D'Amours Guylaine (Orcid ID: 0000-0002-1068-3154)

Refining the phenotype associated with biallelic *DNAJC21* mutations

Running title: Refined phenotype in *DNAJC21* mutations

Guylaine D'Amours[1,2], Fátima Lopes[3,4,5], Julie Gauthier[6], Virginie Saillour[3,7], Christina Nassif[3], Robert Wynn[8], Nathalie Alos[9,12], Thierry Leblanc[10], Yline Capri[11], Sonia Nizard[1,12], Emmanuelle Lemyre[1,12], Jacques L. Michaud[1,3,7,12], Véronique-Anne Pelletier[12,13], Yves D. Pastore[12,14], Jean-François Soucy[1,6,12]

1. Service de Génétique Médicale, CHU Sainte-Justine, Montréal, Canada

2. Faculté de Médecine, Université de Montréal, Montréal, Canada

3. Centre de Recherche, CHU Sainte-Justine, Montréal, Canada

4. Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal

5. ICVS/3B's - PT Government Associate Laboratory, Braga/Guimarães, Portugal

6. Laboratoire de Diagnostic Moléculaire, CHU Sainte-Justine, Montréal, Canada

7. Centre Intégré de Génomique Clinique Pédiatrique, Montréal, Canada

8. Blood and Marrow Transplant Unit, Royal Manchester Children's Hospital, Manchester, UK

9. Service d'Endocrinologie, CHU Sainte-Justine, Montréal, Canada

10. Département d'Hématologie Pédiatrique, CHU Robert-Debré, Paris, France

11. Service de Génétique Clinique, CHU Robert-Debré, Paris, France

12. Département de Pédiatrie, Université de Montréal, Montréal, Canada

13. Département de Pédiatrie, CHU Sainte-Justine, Montréal, Canada

14. Service d'Hématologie-Oncologie, CHU Sainte-Justine, Montréal, Canada

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Correspondence to: Jean-François Soucy, Service de Génétique Médicale, CHU Sainte-Justine, Montréal (QC), Canada H3T 1C5; jean-francois.soucy@umontreal.ca

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ABSTRACT

Inherited bone marrow failure syndromes (IBMFS) are caused by mutations in genes involved in genomic stability. Although they may be recognized by the association of typical clinical features, variable penetrance and expressivity are common, and clinical diagnosis is often challenging. *DNAJC21*, which is involved in ribosome biogenesis, was recently linked to bone marrow failure. However, the specific phenotype and natural history remain to be defined. We correlate molecular data, phenotype, and clinical history of five unreported affected children and all individuals reported in the literature.

All patients present features consistent with IBMFS: bone marrow failure, growth retardation, failure to thrive, developmental delay, recurrent infections, and skin, teeth or hair abnormalities. Additional features present in some individuals include retinal abnormalities, pancreatic insufficiency, liver cirrhosis, skeletal abnormalities, congenital hip dysplasia, joint hypermobility, and cryptorchidism.

We suggest that *DNAJC21*-related diseases constitute a distinct IBMFS, with features overlapping Shwachman-Diamond syndrome and Dyskeratosis congenita, and additional characteristics that are specific to *DNAJC21* mutations. The full phenotypic spectrum, natural history, and optimal

management will require more reports. Considering the aplastic anemia, the possible increased risk for leukemia, and the multisystemic features, we provide a checklist for clinical evaluation at diagnosis and regular follow-up.

