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The Congenital Dyserythropoieitic Anemias: Genetics and Pathophysiology

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Abstract

Purpose of review—The congenital dyserythropoietic anemias (CDA) are hereditary disorders characterized by ineffective erythropoiesis. This review evaluates newly developed CDA disease models, the latest advances in understanding the pathogenesis of the CDAs, and recently identified CDA genes.

Recent findings—Mice exhibiting features of CDAI were recently generated, demonstrating that Codanin-1 (encoded by *Cdan1*) is essential for primitive erythropoiesis. Additionally, Codanin-1 was found to physically interact with CDIN1, suggesting that mutations in *CDAN1* and *CDIN1* result in CDAI via a common mechanism. Recent advances in CDAII (which results from *SEC23B* mutations) have also been made. SEC23B was found to functionally overlap with its paralogous protein, SEC23A, likely explaining the absence of CDAII in SEC23B-deficient mice. In contrast, mice with erythroid-specific deletion of 3 or 4 of the *Sec23* alleles exhibited features of CDAII. Increased SEC23A expression rescued the CDAII erythroid defect, suggesting a novel therapeutic strategy for the disease. Additional recent advances included the identification of new CDA genes, *RACGAP1* and *VPS4A*, in CDAIII and a syndromic CDA type, respectively.

Summary—Establishing cellular and animal models of CDA is expected to result in improved understanding of the pathogenesis of these disorders, which may ultimately lead to the development of new therapies.

Keywords

Congenital Dyserythropoietic Anemia; Red Blood Cells; Erythropoiesis; Hereditary anemia; Molecular genetics

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Introduction

The congenital dyserythropoietic anemias (CDAs) are a group of hereditary disorders collectively characterized by anemia of variable severity and increased percentage of bone marrow bi/multinucleated erythroblasts. Historically, the CDAs have been divided into three types (CDA I, CDA II, and CDA III); however, additional CDA types have been described. CDA II is the most common CDA, followed by CDA I, with an estimated prevalence of 0.71 and 0.24 cases/million, respectively [1, 2]. However, the CDAs are likely underdiagnosed and underreported, as suggested by a more recent estimate of CDA I incidence of 5 cases/million live births [3*]. Though several reviews that discuss the CDAs have been published in the last few years [4–9], this manuscript focuses primarily on the most recent advances in CDA genetics and pathophysiology.

Clinical and laboratory characteristics shared by most CDAs

The hematopoietic defect in the CDAs is restricted to the erythroid lineage, except for *GATA1*-mutated CDA in which both the erythroid and megakaryocytic lineages are affected. Although the anemia in CDA results predominantly from ineffective erythropoiesis (characterized by differentiation block and/or death of erythroid precursors in the bone marrow), CDAs are also characterized by a hemolytic component, often resulting in gallstone formation and intermittent jaundice, and commonly accompanied by splenomegaly. Therefore, the lactate dehydrogenase and indirect bilirubin levels are often elevated in CDA (due to hemolysis), but the reticulocyte count is normal or suboptimally elevated for the severity of the anemia (due to ineffective erythropoiesis). The severity of the anemia in CDA is highly variable, ranging from mild to transfusion dependent. Most patients with CDA I or CDA II are diagnosed in infancy or childhood following a workup for mild to moderate anemia, though delayed presentations, even in late adulthood, are not uncommon when the disease is mild [10]. Rarely, the anemia in CDA is very severe resulting in hydrops fetalis [11, 12]. Most CDA patients develop secondary hemochromatosis, regardless of transfusion requirement, due to increased iron absorption [13–17]. In addition to the characteristic findings shared by all CDAs, each CDA subtype has distinguishing features, as discussed below.

