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ORIGINAL ARTICLE

Further evidence supporting the role of *DUT* gene in diabetes with bone marrow failure syndrome

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Abstract

In 2017, a homozygous *DUT* mutation was reported to cause a syndrome of diabetes and bone marrow failure. However, no further patient with this combination has been reported and the phenotype of heterozygous *DUT* mutation is unknown. We describe the genotype, phenotype, and post bone marrow transplantation (BMT) data of two unrelated families with this rare syndrome. Whole-exome and/or direct sequencing of the *DUT* gene were performed in all family members. Each family has two children presented within the first 10 years of life with thrombocytopenia, macrocytosis, with or without anemia, followed by non-autoimmune diabetes. The same homozygous missense *DUT* mutation, reported in 2017 (c.425A>G p.(Tyr142Cys), was detected in all affected children. The heterozygous carriers have no BM failure, one developed type 2 diabetes, and the rest have normal fasting glucose, insulin, HbA1c, and c-peptide. Multiple nevi were detected in homozygous and heterozygous mutation carriers. Allogenic BMT normalized BM aplasia without impact on diabetes. Post BMT follow-up revealed normal puberty and school performance; but three have height <2.5 SDS. We add two families with this syndrome supporting a role of *DUT* in bone marrow and β-cell function. The heterozygous carriers of this *DUT* mutation appear to be healthy.

KEYWORDS
bone marrow aplasia, bone marrow transplantation, childhood diabetes, DUT gene, monogenic diabetes

1 | INTRODUCTION

The combination of diabetes and extra pancreatic features raises the possibility of monogenic diabetes mellitus (MGD), which accounts for 1%–6.3% of diabetes caseload in children and young adults (Delvecchio et al., 2017; Kim et al., 2021). However, identifying this rare form of diabetes can guide the clinical management for the patients and their families (Hattersley et al., 2018). To date, mutations in more than 50 genes are associated with isolated and syndromic MGD (Riddle et al., 2020) and further genetic studies would identify more MGD forms and develop our understanding of disease mechanisms.In 2017, Dos Santos et al. described a new autosomal recessive syndrome characterized by early onset diabetes and bone marrow failure in two consanguineous French and Egyptian families. Each of these families have two siblings with diabetes and variable degrees of bone marrow failure including macrocytosis, anemia, and thrombocytopenia. The hematological features were detected at birth or during infancy while diabetes presented between the age of 5 and 28 years. An 11-year-old girl died of brain hemorrhage following severe thrombocytopenia, while a man, died at 22 years of severe graft-versus-host disease following bone marrow transplantation (BMT) for acute lymphoblastic leukemia. The parents of both families appeared to be healthy but were not available for clinical and laboratory assessment. Genome-wide linkage analysis and whole-exome sequencing (WES) of

the index case of one family identified a homozygous missense mutation (c.425A>G p.(Tyr142Cys) in the *DUT* gene (OMIM *601266). This mutation was replicated by Sanger sequencing of the *DUT* gene in another patient, with similar phenotype, from an unrelated family. The *DUT* gene is mapped to chromosome 15 and encodes the dUTPase enzyme, which is essential for nucleotide metabolism by hydrolyzing the deoxyuridine triphosphate (dUTP) to deoxyuridine monophosphate (dUMP) and pyrophosphate (Vértessy & Tóth, 2009). This reaction generates the dUMP, for the synthesis of thymine nucleotides needed for DNA replication. It also reduces the intracellular dUTP, which prevents the integration of uracil into DNA that leads to DNA toxicity and cell death (Koehler et al., 2004; Vértessy & Tóth, 2009; Horváth & Vértessy, 2010).

To the best of our knowledge, no further patient with this syndrome has been reported and the phenotype of heterozygous carriers of *DUT* mutations has not been detailed. We describe two unrelated Libyan families in whom some members were homozygous, and others were heterozygous for the above *DUT* mutation. We also report the impact of BMT on this condition.

2 | METHODS

The study was approved by Tripoli University Hospital ethics committee and was conducted in accordance with the principles of Helsinki Declaration as revised in 2008.

2.1 | Patients and family

We studied two unrelated consanguineous Libyan families under regular follow-up in our institution. Each family has two children with diabetes and bone marrow aplasia. Clinical, laboratory, and genetic assessment were done for both families, while bone marrow biopsy, and pancreatic autoantibodies as clinically indicated. We compared clinical and laboratory variables pre and post BMT.