Key words: BMFS3, bone marrow failure syndrome, founder effect, genomic instability, genotype-phenotype, management, natural history, ribosome, telomere

INTRODUCTION

Inherited bone marrow failure syndromes (IBMFS) are characterized by cytopenia(s) due to impaired hematopoiesis, and to a varying degree, cancer predisposition. Most present with additional manifestations such as bone marrow failure, growth and developmental delay, osteopenia, and recurrent infections. Many IBMFS may be recognized by the association of distinct clinical or laboratory features: radial ray defects and increased chromosomal breaks in Fanconi anemia (FA); the presence of a classic triad (oral leukoplakia, nail dystrophy, and reticular hypopigmentation), associated with very short telomeres in Dyskeratosis congenita (DC); and chronic neutropenia, with exocrine pancreatic insufficiency and skeletal abnormalities in Shwachman-Diamond syndrome (SDS). However, variable penetrance and expressivity are common, making clinical diagnosis often challenging. So far, over 50 genes have been associated with IBMFS.[1] They are involved in genomic stability, DNA repair, telomere maintenance, and ribosome biogenesis. *DNAJC21*, which is required for 60S ribosomal subunit maturation, was recently linked to bone marrow failure in four individuals.[2] Six other individuals with a biallelic mutation in this gene have been reported since.[3,4] Full phenotypic spectrum, natural history, and management recommendations of this new entity remain to be defined. We describe molecular data, phenotype, and clinical history of five affected individuals from two families carrying the same biallelic mutation, compare molecular data and clinical information with all individuals reported in the literature, and suggest clinical management and follow-up that should be considered in all affected individuals.

PATIENTS AND METHODS

We describe five previously unreported children from two families of the same Canadian First-Nation origin, as well as updated clinical information on three affected individuals from two previously reported families.[2,4] All patients were evaluated in a clinical setting by multiple specialists, including a

geneticist. Approval for genomic studies was obtained from the Research Ethics Board of the CHU Sainte-Justine, and informed consent to publication of clinical information and photographs was obtained from parents or guardians.

RESULTS

Molecular data and clinical information are summarized in **table 1** and detailed in **table S1**. Pedigrees are available in **figure S1**. All children presented features consistent with IBMFS: postnatal growth retardation, global developmental delay, skin, teeth and hair abnormalities, skeletal abnormalities, and bone marrow failure. The differential diagnosis included DC, SDS and Rothmund-Thomson syndrome, although they lacked the classic features of these disorders, and single gene sequencing failed to identify a mutation in any of the associated genes. Exome sequencing performed in patient 2 identified a homozygous variant in *DNAJC21*. This variant was then confirmed by Sanger sequencing in all affected. Available parents were heterozygous (**figure S1**).

The identified mutation, NM_001012339.2:c.100A>G:p.Lys34Glu, deemed likely pathogenic (PM2, PM1, PP3, PP1),[5] has since been reported in two siblings from a Canadian First-Nation tribe.[3] Including the patients in the current report, a total of 15 individuals carrying 9 different mutations, are now described with clinical information (summary in **table 1**, details in **table S1**). This includes seven patients, from three unrelated families, with the same missense mutation. All mutations are private, and all but one affected individual are homozygous. Four mutations are missense, within the J-domain of the protein, while the other five are truncating (**figure 1A**).

DISCUSSION

Previous reports

Bone marrow failure syndrome 3 (BMFS3, OMIM #617052) was first reported in four unrelated individuals with bone marrow failure and growth delay.[2] Half (2/4) had dental and skin abnormalities, and one had retinal dystrophy. Since that original report, six individuals with biallelic mutations in *DNAJC21* have been reported.[3,4] Four individuals reported by Dhanraj were clinically diagnosed with SDS. They presented bone marrow failure, skeletal abnormalities, pancreatic insufficiency and mild liver fatty changes or enzymes elevation. Three had short stature and cognitive or motor delay. Half (2/4) had skin abnormalities, and one had abnormal dentition. Although fulfilling the criteria for SDS, two had retinal dystrophy, and another had dysmorphic features, which is not typically found in SDS. Bluteau's report included three individuals with *DNAJC21* variants, out of a large bone marrow failure cohort (179 individuals), therefore phenotypic information was limited.

