



Fetal and neonatal immune thrombocytopenia caused by maternal alloantibodies and isoantibodies in Caucasian and Asian populations: a narrative review

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Objective: The aim of this review is to renew our knowledge about the role of platelet antibodies (allo- and isoantibodies) in fetal neonatal and alloimmune thrombocytopenia (FNAIT) among Caucasian and Asian populations and to provide additional new insights which may be responsible for the various clinical pictures of this serious immune disease.

Background: During the pregnancy, maternal allo- and isoantibodies can cross the placenta via the neonatal Fc receptor (FcRn) and cause the clearance of fetal platelets and endothelial dysfunction, resulting in FNAIT, which is often associated with bleeding complications of the fetus and neonate. In the last years, great progress has been made in the field of alloantigen-related FNAIT, especially caused by alloantibodies against human platelet antigen (HPA)-1a located on $\beta 3$ integrins ($\alpha IIb\beta 3$ and $\alpha v\beta 3$ integrins). However, little attention was paid to the role of isoantibodies, particularly against CD36, which turn out to be one of the most important antibodies responsible for FNAIT in Asian populations.

Methods: In this review, we described the currently available information about alloantibodies and isoantibodies with respect to allele frequencies, the incidence of immunization, clinical relevance, and the pathophysiology of FNAIT.

Conclusions: Apart from platelet alloantibodies, isoantibodies against platelet glycoproteins play an important role in the pathomechanism of FNAIT. In a globalized world, diagnosis and therapy of anti-HPA-1a- and anti-CD36-related FNAIT should be available, even if anti-HPA1a is uncommon in Asian populations and anti-CD36 is very rare in Caucasians. Most of these antibodies not only bind to platelets, but also react with endothelial cells and other blood cells (such as monocytes) which may contribute to the pathomechanism of FNAIT. In addition, recent evidence indicated that maternal antibodies are heterogeneous with respect to their epitopes, and their ratio may differ from one case to other. All of these facts may reflect the various clinical pictures of FNAIT and consequently require adapted treatment strategies. Therefore, further improvement on laboratory diagnostics, both on serological and functional analysis of platelet antibodies, is mandatory for the better prediction and management of FNAIT. To achieve this goal, a further understanding of the nature of the pathogenic antibodies will be necessary.

Keywords: Fetal and neonatal alloimmune thrombocytopenia; alloantibodies; isoantibodies

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Human platelet antigens (HPAs) associated with fetal neonatal and alloimmune thrombocytopenia (FNAIT)

Common HPAs

Alloantigens

Twelve well-established HPAs are included in six diallelic systems: HPA-1, HPA-2, HPA-3, HPA-4, HPA-5 and HPA-15. HPAs are numbered in their order of discovery, with the higher frequency antigen designated as 'a' and the lower frequency antigen designated as 'b'. The lower frequency antigens arose from single nucleotide mutations on the respective gene leading to missense amino acid exchanges and resulting in new antigenic determinants (epitopes). The frequencies of HPAs were intensively studied in Caucasian populations, and investigated in other ethnic groups.

Nonself antigens causing immune responses in members of the same species are called alloantigens or isoantigens. Alloantigens (such as HPA) differ only in the polymorphic structure caused by mutational changes (e.g., single amino acid substitutions) of glycoprotein, and isoantigens are recognized by individuals lacking an entire cellular glycoprotein present in cells of normal individuals. Accordingly, the corresponding immune responses are called alloimmunization or isoimmunization. Until today, isoantigens have not been included in the HPA nomenclature.

Three transmembrane glycoprotein complexes, namely, α IIb β 3, α 2 β 1, and GPIb/IX/V, and a glycosylphosphatidylinositol (GPI)-linked glycoprotein, CD109, are known as carriers of antigenic determinants. HPA-1, HPA-3, and HPA-4 reside on α IIb β 3, whereas HPA-5 resides on α 2 β 1, and HPA-15 is found on CD109. In the last three decades, a large number of rare HPAs have been identified. This progress is due in particular to the introduction of a platelet crossmatch between maternal serum and paternal platelets (carrier of rare antigens) in the antigen capture assay (MAIPA), in addition to antibody screening of maternal serum using standard platelet panels. As a result, the first low-frequency HPA (HPA-8b) could be discovered (1). Most of them are located on the extracellular domain of the integrin α IIb β 3 (<https://www.versiti.org/medical-professionals/precision-medicine-expertise/platelet-antigen-database/hpa-gene-database>).