CDA I

Clinical and laboratory characteristics

CDA I is characterized by macrocytic anemia in most patients, but in ~30% of patients, the anemia is normocytic. The percentage of binucleated erythroblasts in the CDA I marrow (~2–10% of late erythroblasts) is generally lower than that observed in CDA II. In contrast to other CDAs, distinguishing features observed in the CDA I marrow include internuclear chromatin bridging in ~1–8% of erythroblasts [18] and “Swiss-cheese” appearance of the heterochromatin observed in ~60% of erythroblasts [19, 20].

Non-hematologic abnormalities have been reported in CDA I, including dysmorphic bone features mostly involving the hand and/or foot (in ~10% of patients) [19], short stature [21], osteoporosis, pulmonary hypertension of the newborn [22], and retinal angioid streaks

[23]. In addition, left ventricular noncompaction (a form of cardiomyopathy) appears to be more prevalent in CDA I patients compared to age and gender-matched controls [24], independently of the iron storage status; however, the clinical significance of this finding remains unknown, particularly that no adverse clinical cardiac outcome was identified in this study [24].

Genetics and pathophysiology

CDA I is an autosomal recessive disease resulting from loss-of-function mutations in *CDAN1* [25] or *CDIN1* (previously *C15Orf41*) [26], accounting for ~80% and ~10% of the disease, respectively. The remaining ~10% of patients may have mutations in noncoding regulatory elements of *CDAN1* or *CDIN1* or in yet unidentified CDA I-causing genes.

Germline deletion of *Cdan1* in the mouse results in embryonic lethality at embryonic day 6.5, prior to the onset of hematopoiesis [27], suggesting a critical role for Codanin-1 (the protein encoded by *CDAN1*) in development, unrelated to erythropoiesis. Consistent with this finding, humans with bi-allelic null mutations in *CDAN1* have not been reported, suggesting that complete loss of Codanin-1 is lethal.

Initial efforts aimed at studying the function of Codanin-1 were performed using a cervical cancer cell line (HeLa) and an osteosarcoma cell line (U-2-OS); these studies demonstrated that Codanin-1 localizes to the heterochromatin during interphase and cytokinesis, but that Codanin-1 was phosphorylated during mitosis resulting in its exclusion from condensed chromosomes [28]. In contrast, three independent reports [27, 29, 30*], two of which used validated antibodies [27, 29], showed that Codanin-1 is localized mostly to the cytosol [27, 29, 30*], a finding confirmed at the endogenous expression level in primary human erythroblasts, CDA I erythroblasts, and murine erythroblasts [27]. While one of the latter reports showed that the Golgi apparatus of CDA I erythroblasts aberrantly accumulates HP1α (a member of the heterochromatin protein family) [27], another report showed that Codanin-1 interacts with and sequesters Asf1 in the cytoplasm, resulting in inhibition of DNA replication due to impaired delivery of histones to the nucleus by Asf1 [29].

Adding to the puzzle, Codanin-1 was recently reported to be enriched in the nucleolus by immunofluorescence studies in two independent reports [3*, 31*]; however, both reports used the same antibody that was appropriately validated for Western Blot, but not validated for immunofluorescence [3*, 31*]. Recently, a Human Umbilical Cord Blood-Derived Erythroid Progenitor-2 (HUDEP-2) cell line expressing FLAG-tagged Codanin-1 from the endogenous locus of *CDAN1* was established [32]. Using well-validated anti-FLAG antibodies, this cell line may help reconcile the discrepant cellular localizations reported for Codanin-1.

To define the role of Codanin-1 in erythropoiesis, a mouse with a conditional *Cdan1* allele was generated, demonstrating that Codanin-1 is essential for primitive erythropoiesis [33**]. Deletion of *Cdan1* in the erythroid compartment resulted in mid-embryonic lethality, with the mutant embryos exhibiting several of the CDA I features [33**]. Unlike previous reports that suggested that human CDA I erythroblasts exhibit cell cycle arrest at the S phase [34, 35], Codanin-1 deficiency in murine erythroid cells appeared to result in cell cycle arrest

at the G0/G1 phase [33**]. Possible explanations for these discrepant cell cycle findings observed in human and mouse CDA I erythroblasts include species-specific differential roles of Codanin-1 in cell cycle regulation or disparate roles of Codanin-1 in primitive versus definitive erythroid cells.