Current report

We report the largest group of children with the same biallelic mutation in *DNAJC21*. They presented cytopenia(s), post-natal growth delay, failure to thrive (**appendix S1**), progressive microcephaly, motor or global development delay, mild dysmorphic features (**figure S2**), severe/precocious osteopenia, skeletal irregularities (**figure 1B**, and **figure S3**), congenital hip dysplasia, joint hypermobility, and skin or adnexa abnormalities (sparse fine hair, nail hypoplasia/dystrophy, microdontia or conical teeth, enamel abnormalities, carious teeth). Most (4/5) had recurrent and/or refractory infections in infancy, and both males had cryptorchidism. Three of the four tested had sensorineural hearing impairment, and two had retinal abnormalities. Short (between 1st and 10th

percentile) and/or very short (below 1st percentile) telomeres were observed in most affected individuals (**figure S4**).

This contrasts with Tummala's report, where all individuals had normal telomere length.[2] This discrepancy could be the result of the measurement method used,[6,7] disease severity, or each mutation's pathogenic mechanism. Although telomere shortening has been described in other non-DC IBMFS, such as SDS and FA,[8] it remained above the 1st percentile for most patients with SDS (12/14). In contrast, all patients tested in our cohort had at least one subpopulation at or below the 1st percentile, with most between 1st and 10th percentile, which is consistent with some level of telomere maintenance defect. Indeed, previous reports showed that defining normal telomere length as above the 1st percentile would miss children with telomeropathies,[9] considering that up to one in seven are in the 1st to 10th percentile range.[8]

In contrast to Dhanraj's report,[3] although two individuals in our cohort had pancreatic hyperechogenicity (patients 1 and 2), none demonstrated clear evidence of pancreatic insufficiency (**table S1**). Both had mild liver enzymes elevation, one developed cirrhosis by age 11, which is not typical of SDS. The siblings from Dhanraj's report carrying the same mutation also had signs of liver disease, suggesting an association with this specific mutation.

Finally, previously unpublished clinical information reveals that there may be additional recurrent features in this syndrome. Indeed, in addition to pancytopenia and growth delay, two siblings (Patient 7 and 8, previously reported[2,4]) had motor delay and skin abnormalities (hypopigmented skin, hyperkeratosis or eczema). One also had retinal dystrophy, microdontia, abnormal teeth morphology, osteoporosis, hip dislocation, and growth hormone deficiency, while her brother had microcephaly and a cardiac malformation. Neither had evidence of pancreatic insufficiency.

Therefore, we suggest BMFS3 constitutes a condition distinct from SDS and DC, with features overlapping both syndromes, and additional characteristics that are specific to *DNAJC21* mutations (**figure 1C**). It would be premature to restrict DNAJC21's role to ribosome biogenesis, considering there are few human studies on this RNA-binding protein. Although no data supporting a role in telomere maintenance is available at this time, many features observed in affected individuals are not in the usual SDS spectrum, but rather evocative of dyskeratosis congenita, a telomeropathy. One of the associated gene, *DKC1*, is one example of a protein involved both in ribosome maturation and telomere maintenance.[10] The phenotypic variations observed in the individuals reported so far could result from differential pathogenic mechanisms or variable expressivity. It is plausible that missense mutations within the J domain lead to gain-of-function interfering with other cellular processes, while truncating mutations are limited to 60S subunit maturation impairment. It is also probable that individual genetic background influences the expressed phenotype, considering DNAJC21's involvement in crucial cellular processes.

Based on the clinical features found in affected individuals, we suggest a thorough clinical evaluation at diagnosis and regular follow-up (**table 2**).

Natural history

All children in our cohort demonstrated various degree of bone marrow failure, but none of them required bone marrow transplant (BMT) nor developed leukemia (details in **appendix S2**). Moreover, although our cohort is small, all patients followed at our center showed improvement in their cell counts with age, except for lymphocytes (**figure S5**), and none required transfusions past 5 years old.

It is worth mentioning that an acquired 17p13 deletion encompassing *TP53* appeared in the hypocellular bone marrow of a 5 ½ year-old boy (patient 3). There is no dysplasia in his bone marrow, and the significance of this cytogenetic abnormality remains unknown (details in **appendix S2**). This

deletion may represent an initial event that could lead to tumorigenesis, or a rescue mechanism that could help recover hematopoiesis, or both.

