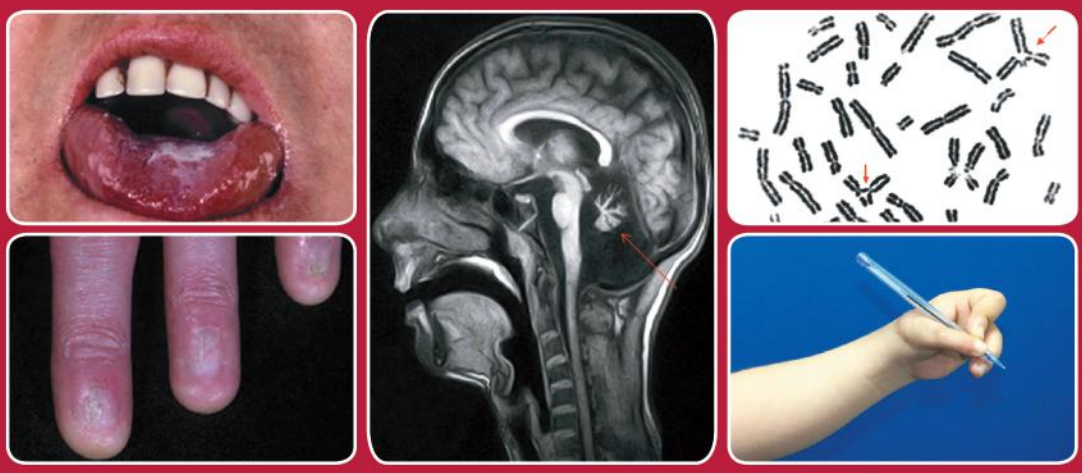
FANCONI ANEMIA AND OTHER INHERITED BONE MARROW FAILURE SYNDROMES

Editor

ŞULE ÜNAL CANGÜL



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Preface

Over the last century, the data on hematopoiesis and the hematopoietic stem cells increased tremendously. This information was obtained not only from the pre-clinical studies, but also through understanding the pathophysiology of bone marrow failure syndromes. Bone marrow failure syndromes can be either acquired or inherited and inherited bone marrow failure syndromes are importantly higher in populations with higher consanguineous marriages. Inherited bone marrow failure syndromes are a group of disorders characterized with congenital defects and increased propensity to cancer, accompanying cytopenias. Interestingly, almost all of these disorders are multigenic and the phenotype may also be different even within the same family, indicating a very heterogeneous group of disorders. This book has been written for the purpose of giving an insight to clinicans who diagnose and treat these patients .