2.2 | Molecular genetic testing

In both families, DNA was collected from buccal smear of affected children as the tests were conducted post BMT, while in other family members DNA was extracted from whole blood. The analyzed DNA from the two tissues covers the two isoforms of the gene. WES was performed in the affected children and Sanger sequencing was used to confirm the detected *DUT* variant in the affected children and to sequence *DUT* gene in the asymptomatic members of both families.

2.3 | Whole-exome sequencing

Genomic DNA were fragmented using a Covaris E220 evolution (Covaris). The performed WE trio included both nuclear and mitochondrial isoforms of the *DUT* gene. Libraries were prepared using NEB Ultra II kits (New England Biolabs) and enriched by Roche SeqCap EZ MedExome V1 target enrichment (Roche). Sequencing was performed on an Illumina NovaSeq 6000 system (Illumina). NGS data were aligned to the hg19 genome assembly. Variant calling and annotation were performed by developed bioinformatics pipeline (Bioscientia). Identified SNVs and indels were filtered against external and internal databases focusing on rare variants with a Minor Allele Frequency (MAF) in gnomAD of 1% or less and removing known artifacts and variants in regions with highly homologous regions. Classification of variants was conducted based on ACMG guidelines considering database entries (incl. HGMD, Qiagen), bioinformatics prediction tools and literature status.

2.4 | Sanger sequencing

The *DUT* gene was sequenced in patients and unaffected members of both families to identify the mutation detected by WES. The corresponding coding regions of *DUT* exon were amplified by polymerase chain reaction and analyzed by direct sequencing on an AB 3500 xL sequencer (Applied Biosystems). The resulting sequence data were compared with the reference sequence NM_001025248.1 (SeqPilot, JSI medical systems).

3 | RESULTS

The demographics, clinical, and laboratory details of the affected individuals pre and post BMT and the heterozygous carriers in both families are summarized in Tables 1 and 2. The pedigrees of both families with mutation chromatograms are illustrated in Figure 1

Family A: the parents were first cousins with two affected sons (A.1 and A.2) and a healthy younger daughter. The boys presented at four and two and half years, respectively, with macrocytosis, thrombocytopenia. Within few weeks, their hemoglobin (Hb) and platelets levels deteriorated, but WBC remained normal. They were not dysmorphic, with appropriate growth and development without deafness or skeletal deformities. Coombs test, vitamin B12, and folic acid were normal, and BM showed hypocellular picture. Cyclosporine and steroid were unhelpful and regular blood transfusion was started. Patient A.1 presented at 6.8 years with symptomatic hyperglycemia. His glycosylated hemoglobin (HbA1c) was 12.6% (114 mmol/mol) and subcutaneous insulin at 0.5 units/kg/day was started. HbA1c remained above 12% despite an insulin dose of 1.0 units/kg/day but dropped to 8.1% (65 mmol/mol) on continuous subcutaneous insulin infusion (CSII) 0.6 units/kg/day. Patient A.2 presented at 6.3 years with symptomatic hyperglycemia and HbA1c of 7% (53 mmol/mol). He needed insulin dose of 0.4 units/kg/day and HbA1c remained around 6.5% (48 mmol/mol). He experienced recurrent hypoglycemia, which disappeared with CSII. Both boys had unrecordable c-peptide and negative pancreatic autoantibodies (ICA, IA2, GAD65, tyrosine phosphatase, and zinc transporter 8) measured 4 years following the

TABLE 1 Demographic, clinical, and laboratory characteristics of the affected children with pre and post bone marrow transplantation (BMT) data

