

ASSOCIATION OF X-LINKED CHRONIC GRANULOMATOUS DISEASE WITH THE RARE MCLEOD PHENOTYPE - A CASE REPORT

A. Siderow¹, J. Ries¹, B. Grossrieder¹, J. Reichenbach², R. Seger², M. Hergersberg³, R. Röthlisberger³ and B.M. Frey¹

¹Blutspende Zürich, Rütistrasse 19, 8952 Schlieren, Switzerland

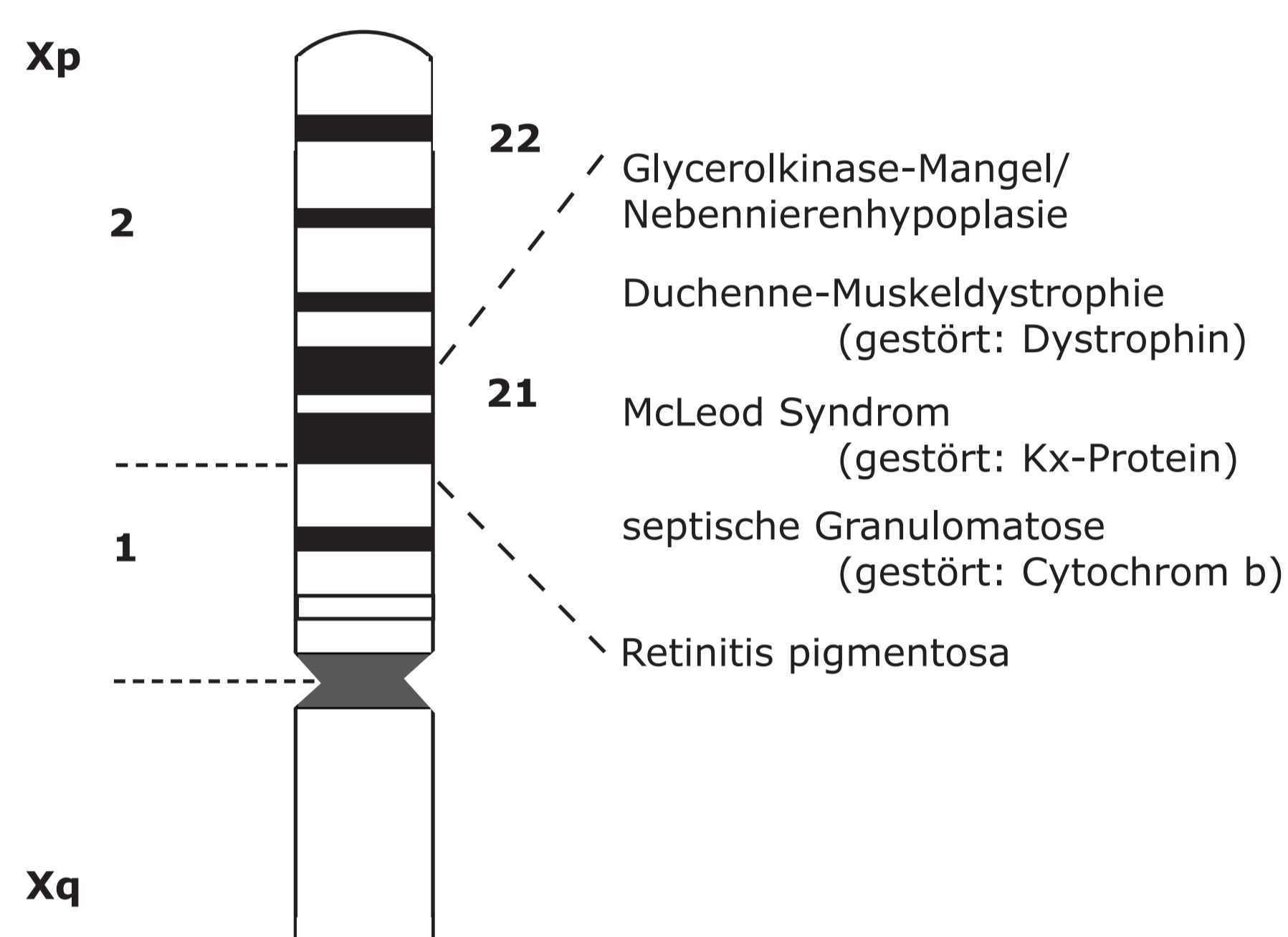
²Kinderspital Zürich, 8032 Zürich, ³Zentrum für Labormedizin, Kantonsspital, 5000 Aarau
www.blutspendezurich.ch