Since the discovery that ~10% of CDA I patients have a mutation in *CDIN1*, several groups independently identified a physical interaction between the Codanin-1 and CDIN1 proteins [3*, 30*, 36*]. While reduced expression of CDIN1 had no impact on the Codanin-1 level, loss of codanin-1 resulted in concurrent depletion of CDIN1[3*], suggesting that the stability of CDIN1 depends on Codanin-1. Consistent with these results, concurrent overexpression of Codanin-1 and CDIN1 results in higher CDIN1 level compared to overexpression of CDIN1 alone [30*]. Interestingly, the cellular localization of CIDN1 appears to also depend on Codanin-1; combined overexpression of Codanin-1 and CDIN1 results in a shift in the localization of CDIN1 from the nucleus to the cytoplasm [30*, 36*]. In contrast, two recent reports suggested that at the endogenous level of expression, CDIN1 localizes (with Codanin-1) primarily to the nucleolus by immunofluorescence [3*, 31*]; while intriguing, this finding remains to be confirmed with an antibody validated for immunofluorescence [3*, 31*]. While CDIN1 is predicted to be a nuclease, no nuclease activity was detected when CDIN1 was complexed with the C-terminal fragment of Codanin-1 [36*].

Recently, CD34+ hematopoietic stem and progenitor cells were isolated from CDA I patients and differentiated into erythroid cells, demonstrating increased proliferation, delayed differentiation, and altered regulatory landscape as determined by chromatin accessibility [31*]. A striking feature in CDA I erythroblasts was reduced chromatin accessibility at sites that contain a binding motif for the NF-E2 family of transcription factors and disruption of the nucleoli structure [31*]. Whether these findings are responsible for the erythroid differentiation defect in CDA I or merely associated with impaired erythroid differentiation remain to be determined.

While several advances have been made in the study of CDA I, the specific roles of CDAN1 and CDIN1 in erythropoiesis and the mechanism by which *CDAN1* and *CDIN1* mutations result in a predominantly erythroid disorder remain to be elucidated.

Treatment

Management of CDA I depends largely on the severity of the anemia. Some patients with severe anemia require transfusion support. This requirement may be transient (such as perinatally or in the setting of bone marrow/erythroid stress), but ~4% of CDA I patients are chronically transfusion dependent [20].

Secondary hemochromatosis is common; therefore, iron studies need to be monitored periodically, as does myocardial T2* magnetic resonance imaging (MRI) and hepatic R2* MRI. A consensus for the frequency of monitoring for iron overload has not been established, but yearly studies starting in adolescence have been suggested. If myocardial or hepatic iron overload is observed or if the ferritin reaches 500–1000 mg/L, iron depletion

should be initiated, either by phlebotomy if the anemia is mild or using iron chelators in patients for whom phlebotomy cannot be safely performed.

Several reports have shown improvement in the CDA I anemia with interferon treatment [37–41]. A recent cohort of CDA I patients showed that six out of seven patients achieved transfusion independence with pegylated interferon alpha-2a [42*]. Notably, patients treated with pegylated interferon alpha-2a appear to have reduced hemolysis but continue to have high ferritin levels. It is possible that interferon prevents destruction of erythroid cells in CDA I without relieving the ineffective erythropoiesis, but more work is required to determine the mechanism by which interferon improves the erythroid defect of CDA I.

Bone marrow transplantation is curative for CDA I [43–45] and should be considered in patients with severe transfusion-dependent anemia.