Alloantibodies and FNAIT

In this section, we will discuss the recent progress on the most clinically important human platelet antigens, namely,

HPA-1, -3, and -4 residing on integrins α IIb β 3, and HPA-5 on α 2 β 1 (*Figure 1A,1B*) as well as HPA-2 and HPA-15 located on GPIb/IX/V complex and CD109, respectively. We present the following article in accordance with the Narrative Review reporting checklist (available at <https://dx.doi.org/10.21037/aob-21-47>).

HPA-1 and HPA-4 on β 3 integrin

HPA-1 is the most relevant alloantigen system associated with FNAIT in Caucasians. Alloantibodies against HPA-1a are responsible for approximately 80% of FNAIT cases (4,5). The incidence of FNAIT is about 1:1,000 in newborns (6). In a retrospective study, intracranial hemorrhage (ICH) was encountered in approximately 15% of these cases (4), which may lead to fetal death or persistent neurological sequelae (7). In a prospectively studied cohort of pregnancies, the incidence of ICH was lower. In 79 newborn babies with FNAIT (anti-HPA-1a), 2 (2.5%) developed ICH. In both cases, platelet counts were $<50 \times 10^9/L$ (8). Among Caucasian populations, the frequency of the rare HPA-1b allele ranges from 0.133 to 0.190. In contrast, HPA-1b gene frequencies are much lower in East Asian populations (ranging from 0.002 to 0.012) (9). Accordingly, alloimmunization against HPA-1a is unlikely in Asian populations. Recently, the first case of FNAIT due to anti-HPA-1a antibodies was found in a blood-related Chinese family (10).

HPA-1a and -1b are controlled by the point mutation leucine > proline at position 33 (Leu33Pro) located on the PSI (plexins, semaphorins and integrins) domain of the β 3 integrin subunit (*Figure 1A*). According to the allele distribution, the estimated risk of an antigenic incompatibility allowing immunization against HPA-1b is higher compared to HPA-1a (13.51% versus 2.17% for a first pregnancy). However, alloimmunization against HPA-1a is much more common than immunization against HPA-1b during pregnancy. In addition, only a few cases of FNAIT caused by anti-HPA-1b were reported (11), whereas, anti-HPA-1b antibodies are encountered more frequently than anti-HPA-1a in patients immunized by blood transfusion. Until today, the reason for this discrepancy is unclear.

Although the Leu33Pro mutation responsible for the formation of HPA-1a and -1b could be identified, little is known about the exact epitopes recognized by anti-HPA-1a antibodies. Accumulated data demonstrated that the epitopes of anti-HPA-1a antibodies are heterogeneous. Some anti-HPA-1a react solely with the PSI domain carrying the polymorphic amino acid residue 33 (called type 1), and some recognize conformational epitopes formed by the