Sule Unal. M.D.
2021, Ankara

Contents

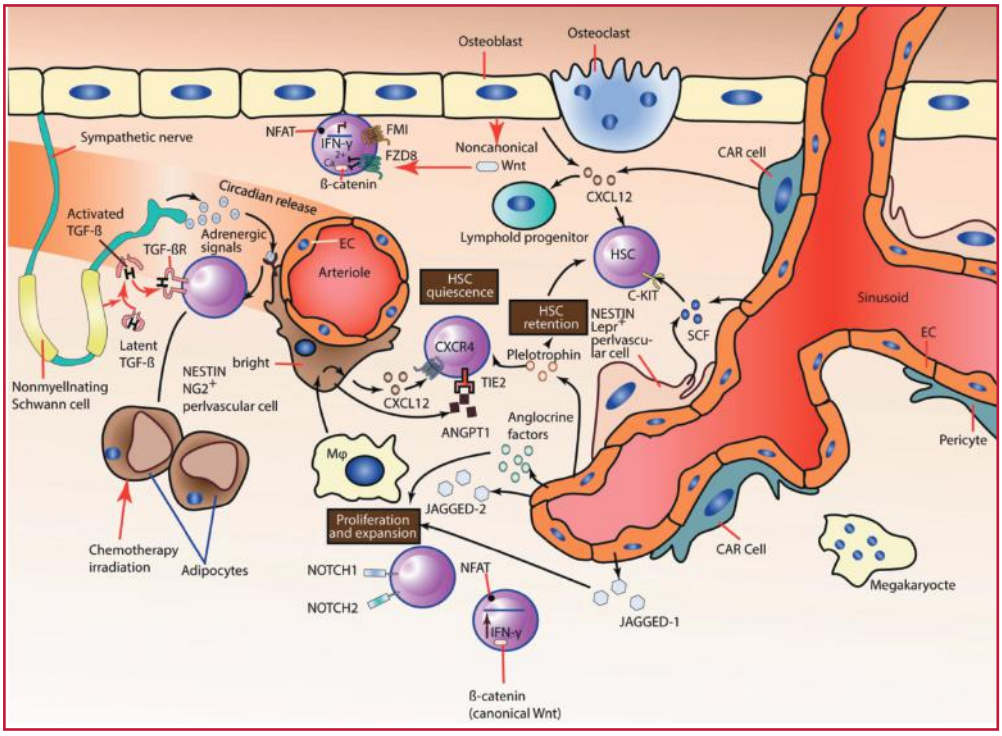


Figure 3 • Various cell types forming niche have been implicated for their roles in promoting HSC maintenance, including perivascular stromal cells, endothelial cells (ECs), macrophages, CAR cells, sympathetic neurons and nonmyelinating Schwann cells. Although established regulators of HSC maintenance include CXCL12 and SCF, other regulatory factors include pleiotrophin, angiopoietin 1 (ANGPT1) and TGF-β and signaling pathways including Notch and Wnt. Osteoblasts are also dispensable for HSC maintenance but may have a role in regulating lymphoid progenitor cells. Certain cell types have been shown to negatively affect HSC maintenance, including adipocytes, which are increasingly present after chemotherapy and radiation. Regional localization of HSCs during quiescence and after activation revealed that quiescent HSCs associate with arterioles ansheathed with NG2+ pericytes but after activation relocate near the Lepr-expressing perisinusoidal area (Redrawn from Mendelson et al, reference no 24)

Location of the niche: Several imaging studies have suggested that HSCs may lodge in specific areas of blood vessels, possibly because of endothelial adhesive molecules. Homeostatic HSCs are homogenously distributed, whereas transplanted HSCs preferentially home to the trabecular bone region. These HSCs seem to have enhanced regenerative and self-renewal capacities compared with those that localize to the diaphysis region. The use of intravital microscopy imaging of the mouse calvarium recently revealed that after injection into non-irradiated mice, all HSCs and progenitor cells homed and localized very close (within 16 μm) to the vasculature. After transplantation into irradiated mice, however, most HSCs were found closer (within 15 μm) to the endosteum, where they were able to generate all peripheral blood

Table 1 • Congenital Anomalies and Clinical Manifestations in Fanconi Anemia

Organ, System Findings	Abnormalities
Skin	Generalized hyperpigmentation, café au lait spots, hypopigmentations, Hyper- and hypopigmented patches of skin, warts, basal or squamous cell carcinoma (SCC), actinic keratosis, melanoma
Height	Short stature
Upper Limbs	**Thumbs:** Absent or hyoplastic, bifid duplicated rudimentary, triphalangeal, attached by thread, long, low set, digitized **Radii:** Shortened, absent or hypoplastic (only with abnormal thumbs), curved, absent or weak pulse **Ulnae:** Short, dysplastic, absent **Hands:** Absent first metacarpal, clinodactyly, polydactyly, abnormal fingers, short fingers, transverse crease **Thenar-eminence:** Flat, absent, hypoplastic
Lower Limbs	**Hips:** Congenital hip dislocation, dysplasia malrotation **Feet:** Toe syndactyly, abnormal toes, club feet
Other Skeletal	**Spine/vertebral:** Spina bifida, scoliosis,kyphosis, abnormal ribs, hemivertebrae, coccygeal aplasia, Klippel-Feil
Head	Microcephaly
Facial	FA facies, triangular face, birdlike, dysmorphic, mid-face hypoplasia, micrognathia, pointed chin, facial nerve palsy,microsomia
Neck	Sprengel, Klippel-Feil, short, low hairline, web
Eyes	Microphthalmia, strabismus, epicanthal folds, close-set, hypotelorism, hypertelorism, cataracts, ptosis, astigmatism, almond shaped fissures, microcornea
Ears/Otology	Hearing loss (conductive, sensorineural or mixed), abnormal shape, atresia, dysplastic, abnormal narrow canal, abnormal middle ear bones, abnormal pinna, Speech: delayed, unclear
Renal	Ectopic, pelvic, horseshoe, hypoplastic, dysplastic, absent, hydronephrosis or hydroureter
Cardiac	Patent ductus arteriosus, atrial septal defect, ventricular septal defect, coarctation, situs inversus, truncus arteriosus, iron overload
Gastrointestinal	Esophageal atresia (EA) Esophageal atresia with tracheoesophageal fistula (TEF) Duodenal atresia Jejunal atresia Annular pancreas Intestinal malrotation **Anorectal malformations:** Imperforate anus, ectopic anus, bifurcated anus, gastric emptying delay, poor weight gain, poor feeding, esophageal SCC
Liver	Cirrhosis, fibrosis, elevated enzymes, iron overload, androgene toxicity, adenoma, hepatocellular carcinoma, peliosis hepatis
Gonads	**Males:** Hypogenitalia, undescended testes, small or absent testis, hypospadias, micropenis, microphalus, infertility **Females:** Hypoplastic, absent or bicornuate uterus; gonadal dysgenesis small ovaries; rectovaginal fistula; Hypogenitalia, vaginal atresia; abnormal menses, late menarche, early menopause, infertility, vulvar SCC, breast cacer

