Disorder	Mode of inheritance	Molecular basis of pathology	Clinical presentation
Retinoblastoma	Autosomal dominant[1]	Mutation in *RB1*, a tumor suppressor, which inactivates transcription factor E2F. Incomplete penetrance may be explained by two hit model for oncogensis	Visible tumor on retina
Neurofibromatosis-1	Autosomal dominant	Mutation in *NF1*, a regulator in growth pathway; *de novo* mutations account for half of all cases	Café-au-lait macules, axillary & inguinal freckling, neurofibromas, lisch nodules (iris hamartomas), bony lesions (*e.g.* tibial bowing); penetrance is 100% with clear diagnosis by age 6
Marfan syndrome	Autosomal dominant	Mutation in *FBN1* gene which codes for structural fibrilin protein important in extracellular matrix and sequestration of growth factor TGF-β; 25% *de novo*	Dialted aortic root, ectopia lentis, skeletal changes, tall long arms; diagnosis without family history usually requires aortic dilation
Achondroplasia	Autosomal dominant	Mutation in fibroblast growth receptor 3 *FGFR3* gene, a negative regulator bone growth. The mutation is a gain of function, abnormal bone growth, rhizomelic shortening of arms and leg. Most pathogenic variants are in *G1138A* 80% of which are *de novo*. Homozygosity is generally considered lethal	Short-limbs, macrocephaly, skeletal and CNA complication, depressed nasal bridge, hypotonia, compression of spinal cord or upper airway
Sickle cell anemia	Autosomal recessive	Point mutation causes misfolding of hemeglobin proding HbS, which sickle under low pH or deoxygenation; heterzygtoes have 40% Hbs while homozygotes have 100%	Pain, bruising
Cystic Fibrosis	Autosomal recessive	Mutations in *CFTR*, which codes for chloride channel. Can block transcription, processing, regulation, translation, or alter conductance. Prevents section of chloride ions into lumen causing hyperabsorption of Na^+ and water casing mucociliary transport to fail	Chronic respritory infections, nasal polyposis, delayed puberty, azoospermia, chronic diarrhea in infants, pneumonia
Phenylketonuria	Autosomal recessive	Mutation in gene that codes for phenylalanine hydroxylase causing silencing; phenylalanine cannot be made into tyrosine (a precursor for melanin) and willaccumulate in the brain	Eczema, hypopigmentation, patient families report must odor; can cause brain damage, microcephaly, decreased cognitive function, epilepsy

[1] 10% of obligate carriers have no symptoms

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Trisomy 21	Only transmitted if parent has robertsonina transolcation (*e.g. 45,XY,t(21;21)*)	Not well documented; the cause of trisomy is ususally nondisjuction in females during meiosis I, maternal age does not play a role in robertsonian tanslocation	Oblique palperbral fissures, overfolded helices, single palmar transverse creases, short bent 5^{th} fingers; Hypothyroidsim, lower cognitive function, congenital heart diseases
Trisomy 13	—	Autosomal anupolidy	Low frontal hairline, short palpebral fissures, blunt nasal tip, small nostrils and chin, low rotated unfurled ears, high nasal bridge, clenched fists
Trisomy 18	—	Autosomal anupolidy	Haloprosencephaly, premaxillary agenesis (median clef lip/palate), microphthalmia, flexed fingers, polydactyly, cardiac and renal defects, abnormal scrotum, "rocker-bottom" feet
5p- syndrome	—	Micro deletion of p on chromosome 5	*Cri du chat* due to laryngeal abnormality, hypotonia, microcephaly, round face, widely spaced eyes, single palmar creasess, diminished cognitive function
22q11.2	Autosomal dominant	Deletion of genes associated with facial features due to non-allelic homologous recombination (NAHR), an error in cross-over	Cleft palate, facial dysmorphia, abnormal 4^{th} branchial arch and 3^{rd}&4^{th} pharyngeal pouches, interrupted aortic arch, broad face, ear dysmorphia, thymus & parathyroid abnormalities, slow development, long narrow tubular nose
WAGR syndrome	—	11p13 micro deletion of *WT1* and *PAX6*	Wilms tumor or kidney ($\sim$ 40%), Aniridia, Genital anomalies, Retardation of development
Williams syndrome	—	Micro deletion on 7q11.23 affecting many genes	Depressed nasal bridge, eye puffiness, stellate pattern in blue eyes, long philturm, wide mouth, delayed development, "cocktial personality, supravalvar aortic stenosis (75%), hypercalcemia (33%)

