Abstract

Diamond-Blackfan anemia (DBA) is a rare congenital syndrome that presents with anemia and selective deficiency of erythroid precursors, while other blood lineages are usually unaffected. Approximately half of the patients display additional somatic anomalies and growth retardation. The therapy is mostly symptomatic and is dominated by corticosteroids, other modalities include regular blood transfusions or hematopoietic stem cell transplantation.

At the beginning of this work, only two DBA causal genes were known, *RPS19* and *RPS24*, being mutated in approximately 1/4 of all DBA patients. The goals of this work were to study the consequences of the known DBA causal mutations on cellular level and to find novel DBA causal genes.

To date, over a half of DBA patients have been reported to carry a mutation in one of nine known DBA causal genes, including RPS17, RPL11 and RPL5, that are reported in this dissertation. All confirmed DBA causal genes encode for ribosomal proteins (RPs) that were essential for ribosome assembly. We further hypothesized a non-ribosomal protein participating in this process might be involved in DBA pathogenesis, too. In one DBA patient, we identified a rare sequence variant in one such candidate, a protein arginine methyltransferase 3 (PRMT3). We reported that the patient PRMT3 variant was not fully active, however, we didn't confirm its causative role for DBA. In conclusion, our findings broadened the spectrum of known DBA causal genes and supported the hypothesis, that the mechanism of pathogenesis is a ribosomal defect.

Keywords

Diamond-Blackfan anemia, congenital anemia, ribosomopathy, ribosomal protein, ribosome biogenesis, protein arginine methyltransferase, RPS17, RPL5, RPL11, PRMT3