controlling AP1 and OCRL-bearing vesicles. *Dev Cell.* 2012;23(5):954-967.

6. Chen J, Shetty S, Zhang P, et al. Aspirin-triggered resolvin D1 down-regulates inflammatory responses and protects against endotoxin-induced acute kidney injury. *Toxicol Appl Pharmacol.* 2014;277(2): 118-123.

7. Marsh RA, Rao K, Satwani P, et al. Allogeneic hematopoietic cell transplantation for XIAP deficiency: an international survey reveals poor outcomes. *Blood.* 2013; 121(6):877-883.

8. Ferretti M, Gattorno M, Chiocchetti A, et al. The 423Q polymorphism of the X-linked inhibitor of apoptosis gene influences monocyte function and is associated with periodic fever. *Arthritis Rheum.* 2009; 60(11):3476-3484.

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Transfer RNA and syndromic sideroblastic anemia

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In this issue of *Blood*, Chakraborty et al[1] reported loss-of-function of TRNT1 gene causes a syndromic form of congenital sideroblastic anemia (SA) associated with B-cell immunodeficiency, periodic fevers, and developmental delay (SIFD). This new syndrome, inherited with a recessive pattern, was described in this Journal 1 year ago studying 12 subjects from 10 different families.[2] It is a severe condition with neonatal or infancy onset and systemic tissue involvement that can partially benefit from bone marrow transplantation.

Identification of TRNT1 mutations as SIFD-causing genetic alterations was achieved by using 2 independent technical approaches: genome-wide next-generation sequencing and descendent mapping linkage analysis. Both methods identified germline point mutations of the TRNT1 gene (EC 2.7.7.25) that encodes an essential enzyme that catalyzes the addition of the CCA terminus to the 3′ end of transfer RNA (tRNA) precursors. This reaction is a fundamental prerequisite for mature cytosolic and mitochondrial tRNA aminoacylation and quality control as well as for stress response.

Inherited SAs comprise heterogeneous phenotypes depending on the original function(s) of the mutated genes but all characterized by the presence of ringed sideroblasts in the bone marrow aspirate. The latter are erythroblasts with pathological coarse granules of iron deposition in mitochondria, as demonstrated by electron microscopy. Such iron-encrusted mitochondria surround the nucleus of the erythroid cell forming a characteristic "ring," when stained with Perls' Prussian blue.

Inherited SA is rarer than the acquired form and could be syndromic or not syndromic, with heterogeneous patterns of inheritance. To date, several genes responsible for inherited SA have been identified and they all play important roles in heme biosynthesis, Fe-S cluster biogenesis, or biology of mitochondria[3] (see figure).

