Key Points for Clinical Practice

Dermatological Pathologies With Only Anecdotal Occurrences in Trisomy 21

- **Pityriasis Rubra Pilaris:** Only juvenile forms of PRP have been documented in individuals with Trisomy 21, with two out of three cases presenting as localized disease. The etiology is unclear, though occasionally associated with autoimmune or autoinflammatory conditions. The diagnosis of PRP is based on clinical features and should be confirmed histologically to differentiate it from psoriasis. Treatment is the same as for neurotypical patients. Most cases (80%) regress within 18 months to three years.

- **Keratosis Pilaris Atrophicans**: Rare variants of keratosis pilaris that progress to atrophic scarring and/or alopecia. Only two cases in individuals with Trisomy 21 have been documented in a familial context: one case of Keratosis follicularis spinulosa decalvans (Siemens syndrome) and one case of atrophoderma vermiculata. These variants involve causal germline mutations in different genes.

- **Generalized Perforating Granuloma Annulare:** This rare subtype of granuloma annulare is marked by transepidermal elimination of necrotic collagen, and typically features ten or more coexisting lesions. It is occasionally associated with autoimmune conditions. Only one case has been documented in a young adult with Trisomy 21. Lesions typically regress spontaneously within a few years.

- **Cutaneous Leishmaniasis:** This parasitic infection, the most common clinical form of leishmaniasis, presents as ulcers on exposed skin that may lead to permanent scarring. Immunological dysregulation in Trisomy 21 should be considered an exacerbating factor. Four cases have been reported in individuals with Trisomy 21 in regions where leishmaniasis is endemic: Iran, Brazil, Sardinia, and Saudi Arabia. Treatment efficacy is not affected by the presence of Trisomy 21.

- **Eruptive Collagenoma:** These rare benign lesions, characterized by multiple, asymptomatic, flesh-colored papules, typically occur on the upper back and shoulders in young adults without identifiable triggers or family history. Histology reveals thickened, intensely eosinophilic dermal collagen fibers. Five cases have been reported in individuals with Trisomy 21, possibly linked to COL6A1 gene triplication (implicated in collagen VI anomalies) and SOD1 (associated with premature skin aging).

- **Acquired Reactive Perforating Collagenosis:** This rare acquired perforating disorder presents with papulonodular eruptions and transepidermal elimination of collagen. Often associated with diabetes, chronic renal failure on dialysis, autoimmune disease, or immunodeficiency, it has been reported in two cases involving individuals with Trisomy 21. Lesions generally regress within 6–8 weeks, sometimes leaving atrophic, hypopigmented scars. Recurrence and Koebner phenomenon are common.

Dermatological Pathologies

- **Calcinosis Cutis:** Characterized by calcium salt deposits in the skin and subcutaneous tissue. Diagnosis is confirmed by the appearance of firm, whitish yellow infiltrated papules, plaques or nodules, which are typically asymptomatic, radio-opaque, and often painless. Three cases have been documented in individuals with Trisomy 21: two cases of dystrophic CC (related to skin trauma/connective tissue disease) and one case of idiopathic tumoral calcinosis (without prior skin lesions). All three cases showed normal calcium and phosphorus levels.

- **Miescher's cheilitis granulomatosa:** This rare inflammatory condition manifests as painless swelling of one or both lips (macrocheilia). The etiology is unknown; food allergens such as cinnamon and sodium benzoate may be involved. Three cases have been documented in individuals with Trisomy 21: two isolated cases and one associated with Melkersson-Rosenthal syndrome (macrocheilia, facial palsy, and fissured tongue). Treatment is challenging, predominantly medical, with surgical intervention rarely required.

- **Cutaneous Tumors:** Compared to the general population, individuals with Trisomy 21 have a significantly reduced risk of skin cancer, including melanoma. However, the risk is not zero, and cutaneous melanoma is the skin cancer most frequently reported in the literature in children and adults with Trisomy 21. It is important to monitor any suspicious lesions on previously healthy skin, changes in stable nevi, or evolving lentigines, especially in older adults. Preventive measures for skin protection are also advised, given the increasing life expectancy and susceptibility to premature skin aging in individuals with Trisomy 21.

- **Pediatric Cutaneous Mastocytosis:** These rare genodermatoses, linked to clonal mast cell proliferation in the skin, are associated in over 80% of cases with a gain-of-function somatic mutation in the KIT gene, coding for the receptor with tyrosine kinase activity, KIT. The maculopapular form with polymorphic expression is the most common form in children. Only one case has been reported in a child with Trisomy 21, in an extremely rare familial form.

- **Dystrophic Epidermolysis Bullosa:** A common form of hereditary epidermolysis bullosa, characterized by skin and mucosal fragility, leading to superficial vesicles and ulcerations starting in infancy that heal with significant scarring. It results from mutations in the COL7A1 gene, causing type VII collagen abnormalities resulting in cutaneous fragility. Only one autosomal dominant case has been documented in a child with Trisomy 21. To date, the association with Trisomy 21 is anecdotal and does not appear to alter the clinical presentation.

- **Hereditary Ichthyosis – Collodion Baby:** The clinical presentation of collodion baby signifies the congenital and initial expression of various rare, hereditary forms of ichthyosis, both non-syndromic and syndromic, and does not predict disease severity. To date, only one case has been reported in a newborn with Trisomy 21.

- **Riga-Fede Disease:** This benign, rare condition typically affects children under two years old and manifests as traumatic ulceration, usually on the ventral tongue or less commonly, the inner lower lip mucosa. Four cases have been documented in individuals with Trisomy 21, three associated with natal or neonatal teeth (which are known to be common in Trisomy 21 and may warrant discussion regarding extraction), and one late-onset case linked to repetitive lower lip sucking and nibbling movements against the lower incisors.