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| Gene | TP63 |
| Summary | TP63-related disorders are a group of autosomal dominant syndromes involving developmental anomalies affecting ectodermal structures, limbs, face, and orofacial region. The main overlapping clinical entities are: ankyloblepharon-ectodermal defects-cleft lip/palate (AEC) syndrome, ectrodactyly-ectodermal dysplasia-cleft lip/palate syndrome 3 (EEC3), acro-dermo-ungual-lacrimal-tooth (ADULT) syndrome, limb-mammary syndrome, split-hand/foot malformation type 4 (SHFM4), and isolated cleft lip/palate (Orofacial cleft 8). Common features include ectodermal dysplasia (hair, nails, teeth, skin), cleft lip/palate, limb anomalies and lacrimal duct obstruction. Clinical presentation and severity vary between and within syndromes. Management is multidisciplinary and symptomatic, including surgical, dermatologic, dental, ophthalmologic, and psychological interventions. Pathogenic variants are most often missense changes affecting protein domains of p63, a master regulator of epithelial and limb development. |
| Clinical\_untreated | If untreated, affected individuals may have chronic skin erosions (risk of secondary infection, dehydration, malnutrition), significant dental anomalies (hypodontia), conductive hearing loss, persistent clefts of lip and/or palate leading to feeding and speech problems, split-hand/foot malformations affecting function, persistent lacrimal obstruction leading to chronic conjunctivitis, and potential psychosocial adversity. Severe forms (notably AEC syndrome) may have life-threatening skin erosions and infections in infancy. Growth retardation and failure to thrive can occur in early childhood. Developmental delay is possible due to medical complications and hearing loss. |
| Clinical\_treated | With early multidisciplinary intervention, many complications are manageable. Skin erosions can be minimized and infection risk reduced through wound care and infection control; specialized dental and prosthodontic care can address hypodontia; hearing loss can be improved with myringotomy and amplification; surgical repair of clefts and correction of limb anomalies help optimize function. Psychosocial support ameliorates quality of life. Growth and nutritional status usually improve with intervention. Regular monitoring of dental and hearing status is important. |
| Variants | The major variants are: AEC syndrome (includes Rapp-Hodgkin syndrome; prominent skin erosions, ankyloblepharon), EEC3 (split-hand/foot malformation, ectodermal dysplasia, clefting), ADULT syndrome (acro-dermo-ungual-lacrimal-tooth; mild ectodermal, freckling, breast/nipple hypoplasia), limb-mammary syndrome (limb anomalies and mammary/nipple hypoplasia, minor ectodermal features), SHFM4 (mainly split-hand/foot malformation, little/no ectodermal or clefting), and isolated Orofacial cleft 8 (minimal features besides cleft). Clinical severity, affecting skin, teeth, hair, limbs, and clefts, as well as penetrance, ranges by variant. ADULT and limb-mammary show breast/nipple involvement; AEC is distinguished by severe erosions; SHFM4 lacks ectodermal and clefting features. |
| Genetics | TP63-related disorders are caused by heterozygous pathogenic variants in TP63, primarily missense variants, but also deletions, nonsense, and splice site mutations. Pathogenic effects are mostly dominant-negative or (in ADULT syndrome) gain-of-function. Over 100 unique pathogenic mutations have been identified and validated. Genotype-phenotype correlation is observed: AEC typically involves SAM domain or N-terminal truncations, EEC3 by DNA-binding domain missense mutations, ADULT by DNA-binding domain changes, limb-mammary by mutations between TA and DNA domains, and SHFM4 by TA or DNA domain variants. |
| Incidence | Exact incidence is unknown, but TP63-related disorders are rare. Combined, they likely account for fewer than 1 in several hundred thousand live births. Prevalence by country/ethnic group is not established due to rarity; de novo mutations are frequent (about 70% of cases), while ~30% are inherited. |
| Diagnosis | Diagnosis in newborns is suspected in those with clefts, skin erosions, limb malformations, ectodermal dysplasia, together with suggestive family history. Genetic confirmation is by sequencing of TP63 (sequence analysis identifies ~99% of cases). Gene-targeted deletion/duplication analysis detects rare copy number changes. High-throughput panels or genomic sequencing can be used if the phenotype is non-specific. TP63 is not part of standard metabolic newborn screening; recognition is clinical with rapid molecular confirmation. |
| Differential\_diagnosis | Differential diagnoses include: epidermolysis bullosa simplex (EBS: EXPH5, KRT5, KRT14, TGM5), autosomal recessive congenital ichthyosis (ABCA12, etc., with collodion membrane), Curly hair-ankyloblepharon-nail dysplasia syndrome (RIPK4), cocoon syndrome (CHUK), SHFM1 (DLX5), SHFM3 (10q24 duplication), SHFM6 (WNT10B), and hypohidrotic ectodermal dysplasia (HED; EDA, EDAR, EDARADD, WNT10A). Distinction is based on clinical features (pattern of ectodermal/limb involvement, presence of clefts, hair/nail/skin findings, lack/severity of hypohidrosis, genetic testing). |
| Treatment | Treatment is multidisciplinary and tailored to manifestations: gentle wound care and bleach soaks for skin erosions; antibiotics for infections; hydration/nutritional support for infants; wigs for alopecia; dental prosthesis or implants for hypodontia; surgical repair for cleft lip/palate; ophthalmologic interventions for lacrimal duct atresia/obstruction; myringotomy for chronic otitis with hearing loss; occupational/physical therapy and surgery for limb malformations; plastic surgery for breast/nipple asymmetry; developmental assessment and psychosocial/psychological support as needed. Regular surveillance for dental and hearing needs. |
| Prognosis | Prognosis is good if identified and treated early. Morbidity is minimized and life expectancy is normal with appropriate multidisciplinary care. Most children achieve good functional outcomes and quality of life, though some features (e.g., dental or limb anomalies) are lifelong and may require repeated interventions. Delay in treatment, particularly for skin erosions, feeding/nutrition, or hearing loss, can result in increased risk of infection, malnutrition, developmental delays, or psychosocial difficulties. |