Patient	A.1	A.2	B.1	B.2
Gender	Male	Male	Female	Male
Birth weight (kg)	2.5	3.0	3.2	2.6
Age at presentation	4 years	2.5 years	4.5 years	8.3 years
Presenting features	Macrocytosis and thrombocytopenia	Macrocytosis and thrombocytopenia	Macrocytic anemia and thrombocytopenia	Macrocytic anemia and thrombocytopenia
Age at diabetes diagnosis	6.7 years	6.3 years	6.9 years	9.7 years
Age at BMT	8.2 years	6.6 years	7.5 years	9.7 years
Hb (NR = 11.6–15.5 g/dl)				
Presentation	11.2	12.1	3.4	5.0
Pre BMT	9.7	9.0	11.1	7.4
Post BMT	14.3	11.9	12.5	13.9
MCV (NR = 80–100 fl)				
Presentation	122.9	104.9	98	105
Pre BMT	112	102	90.3	100.4
Post BMT	86	85	89.7	87
Platelets (NR = 150–450 $\times 10^9$/L)				
Presentation	114	36	46	17
Pre BMT	63	56	42	59
Post BMT*	285	414	266	219
WBC (NR = 3.5–11.2 $\times 10^9$/L)				
Presentation	7.2	6.3	5.7	6.1
Pre BMT	4.2	3.7	4.6	5.2
Post BMT	7.9	11.5	7.6	5.6
Serum ferritin (7–140 ng/ml)				
Pre BMT	1209	999	2075	3514
Post BMT	635	318	828	412
HbA1c% (mmol/mol)				
Presentation	12.6 (114)	7.0 (53)	9.0 (75)	9.0 (75)
Pre BMT	8.6 (70)	6.5 (48)	12 (108)	9.0 (75)
Post BMT	8 (64)	5.8 (40)	13 (119)	10.3 (89)
Current age (on submission)	13.5 years	12.0 years	15.2 years	13.5 years
Insulin dose and regimen	CSII (1.1 IU/kg/day)	CSII (0.6 IU/kg/day)	MDI (2 IU/kg/day)	MDI (2.2 IU/kg/day)
Weight SDS	−1.7	−2.1	+0.54	−2.7
Height SDS	−1.3	−2.9	−3.4	−2.5
Bone age (Greulich and Pyle)	11.5 years	9 years	Closed	12 years
BMI (kg/m^2)	16	16.1	27	15.2
Puberty Tanner stage	IV	II	Menarche at 12 years	III

Abbreviations: BMI, body mass index; CSII, continuous subcutaneous insulin infusion; Hb, hemoglobin; IU, international unit; MCV, mean corpuscular volume; MDI, multiple daily injection; WBC, white blood cells.

diagnosis. They have multiple nevi on the face and trunk, with a maximum diameter of 1 cm (Figure 2).

Allogenic BMT was conducted on A.1 at 8.2 years and on A.2 at 6.6 years old. Five years post BMT, their Hb, MCV, WBC, and platelets remained normal without significant change in HbA1c levels. They have appropriate puberty and school performance, but A.1 height was −2.9 SDS compared with −1.9 in A.2.

The parents and the sister, all heterozygous for the *DUT* mutation, have multiple nevi with similar distribution to the homozygous boys. Their Hb, WBC, platelets, and MCV were normal. The mother and her daughter had normal fasting glucose, HbA1c, insulin, and c-Peptide (Table 2), but the father presented at 48 years with hyperglycemia and HbA1c 8% (64 mmol/mol). He has mild acanthosis nigricans, BMI of 33 and his diabetes was controlled on metformin. Two years after

TABLE 2 Demographic and laboratory characteristics of the heterozygous carriers of the missense *DUT* mutation (c.425A>G p.(Tyr142Cys)) from the two families

	Family A			Family B	
Family member	Father	Mother	Daughter	Father	Mother
Age (years)	48	38	7.5	50	39
BMI (kg/m^2)	33.1	34	16.2	24.2	35.3
Hb (g/dl)	15.3	11.1	14.1	12.2	12.8
MCV (80–100 fl)	88	85	89	93.5	88.1
Platelets (135–450 × 10^9/L)	198	426	279	149	233
WBC (3.5–11 × 10^9/L)	6.7	8.82	6.14	7.3	5.97
HbA1c (<6.5%)	8.0	5.5	4.6	6.0	5.5
Fasting glucose (mg/dl)	145	94	87	101	95
Fasting insulin (2.0–25.0 mU/L)	9.1	8.6	5.1	8.7	10.2
Fasting c- peptide (1.1–4.4 ng/ml)	4.4	3.47	1.58	3.4	2.57

his diagnosis with diabetes, biochemical assessment revealed normal fasting insulin level and high normal fasting C-peptide (Table 2).