BLUTSPENDE ZÜRICH
● ● ● ● ●

Background

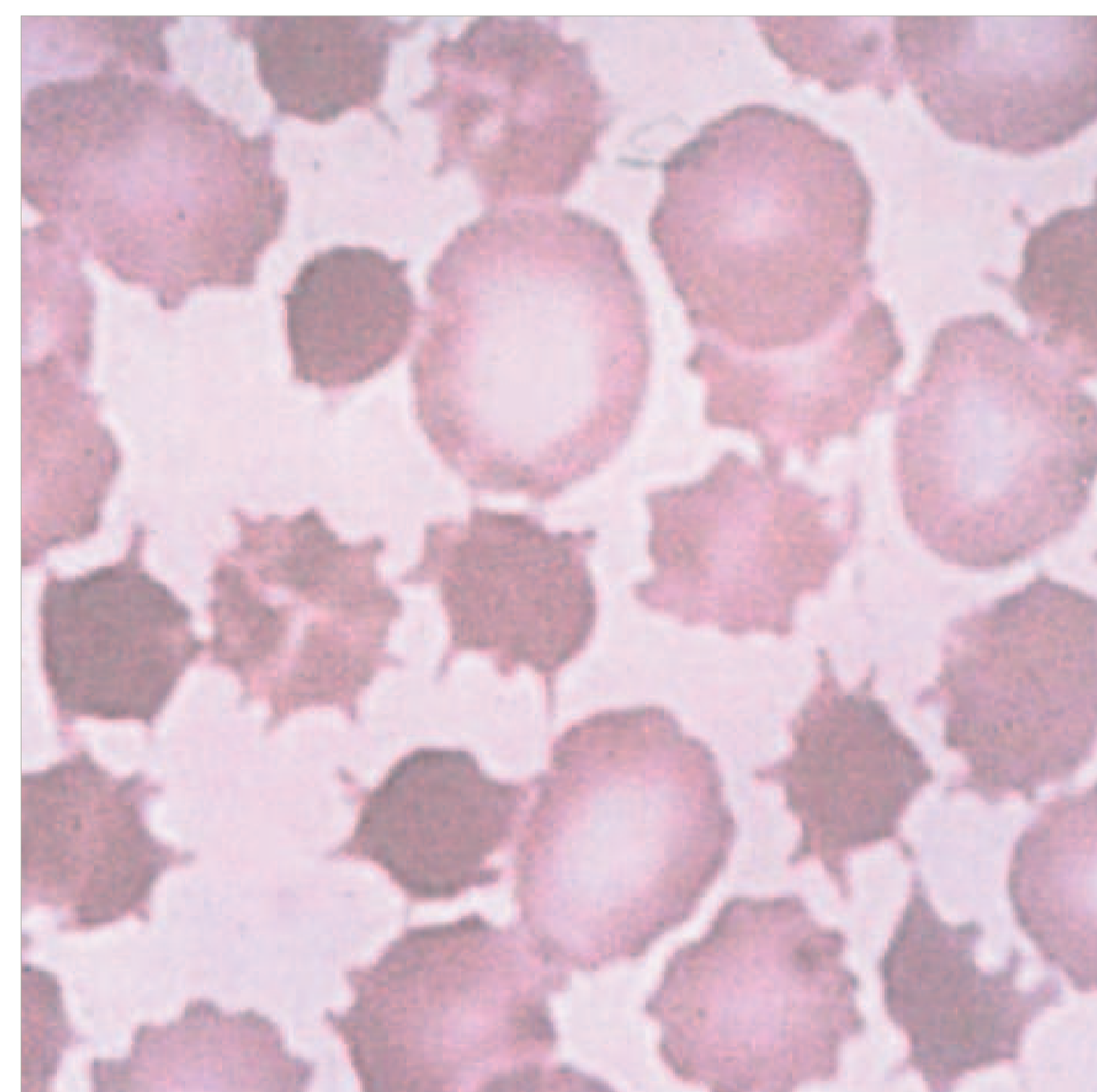
McLeod syndrome (MLS) is characterized by the absence of the high frequency red blood cell (RBC) antigen Kx (> 99.9%), weakened expression of KEL antigens, acanthocytosis and hemolytic anemia. MLS results from mutations in the XK-Gen at Xp21.1. The XK-Locus is neighbouring the CYBB-Locus. Mutations of the X-chromosomal gene encoding gp91-phox (CYBB), a subunit of cytochrome b (-245) cause the X-linked granulomatous disease (X-CGD). X-CGD caused by deletion of the CYBB locus might be associated with the rare MLS. In these cases, the XK gene locus at Xp21.1 adjacent to CYBB locus is affected by an extend deletion of CYBB including Xp21.1 leading to disturbed expression of XK-KEL protein complex on RBC membrane and Kx neg RBC phenotype. To date, 8 different mutations translating into X-CGD associated MLS are known. All affected carriers are males as is expected in X-linked hereditary diseases.

