Dyskeratosis congenita

Genetics

-Genes: DKC1 (XL; 20-25%); TINF2 (AD; 12-20%); TERC (AD; 5-10%); RTEL1 (AD/AR; 2-8%); TERT (AD/AR; 1-7%); unknown 20-30%

Clinical findings/Dysmorphic features

-1) dysplastic nails; 2) lacy reticular pigmentation of upper chest/neck, 3) oral leukoplakia

-Increased risk for: pulmonary fibrosis, progressive bone marrow failure, myelodysplastic syndrome, acute myelogenous leukemia, solid tumors (squamous cell carcinoma of head/neck or anogenital cancer); bone marrow failure

Etiology

-Rare, 2015: 400 families

Pathogenesis

-TTAGGG nucleotide repeats fold back to create a t-loop --> many proteins bind to t-loop and others bind to those proteins to form a stable telomere "cap".

-11 genes (DKC1, TERC, TERT, TINF2, NOP10, NHP2, WRAP53, ACD, RTEL1, PARN, CTC1) encoding critical components of telomere can be mutated in individuals with DC

Genetic testing/diagnosis

-Individuals with DC have abnormally short telomeres for their age --> multicolor flow cytometry fluorescence in situ hybridization (flow-FISH) on white blood cell subsets

-Serial single-gene testing or multigene panel; in AJ testing for c.3791G> A (p.Arg1264His) in RTEL1 can be considered first