We report updated clinical information on three previously reported patients (details in **table S1**, pedigrees in **figure S1**). To our knowledge, only one individual with a *DNAJC21* mutation developed leukemia (patient 6). He died from transplant-related morbidity, after a mismatched BMT for acute megakaryoblastic leukemia. Another 2-year-old male (patient 8) is currently stable and no longer transfusion-dependent, 9 months after an uncomplicated matched BMT performed for severe pancytopenia (details in **table S1**). His sister (patient 7) required transfusions in infancy, but her counts have stabilized since. Two siblings reported by Dhanraj died: one from sepsis, and one from EBV-associated lymphoproliferative disorder shortly after BMT. Neither had leukemia, but one had a bone marrow karyotype abnormality: der(15)t(1;15)(q12;p11).

Biallelic mutations in *DNAJC21* cause a distinct IBMFS, with some clinical overlap with SDS and DC, and additional features such as retinal abnormalities, liver cirrhosis, congenital hip dysplasia, joint hypermobility, and cryptorchidism. More reports are needed to understand the full phenotypic spectrum and long-term evolution of affected individuals, and establish optimal management, including BMT indications and protocol. Aplastic anemia, and a possible increased risk for leukemia warrants regular hematological follow-up, and multidisciplinary care to address all other potential medical issues.

REFERENCES

1. Wegman-Ostrosky T, Savage SA. The genomics of inherited bone marrow failure: from mechanism to the clinic. *Br J Haematol*. 2017;177(4):526-542.

2. Tummala H, Walne AJ, Williams M, et al. DNAJC21 Mutations Link a Cancer-Prone Bone Marrow Failure Syndrome to Corruption in 60S Ribosome Subunit Maturation. *Am J Hum Genet*. 2016;99(1):115-124.

3. Dhanraj S, Matveev A, Li H, et al. Biallelic mutations in DNAJC21 cause Shwachman-Diamond syndrome. *Blood*. 2017;129(11):1557-1562.

4. Bluteau O, Sebert M, Leblanc T, et al. A landscape of germline mutations in a cohort of inherited bone marrow failure patients. *Blood*. November 2017.

5. Richards CS, Bale S, Bellissimo DB, et al. ACMG recommendations for standards for interpretation and reporting of sequence variations: Revisions 2007. *Genet Med*. 2008;10(4):294-300.

6. Gutierrez-Rodrigues F, Santana-Lemos BA, Scheucher PS, Alves-Paiva RM, Calado RT. Direct comparison of flow-FISH and qPCR as diagnostic tests for telomere length measurement in humans. *PLoS ONE*. 2014;9(11):e113747.

7. Gadalla SM, Khincha PP, Katki HA, et al. The limitations of qPCR telomere length measurement in diagnosing dyskeratosis congenita. *Mol Genet Genomic Med*. 2016;4(4):475-479.

8. Alter BP, Giri N, Savage SA, Rosenberg PS. Telomere length in inherited bone marrow failure syndromes. *Haematologica*. 2015;100(1):49-54.

9. Alder JK, Hanumanthu VS, Strong MA, et al. Diagnostic utility of telomere length testing in a hospital-based setting. *Proc Natl Acad Sci U S A*. 2018;115(10):E2358-E2365.

10. Mochizuki Y, He J, Kulkarni S, Bessler M, Mason PJ. Mouse dyskerin mutations affect accumulation of telomerase RNA and small nucleolar RNA, telomerase activity, and ribosomal RNA processing. *Proceedings of the National Academy of Sciences*. 2004;101(29):10756-10761.