Figure 1



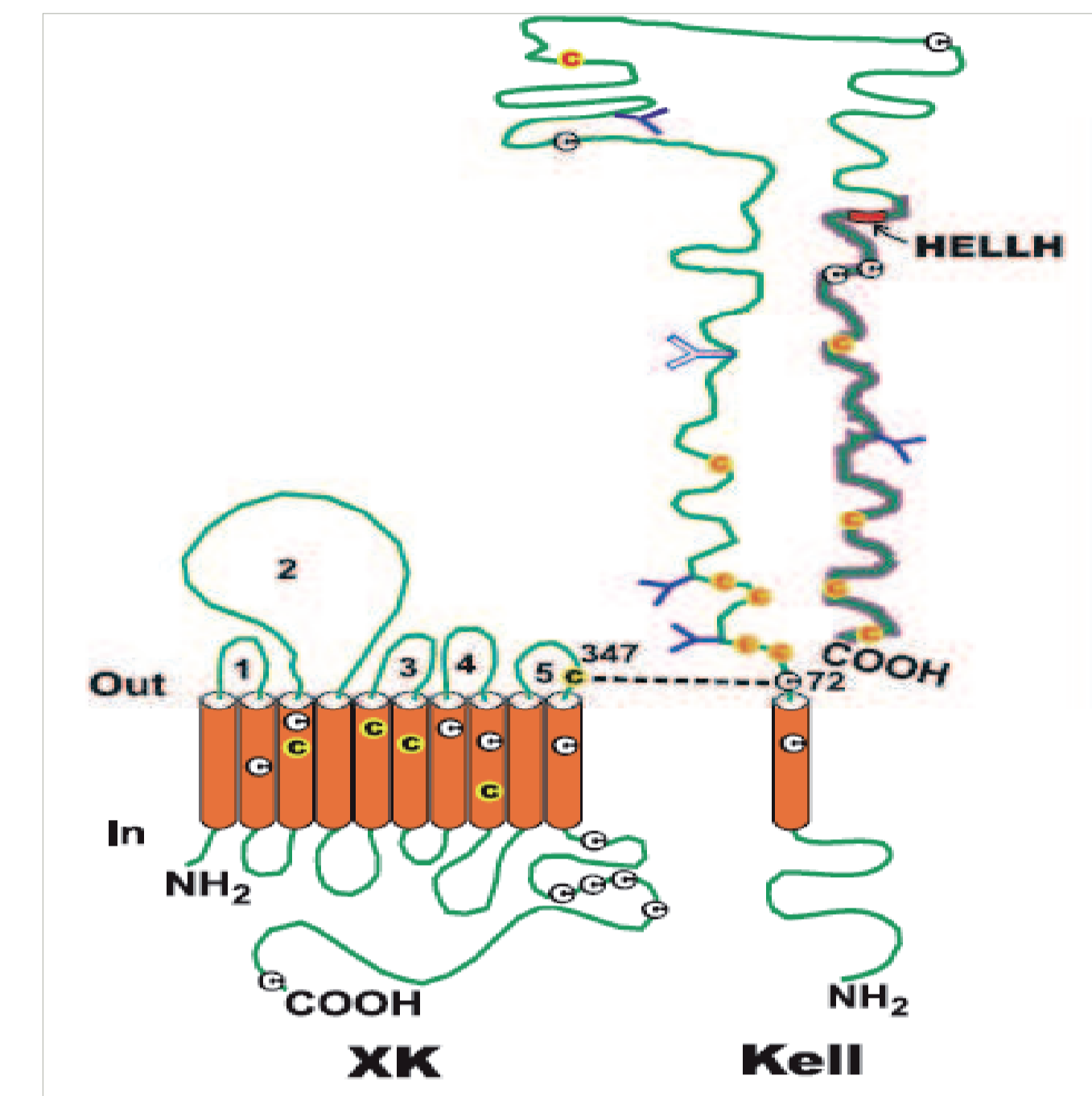
Short arm of X-chromosome with neighbouring loci of McLeod locus

Figure 2



Pathognomonic red blood cell changes (acanthocytes) in carriers of McLeod mutation