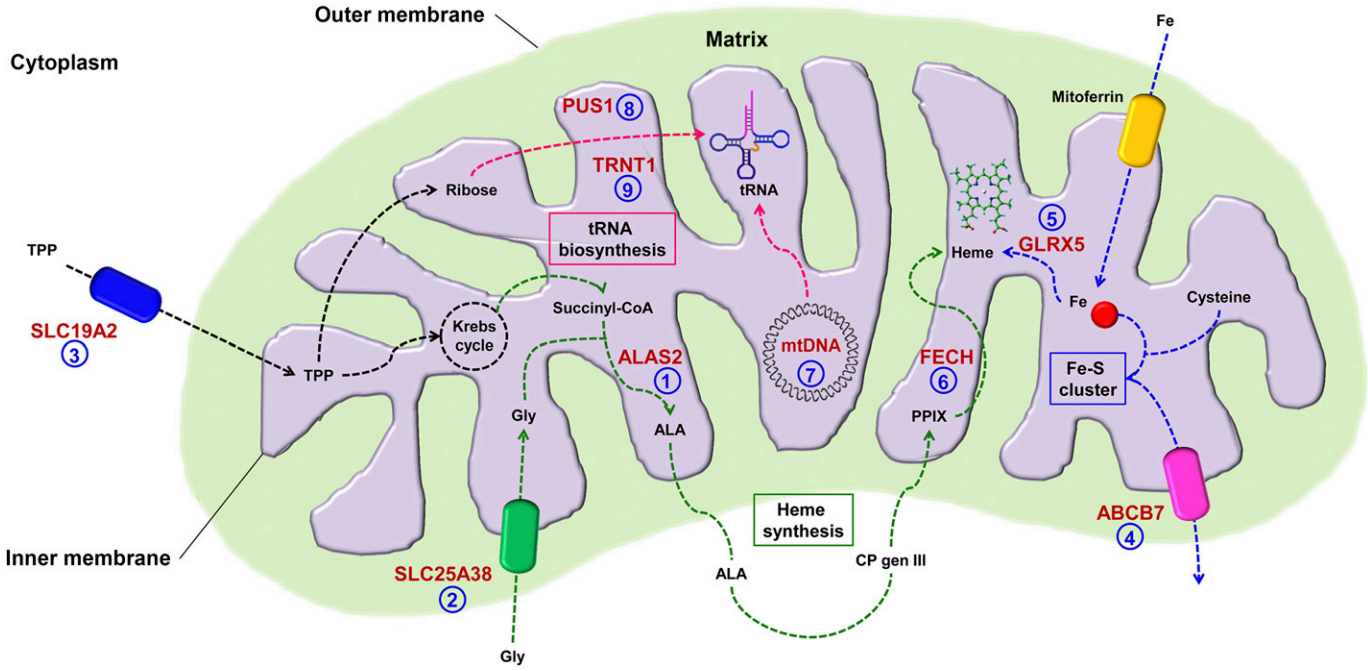
The most frequent form is X-linked SA (XLSA), caused by mutations in the erythroid-specific *d*-aminolevulinate synthase gene (ALAS2). Bergmann et al[4] systematically examined gene mutations in 60 inherited SA probands, and identified mutations of ALAS2, SLC25A38, mitochondrial DNA, and PUS1 in 37% 15%, 2.5%, and 2.5% of cases, respectively. Disease-causing mutations were not found in the remaining 43% of cases, suggesting that there are as-yet-unidentified gene mutations that can cause inherited SA.

The observations of Chakraborty et al[1] reduce the number of syndromic forms lacking a causative gene, in particular those with SIFD. Because of the large heterogeneity of SIFD expressivity, it is difficult to calculate the exact percentage of patients carrying TRNT1 mutations because many cases might be misdiagnosed for their mild phenotype. Such cases could now be identified by TRNT1 gene sequencing. The loss of function effect of SIFD-associated TRNT1 mutations was clearly shown in both human fibroblasts and in yeast, although the specific mechanism by which these mutated proteins cause specifically anemia, immunodeficiency, fever, and developmental delay is still largely unknown. This is another example of an inherited disease in which insufficiency of a single protein, TRNT1, simultaneously promotes the deficiency of many other proteins via the perturbation of protein biosynthesis pathway. Noteworthy is that TRNT1 gene function appears crucial and not redundant for cellular homeostasis and fitness, as demonstrated by the observations that almost all patients retain some enzyme activity and most mutations are hypomorphic. In addition, silencing of the TRNT1 gene is accompanied by cell death in vitro.

However, as in Diamond–Blackfan anemia for the ribosome synthesis[5] and in congenital dyserythropoietic anemia type II for COPII assembly, even if the mutated gene is expressed in a variety of tissues, the clinical symptoms appeared limited to a single or few organs and tissues.[6] How can such an oddness be explained? One possibility could be that, in SIFD, tissues devoted to producing a large amount of a limited set of proteins or even a single one (as hemoglobin for erythroid precursors or immunoglobulin for B lymphocytes) could suffer more from inefficient protein synthesis.

In both the syndromic and not-syndromic forms of SA, the final effect is deregulation of iron metabolism that causes an iron overload in the erythroblast mitochondria associated with increased mitochondrial ferritin, which is, indeed, the hallmark of these anemias. Thus, such iron excess in these organelles needs to be sheltered by mitochondrial ferritin to avoid Fenton-type reactions and iron-induced oxidative damage.[7]

In several nonsyndromic cases (such as those caused by mutations of XLSA, SLC25A38, GLRX5, and FECH), the iron overload appears as a direct consequence of the involvement of a gene whose product is directly related to iron or heme metabolism. In these cases, the symptoms are mainly confined to anemia. On the other hand, syndromic forms appear to be associated with a defect in mitochondrial/cytosolic protein translation (ABCB7, SIFD, Pearson syndrome, myopathy lactic acidosis and SA, thiamine-responsive megaloblastic anemia) and in particular with abnormal tRNA function caused by defects in tRNA maturation/modification or even