Table 1. Molecular data and summary of clinical features found in all reported individuals with biallelic mutations in *DNAJC21*.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6[†]	Patient 7[‡]	Patient 8[§]	Tummala Subject 4	Dhanraj Patient 1	Dhanraj Patient 2	Dhanraj Patient 3	Dhanraj Patient 4	Bluteau Patient 54[¶]	Bluteau Patient 114
Mutation (cDNA)	100A>G	100A>G	100A>G	100A>G	100A>G	94C>G	983+1G>T	983+1G>T	793G>T	520C>T	100A>G	100A>G	438-?_894+?del	517C>T	14A>G/1143_1146del
Protein change	Lys34Glu	Lys34Glu	Lys34Glu	Lys34Glu	Lys34Glu	Pro32Ala	Gly299Alafs*2	Gly299Alafs*2	Glu265*	Gln174*	Lys34Glu	Lys34Glu	Val148Lysfs*30	Arg173*	Tyr5Cys/Lys381fs
Mutation feature	Missense	Missense	Missense	Missense	Missense	Missense	FS + stop gain	FS + stop gain	Stop gain	Stop gain	Missense	Missense	FS + stop gain	Stop gain	Missense / In-frame deletion
Protein domain	J domain	J domain	J domain	J domain	J domain	J domain	Interdomain	Interdomain	Coiled coil	Interdomain	J domain	J domain	Interdomain	Interdomain	J domain / Interdomain
Gender	M	F	M	F	F	M	F	M	F	F	M	M	M	F	F
Age (initial/last evaluation)	5m/ 12y1m	8m/ 9y10m	2y6m/ 5y7m	13m/ 5y1m	2m/14m	12y/uk	6y/ 14y6m	6m/2y	6y/uk	2y6m/14y	Birth/18m	Birth/7y4m	Birth/11y	3y/uk	14m/uk
Growth delay ± FTT	+	+	+	+	+	+	+	+	+	+	-	+	+	+	uk
Pancytopenia/BMF	+	+	+	+	+	+	+	+	+	+	+	+	+	+	uk
Dysmorphic facial features	+		+	+	+	uk	-	-	uk	+	-	-	-	uk	uk
Neurological features	+	+	+	+	-	uk	+	+	uk	+	-	+	+	uk	+
Microcephaly	+	-	+	+	-	-	-	+	-	uk	uk	uk	uk	+	uk
Eye abnormalities	+	+	+	-	uk	uk	+	-	uk	+	-	-	+	uk	uk
Skeletal abnormalities	+	+	+	+	+	uk	+	uk	uk	+	+	+	+	uk	uk
Skin & adnexa abnormalities	+	+	+	+	+	+	+	+	uk	+	-	-	+	uk	uk
Recurrent/severe infections	+	+	+	+	-	uk	-	-	uk	+	+	-	-	uk	uk
Digestive system abnormalities	+	+	-	-	-	uk	+	-	+	+	+	+	+	uk	uk
Genitourinary abnormalities	+	-	+	+	-	uk	-	-	uk	uk	-	-	uk	uk	uk
Other	Fetal cystic hygroma					GH deficiency. Deceased post-BMT (TRM)	GH deficiency	Bicuspid aortic valve, ventricular septal defect			Deceased pre-BMT (sepsis)	Deceased post-BMT (EBV-associated PTLD)			
Short telomeres	+	+	+	+	+	-	±	-	-	-	uk	uk	uk	-	uk
Bone marrow cytogenetic abnormality	-	-	del(17p13.1) (63% of cells at 5y6m)	del(20q) (9.7% of cells at 17m)	-	uk	uk	uk	uk	-	-	der(15) t(1;15)(q12; p11) (8m-7y)	-	47-51,XX, +X,+8,+13,+21,+22	uk
Malignancy	-	-	-	-	-	AML-M7	-	-	-	-	-	-	-	-	-

BMT	-	-	-	-	-	+	-	+	uk	-	-	+	+	uk	uk
Alive	+	+	+	+	+	-	+	+	uk	+	-	-	+	uk	uk

F, female; M, male; m, months; y, years; +, present; -, not present; uk, unknown.
BMF, bone marrow failure; BMT, bone marrow transplant; FS, frameshift; FTT, failure to thrive; GH, growth hormone; PTLD, post-transplant lymphoproliferative disorder; TRM, transplant-related mortality.
Previously reported patients: † Tummala *et al.* (subject 3); ‡ Tummala *et al.* (subject 2); § Bluteau *et al.* (Patient 91); ¶ Tummala *et al.* (subject 1).