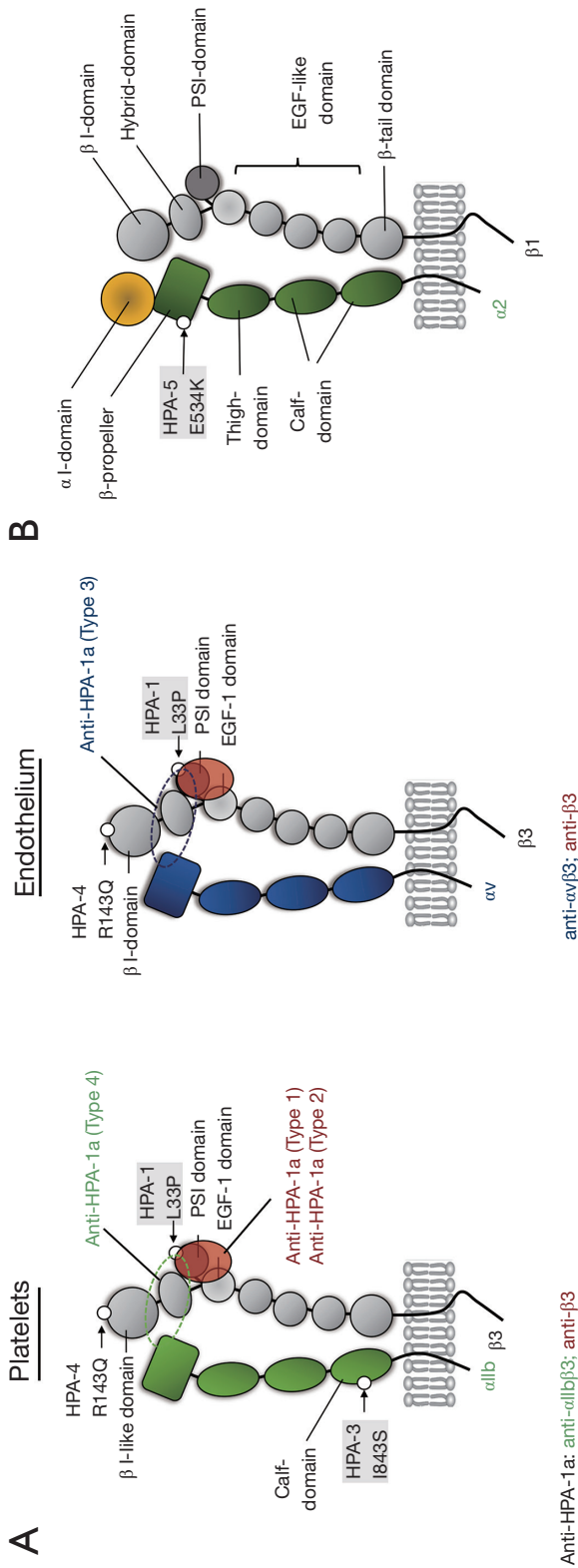


Figure 1 Integrins carrying human platelet alloantigens (HPAs). (A) Integrins $\alpha\text{IIb}\beta3$ and $\alpha\text{v}\beta3$ on platelets and endothelium carrying HPA -1, -3, and -4. The positions of amino acid exchanges (L33P; R143Q and I843S) located on $\beta3$ and αIIb subunits responsible for the formation of HPA-1, HPA-4, and HPA-3 are indicated. Alloimmunization during pregnancy can lead to the development of different anti-HPA-1a antibody types and FNAT. Left panel: two different types of anti-HPA-1a antibodies (type 1 and type 2) recognizing the polymorphic $\beta3$ subunits independent from α subunits (neither αIIb nor αv) were found [Zhi *et al.*, 2018, (2)]. In contrast to type 1, type 2 anti-HPA-1a antibodies recognize epitopes formed by not only the PSI but also the EGF-1 domain. Theoretically, mothers could also develop anti-HPA-1a antibodies reacting with compound epitopes formed by platelet αIIb and $\alpha3$ subunits (type 4). Right panel: the third type of anti-HPA-1a antibodies (type 3) react with compound epitopes formed by αv and $\alpha3$ subunits expressed predominantly in the endothelium [Santoso *et al.*, 2016, (3)]. (B) Integrin $\alpha2\beta1$ on platelets carrying HPA-5. The positions of amino acid exchange E534K located on the b-propeller domain of $\alpha2$ subunits responsible for the formation of HPA-5 are indicated. In contrast to αIIb , the $\alpha2$ integrin subunit contains a α I-domain.