CDAII

Clinical and laboratory characteristics

CDA II is the most common CDA [1, 2, 5, 46]. The diagnosis of CDA II is suggested when a bone marrow biopsy demonstrates an increased percentage (10–30%) of bi-nucleated erythroid precursors [19]. However, in contrast to CDA I, internuclear chromatin bridging between erythroblasts is not a characteristic feature of CDAII. Gaucher-like cells, which result from erythroblast phagocytosis by macrophages, are found in ~60% of CDA II patients. An additional highly characteristic feature of CDA II is a double membrane appearance of the red blood cell (RBC) plasma membrane by electron microscopy, with the inner membrane representing residual endoplasmic reticulum (ER) [47]. Furthermore, CDA II is characterized by as narrower band size and increased migration of the RBC plasma membrane proteins band 3 and band 4.5 on sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE) [48], resulting from reduced glycosylation of these proteins.

Genetics and pathophysiology

CDA II is an autosomal recessive disease resulting from loss-of-function mutations in *SEC23B* [14], which encodes a component of coat complex II (COPII) vesicles that traffic ~7,000 mammalian secretory proteins from the ER to the Golgi apparatus [49, 50]. Though the genetic defect underlying CDA II was identified more than a decade ago [14], the pathophysiology of the disease remains poorly understood. For many years, one of the chief obstacles to studying the pathogenesis of CDA II has been the lack of a cell or animal model that recapitulate features of CDA II. However, recent generation of human erythroid cell lines (such as HUDEP-2) that can be differentiated efficiently into more mature erythroid cells resulted in the successful generation of a cellular model for CDA II [51*]. SEC23B deficient HUDEP-2 cells exhibited no survival or expansion defect when maintained in the pro-erythroblasts phase; however, upon differentiation into mature erythroid cells, *SEC23B* deleted HUDEP-2 cells exhibited reduced survival and expansion, a differentiation defect, and increased bi-nucleated cells, characteristic features of CDA II [51*]. The CDA II cell line model is expected to result in improved understanding of the pathophysiology of CDA II and to test the effectiveness of future therapies developed for the disease.

Initial attempts at generating a murine model of CDA II were unsuccessful. Surprisingly, in contrast to humans, mice with germline deletion of *Sec23b* exhibit perinatal mortality due to pancreatic degeneration [52–54], while mice with erythroid-specific or pan-hematopoietic *Sec23b* deletion do not exhibit an erythroid defect [55], nor do lethally irradiated mice transplanted with *Sec23b* deleted hematopoietic stem cells [55]. To address the discrepant mouse and human phenotypes resulting from SEC23B deficiency, a large body of work was performed demonstrating that SEC23B functionally overlaps with its closely related paralogous protein SEC23A. The functional overlap between SEC23A and SEC23B was supported by several lines of evidence, including studies showing overlapping interactomes for SEC23A and SEC23B [56], complementation of the yeast *sec23* by both murine and human SEC23 paralogs [56], and rescue of the perinatal mortality and pancreatic degeneration resulting from murine SEC23B deficiency by expressing *Sec23a* from the endogenous locus of *Sec23b* [51*, 56]. Examination of the expression levels of SEC23A and SEC23B in wildtype mouse and human bone marrow and pancreas tissues demonstrated a greater dependency for SEC23B in human bone marrow and mouse pancreas tissues [56–58], consistent with the SEC23B deficient phenotypes in these species.

Based on the functional overlap between the two SEC23 paralogs, mice with erythroid-specific deletion of all combinations of the 4 *Sec23* alleles were generated. Mice with deletion of all 4 *Sec23* alleles die in mid-embryonic development exhibiting anemia and dyserythropoiesis, while mice with biallelic *Sec23a* deletion combined with *Sec23b* haploinsufficiency exhibit mild anemia [51*], and mice with *Sec23a* haploinsufficiency combined with bi-allelic *Sec23b* deletion exhibit an intermediate phenotype between mice of the former two genotypes [51*]. Analysis of the expression levels of SEC23A and SEC23B in mouse erythroid cells demonstrated an inverse relationship between the total SEC23 (SEC23A + SEC23B) level and the severity of the erythroid phenotype.