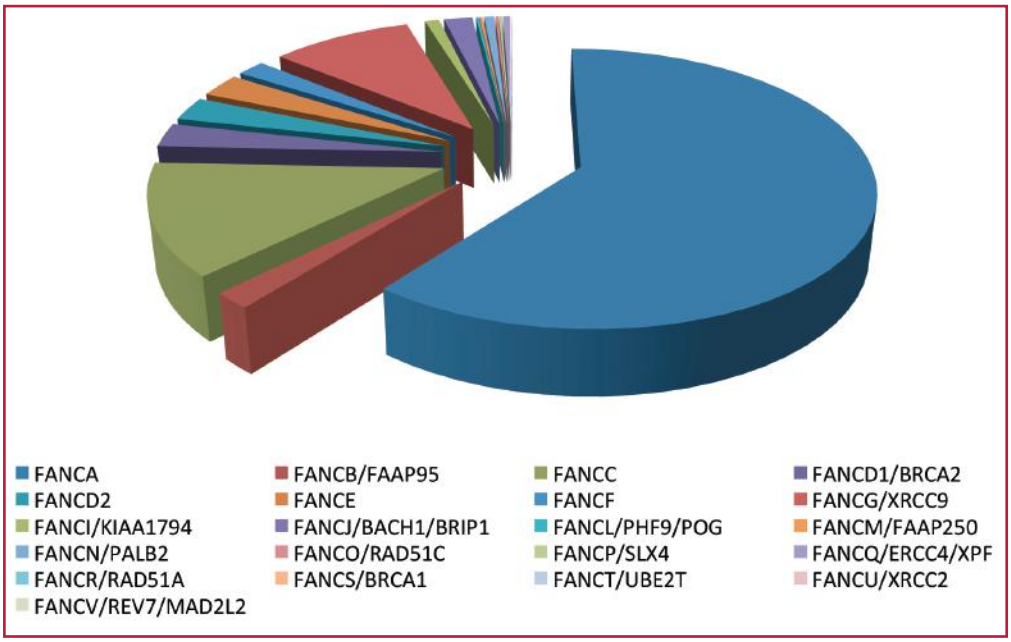


Figure 2 • Frequency distributions of total FA gene mutations.

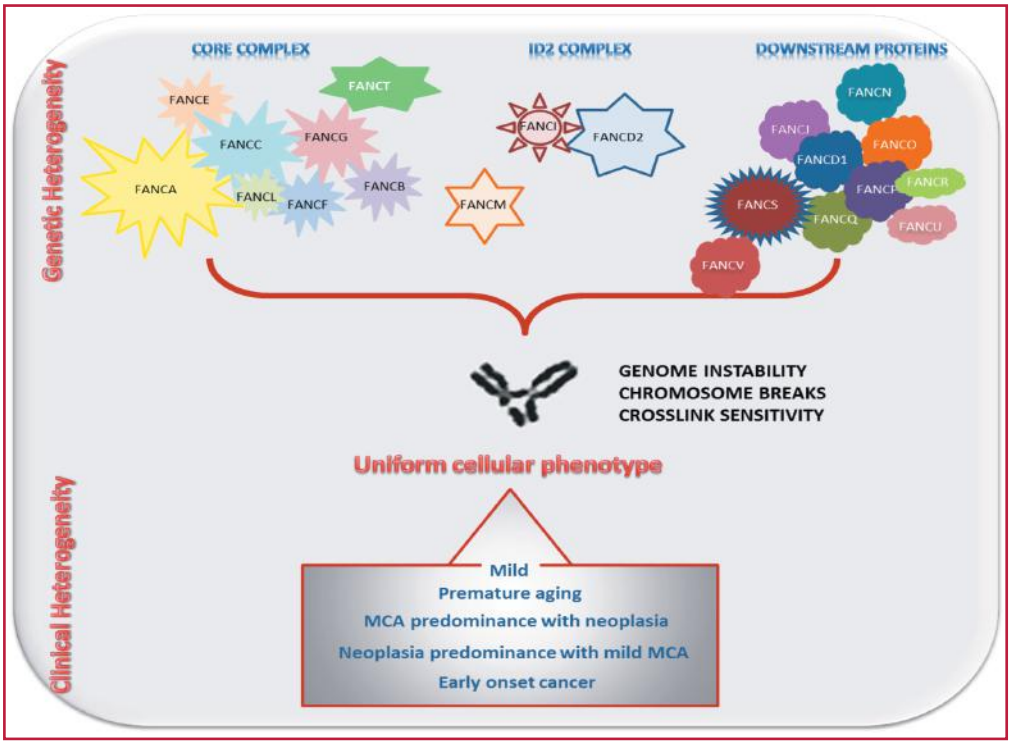


Figure 3 • Uniform cellular phenotype with heterogeneity of molecular etiology and clinical findings in FA.

