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	• Tay-Sachs disease • Charcot-Marie-Tooth type X
	Spontaneous		Caused by DNA replication and editing errors	
		In gamete	Includes triplet repeat expansions and imprinting errors	• Achondroplasia • Prader-Willi syndrome • Angelman syndrome
		In somatic germ cell	Affects offspring of individual with mutation; may affect >1 child	• Duchenne muscular dystrophy
		In somatic embryonic cell	Leads to somatic mosaicism	• McCune-Albright syndrome
		In somatic cell leading to unrestricted cell division	Leads to tumor formation (cancer/neoplasia)	• Breast cancer • Lung cancer
Location of the defect	Autosomal chromosomes		Few differentiators among the 22 autosomal chromosomes No gender bias	• Cystic fibrosis • Canavan disease
	X chromosome		Recessive disorders affect more men than women; dominant disorders affect more women than men	• Lesch-Nyhan syndrome • X-linked hypophospatemia
	Y chromosome		Affect only males	• Mutations in azoospermia factor c
	Mitochondrial DNA		Inherited through maternal line Variable phenotypes due in part to heteroplasmy	• MERRF • MELAS • Kearns–Sayre syndrome
Physical nature of the defect	Single-gene defects		Most genetic disorders have been associated with multiple types of defects (point mutations, deletions, etc.)	
		Point mutations	Result in synonymous, missense, nonsense, and splice site mutations	• Achondroplasia
		Deletions	Vary in size from one base pair to >1 gene Effect can be worse with frame shift	• Cri-du-chat syndrome
		Insertions	Vary in size Effect can be worse with frame shift	• Myotonic dystrophy
		Inversions	DNA sequence is reversed	• Hemophilia A
		Duplications	Entire gene is duplicated	• Charcot-Marie-Tooth, type 1A
	Chromosomal abnormalities			

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		Monosomy		• Turner syndrome (monosomy X)
		Trisomy	Trisomy 21 is only known viable autosomal trisomy.	• Down syndrome (trisomy 21) • XXY, (Klinefelter syndrome), XXX, XYY
		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	• Partial trisomy of chromosome 11q
		Uniparental disomy	Results in disorder when chromosome contains imprinted regions (chromosomes 7, 11, 14 and 15)	• Angelman syndrome • Prader-Willi syndrome
		Ring chromosomes	Effect depends on chromosome involved and extent of chromosome loss	• Ring 18 syndrome
		Translocations	May create fusion genes or affect expression	• 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	• 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	• Cystic fibrosis • Canavan disease
		Dominant (only one gene needs to be defective)	Causes include haploinsufficiency or harmful structural defect	• Huntington disease • Marfan syndrome
	Disorders with incomplete penetrance	Polygenic	Exhibit weak aggregation within families	• Hirschsprung disease • Chronic myelogenous leukemia • Type II diabetes (suspected)
		Requiring environmental factors and one or more genetic factors	Have a genetic basis but also require environmental factors (radiation, drugs, etc.) Exhibit familial aggregation but less than 100% penetrance	• 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	• Duchenne muscular dystrophy • Acute intermittent porphyria
	Excessive expression		Usually dominant	• 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	• Galactosemia • Alport syndrome, X-linked
	Excess activity		May involve higher efficiency than wild-type or inability to be degraded	• Factor V Leiden thrombophilia • Multiple endocrine neoplasia type 2
	Impairment of other cellular functions		May involve aggregation of protein into structures	• 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		• Achondroplasia
		Onset in infancy	Many enzyme deficiencies are noticed in infancy	• Lesch-Nyhan syndrome • Galactosemia
		Onset in childhood		• MELAS
		Onset in adolescence		• Ankylosing spondylitis
		Onset in adulthood		• Acute intermittent porphyria • Leber's hereditary optic neuropathy
	Progression	Stabilizing	Progression often related to molecular pathway or organ system involved	• Leber's hereditary optic neuropathy
		Steadily progressive		• ALS • Duchenne muscular dystrophy
		Relapsing/remitting		• 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	• X-linked dilated cardiomyopathy • X-linked hypophosphatemia
		Hormonal effects		• Luteinizing hormone receptor mutations

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		Reason unknown	Autoimmune diseases often affect more women than men for reasons not yet understood	• Leber's hereditary optic neuropathy • Systemic lupus erythematosus
	Person-to-person variations	Allelic variances	Severity of triplet expansion diseases increases with repeat length	• Hereditary hemochromatosis • Myotonic dystrophy
		Mitochondrial DNA heteroplasmy	May affect severity and appearance of symptoms	• MELAS
		Somatic mosaicism	Severity and type of tissue affected may vary among individuals Mutations may accumulate with age	• McCune-Albright syndrome
		Environmental factors	Environmental factors may cause the disease to become manifest or may trigger symptoms	• Phenylketonuria • Acute intermittent porphyria
		Other genetic factors (epistasis)	Epistatic factors may be beneficial or detrimental	• Sickle cell anemia

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