Consistent with the findings described in mice, SEC23A was also shown to functionally overlap with SEC23B in human erythroid cells. Indeed, increased expression of endogenous SEC23A rescues the erythroid differentiation defect and the increased bi-nuclearity observed in differentiating *SEC23B* deleted HUDEP-2 cells [51*]. A dose response relationship between the level of increased SEC23A expression in *SEC23B* deleted HUDEP-2 cells and the degree of rescue of the erythroid differentiation defect was noted. Increased expression of SEC23A by as little as 30% and 5% in undifferentiated and differentiated HUDEP-2 cells, respectively, resulted in significant improvement of the erythroid defects resulting from SEC23B deficiency [51*]. Taken together, these findings indicate that strategies aimed at increasing SEC23A level, even by moderate amounts, are expected to be of therapeutic value for CDA II. Supporting this approach, CDA II patients with higher SEC23A expression levels appear to have a milder phenotype than those with lower SEC23A expression [59].

Treatment

Similar to CDA I, current management of CDA II patients is limited to transfusion support if/when needed and treatment of iron overload with either phlebotomy (if the anemia is mild) or iron chelators. In patients with severe transfusion-dependent anemia, allogeneic

bone marrow transplantation should be considered, as it remains the only curative modality for the disease [60–68].

Recently, luspatercept, a ligand trap for transforming growth factor beta (TGF-β), was shown to enhance erythroid maturation and improve the anemia of ineffective erythropoiesis observed in myelodysplastic syndrome [69] and β-thalassemia [70]. Since CDA II is also characterized by ineffective erythropoiesis, another ligand trap for TGF-β, RAP-011, was tested in an immortalized erythroleukemia K562 cell line in which *SEC23B* was genetically silenced, demonstrating restoration of expression of erythroid differentiation markers [71]. These studies support future clinical trials that aim to test the clinical utility of TGF-β traps in CDA II, and possibly other CDAs.

Though overexpression of the transcription factor CREB3L2/BBF2H7 has been shown to result in increased SEC23A expression [72–74] and improvement of the band-3 hypoglycosylation defect observed in CDA II [74], additional regulators of SEC23A expression that may be better targetable with less off-target effects need to be identified. Future areas of investigations should include efforts at identifying small molecules that may result in increased SEC23A expression.

CDA III

Clinical and laboratory characteristics

CDA III is less common than CDA I and II. Though several families and sporadic cases have been reported [75–86], much of the knowledge gained about CDA III originates from studying one large Swedish family with more than 20 affected members [87]. In this family, affected individuals were found to be at risk of developing retinal angioid streaks [88] and monoclonal gammopathies [89]. Unlike CDA I and II, iron overload and splenomegaly are not common in CDA III. The percentage of multinucleated erythroblasts in the CDA III bone marrow has been reported to range from 12% to 35% [75, 79, 80]. In contrast to CDA I and II, CDA III is characterized by giant multinucleated erythroblasts containing up to 12 nuclei per cell [19, 90], a feature highly specific for CDA III.

Genetics and pathophysiology

CDA III is an autosomal dominant disease resulting from mutations in the Kinesin Family Member 23 gene (*KIF23*), which encodes the Mitotic Kinesin-Like Protein 1 (MKLP1) [81, 91]. An identical mutation in *KIF23* (c.2747C>G resulting in p.P916R) was identified in the large Swedish family and in an unrelated family from the United States, but recently a different mutation (c.2833delC resulting in p.Leu945Trpfs*31) was identified in a separate family [81]. MKLP1 is a component of centralspindlin, a key regulator of cytokinesis [92–94]. Depletion of MKLP1 results in binucleated cells due to cytokinesis failure [91], suggesting that a defect in cytokinesis underlies the pathophysiology of CDA III.