Table 1 • Follow-up According to Severity of Bone Marrow Failure and Clonality (modified from references 1,3)

	Normal	Mild	Moderate	Severe	Non-poor risk Cytogenetics (+1q, -20, -11q, -5q, -Y)	Poor-risk Cytogenetics (-7q, +3q, complex, RUNX1 mutations)
Absolute neutrophil count	>1.500/ mm^3	<1.500/ mm^3	<1.000/ mm^3	<500/mm^3	-	-
Platelets	>150.000/ mm^3	50.000-150.000/ mm^3	<50.000/ mm^3	<30.000/ mm^3	-	-
Hemoglobin	Normal for age	>8 g/dl	<8 g/dl	<8 g/dl	-	-
Hemogram with differential	If no clonality, q 3-4 months	If no clonality, q 3-4 months	If no clonality, q 6–8 weeks	HSCT should be prompted.	q 6–8 weeks	HSCT should be prompted.
Bone marrow biopsy, aspirate and cytogenetics	At diagnosis, If no clonality at last BM, then starting from 2 years of age, annually	At diagnosis, If no clonality at last BM, then starting from 2 years of age, annually	If no clonality, q 3–4 months	HSCT should be prompted.	q 3–4 months	HSCT should be prompted.

BM: bone marrow; HSCT: Hematopoietic stem cell transplantation; q: every

do not protect from MDS/AML. The exact mechanism of effect is not fully understood, but oxymetholone has been reported to decrease the quiescence and increase proliferation of hematopoietic stem cells in Fancd2-/- mice (17). Another potential mechanism has been postulated through the induction of telomerase expression (18). Some of the patients may loose their response over time; wheras 10-20% may be transfusion independent for long time without any need for HSCT, unless MDS/AML develop (3,14).

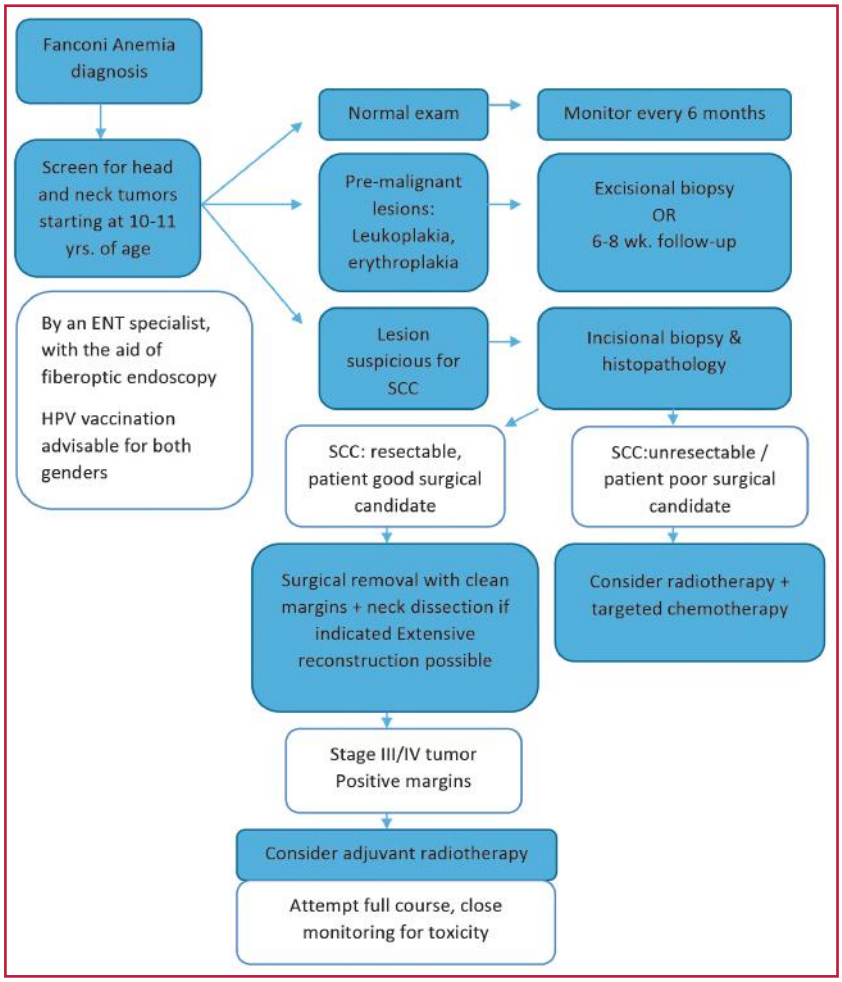
Main adverse events ralated to androgen use are masculization/virilization in females, acnea, elevation in liver enzymes and risk for benign hepatic adenomas and rarely hepatocellular carcinoma (3,18-20). Another complication is peliosis hepatis, dilatation hepatic sinusoids, that have a potential risk of rupture. Peliosis hepatis usually regresses after androgen therapy was ceased (3). Patients should be monitored by liver function tests and liver ultrasonography, every 3 months and every 6 months, respectively.

It is quite plausible that HSCT, its associated conditioning regimen and the resulting immune compromise from GVHD contribute to the deficiency in the already weakened immune surveillance against malignancy in FA, further increasing the susceptibility to solid tumors.