Table 2. Recommended management.

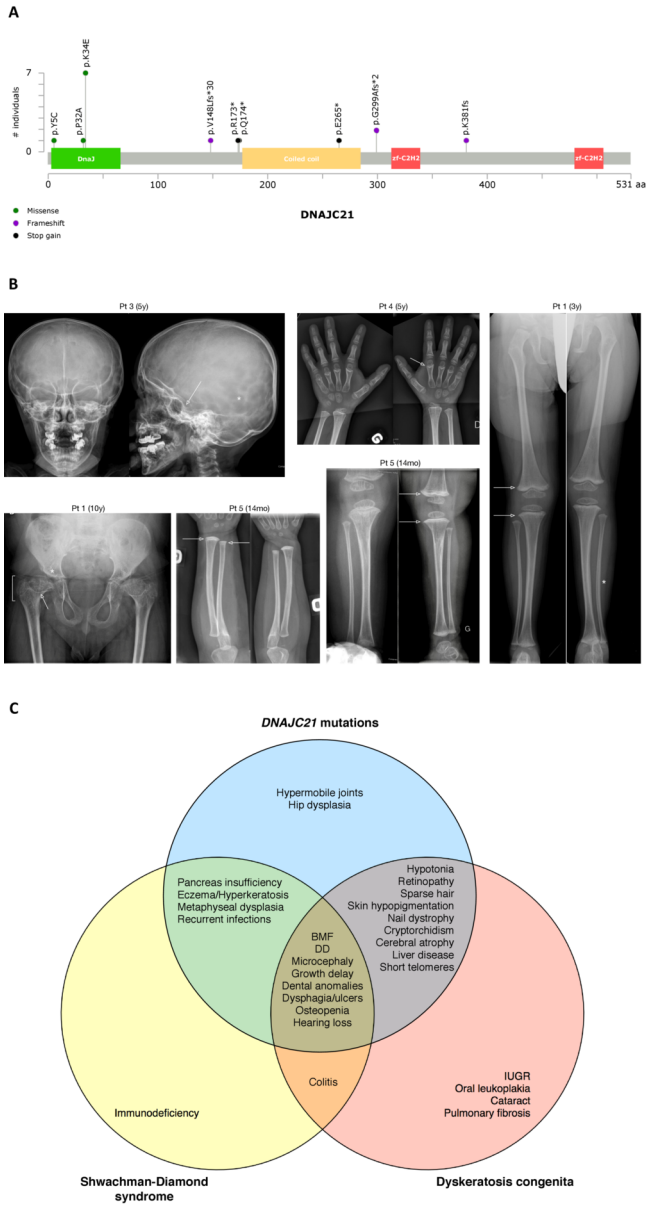
	Investigation/intervention	At Diagnosis	At Follow-up
Genetics	Gene testing (familial mutation if known, or sequencing; patient, family member if HSCT donor)	Yes	If not done at diagnosis
	Genetic counseling ± molecular testing (adult carrier)	-	Yes
	Telomere length testing (patient, family member if HSCT donor)	Yes	-
Hematology	Complete blood count, reticulocytes	Yes	Every 3-4 months or as clinically indicated
	Bone marrow aspirate & biopsy + microarray or karyotype & FISH panel	Yes	Every 1-3 years or as clinically indicated
	Iron, vitamin B12, folate	Yes	As clinically indicated
	Fetal hemoglobin	Yes	-
	HLA typing (affected, siblings and parents)	As clinically indicated	As clinically indicated
Neurology	Head circumference measurement	Yes	Yearly
	Cerebral imaging (MRI)	-	As clinically indicated
	Neurodevelopmental evaluation	Yes	Every 6 months until 6 years, then screening at 11-13 years old, or as clinically indicated
	Physiotherapy, occupational therapy, speech therapy	-	As clinically indicated
Ophthalmology	Standard eye exam	Yes	Yearly
	Electroretinography	Yes	Every 2 years
Audiology	Audiogram or auditory brain-stem evoked response testing	Yes	As clinically indicated
Growth, skeletal	Weight & height	Yes	Yearly
	Hip dysplasia screening ± orthopedics referral	Yes	-
	Bone mineral density measurement	Yes	Every 2 years, or as clinically indicated
	Skeletal survey (metaphyseal dysplasia, compression fractures)	Yes	Before age 5, then as clinically indicated
	Bone age	-	As clinically indicated
	Parathyroid hormone level	Yes	-
	Calcium (ionized), phosphorus	Yes	Every 2 years
Endocrine	IGF-1 or GH stimulation test (GH deficiency)	Yes	As clinically indicated
	Thyroid stimulating hormone	Yes	As clinically indicated
Immunologic	Lymphocyte phenotype	Yes	As clinically indicated
	IgG, IgM, IgA levels	Yes	-
	Post vaccination serologies	-	As clinically indicated
	Antibiotic prophylaxis	-	As clinically indicated
Gastrointestinal & hepatic	Pancreatic function testing: fecal elastase, trypsinogen (d 3y) or pancreatic isoamylase (e 3y)	Yes	Yearly until 5 years old, then as clinically indicated
	Liver enzymes, albumin, bilirubin, prothrombin time	Yes	Yearly or as clinically indicated
	Nutritional status: lipid panel, vitamins A, D, E	Yes	Yearly
	Abdominal ultrasound (pancreas & liver)	Yes	Every 2 years until 6 years old, then as clinically indicated
	Dental care (caries, gingivitis)	Yes	Every 6-12 months
	Esophagram, endoscopy	-	As clinically indicated
Dermatologic	Skin & nail examination, cancer surveillance	Yes	Yearly
	Eczema treatment	-	As clinically indicated
Other	Pelvic ultrasound (kidney, testicles)	Yes	-
	Echocardiogram	Yes	-
	Pulmonary function tests, pulse oximetry, diffusion capacity of the lung for carbon monoxide testing, six-minute walk test	-	As clinically indicated
	Chest computed tomography (pulmonary fibrosis)	-	As clinically indicated
	Avoid: prolonged use of cytokines and hematopoietic growth factors, unnecessary radiograph studies		