To study the pathogenesis of CDA III, a mouse with a *Kif23* mutation (c.2726 C>G resulting in p. P909R) corresponding to the human c.2747C>G *KIF23* mutation was recently generated [95]. Surprisingly, mice heterozygous for the *Kif23* mutation did not exhibit a phenotype reminiscent of human CDA III, nor did mice homozygous for the *Kif23* mutation

[95]. Further investigation is needed to explain why *Kif23* mutant mice do not exhibit CDA III and to establish a CDA III model to study the pathophysiology of the disease.

Recently, mutations in *RACGAP1*, which encodes the Rac GTPase-activating protein 1 (MgcRacGAP, also known as CYK-4), have been described in families with an autosomal recessive form of CDA III [96**, 97], raising the possibility that defects in *KIF23* and *RACGAP1* may result in CDA III via a common mechanism, as both proteins are components of centralspindlin [98]. However, this remains speculative and requires further investigation.

CDA IV

Clinical and laboratory characteristics

The severity of CDA IV is variable. In the most severe cases, CDA IV results in hydrops fetalis followed by transfusion dependence postnatally [99]. Other affected individuals may exhibit a milder disease, with postnatal anemia that may improve/resolve over time [99]. Characteristic features of CDA IV include elevated fetal hemoglobin, absence of erythrocyte CD44 and aquaporin 1 expression, hemolysis, splenomegaly, and high levels of circulating nucleated erythroid cells [100]. Therefore, the presence of an elevated fetal hemoglobin and/or severe hemolysis in the setting of a CDA should raise the suspicion of CDA IV. Some, but not all, CDA IV cases have been associated with urogenital anomalies and growth defects [99, 100]. As in other CDAs, bone marrow biopsy in CDA IV demonstrates erythroid hyperplasia and increased percentage of bi/multinucleated erythroblasts. Additional bone marrow findings reported in CDA IV include atypical cytoplasmic inclusions and intercellular (rather than internuclear) bridges [100, 101].

Genetics and pathophysiology

CDA IV is an autosomal dominant disease resulting from defects in the erythroid transcription factor *KLF1* [100]. Patients with CDA IV share the same *KLF1* E325K mutation, affecting the second zinc finger of the protein [100]. Mutation in the corresponding residue of mouse *Klf1* (E339D) was observed in the *Nan* mouse, which is characterized by neonatal hemolytic anemia [102–104] but without persistence of fetal globin elevation [105].

The *KLF1* E325K mutation results in poor binding of KLF1 to its canonical recognition motif and aberrant binding to other sites [106, 107], resulting in altered expression of *KLF1* target genes [106–109] as well as ectopic expression of non-erythroid genes [108], likely explaining the erythroid defect observed in CDA IV patients, especially since patients with other heterozygous missense mutations in *KLF1* exhibit no or mild erythroid defects [110–114].

Recently, a patient with a CDA IV-like phenotype but without the *KLF1* E325K mutation was reported [115]. Compound heterozygous mutations in *KLF1* (p.His295Leufs*58 and p.Arg301Leu) was identified in the patient [115]; however, it remains unknown if these *KLF1* variants are causative for the disease, as studies that establish a causal relationship between these variants and the disease were not performed [115].

Other CDAs

Several additional CDA variants have been described. Some of these disorders are characterized by an erythroid predominant or erythroid restricted defect, while others are associated with syndromic disorders (Table 1).

Two forms of X-linked CDAs have been reported, one (X-linked recessive) resulting from *GATA1* mutations and characterized by macrothrombocytopenia in addition to the erythroid defect, and the other (X-linked dominant) resulting from *ALAS2* mutations and characterized by macrocytic anemia. While *ALAS2* mutations result in a CDA in females, *ALAS2* mutations result in sideroblastic anemia in males [116].

