Southeast Asian ovalocytosis (SAO) is a dominantly inherited disorder that is widespread in certain ethnic groups of Malaysia, Indonesia, Papua New Guinea, and the Philippines. The SAO red blood cells (RBCs) are ovalocytic in shape, rigid, and resistant to invasion by different strains of malaria parasites. Membranes of SAO RBCs do not undergo salt-induced crenation, and several blood group antigens, but not the Gerich antigens, have a reduced level of expression. Affected heterozygous individuals are asymptomatic, with no clinically detectable hemolysis, although one subject has been described with compensated hemolysis.

The underlying molecular defect in SAO is a deletion of 27 bp in the band 3 gene resulting in the absence of 9 amino acids at the boundary of the cytoplasmic and membrane domains of band 3. This defect is tightly linked in all cases of SAO to the band 3 Memphis I polymorphism, a point mutation causing a lys 56 → glu substitution. The prevalence of SAO in other population groups is not known, but one Mauritian subject of Indian extraction and one African-American family have been reported.

We now describe the first instance of dominantly inherited SAO in a four-generation South African Cape Colored family that also showed two additional unusual features. Firstly, all affected subjects exhibited varying degrees of hemolytic anemia. Secondly, the band 3 Memphis I polymorphism was not linked to the SAO band 3 deletion in all subjects. The family members studied consisted of seven affected and three normal individuals. Clinically, all affected subjects showed evidence of hemolysis, ranging from a severe transfusion-dependant condition to compensated hemolysis. One individual continued to hemolyse after splenectomy. Other causes of hemolysis, such as hemoglobinopathies or enzyme deficiencies, were ruled out. RBCs from affected individuals showed the characteristic spoon-shaped stomatocytic ovalocytic morphology and incubation of SAO RBC ghosts in isotonic saline did not alter the morphology, in contrast to control ghosts that became smaller and echinocytic. In vitro infection of SAO and normal RBCs with Plasmodium falciparum and culturing for two cycles of parasite invasion and growth showed a markedly decreased level of parasitemia in SAO cells. Several blood group antigens, including the Gerich antigens, were depressed.

Polymerase chain reaction (PCR) amplification of genomic DNA using primers flanking the SAO deletion in exon 11 of the band 3 gene showed two products of 175 and 148 bp, indicating that the affected individuals were heterozygous for the 27-bp SAO band 3 gene deletion. Normal family members only showed amplification of the 175-bp fragment. The presence of the band 3 Memphis I polymorphism was analyzed by limited tryptic digestion of RBC ghosts followed by electrophoresis and immunoblotting with an anti-band 3 antibody. The protein findings were confirmed by PCR amplification of the band 3 gene and DNA sequencing. Interestingly, six SAO subjects and all three normal family members were heterozygous for the band 3 Memphis I polymorphism (Lys 56 → Glu) and one SAO subject was homozygous.

The Cape Coloreds are a hybrid people into whose ancestry a Caucasoid element has entered. The other element is usually of African origin (Khoi, San, or Negro), but may also be the hybrid Caucasoids from Malaysia or India. The origin of this Cape Colored family is not known, but we speculate that the SAO gene was introduced into the family ancestors during the 17th or 18th century by a Malaysian or Indonesian forebear who came to the Cape Town settlement with the Dutch East India Company. Alternatively, the SAO gene deletion could have arisen independently in this family. This may be less likely because it is a relatively large deletion (27 bp) and, in addition, the Cape region of South Africa is not an endemic malaria area. It has been postulated that the SAO mutation is an ancient one probably selected for by the protection the gene affords against malaria.

In summary, our results indicate that the SAO phenotype also occurs in the South African Cape Colored population and is not always clinically asymptomatic. Furthermore, the inheritance of the band 3 Memphis I polymorphism in an affected family is not necessarily indicative of SAO.

References:

Southeast Asian ovalocytosis in a South African kindred with hemolytic anemia [letter]

TL Coetzer, L Beeton, D van Zyl, SP Field, A Agherdien, E Smart and GL Daniels