There is recent evidence that a fludarabine-based reduced intensity conditioning regimen for HSCT significantly reduces the incidence of acute and chronic GVHD in FA patients(40). It seems probable that minimization of the immunologic phenomena that accompany HSCT may also reduce the risk of SCC development in the transplanted FA population, yet validation of this premise requires further research.

ALGORITHM

Although there are no evidence based guidelines for FA patients under risk of solid tumor development yet, the following algorithm summarizes the authors' broad recommendations on general approach to head and neck tumors in FA.



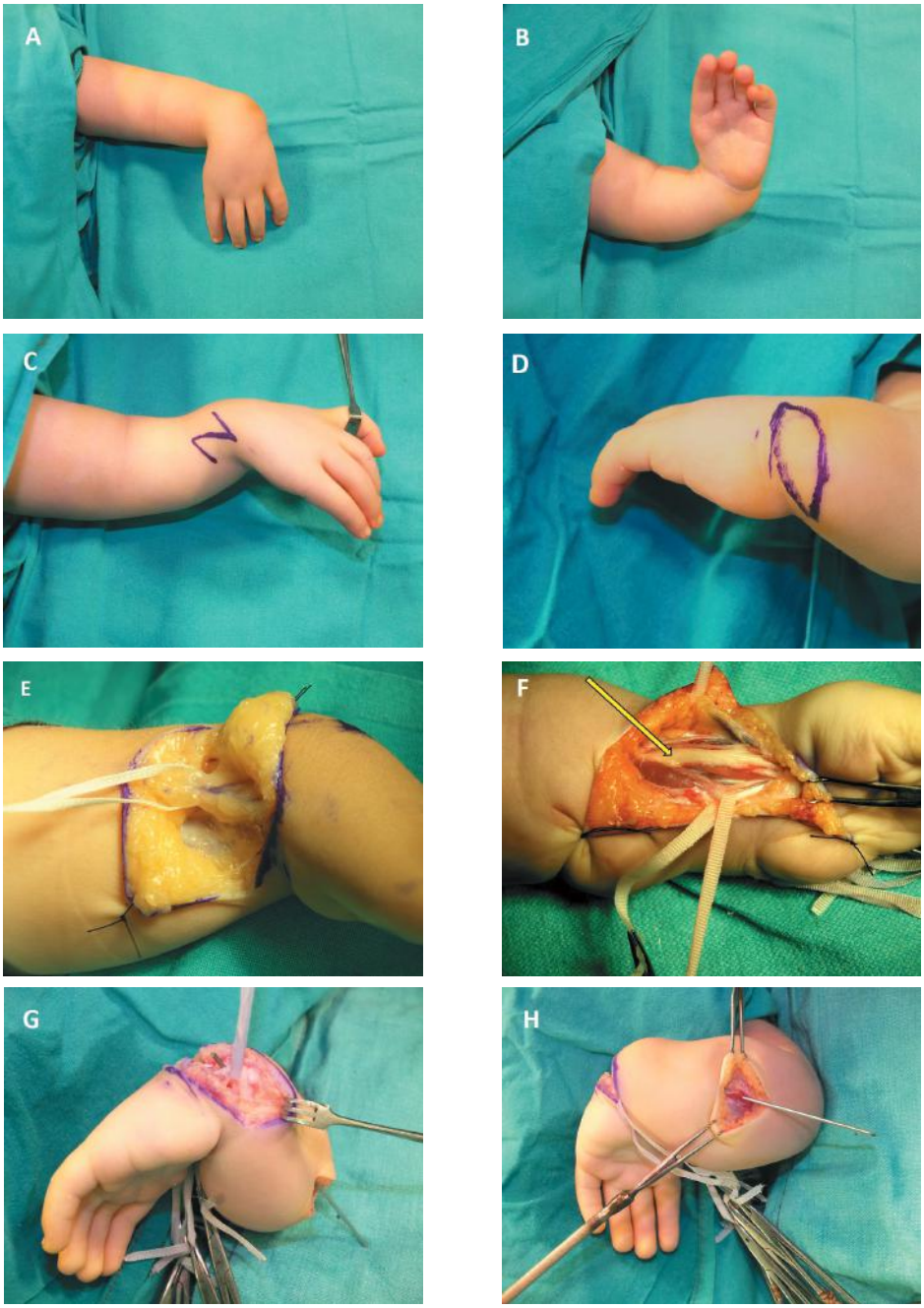


Figure 2 • Steps of centralization procedure. **A.** Radial clubhand, dorsal aspect. **B.** Radial clubhand, volar aspect. **C.** Z-plasty on the radial side. **D.** Elliptical excision of the excess skin on the ulnar side. **E.** Isolation and preservation of superficial radial nerve (if present) and superficial veins on the radial side. **F.** Release of the fibrous anlage on the flexor and radial aspect and exposure of the extrinsic flexor muscles/tendons and the median nerve. Note that the median nerve is localized on the radial side, rather than at the midline, which is also called as "radian" nerve (arrow).