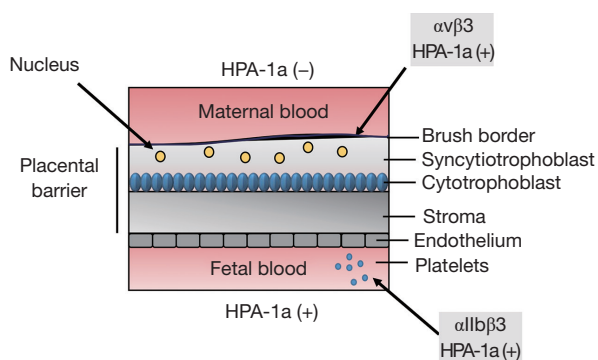


Figure 2 Possible alloimmunization of HPA-1a (-) mother by HPA-1a (+) fetus [Vanderpuye *et al.*, *Biochem J* 1991, (21); Kumpel B *et al.*, *Transfusion* 2008, (22)]. Simplified representation of fetal-maternal placenta interface is illustrated. HPA-1a (+) fetal and HPA-1a (-) maternal platelets expressed abundantly on $\alpha IIb \beta 3$, but little on $\alpha v \beta 3$ is indicated. The expression of HPA-1a (+) on $\alpha v \beta 3$ in syncytiotrophoblast is shown. Theoretically, sensitization of the mother may occur by direct contact of maternal blood with syncytiotrophoblast or/and through the shedding of trophoblast microparticles into the maternal circulation or by fetal platelets resulting from obstetrical, trauma related complications or at parturition. HPA, human platelet alloantigen.

PSI-together with the epidermal growth factor-1 (EGF-1) domain (called type 2) (2,12-14) (*Figure 1A*). Recent studies showed that both antibody types bind independently from the α subunits (neither αIIb nor αv) (15). Furthermore, current evidence indicated that most anti-HPA-1a represent type 2 antibodies (13). Therefore, it is tempting to speculate that type 1 and type 2 antibodies represent successive affinity maturation stages during the course of the immune response (13). A study demonstrated that anti-HPA-1a antibodies are also heterogeneous in their ability to interfere with fibrinogen binding and consequently have a different impact on bleeding in FNAIT (16). It is currently unclear whether this functional heterogeneity is related to type 1 and type 2 anti-HPA-1a antibodies.

It is known that the integrin $\beta 3$ common subunits can form heterodimers with either αIIb or αv chains and function as a receptor for fibrinogen ($\alpha IIb \beta 3$) and vitronectin ($\alpha v \beta 3$), respectively (*Figure 1A*). Recently, another type of anti-HPA-1a antibody recognizing compound epitopes formed by the αv , and the polymorphic $\beta 3$ subunit was found in FNAIT cases, predominantly found in FNAIT cases with ICH. However, the exact position and conformation of binding sites of this antibody type are

not known. In comparison to the previous antibody types, this anti-HPA-1a type could alter angiogenesis (3). Similar observations were made in an animal model suggesting that maternal anti- $\beta 3$ antibodies suppressed fetal angiogenesis and caused trophoblasts destruction by natural killer cells leading to ICH, placental dysfunction and miscarriage (17,18). It remains to be elucidated which types of anti- $\beta 3$ antibodies produced by immunized mice in this animal model are directly responsible for this dysfunction.

Recent observations indicated that anti-HPA-1a antibodies recognizing the $\alpha v \beta 3$ complex did not significantly induce platelet clearance by macrophages, most probably due to the low copy number of $\alpha v \beta 3$ on the platelet surface when compared to $\alpha IIb \beta 3$ (500 versus 50,000 molecules/platelet) (Santoso *et al.*, in preparation). HPA-1a antibodies have been shown to suppress megakaryopoiesis by inducing early cell death (19). Later, Zeng *et al.* demonstrated that anti- $\alpha v \beta 3$ autoantibodies from patients with immune thrombocytopenia (ITP) could aggravate thrombocytopenia by impeding megakaryocytes migration and adhesion to the vascular niche (20). Thus, maternal anti-HPA-1a reacting specifically with fetal $\alpha v \beta 3$ may alter fetal/neonatal platelet counts by inhibiting thrombopoiesis.

Finally, although the three-dimensional structures of the isolated PSI domain in $\alpha v \beta 3$ and $\alpha IIb \beta 3$ are nearly superimposable, this domain showed distinct conformational states when placed in the context of the entire $\beta 3$ pairing either with αv or αIIb subunit. This structural difference could be recognized by the immune system (3). Therefore, it is possible that different patterns of anti-HPA-1 antibody types may develop by immunization with platelets or endothelial cells.

Recent data indicated that maternal immunization to HPA-1a occurs during pregnancy by exposure to $\beta 3$ on syncytiotrophoblast or platelets (*Figure 2*). In addition, immunization by fetal platelets may occur from obstetrical, trauma complications, or at parturition (6). As HPA-1a is expressed on $\alpha v \beta 3$ integrin in the fetal trophoblast, one might speculate that contact of maternal blood with trophoblast or circulating microparticles in maternal blood result in maternal alloimmunization against HPA-1a on $\beta 3$ and $\alpha v \beta 3$ complex (21-23). In addition, if immunization occurs to HPA-1a fetal platelets residing on $\alpha IIb \beta 3$, anti-HPA-1a antibodies against $\beta 3$ and $\alpha IIb \beta 3$ complex may develop (*Figure 1A*).

