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Regulatory Function of the Anticoagulant Protein S in Patients with Chuvash Polycythemia

Background: Chuvash polycythemia is a hematological disorder that is present worldwide but endemic to the Chuvash population, a Turkish ethnic group, in Russia. The disorder is caused by a homozygous germline mutation (R200W) in the von Hippel Lindau gene. This mutation impairs binding of pVHL to hypoxia-inducible factor 1-alpha (HIF-1α); lack of this interaction prevents degradation of HIF-1α. The resultant upregulation of HIF-1α, even in a normal oxygen state, increases the activity of erythropoietin, thereby causing polycythemia. Affected individuals experience increased rates of arterial and venous thrombosis unrelated to the increased concentration of hemoglobin.

Aims: To determine whether upregulation of HIF-1α in patients with Chuvash polycythemia causes a decreased level of the antithrombotic agent Protein S. A decreased level of Protein S may explain the increased risks of arterial and venous thromboembolic events in this population.

Methods: Enzyme-linked immunosorbent assay (ELISA) will be performed to measure total and free Protein S concentration in Chuvash and control plasma. Immunoblotting will be performed to confirm the ELISA measurements. Additional assays will be performed if Chuvash plasma is found to have a decreased Protein S concentration.

Results: Total Protein S concentration measured by ELISA was lower in Chuvash individuals compared with control. Free Protein S levels could not be determined in either the Chuvash or control samples because the samples had undergone many freeze-thaw cycles that caused degradation of free Protein S. We have asked the lab that provided the samples to supply fresh plasma~~s~~ so that we can accurately measure free Protein S levels and obtain additional total Protein S data. Meanwhile, we are performing immunoblotting on the samples we currently possess~~samples~~.

Conclusion: Our preliminary results suggest a decreased level of total Protein S in individuals with Chuvash polycythemia. Because an increased hemoglobin concentration does not increase the rates of thromboembolic events in this population, our finding of a reduced amount of anticoagulant Protein S may explain the hypercoagulability that Chuvash individuals experience.