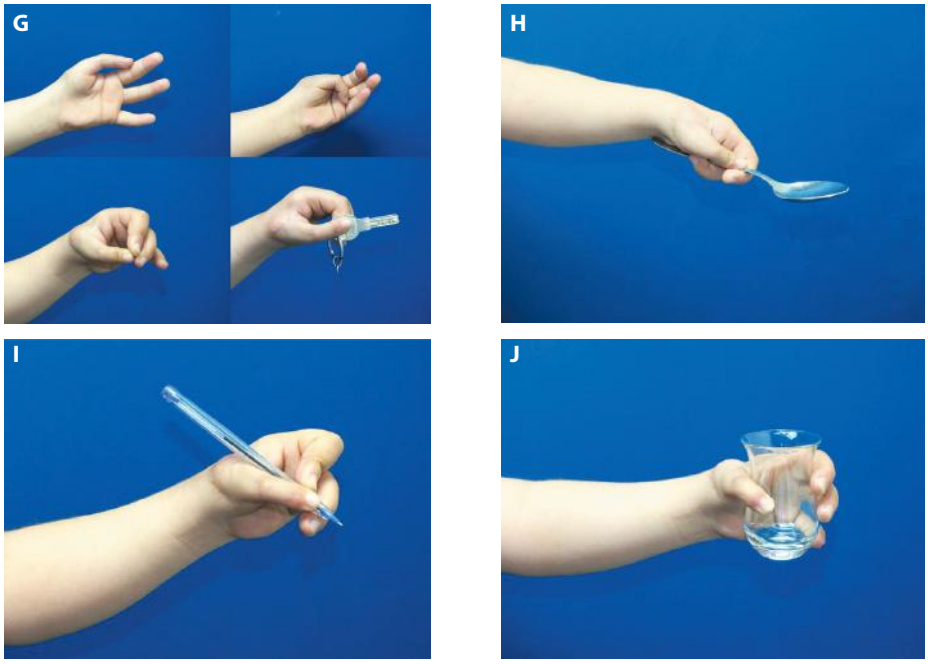


Figure 9 • Steps of pollicization procedure. **A.** Left hand with type 5 thumb hypoplasia. **B.** Elevation of skin flap and preservation of dorsal veins. **C.** Ligation of proper digital artery on adjacent finger. **D.** Interfascicular dissection of the common digital nerve. **E.** Intrinsic muscle transfers. **F.** Extension, flexion, pulp-to-pulp pinch and opposition after pollicization. **G.** Side-pinch, adduction-opposition, three-point pinch and key-pinch after pollicization. **H,I,J.** Some basic hand functions in daily life.

CONCLUSIONS

Fanconi anemia is a heterogenous clinical condition requiring a multidisciplinary approach whereas these patients are frequently born with upper limb anomalies and are often referred to a hand surgeon long before the diagnosis of the underlying disease. Hand specialists have the responsibility to refer these patients with high risk to pediatrics/hematology specialists for Fanconi testing.

Treatment of congenital differences of the upper extremity is a significant challenge. From the perspective of hand surgery, the goal is to achieve a functioning limb that should be satisfactorily treated for the child's physical, social and emotional development. In means of postoperative results, specialized therapy and rehabilitation is as important as proper evaluation and skillful surgical approach.

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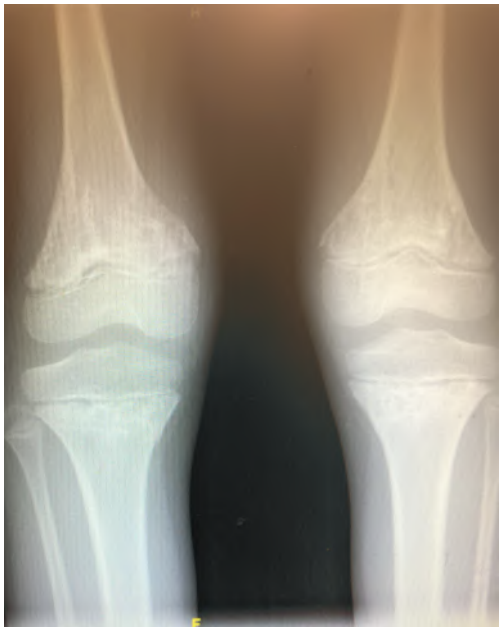

Figure 1 • Metaphyseal dysplasia prominent in distal metaphyses of femur.

Hepatic failure manifested as cholestasis and fibrosis in a 15 year old patient with SDS (24). Hepatic fibrosis, cirrhosis have also been reported as rare liver findings in patients with SDS (25).

Short stature is common (52-95%) and is not only related to malabsorption. At one year of age more than half of the patients' heights have been reported to be lower than 3rd percentiles for their age and gender appropriates. Although, pancreatic enzyme replacement therapies normalize the height velocity in most of the patients, the height of the patients remain below 3rd percentile in most (26).