Syndromic forms of CDA, all autosomal recessive, include (i) Majeed syndrome (due to mutations in *LPIN2*) characterized by multifocal osteomyelitis, inflammatory dermatosis, and microcytic CDA; (ii) early infantile epileptic encephalopathy-50 (due to mutations in *CAD*) characterized by neurodegenerative disease, epilepsy, mild CDA, and abnormal glycosylation of the red cell membrane proteins band-3 and RhAG; (iii) mutations in *COX4I2*, which results in pancreatic insufficiency, calvarial hyperostosis, and dyserythropoiesis; and (iv) *MVK* mutations resulting in recurrent fevers and abdominal pain in the setting of CDA (Table 1).

Recently, *de novo* mutations in *VPS4A* affecting amino acids 284 and 203 (p.Arg284Trp, p.Arg284Gly, and p.Glu206Lys) have been reported in 6 unrelated patients with structural brain abnormalities, microcephaly, severe neurodevelopmental delay, dystonia, cataract, and growth retardation [117]. Three of the 6 patients had anemia, 2 of whom showed evidence of dyserythropoiesis [117]. In a separate report, 3 additional unrelated patients with a similar neurologic syndrome-associated CDA have been described [118**]; 2 patients with *de novo* heterozygous mutations (p.Arg284Trp and p.Gly203Glu) and 1 patient with a homozygous mutation in *VPS4A* (p.Ala28Val) [118**].

Patients with *VPS4A* mutation exhibit macrocytic anemia, hemolysis, reticulocytosis, splenomegaly, and iron overload. In contrast to red blood cells isolated from unaffected individuals, a subset of mature red blood cells from patients with *VPS4A* mutation retain CD71 on their surface [118**]. In addition to increased levels of binucleated erythroblasts, bone marrow analysis demonstrates cytoplasmic bridges [118**].

VPS4A regulates the function of the Endosomal Sorting Complex Required for Transport (ESCRT)-III complex, which is required for formation of multi-vesicular bodies, endosomal trafficking, and abscission [119]. The cytokinesis defect might explain the increased percentage of bi-nucleated erythroblasts, as erythroblasts cultured from a patient-derived induced pluripotent stem cell (iPSC) line exhibited altered VPS4 distribution in the midbody during cytokinesis [118**]. The *VPS4A* mutations (p.Arg284Trp, p.Arg284Gly, and p.Glu206Lys) appear to have a dominant negative effect [117], similar to a previously reported dominant negative *VPS4A* mutation in which the ATPase function of the protein was defective [120].

More recently, an additional patient with a severe neurodevelopmental disorder resulting from *VPS4A* mutation (p.Arg284Trp) has been reported [121]. This patient had severe transfusion-dependent anemia with brisk reticulocytosis, but no evidence of dyserythropoiesis on bone marrow evaluation [121]. Notably, subtle dyserythropoitic findings can be seen in disorders of hereditary chronic hemolytic anemias such as pyruvate kinase deficiency [122] and hereditary xerocytosis [122, 123]. Therefore, this report raises the question whether the anemia in patients with *VPS4A* mutation results primarily from hemolysis or from ineffective erythropoiesis.

Conclusion and future directions

Though several CDAs are characterized by distinguishing features identified using specialized tests (such as erythroblast electron microscopy, Ham's test, or others), genetic studies may obviate the need for such specialized tests if the clinical picture, bone marrow morphologic findings, and the genetic tests all point to a specific CDA type. Another reason to obtain genetic testing to support a diagnosis of CDAs is that some hemolytic disorders (such as hereditary spherocytosis, pyruvate kinase deficiency, or others) may exhibit overlapping morphologic bone marrow findings with the CDAs [122].

It is important to note that family members of CDA patients may carry the same disease-causing mutation(s) as their affected relatives, without developing the disease (incomplete penetrance) [31*, 81]. Therefore, the diagnosis of CDA relies not only on the genetic test results, but also on identifying characteristic bone marrow findings (and potentially other tests if needed). Furthermore, if a bone marrow transplantation is to be performed using hematopoietic stem cells isolated from a sibling donor, testing for the genetic mutation(s) in the sibling is recommended.