Family B: The parents were healthy first cousins with an affected daughter (B.1) and son (B.2). They presented at 4.5 and 8.3 years old, respectively, with severe macrocytic anemia and thrombocytopenia. They were not dysmorphic, with normal growth and development without hearing defects or skeletal deformities. Coombs test, vitamin B12, and folic acid were normal with hypocellular bone marrow. Monthly blood transfusions with chelation were started. Patient B.1 presented at 6.9 years with symptomatic hyperglycemia, ketonuria, and HbA1c of 9% (75 mmol/mol). Insulin at 0.5 units/kg/day was started, but over the years HbA1c raised to 12% (108 mmol/mol) despite insulin requirement of 1.1 unit/kg/day. At the age of 7.5 years, she received allogenic BMT. Patient B.2 presented at 9.7 years with diabetes, mild ketonuria, and HbA1c of 10% (86 mmol/mol). Insulin was started at 0.5 units/kg/day and a few weeks later he received allogenic BMT. Prior to BMT, they have negative pancreatic autoantibodies and unmeasurable c-peptide. They have multiple nevi with similar size and distribution to patients A.1 and A.2. Follow-up at 7.7 years and 3.4 years post BMT, their Hb, MCV, platelets, and WBC remained normal, but their HbA1c and serum ferritin remained high. Puberty and school performance were appropriate, but their height SDS were <−2.5.

The parents were asymptomatic but have multiple nevi with similar size and distribution to their children. Their Hb, platelets, WBC, HbA1c, fasting glucose, insulin, and c-peptide were all normal (Table 2).

3.1 | Genotype

WES identified a homozygous c.425A>G p.(Tyr142Cys) (chr15:48626619; hg19) mutation in the *DUT* gene (OMIM *601266; chromosome 15q21.1) in four affected children of both families. Sanger sequencing confirmed this variant in the mitochondrial and nuclear isoforms of the *DUT* gene of the affected children. The detected mutation was also identified in heterozygous state in parents of both families and an asymptomatic girl in family A (Figure 1). This *DUT* mutation is identical to the one previously identified in the homozygous status in patients affected by diabetes and bone marrow failure and described as causative to this syndrome (Dos Santos et al., 2017). Thus, our finding replicates this previous finding in patients from two additional independent families presenting with the same syndrome.

4 | DISCUSSION

We describe four children from two unrelated families with non-autoimmune diabetes, bone marrow failure, and homozygous *DUT* mutation making a total number of four families reported with this syndrome to date (Dos Santos et al., 2017). The BMT resolved the hematological features, and the heterozygous carriers of this mutation are healthy confirming autosomal recessive transmission.

Dos Santos et al. showed that silencing the *DUT* gene, by two independent mechanisms, increased the apoptosis in human and rat pancreatic β-cell (Dos Santos et al., 2017). This finding indicated a role of *DUT* in maintaining β-cell integrity and explains the insulin-dependent MGD with very low c-peptide in their patients and ours. The exact explanation for the hematological consequences of *DUT* mutation is not clear; however, the initial picture and the progressive nature of the bone marrow failure mimic other hematological conditions of impaired DNA repair such as Fanconi anemia (FA) (Petryk et al., 2015). Interestingly, our patients and others reported by Dos et al. developed diabetes years after the hematological manifestations. This delayed diabetes presentation could reflect a variable tissue response to impaired *DUT* function. Bone marrow has higher cell division and turnover and therefore cells would be more vulnerable to apoptosis following *DUT* mutation compared with pancreatic β-cells, which have slow division (Lam et al., 2017; Oram et al., 2019).

All reported patients with this phenotype were homozygous for the only described *DUT* mutation in human. However, we noticed a wide variation in the severity and age of onset even between siblings of the same gender. This phenomenon was reported in other

