Cornelia de Lange syndrome

Genetics

-NIPBL, SMC1A, SMC3, HDAC8, RAD21

-AD (NIPBL, RAD21, SMC3), XLR (SMC1A, HDAC8; almost all de novo)

Clinical findings/Dysmorphic features

-Growth retardation (prenatal onset; <5th centile throughout life), moderate to severe ID; hirsutism (excessive body hair); upper-limb reduction (subtle phalangeal abnormalities to oligodactyly); diaphragmatic hernia; pulmonary valve stenosis and/or VSD

-Facial features: microbrachycephaly; synophrys, arched eyebrows; low‐set posteriorly rotated and/or hirsute ears with thickened helices; depressed or broad nasal bridge; upturned nasal tip with anteverted nares; long smooth philtrum; thin vermillion border of the upper lip (midline "drip" appearance); downturned corners of the mouth; high and arched palate with clefts; small widely‐spaced teeth; micrognathia; short neck; ptosis; nystagmus; long eyelashes

Etiology

-Approx. 1:50,000 for the classic form of CdLS (ind. with milder features under-diagnosed)

Pathogenesis

-Unknown, majority of mutations are truncating --> haploinsufficiency

-Cohesinopathy; mutations in cohesin structural/regulatory proteins --> cohesin loading defects

Genetic testing/diagnosis

-Serial single-gene testing/multigene panel/more comprehensive genomic testing

-NIPBL (60%), SMC1A (5%), HDAC8 (4%), SMC3 (1-2%), RAD21 (<1%)

Others

-Many individuals demonstrate autistic and self-destructive tendencies

-Frequent: cardiac septal defects, GI issues, HL, myopia, cryptorchidism/hypoplastic genitalia