Skeletal abnormalities, such as progressive metaphyseal dysplasia/thickening and irregularities in the distal and proximal ends of the long bones/costochondral junctions are common (3,22). Metapyhyseal findings are exhibited in Figure 1. Thoracal abnormalities might be seen in 12-92% of the patients and include asphyxiating thoracic dystrophy, flared ribs and widening in the costochondral junctions (3). Delayed appearance of secondary ossification centers (delayed bone age), delay in epiphyseal maturation, cortical thinning in long bones indicating generalized osteopenia, wormian appearance of skull bones are also among the skeletal abnormalities that might be seen in patients with SDS (27). Osteoporosis may end up with vertebral compression fractures and may also be aggrevated by the accompanying vitamin D and K deficiencies (3). Although, epiphyseal maturation is completed at later ages, the abnormalities in metaphyses usually worsen by age (27). Abnormal chondrogenesis may rarely cause subglottic stenosis (25). Severity of skeletal findings may vary even in the patients with the same mutations at similar ages (27).

Cardiac abnormalities have been reported in 7 out of 37 (19%) of the patients in the North American Registry and 12 out of 102 (12%) of the patients in the French Registry (4,12).

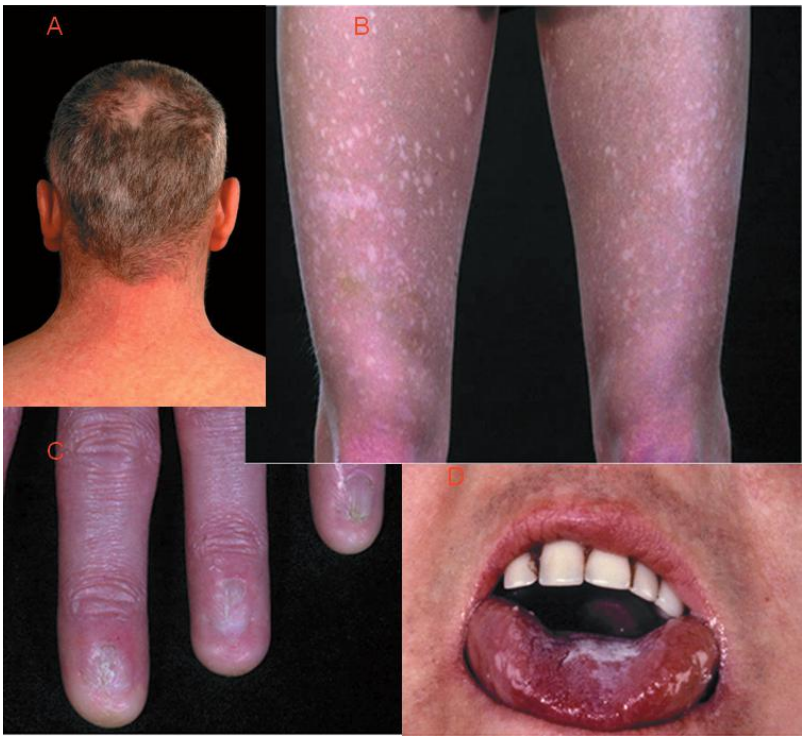

Figure 1 • Mucocutaneous features of DC: Abnormal skin pigmentation **(A, B)**, oral leucoplakia **(D)** and nail dystrophy **(C)**. Note A also shows premature greying of scalp hair

BM failure by the age of 30 years. But there is marked variation between patients with respect to the age of onset and disease severity even within the same family. This causes difficulty in making a diagnosis. Equally it is not uncommon for the BM failure or immune deficiency or an abnormality in another system to present before the more classic mucocutaneous features and this is being recognised increasingly since the advances in its genetics.

The minimal clinical criteria for diagnosis of DC includes the presence of at least 2 out of the 4 major features (abnormal skin pigmentation, nail dystrophy, leukoplakia and BM failure) and two or more of the other somatic features (Table 1) known to occur in DC (3). Since 1998, 11 DC genes have been identified and these account for approximately two thirds of DC cases (Table 2).

B. GENETICS AND DIFFERENT SUBTYPES OF DC

X-linked Recessive DC and the Hoyeraal-Hreidarsson Syndrome

DKC1 (dyskeratosis congenita 1)

The gene (*DKC1*) responsible for X-linked DC was mapped to Xq28 in 1986 and identified through positional cloning in 1998. This gene is highly conserved and encodes the protein