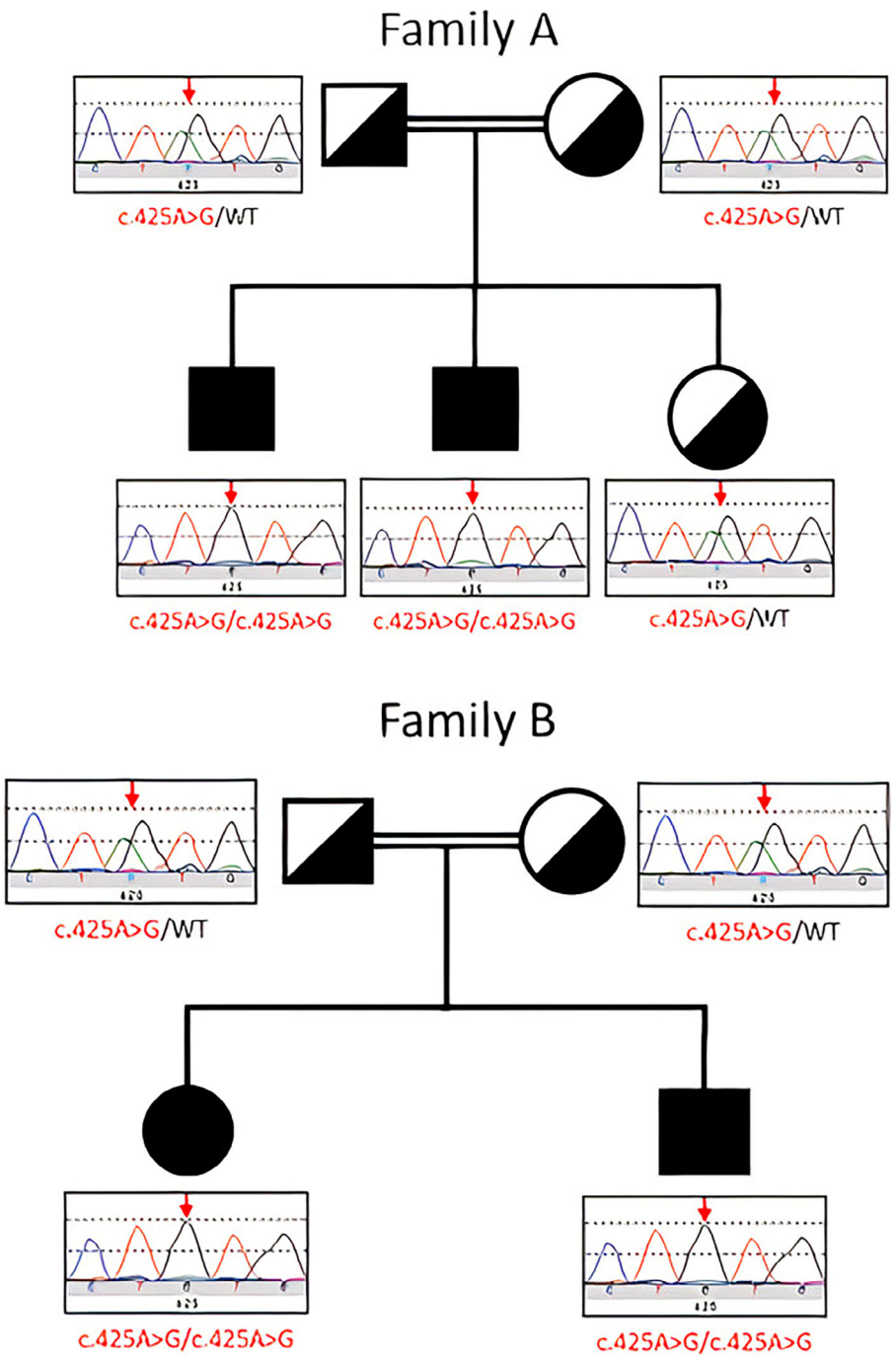

FIGURE 1 Family 1 pedigree with *DUT* mutation chromatograms

MGD syndromes (Habeb, 2013; Habeb et al., 2018) and could be related to environmental factors or the presence of other modifying genes. Multiple naevi on the face and trunk were seen in all our patients and heterozygous family members for this *DUT* mutation. This feature was also seen in siblings of a family reported by Dos Santos et al., but the remaining members of that family were not available for assessment. Benign naevi can be associated with DNA repair defect (Stark et al., 2020); however, because nevi are relatively common finding, evaluation of more patients with *DUT* mutations is needed before considering nevi as a feature of this syndrome.

We were able to explore the clinical consequences of carrying this *DUT* mutation in heterozygous state, which has not been previously reported (Dos Santos et al., 2017). Our assessment revealed that the heterozygous carriers for this mutation have no evidence of BM failure or diabetes and appear healthy apart from multiple nevi, similar to individuals with homozygous *DUT* mutations. Although one father developed diabetes, he was obese and his good response to metformin suggests that he has common type 2 diabetes rather than MGD. The remaining heterozygous individuals appear to have normal β-cell function based on normal fasting insulin, c-peptide, glucose, and HbA1c levels. However, the families were reluctant to undergo