GH, growth hormone; HSCT, hematopoietic stem cell transplant

FIGURE LEGEND

Figure 1. Biallelic mutations in *DNAJC21* cause features overlapping with Dyskeratosis congenita and Shwachman-Diamond syndrome.

(A) Number and mutations types reported, with corresponding position in DNAJC21 protein and its domains. The missense homozygous mutations found in our cohort (p.K34E) and in subject 3 from Tummala's cohort (p.P32A) are located in the J-domain. Other reported homozygous mutations are outside of the J-domain. (B) Representative X-rays of children in this report showing skeletal anomalies. Pt 3 (5y): marked copper beaten aspect of the skull (asterisk), flattened sella turcica (arrow) and brachycephaly. Pt 4 (5y): bilateral irregular and cupped metaphysis of distal metacarpals (arrow). Pt 1 (3y): bilateral metaphysis flaring of distal femur and proximal tibia (arrows), and mild lateral bowing of tibia and fibula (asterisk). Pt 1 (10y): bilateral acetabular dysplasia (asterisk), with sclerotic, irregular and flattened femoral head, coxa magna and breva (bracket), and "sagging rope sign" over femoral metaphysis (arrow). Pt 5 (14mo): bilateral growth lines in distal metaphysis of radius and ulna (arrows). Pt 5 (14mo): bilateral growth lines in metaphysis of distal femur and proximal tibia (arrows). (C) Venn diagram of clinical features found in at least two individuals with *DNAJC21* biallelic mutations, compared with features typically found in Dyskeratosis congenita and Shwachman-Diamond syndrome. (BMF, bone marrow failure; DD, developmental delay; IUGR, intra-uterine growth retardation; mo, months old; Pt, patient; y, years old).



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