</p>	<ul style="list-style-type: none"> Myotonic dystrophy
Inversions		<p>DNA sequence is reversed</p>	<ul style="list-style-type: none"> Hemophilia A 	
Duplications		<p>Entire gene is duplicated</p>	<ul style="list-style-type: none"> Charcot-Marie-Tooth, type 1A 	
Chromosomal abnormalities				
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				<ul style="list-style-type: none"> • Turner syndrome (monosomy X) • Down syndrome (trisomy 21) • XXY, (Klinefelter syndrome), XXX, XYY
	Monosomy			
	Trisomy		Trisomy 21 is only known viable autosomal trisomy.	
	Triploidy		Normally results in miscarriage; liveborn babies usually survive only a few hours or days	
	Partial trisomy/monosomy		Commonly result in mental deficiency and developmental defects	<ul style="list-style-type: none"> • Partial trisomy of chromosome 11q
	Uniparental disomy		Results in disorder when chromosome contains imprinted regions (chromosomes 7, 11, 14 and 15)	<ul style="list-style-type: none"> • Angelman syndrome • Prader-Willi syndrome
	Ring chromosomes		Effect depends on chromosome involved and extent of chromosome loss	<ul style="list-style-type: none"> • Ring 18 syndrome
	Translocations		May create fusion genes or affect expression	<ul style="list-style-type: none"> • Chronic myelogenous leukemia • Burkitt's lymphoma
	Robertsonian translocations		Only viable for chromosomes whose short ends do not contain critical genetic material (13, 14, 15, 21 and 22) Can result in monosomy and trisomy upon meiosis	<ul style="list-style-type: none"> • Angelman syndrome
Number and type of causal factors	Mendelian		Exhibit complete penetrance When stably inherited, exhibit strong familial aggregation	
	Recessive (both genes need to be defective)		Disorders involving insufficient protein production are often recessive	<ul style="list-style-type: none"> • Cystic fibrosis • Canavan disease
	Dominant (only one gene needs to be defective)		Causes include haploinsufficiency or harmful structural defect	<ul style="list-style-type: none"> • Huntington disease • Marfan syndrome
	Polygenic		Exhibit weak aggregation within families	<ul style="list-style-type: none"> • Hirschsprung disease • Chronic myelogenous leukemia • Type II diabetes (suspected)
	Disorders with incomplete penetrance		Have a genetic basis but also require environmental factors (radiation, drugs, etc.) Exhibit familial aggregation but less than 100% penetrance	<ul style="list-style-type: none"> • Xeroderma pigmentosum • Malignant hyperthermia

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Effect on protein expression	Insufficient expression		Often but not always recessive Result from decreased expression of normal protein or expression of unusable protein	<ul style="list-style-type: none"> Duchenne muscular dystrophy Acute intermittent porphyria
	Excessive expression		Usually dominant	<ul style="list-style-type: none"> Charcot-Marie-Tooth, type 1A
Effect on protein structure and function	Reduction in protein effectiveness		Involve impairment of folding, binding, or other functions Generally recessive as long as output of one gene is sufficient and unimpaired; otherwise haploinsufficient or dominant negative	<ul style="list-style-type: none"> Galactosemia Alport syndrome, X-linked
	Excess activity		May involve higher efficiency than wild-type or inability to be degraded	<ul style="list-style-type: none"> Factor V Leiden thrombophilia Multiple endocrine neoplasia type 2
	Impairment of other cellular functions		May involve aggregation of protein into structures	<ul style="list-style-type: none"> DRPLA Sickle cell anemia
Phenotypic characteristics	Effect on system or organ		Few correlations can be made between genotype and systems/organs affected	
	Age of onset	Embryonic onset		<ul style="list-style-type: none"> Achondroplasia
		Onset in infancy	Many enzyme deficiencies are noticed in infancy	<ul style="list-style-type: none"> Lesch-Nyhan syndrome Galactosemia
		Onset in childhood		<ul style="list-style-type: none"> MELAS
		Onset in adolescence		<ul style="list-style-type: none"> Ankylosing spondylitis
		Onset in adulthood		<ul style="list-style-type: none"> Acute intermittent porphyria Leber's hereditary optic neuropathy
	Progression	Stabilizing	Progression often related to molecular pathway or organ system involved	<ul style="list-style-type: none"> Leber's hereditary optic neuropathy
		Steadily progressive		<ul style="list-style-type: none"> ALS Duchenne muscular dystrophy
		Relapsing/remitting		<ul style="list-style-type: none"> Familial Mediterranean fever Rheumatoid arthritis
	Gender-specificity	X- or Y-linkage	Gender effect of X-linked diseases depends on whether they are recessive or dominant	<ul style="list-style-type: none"> X-linked dilated cardiomyopathy X-linked hypophosphatemia
		Hormonal effects		<ul style="list-style-type: none"> Luteinizing hormone receptor mutations

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	Reason unknown	Autoimmune diseases often affect more women than men for reasons not yet understood	<ul style="list-style-type: none"> • Leber's hereditary optic neuropathy • Systemic lupus erythematosus
Person-to-person variations	Allelic variances	Severity of triplet expansion diseases increases with repeat length	<ul style="list-style-type: none"> • Hereditary hemochromatosis • Myotonic dystrophy
	Mitochondrial DNA heteroplasmy	May affect severity and appearance of symptoms	<ul style="list-style-type: none"> • MELAS
	Somatic mosaicism	Severity and type of tissue affected may vary among individuals Mutations may accumulate with age	<ul style="list-style-type: none"> • McCune-Albright syndrome
	Environmental factors	Environmental factors may cause the disease to become manifest or may trigger symptoms	<ul style="list-style-type: none"> • Phenylketonuria • Acute intermittent porphyria
	Other genetic factors (epistasis)	Epistatic factors may be beneficial or detrimental	<ul style="list-style-type: none"> • Sickle cell anemia