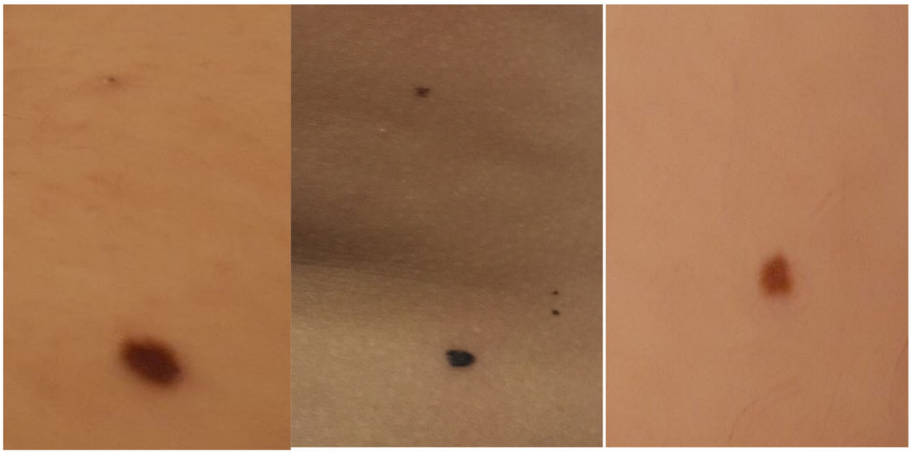

FIGURE 2 Skin nevi in patients A1, A2 and B1

dynamic tests to explore the insulin secretion and action, which is a limitation of our study. More detailed assessment of a larger cohort would provide more insight into the clinical consequences of heterozygous *DUT* mutations.

Recognizing *DUT* mutation syndrome is a challenge as the condition is rare and its phenotype is similar to thiamine responsive megaloblastic anemia (TRMA) (Habeb et al., 2018) and FA (Petryk et al., 2015). In our patients, the normal hearing ruled out TRMA and the absence of severe growth failure and skeletal deformities made FA unlikely. The negative pancreatic autoantibodies and the nonspecific BM histology raised the possibility of syndromic MGD and prompted us to do WES which made the diagnosis. The proper management of this syndrome is not clear; however, our experience indicated that allogenic BMT can reverse the bone marrow failure in patients with this syndrome. Of note, one affected sibling of a patient from the initial report by Dos Santos et al was successfully treated by BMT but he was not available of genetic testing, BMT made no improvement of diabetes control of our patients; however earlier BMT would minimize the risk of iron overload, due to regular transfusion, which can impair the diabetes control as seen in our patients with high serum ferritin.

In conclusion, these two families provide further evidence for the role of the *DUT* gene in maintaining the cell integrity of bone marrow and pancreatic β-cells. Allogenic BMT appears to be a successful option for resolving the bone marrow failure and further studies on larger cohort would clarify the clinical consequences of heterozygous *DUT* mutations.

AUTHOR CONTRIBUTIONS

Millad Ghawil drafted the manuscript, cared for children and families, obtained the families' informed consent, collected and analyzed the data, and contributed to the conception and design of the study. Fathia Abdulrahman, Ibtisam Hadeed, Milad Doggah, and Salem Zarroug cared for children, provided clinical information, and contributed to data analysis and conception of the study. Abdelhadi Habeb designed the study, analyzed the data, and revised and submitted the manuscript. All co-authors reviewed and approved the submitted version of the manuscript.

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CONFLICT OF INTEREST

All authors have no conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

Delvecchio, M., Mozzillo, E., Salzano, G., Iafusco, D., Frontino, G., Patera, P. I., Rabbone, I., Cherubini, V., Grasso, V., Tinto, N., Giglio, S., Contreas, G., di Paola, R., Salina, A., Cauvin, V., Tumini, S., d'Annunzio, G., Iughetti, L., Mantovani, V., … for the Diabetes Study Group of the Italian Society of Pediatric Endocrinology and Diabetes (ISPED). (2017). Monogenic diabetes accounts for 6.3% of cases referred to 15 Italian pediatric diabetes centers during 2007 to 2012. *The Journal of Clinical Endocrinology and Metabolism*, *102*(6), 1826–1834. https://doi.org/10.1210/jc.2016-2490

Dos Santos, R. S., Daures, M., Philippi, A., Romero, S., Marselli, L., Marchetti, P., Senée, V., Bacq, D., Besse, C., Baz, B., Marroquí, L., Ivanoff, S., Masliah-Planchon, J., Nicolino, M., Soulier, J., Socié, G., Eizirik, D. L., Gautier, J. F., & Julier, C. (2017). dUTPase (DUT) is mutated in a novel monogenic syndrome with diabetes and bone marrow failure. *Diabetes*, *66*(4), 1086–1096. https://doi.org/10.2337/db16-0839