In the Japanese population, anti-HPA-4b is the most frequent maternal $\alpha IIb \beta 3$ antibody in FNAIT (24). The

allelic frequency of HPA-4b among the Japanese is 0.00854, whereas the HPA-4 polymorphism is nearly nonexistent in Caucasian populations. Surprisingly, two FNAIT cases caused by anti-HPA-4b have been reported in Caucasian families (25,26). HPA-4a and -4b are formed by the point mutation arginine > glutamine at position 143 located on the β I-domain of the $\beta 3$ integrin subunit (Figure 1A). Currently, it is unknown whether different types of anti-HPA-4 antibodies recognizing different epitopes exist.

HPA-3 on α IIb integrin

In comparison to HPA-1, a greater variation of HPA-3 frequencies was found among different populations. The frequency of HPA-3a and HPA-3b ranges from 0.50 to 0.61 and 0.39 to 0.50, respectively (27). Despite these balanced allele frequencies, anti-HPA-3 antibodies are rarely detected in the sera of women with thrombocytopenic newborns. However, ICH related to anti-HPA-3 antibodies was reported (28-32). Several serological studies showed that anti-HPA-3 antibodies are difficult to detect, most probably because of the heterogeneity of HPA-3 epitopes (33).

HPA-3a and -3b result from the single amino acid Ile843Ser substitution located near the carboxyl terminus of the α IIb extracellular domain (34). Early biochemical studies identified serine 837 as a major O-glycosylation site required for anti-HPA-3a antibody binding (35) (Figure 1A). In this respect, some anti-HPA-3 alloantibodies required intact epitopes formed by O-linked carbohydrates structures or terminal sialic acids that can be lost during platelet storage and platelets' isolation process for antibody testing (28,29,36-38). A similar phenomenon was observed with the rare alloantigen HPA-9 (Val837Met) located six amino acids away from the HPA-3 dimorphism (39). Recently, a rare platelet antigen on α IIb (HPA-30bw) associated with FNAIT was reported. This antigen is formed by the point mutation Glu806His located within the calf-2 domain and also depends on the carbohydrate composition of α IIb subunit. Similar to some anti-HPA-3a, anti-HPA-30bw alloantibodies are sensitive to O-glycanase treatment (40). However, O-glycosylation is regulated differently in non-human, human cell lines, or human platelets, which are likely to express completely different glycan chains. In accordance, anti-HPA-30b antibodies did react with HPA-30b expressed in human (HEK293) cell line but not in non-human (CHO-K1) cells (40). Recently, bioengineered induced pluripotent stem cells (iPSC)-derived megakaryocytes for the detection of HPA-3 and HPA-9bw were generated (41). In the future, the development of *in vitro*-generated HPA-defined iPSC-derived platelets

carrying endogenous carbohydrates moieties may improve the detection of challenging platelet antibodies.

The α IIb and α v subunits of the $\beta 3$ integrin family are apparently different, although both share significant homology (42). The α IIb $\beta 3$ integrin is expressed on platelets but not on endothelial cells (43). Earlier studies demonstrated that anti-HPA-3a did not react with endothelial cells compared to anti-HPA-1a antibodies (44). In the mature protein, the single heavy chain of α IIb (GPIIb α) is disulfide-bonded to the light chain (GPIIb β). Biochemical studies demonstrated the existence of two GPIIb β isoforms, which may lead to the dual proteolytic processing of α IIb (45). Whether this phenomenon may alter α IIb expression on different cells and consequently the binding of some anti-HPA-3 antibodies has not been clarified. Although α IIb is claimed to be a platelet-specific integrin, Rout *et al.* reported high α IIb expression on invasive trophoblast cells in the mice. Together with other integrins, α IIb $\beta 3$ coordinately regulate the adhesion and migration of the differentiating mouse trophoblast (46). Ongoing study in animal models using α IIb deficient and human α IIb transgenic mice indicated that maternal anti- α IIb may target trophoblast cells and lead to placenta dysfunction (47).