Schematic representation of mitochondrial pathways affected by genetic defects in congenital SAs. Genes mutated in congenital SAs (in red) are involved in several pathways: heme synthesis, mitochondrial iron homeostasis, tRNA biosynthesis. Nonsyndromic congenital SAs: 1, XLSA; 2, SLC25A38 deficiency; 5, glutaredoxin 5 deficiency; 6, erythropoietic protoporphyria. Syndromic congenital SAs: 3, thiamine-responsive megaloblastic anemia; 4, X-linked congenital SA with ataxia; 7, Pearson marrow-pancreas syndrome; 8, myopathy, lactic acidosis, and SA; 9. SA, SIFD. ABCB7, mitochondrial transporter for cytosolic Fe-S cluster; ALA, 5-aminlevulinic acid; ALAS2, d-aminolevulinate synthase 2; Co-A, coenzyme A; CP gen III, coproporphyrinogen III; FECH, ferrochelatase; GLRX5, glutaredoxin 5; PPIX, protoporphyrin IX; PUS1, pseudouridylate synthase 1; SLC19A2, transporter of TPP; SLC25A38, transporter of glycine; TPP, thiamine pyrophosphate; TRNT1, tRNA-nucleotidyltransferase 1.

deletion of mitochondrial tRNA genes. In accordance, TRNT1 is essential for the tRNA maturation, and its reduced activity, as in other syndromic SA, is predicted to have profound effects on cell viability by affecting overall protein biosynthesis and causing a plethora of dysfunctions in patients.

In conclusion, the article by Chakraborty et al opens new frontiers for molecular diagnosis in the pre- and postnatal periods and genetic treatment of patients with SIFD, although many efforts still need to be undertaken to understand the molecular mechanism underlying this complex disease phenotype.

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REFERENCES

1. Chakraborty PK, Schmitz-Abe K, Kennedy EK, et al. Mutations in *TRNT1* cause congenital sideroblastic anemia with immunodeficiency, fevers, and developmental delay (SIFD). *Blood.* 2014;124(18):2867-2871.

2. Wiseman DH, May A, Jolles S, et al. A novel syndrome of congenital sideroblastic anemia, B-cell immunodeficiency, periodic fevers, and developmental delay (SIFD). *Blood.* 2013;122(1):112-123.

3. Bottomley SS, Fleming MD. Sideroblastic anemia: diagnosis and management. *Hematol Oncol Clin North Am.* 2014;28(4):653-670.

4. Bergmann AK, Campagna DR, McLoughlin EM, et al. Systematic molecular genetic analysis of congenital sideroblastic anemia: evidence for genetic heterogeneity and identification of novel mutations. *Pediatr Blood Cancer.* 2010;54(2):273-278.

5. Narla A, Ebert BL. Ribosomopathies: human disorders of ribosome dysfunction. *Blood.* 2010;115(16):3196-3205.

6. Russo R, Esposito MR, Iolascon A. Inherited hematological disorders due to defects in coat protein (COP)II complex. *Am J Hematol.* 2013;88(2):135-140.

7. Arosio P, Levi S. Cytosolic and mitochondrial ferritins in the regulation of cellular iron homeostasis and oxidative damage. *Biochim Biophys Acta.* 2010;1800(8):783-792.

● ● ● THROMBOSIS & HEMOSTASIS

Comment on Abdul Sultan et al, page 2872

Postpartum venous thromboembolic risk: one size may not fit all

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In this issue of *Blood,* Abdul Sultan et al describe risk factors for venous thromboembolism (VTE) after pregnancy with consideration of duration of risk in differing clinical circumstances.[1] They provide essential information toward a data-driven foundation on which clinical guidelines may be refined.

Pregnancy-related VTE represents one of the leading causes of maternal mortality and morbidity worldwide.[2,3] In pregnancy and postpartum, several factors converge to increase VTE risk, including altered coagulation factors, mechanical obstruction by the enlarged uterus, and pregnancy-related endothelial changes. Pregnancy-related VTE occurs in ~1 to 2 of every 1000 deliveries.[3,4] Relative to nonpregnant, reproductive age