Hereditary spherocytosis--defects in proteins that connect the membrane skeleton to the lipid bilayer.

The molecular causes of hereditary spherocytosis (HS) have been unraveled in the past decade. No frequent defect is found, and nearly every family has a unique mutation. In dominant HS, nonsense and frameshift mutations of ankyrin, band 3, and beta-spectrin predominate. Recessive HS is most often due to compound heterozygosity of defects in ankyrin, alpha-spectrin, or protein 4.2. Common combinations include a defect in the promoter or 5'-untranslated region of ankyrin paired with a missense mutation, a low expression allele of alpha-spectrin plus a missense mutation, and various mutations in the gene for protein 4.2. In most patients’ red cells, no abnormal protein is present. Only rare missense mutations, like ankyrin Walsrode (V463I) or beta-spectrin Kissimmee (W202R), have given any insight into the functional domains of the respective proteins. Although the eminent role of the spleen in the premature hemolysis of red cells in HS is unquestioned, the molecular events that cause splenic conditioning of spherocytes are unclear. Electron micrographs show that small membrane vesicles are shed during the formation of spherocytes. Animal models give further insight into the pathogenetic consequences of membrane protein defects as well as the causes of the variability of disease severity.