It is becoming more and more apparent that different antibody types produced as a polyclonal response by the mother during the pregnancy may determine the severity of the disease. Therefore, the development of serological identification and functional analysis of such antibody type is an important area to improve the prediction of severity in FNAIT cases.

HPA-5 on $\alpha 2$ integrin

Anti-HPA-5b antibodies were first identified in the maternal sera of patients with FNAIT (48,49). In Caucasian populations, anti-HPA-5b is the second most frequent alloantibody type (9–19%) encountered with FNAIT (5,50,51). Compared to anti-HPA-1a, anti-HPA-5 antibodies were found in higher frequency in unselected female blood donors with at least one pregnancy screened for platelet antibodies (52). Our data showed that 1.7% and 0.1% of female blood donors with at least one previous pregnancy present anti-HPA-5b and anti-HPA-1a, respectively (53). However, the chance for a thrombocytopenic child in immunized pregnant women with anti-HPA-5b is low. This observation is in accordance with a previous prospective study in a large cohort of 933 pregnant women screened to develop platelet alloantibodies. Seventeen of 933 mothers (1.8%) formed

anti-HPA-5b, but in all cases the newborns' platelet counts were above $150 \times 10^9/L$ (54). In a Japanese cohort of FNAIT cases, anti-HPA-5b was also found as the most frequent platelet antibody (24). Although thrombocytopenia in HPA-5b-FNAIT is often moderate, cases with ICH have been observed (55,56). Anti-HPA-5a, directed against the antithetic antigen, has been found in FNAIT and platelet transfusion refractoriness (PTR) (57,58).

HPA-5a and -5b result from the single amino acid substitution Glu534Lys, which is located on the β -propeller-domain of the $\alpha 2$ subunit of the $\alpha 2\beta 1$ integrin (Figure 1B). $\alpha 2\beta 1$, originally characterized on long-term activated T-cells, has been subsequently found on several cell types, including platelets, fibroblast, epithelial cells, and endothelial cells depending on differentiation and activation state. The $\alpha 2\beta 1$ integrin mainly acts as a receptor for collagens, but other non-collagenous proteins, including laminin, proteoglycans, and viruses, have been described as ligands as well (59).

In contrast to $\alpha IIb\beta 3$, only a few copies of the $\alpha 2\beta 1$ integrin (2,000–6,000 copies/platelet) were found on platelets. Similar to the α -subunits of $\beta 2$ -integrin, $\alpha 2$ has a 191-amino acid insert (called the I-domain), which is highly homologous to the A-domain found in the von Willebrand factor (VWF) (60). There are several consistent pieces of evidence for the heterogeneity of $\alpha 2$ expression on platelets. First, two spots with different isoelectric points corresponding to $\alpha 2$ integrin subunits were found (61). Then, a different copy number of $\alpha 2\beta 1$ on the platelet surface associated with an $\alpha 2$ gene polymorphism was reported. Individuals carrying the 807T/873A allele express high levels of platelet $\alpha 2\beta 1$ when compared to individuals carrying the 807C/873G allele (62). Further studies showed a linkage between HPA-5b with C807 (low expresser) and HPA-5a with either C807 or T807 (low and high expresser). This observation indicated that some HPA-5a positive individuals expressed $\alpha 2\beta 1$ in high density on the platelet surface. The HPA-5 polymorphism did not alter platelet adhesion onto collagens (63) but attenuated the adhesion of platelets onto decorin, a small leucine-rich proteoglycan (64).

It is conceivable that the expression of HPA-5 on different cells, depending on the surface density, different state and activation of $\alpha 2\beta 1$ integrin, may enhance antibody binding, alter cellular functions leading to severe cases of FNAIT.