Figure 3

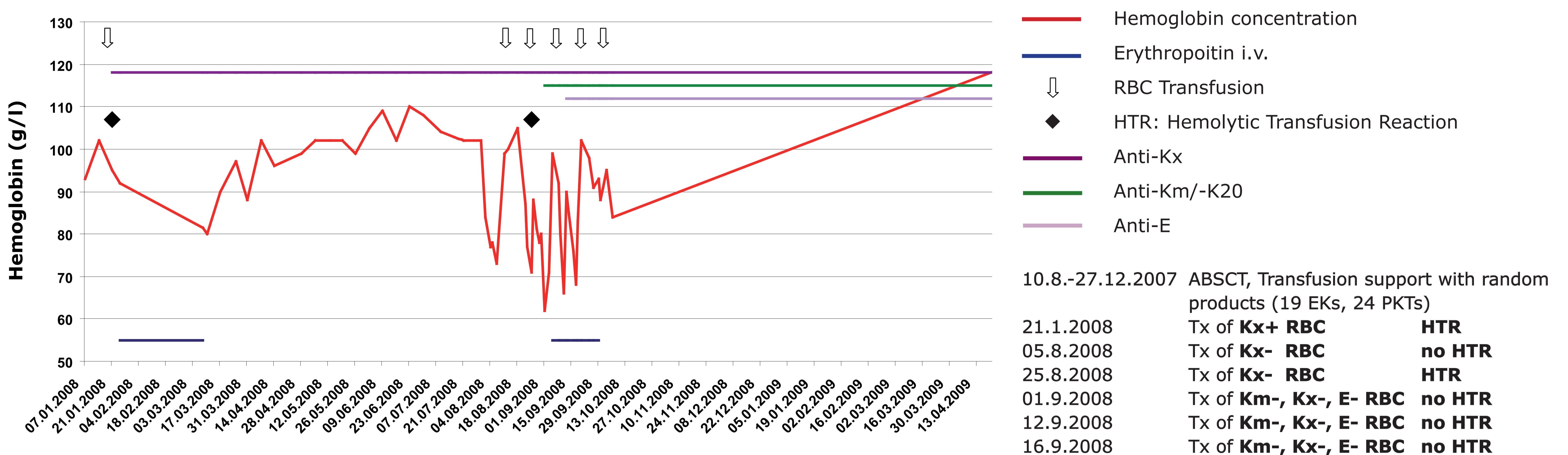


XK-Kell-Komplex as expressed in the normal red blood cell membrane. Mutated or absent XK protein due to McLeod mutations leads to weakened expression of Kell antigens of the Kell protein.

Case

We report a 10-year old boy with X-CGD and therapy refractory pulmonary aspergillosis. Because of lack of HLA-identical stem cell donor, he was treated by genetically (gp91phox) corrected autologous blood stem cell transplantation (ABSCT). Prior to ABSCT, he received repeatedly allogeneic granulocyte transfusions. Following mild conditioning for ABSCT, he became transfusion dependent and he received 19 RBC-units. On pretransfusion compatibility testing he presented with a high-titer anti-Kx antibody (>1:8'000) preventing allocation of compatible allogeneic RBC from blood storage repository. Search of rare donor data files provided one healthy Swiss blood donor carrying McLeod RBC phenotype who was recruited for directed blood donation. Unfortunately, following transfusion of Kx neg RBCs of this donor, the patient developed additional RBC alloantibodies (anti-E, anti-K20) which required worldwide donor search. One compatible donor was identified and provided several units of RBC that were successfully transfused. After sufficient erythropoietic engraftment the patient became transfusion independent again. Later on, following replacement of an infected Port-à-cath system, the patient was again successfully transfused with Kx neg, K20 neg and E neg RBCs. After complete hematologic reconstitution, following gp91phox-modified ABSCT, the patient reached sufficient granulocytic activity with complete clearance of infections, however the RBCs continued to be of McLeod phenotype without sign of hemolysis.

Figure 4: Clinical outcome of a patient with X-CGD associated MLS



Molecular Characterisation of McLeod Mutation

By array comparative genomic hybridization, an exon-specific PCR of the XK-Gen, a deletion at Xp21.1 was identified encompassing the complete XK-gene and the first three (of 13) exons of the CYBB gene. Between the breakpoints 37'381'984+/-1bp and 37'533'472+/-1bp a deletion of 160'000bp was found by sequencing. This so far unknown deletion lead to the clinical phenotype of X-CGD associated MLS.

Conclusions

X-CGD is rarely associated with hereditary MLS harbouring the risk of allosensitisation against the high-frequency RBC antigen Kx which may severely compromise transfusion support. Therefore, such patients require immunohematological work-up and extensive organisational preparation for transfusion support prior to invasive regimens, e.g. surgery and hematopoietic stem cell transplantation. The genetic correction of CGD (CYBB locus) does not correct the genetic defect causing MLS.