Several CDAs result from defects in proteins that play roles in broad cellular processes (such as COPII transport, cytokinesis, etc.), yet many of these CDAs are associated with erythroid restricted phenotypes. Though this finding appears to be well explained in CDA II as discussed above, the reason for the largely erythroid-specific phenotype observed in most CDAs remains unknown and requires further investigation.

Improving our understanding of the pathophysiology of the CDAs is critical for the development of novel therapies for these disorders. Currently, treatment of the CDAs consists primarily of blood transfusion support when needed and iron chelation in the setting of iron overload. Bone marrow transplantation has been shown to be curative for CDA I, CDA II, and CDA III [43–45, 60–68, 80], but due to mortality and morbidity associated with the procedure, it is generally reserved for a subset of patients with severe disease. Most transplants for CDA are performed in childhood (median age is 5.1 years) [68], although adult CDA patients have also successfully undergone bone marrow transplantation [80]. Except for Interferon alpha-2a, which was serendipitously found to reduce/halt hemolysis in CDA I by a yet unknown mechanism [37–42], there are no specific therapies for the CDAs, which reflects our poor understanding of the pathogenic mechanisms underlying these disorders.

Gene therapy is promising for the treatment of monogenic hematologic disorders; however, due to concerns about long-term leukemogenicity, this strategy remains experimental until long-term safety data is available [124]. Therefore, studying the pathogenesis of the CDAs remains critical to advance the field. The development of novel CDA cell [31*, 51*, 96**, 125, 126] and animal models [33**, 51*] as well as advances in iPSC technology, including differentiation of iPSC from CDA patients into erythroid cells that recapitulate the erythroid defects of the disease [109, 118**], are expected to result in improvement of our understanding of the pathophysiology of these disorders, which will ultimately lead to novel therapies.

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Key points:

- Novel murine models of CDA I and CDA II have been recently established and are expected to result in improved understanding of the pathogenesis of these disorders.
- Codanin-1 physically interacts with CDIN1, suggesting that mutations in CDAN1 and CDIN1 result in CDA I via a common mechanism.
- SEC23B overlaps in function with its paralogous protein, SEC23A, suggesting a novel therapeutic strategy for the disease.
- Two new CDA genes, RACGAP1 and VPS4A, have been identified in CDA III and a syndromic CDA type, respectively.

Table 1.

CDA variants. AR, autosomal recessive; AD, autosomal dominant.

Gene	Inheritance	Clinical Features	References
CDA variants			
KLF1	AD	Severe hemolytic anemia Elevated fetal hemoglobin Nucleated RBCs in peripheral blood Growth delay Deficiency of erythroid CD44 and aquaporin Atypical erythroblast cytoplasmic inclusions and intercellular bridges	[8, 100, 127]
GATA1	X-linked recessive	Males Large multinucleated erythroblasts Thrombocytopenia Propensity to bleeding	[128, 129]
ALAS2	X-linked dominant	Females Macrocytic anemia Iron overload	[130]
CDAs associated with Syndromic disorders			
CAD	AR	Early infantile epileptic encephalopathy-50 Global developmental delay, seizures Mild CDA Abnormal glycosylation of erythrocyte band-3 and RhAG Improves with uridine supplementation	[122, 131–133]
COX4I2	AR	Exocrine pancreatic insufficiency Calvarial hyperostosis	[134]
LPIN2	AR	Majeed Syndrome Microcytic anemia Chronic multifocal osteomyelitis Inflammatory dermatosis Inflammatory components improve with IL-1 blockade (unknown if dyserythropoiesis improves)	[135–137]
MVK		Recurrent Fevers Abdominal pain	[138]
VPS4A	Mostly AD (1 case with AR disease)	Structural brain abnormalities Severe neurodevelopmental delay and growth retardation Cataract Dyserythropoiesis in some but not all patients Hemolysis and reticulocytosis Iron overload	[117, 118, 121]