Habeb, A. M. (2013). Frequency and spectrum of Wolcott-Rallison syndrome in Saudi Arabia: A systematic review. *The Libyan Journal of Medicine*, *8*, 21137. https://doi.org/10.3402/ljm.v8i0.21137

Habeb, A. M., Flanagan, S. E., Zulali, M. A., Abdullah, M. A., Pomahačová, R., Boyadzhiev, V., Colindres, L. E., Godoy, G. V., Vasanthi, T., Al Saif, R., Setoodeh, A., Haghighi, A., Haghighi, A., Shaalan, Y., International Neonatal Diabetes Consortium, Hattersley, A. T., Ellard, S., & De Franco, E. (2018). Pharmacogenomics in diabetes: Outcomes of thiamine therapy in TRMA syndrome. *Diabetologia*, *61*(5), 1027–1036. https://doi.org/10.1007/s00125-018-4554-x

Hattersley, A. T., Greeley, S., Polak, M., Rubio-Cabezas, O., Njølstad, P. R., Mlynarski, W., Castano, L., Carlsson, A., Raile, K., Chi, D. V., Ellard, S., & Craig, M. E. (2018). ISPAD clinical practice consensus guidelines 2018: The diagnosis and management of monogenic diabetes in children and adolescents. *Pediatric Diabetes*, *19*(Suppl 27), 47–63. https://doi.org/10.1111/pedi.12772

Horváth, A., & Vértessy, B. G. (2010). A one-step method for quantitative determination of uracil in DNA by real-time PCR. *Nucleic Acids Research*, *38*(21), e196. https://doi.org/10.1093/nar/gkq815

Kim, J. H., Lee, Y., Choi, Y., Kim, G. H., Yoo, H. W., & Choi, J. H. (2021). Etiologic distribution and clinical characteristics of pediatric diabetes in 276 children and adolescents with diabetes at a single academic center. *BMC Pediatrics*, *21*(1), 108. https://doi.org/10.1186/s12887-021-02575-6

Koehler, S. E., & Ladner, R. D. (2004). Small interfering RNA-mediated suppression of dUTPase sensitizes cancer cell lines to thymidylate synthase inhibition. *Molecular Pharmacology*, *66*, 620–626.

Lam, C. J., Jacobson, D. R., Rankin, M. M., Cox, A. R., & Kushner, J. A. (2017). β cells persist in T1D Pancreata without evidence of ongoing β-cell turnover or Neogenesis. *The Journal of Clinical Endocrinology and Metabolism*, *102*(8), 2647–2659. https://doi.org/10.1210/jc.2016-3806

Oram, R. A., Sims, E. K., & Evans-Molina, C. (2019). Beta cells in type 1 diabetes: Mass and function; sleeping or dead? *Diabetologia*, *62*(4), 567–577. https://doi.org/10.1007/s00125-019-4822-4

Petryk, A., Kanakatti Shankar, R., Giri, N., Hollenberg, A. N., Rutter, M. M., Nathan, B., Lodish, M., Alter, B. P., Stratakis, C. A., & Rose, S. R. (2015). Endocrine disorders in Fanconi anemia: Recommendations for screening and treatment. *The Journal of Clinical Endocrinology and Metabolism*, *100*(3), 803–811. https://doi.org/10.1210/jc.2014-4357

Riddle, M. C., Philipson, L. H., Rich, S. S., Carlsson, A., Franks, P. W., Greeley, S., Nolan, J. J., Pearson, E. R., Zeitler, P. S., & Hattersley, A. T. (2020). Monogenic diabetes: From genetic insights to population-based precision in care. Reflections from a diabetes care Editors' expert forum. *Diabetes Care*, *43*(12), 3117–3128. https://doi.org/10.2337/dci20-0065

Stark, M. S., Denisova, E., Kays, T. A., Heidenreich, B., Rachakonda, S., Requena, C., Sturm, R. A., Soyer, H. P., Nagore, E., & Kumar, R. (2020). Mutation signatures in melanocytic nevi reveal characteristics of defective DNA repair. *The Journal of Investigative Dermatology*, *140*(10), 2093–2096.e2. https://doi.org/10.1016/j.jid.2020.02.021

Vértessy, B. G., & Tóth, J. (2009). Keeping uracil out of DNA: Physiological role, structure, and catalytic mechanism of dUTPases. *Accounts of Chemical Research*, *42*, 97–106.

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