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Freidreich Ataxia	Autosomal recessive	Expansion of GAA repeats > 70 in the intron region of the *FXN* gene on *9q21.11* causes transcritptional repression for frataxin protein, which removes iron in cytoplasm and around mitrochondria. Iron build-up causes free radical damage to the mitochondrial membrane	Typically present 5-15 years of age which muscle weakness in arms and legs, loss of coordination, impared vision and hearing, scoliosis, high plantar arches, diabetes, and cardiac disorders
Fragile X syndrome	X-linked dominant	Expansion of CGG repeats in *Xq27* in the $5'$ UTR near the promoter of *familiar mental retardation-1 (FMR1)* gene. 50-200 is a premutation that may present mild symptoms; greater than 200 is considered a full mutation. Expansion occurs during oogenesis. Small mutation causes loss of fucntion of mRNA transport and translation especailly in nurons and testies. Full mutations may cause complete silencing of gene expression.	Patients have large elonged face and chin, high protruding ears, joint laxity, and large testis after puberty. Individuals ususally have a IQ < 70 and present with autism sepctrum disorder
Huntington disease	Autosomal dominant	Expansion of trinucleotide repeats in the coding region of first exon *HTT* gene on *4p16.3* that code for gultamine. The protein interacts with dozens of other proteins that regulat intracelluar transport and shuttling transcription factors out of the nucleus. Affected proteins ususally from inclusion bodies that may be a toxic gain of function or a protective sequestration.	Individuals typically present twitches and ataxia later in life along with dysarthia and chorea

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Xerderma pigmentosum	Autosomal recessive	Mutations in one of 8 genes can cause defects in *nucleotide excision repair*, the mechanism for removing bulking helix distorting lesions	Patients have a 1000-fold increse for basal and squamous cell carcinomas and are extremely susceptible to sunburns and freckling
Ataxia telangiectasia	Autosomal recessive	Mutations in the *ATM* gene cause defects in the homologus repair, translesion DNA replication, and signarling to p53	Begins in infancy, extreme sensitivity to x-rays, incorrdination, nystagmus, telangiectias in bulbar conjunctivae and on joints, causes frequenct infections (via B and T cell dysfucntion), predisposition to malignancy
Hereditary breast cancer	Autosomal dominant	Mutations to the *BRCA1/2* gene case defects in the homologous chromosome repair mechanism	Predisposition to breast, ovarian, and prostate cancer
Werner syndrome	Autosomal recessive	Mutation in *WRN* gene causes defects in the helicase protein that unwinds DNA in homologus recombination and replication	Premature aging, short stature, diabetes, osteoporosis, cancer, etc
Bloom syndrom	Autosomal recessive	Mutation in *BLM* gene causes defect in helicase implcated homologus recombination and decatenation	Sensitivity to sun, narrow face with prominent nose, butterfly facial rash, immunodeficiency, may have MR
Fanconi anemia	Autosomal recessive	Defects in 12 possible *FANC* genes can cause errors in interstrand DNA crosslink repair	Short stature, digit abnormalities, acute myeloid cancers
HNPCC (Lynch syndrome)	Autosomal dominant	Mutation on of the *MSH*, missmatch repair proteins, cases failure of the pathway thereof	Multipule colorectal cancers, testing at 18 is strongly suggested.