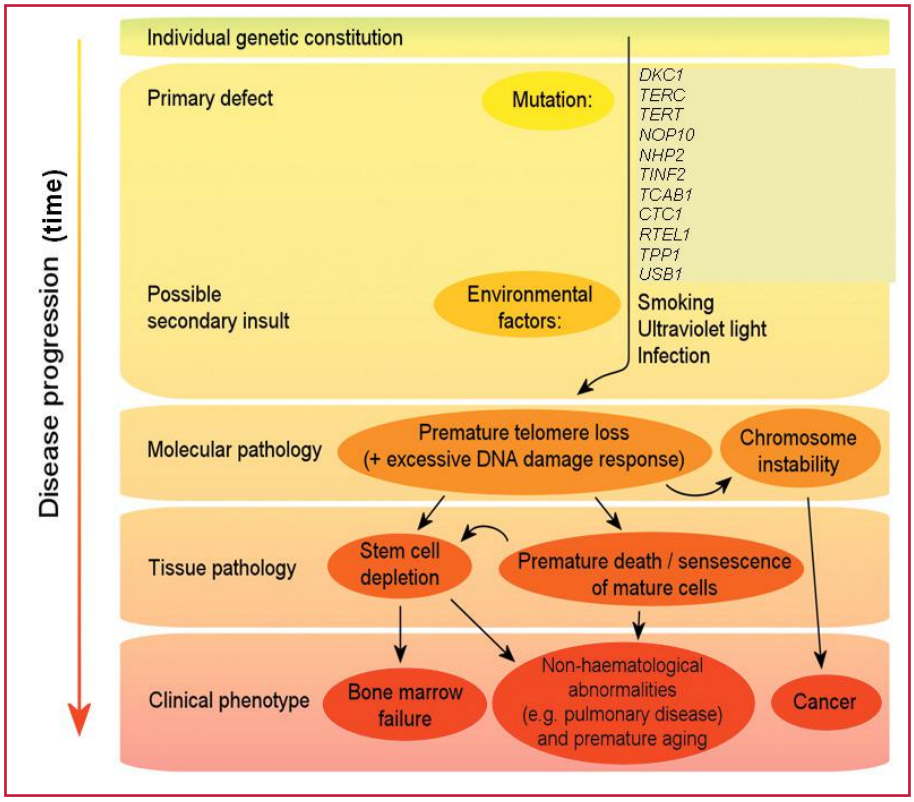

Figure 11 • A model of DC pathophysiology. Constitutional mutations in *DKC1, TERC, TERT, NOP10, NHP2, TINF2, USB1, TCAB1, CTC1, RTEL1* and *TPP1* (primary defect) cause excessive telomere attrition. This together with environmental factors (e.g. smoking), in the context of the overall genetic constitution of the individual, leads to premature cell death and chromosome instability. With increasing age this eventually either reduces/exhausts the stem cell reserve (thereby leading to clinical features such as bone marrow failure, immune deficiency) or results in cancer.

such as bone marrow failure and immune deficiency) or results in hematological and non-hematological cancers.

A study by Alter et al measured telomere length in various blood cell types in patients with DC, their relatives and other patients with different inherited BM failure syndromes (44). They found that DC patients had very short telomeres in the majority of the leukocyte subsets studied (less than 1st centile compared with normal age matched controls). Telomere lengths in the DC patient group also tended to be shorter than in patients with other BM failure syndromes, and because of this telomere length can, with caution, be treated as a surrogate marker for DC but only in the context of BM failure (45). It remains to be validated whether up-front telomere length measurements in new patients with one or more feature of DC can be used to identify the cryptic forms of DC.

Table 2 • Summary Differential Diagnosis of Neutropenia

Condition	Clinic	Diagnosis	References
Infection-induced neutropenia	most common type of neutropenia in newborns and infants. The duration is usually less than 1–3 months. HIV or HCV infections, may be associated with long-lasting neutropenia	history, virology	94,96,97
Alloimune neonatal neutropenia (ANN)	fetomaternal granulocyte mismatch	cross match mother sera vs paternal neutrophils	98
Neonatal alloimmune neutropenia secondary to maternal AIN	neutropenia	history, AIN diagnosis in mother	99,100
Neonatal neutropenia due to maternal drug exposure	smoking (Tobacco), chemotherapy (e.g. taxane), immune therapy (e.g. Rituximab), tocolysis (e.g. Ritodrine)	history, fetal titers/levels	101-104
AIN with autoimmune diseases	Evan´s Syndrome, Lupus erythematosus, Wiskott-Aldrich Syndrome	history, diagnosis of underlying disease	105,106
AIN with neoplasm	e.g. Thymoma/ Good´s Syndrome, Hodgkin´s disease, melanoma	history, diagnosis of underlying disease	95,107-109
Nutrition	copper deficiency, zinc intoxication	micronutrient titer	110
Drug-induced/associated neutropenia	carbimazole, clozapine, dapsone, dipyrone, methimazole, penicillin G, procainamide, propylthiouracil, rituximab, sulfasalazine, and ticlopidinehypoblastic	history,	
Maturation arrest in contrast to AIN	111		
Chemotherapeutic drugs	depending on primary condition and choice of drug	underlying disease and necessary specific treatment protocol	112
Inherited Conditions			
Ethnic neutropenia	Benign condition		
Congenital neutropenia associated with defective differentiation or homeostasis of neutrophil granulocytes	e.g. Hyper IgM Syndrome, Good´s Syndrome, CVID, XLA, SBDS		107,113,114
SCN	Table 1	Table 1	87
SCN with complex disorders	Table 1	Table 1	87

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