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Congenital Dyserythropoietic Anemia type III (CDA III) – diagnostics, genetics and morbidity

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Akademisk avhandling

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Abstract
Congenital Dyserythropoietic Anemia (CDA) type III, is a rare dominantly inherited disorder, characterized by multinucleated erythroblasts in the bone marrow, ineffective erythropoiesis and non-autoimmune hemolysis. A majority of cases belong to a family in Västerbotten, Sweden. The mutation of CDA III has in earlier studies been linked to 15q22.

We show that the novel mutation *KIF23* c.2747C>G (p.P916R) segregates with CDA III in the Swedish family as well as in an American CDA III family. *KIF23* encodes mitotic kinesin-like protein 1 (MKLP1), which plays a central role in the last step of cytokinesis. Knock-down and rescue experiments reveal cytokinesis failure in HeLa cells, resulting in bi-nuclear cells, consistent with appearance of large multinucleated erythroblasts in CDA III patients. We conclude that CDA III is caused by a mutation in *KIF23*.

Flow cytometry with eosin-5´-maleimide (EMA), anti-CD55 and anti-CD59 is commonly used when investigating non-autoimmune hemolytic anemias. Reduced fluorescence of EMA is seen in hereditary spherocytosis and CDA II. Reduction of CD55 and CD59 characterizes paroxysmal nocturnal hemoglobinuria. We studied the flow cytometric profile of EMA, CD55 and CD59 on erythrocytes in CDA III. We found no abnormality of the erythrocyte membrane in CDA III and conclude that standard flow cytometry cannot be used to discriminate between CDA III and normal controls.

In CDA I and CDA II a majority of patients, including those who are not transfusion-dependent, suffer from iron overload. According to earlier studies, this is not the case in CDA III, but we found that individuals of the Västerbotten CDA III family carry mutations in the hemochromatosis (*HFE*) gene. Three CDA III patients with heterozygous and compound *HFE*-mutations need treatment with phlebotomy due to iron overload. One of them carries heterozygous H63D mutation, which is not reported to lead to iron overload by itself in otherwise healthy individuals. We conclude that heterozygous *HFE* mutation, even H63D, can cause iron overload when occurring concomitantly with ineffective erythropoiesis, as in CDA III.

Keywords
congenital dyserythropoietic anemia, *KIF23*, flow cytometry, hereditary hemochromatosis, iron overload,

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