Isoantibodies against $\alpha IIb\beta 3$ and FNAIT

Isoantibodies against $\alpha IIb\beta 3$ produced in mothers with

Glanzmann thrombasthenia (GT) are responsible for fetal and neonatal ITP. GT is a rare autosomal recessive disorder of platelet aggregation caused by mutations in the *ITGA2B* or/and *ITGB3* genes encoding the integrin $\alpha IIb\beta 3$. Three types of GT based on $\alpha IIb\beta 3$ expression/function have been described: type I with absent $\alpha IIb\beta 3$ expression (<5% of normal), type II with reduced expression (5–20% of normal), and type III, which has normal expression but is characterized by non-functional $\alpha IIb\beta 3$. Recurrent bleeding episodes and platelet immunization are common complications of this disease (65). In rare cases, isoantibodies against $\alpha IIb\beta 3$ developed by GT mothers (type I) before or during the pregnancy could cause FNAIT. Such isoantibodies reacted with all platelets derived from healthy blood donors (66–69). A systematic review of the literature among 31 cases comprising 40 pregnancies showed maternal isoimmunization in 73% of pregnancies and was associated with four neonatal deaths (70).

Recently, a unique mutation in the *ITGA2B* gene (G > A substitution at the splice donor site of intron 15) was found within the French Gypsy that showed a strong linkage to the HPA-1b allele (71). Based on the αIIb defect, these homozygous HPA-1bb Gypsy patients fail to express the $\alpha IIb\beta 3$ heterodimer on the platelet surface, but can still express $\alpha v\beta 3$ carrying HPA-1b epitopes. Interestingly, these GT patients developed two types of anti-HPA-1a alloantibodies, one that reacted with $\beta 3$, and another that recognized the $\alpha v\beta 3$ complex (14).

Isoantibodies against CD36 in immune-mediated disorders

Three decades ago, a new platelet antigen (designated Nak^a) involved in PTR was reported for the first time (72,73). By immunochemical analysis, the authors demonstrated that anti-Nak^a antibodies reacted with platelet membrane glycoprotein IV (GPIV, today designated as CD36) from normal donors but not from Nak^a negative subjects. Further study showed that platelets from Nak^a negative platelets failed to express CD36 (CD36null) on the cell surface, suggesting that Nak^a is an isoantigen rather than an alloantigen. Consequently, only transfusions with Nak^a negative platelets were able to raise the platelet counts of the patients. Several cases of PTR associated with anti-CD36 antibodies, primarily in Asian and African populations were reported from this time forward. However, PTR cases caused by anti-CD36 were also found in individuals of Mediterranean descent, including Lebanon, Egypt, Oman, and Palestine (74–81).

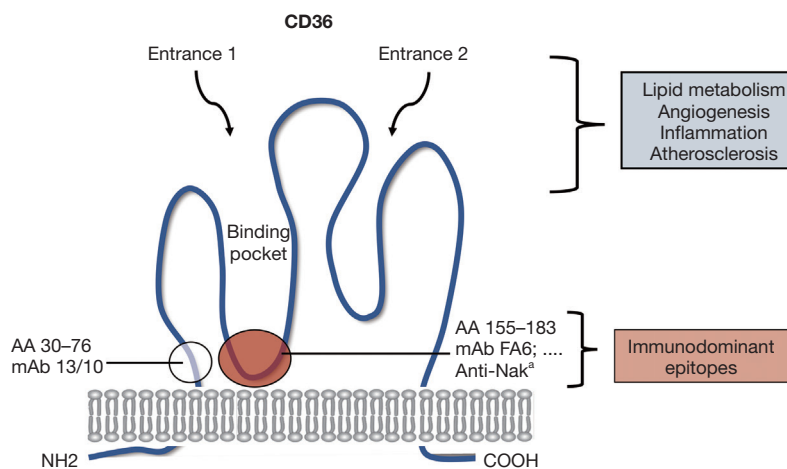


Figure 3 Schematic diagram of the multifunctional receptor CD36. The binding pocket of different ligands and two possible entrances for fatty acid associated with different diseases are illustrated. The region of immunodominant epitopes (amino acid residues 155–183) recognized by several monoclonal antibodies and anti-Nak^a is shown. Another region (amino acid residues 30–76) recognized by mAb 13/15 is indicated.

Meanwhile, several anti-CD36 immune-mediated diseases were described, including thrombotic thrombocytopenic purpura (TTP) (82-84), hemolytic uremic syndrome (HUS) (85), adverse transfusion reactions (86,87), post-transfusion purpura (PTP) (88), and FNAIT (89,90). Interestingly, transfusion-related acute lung injury (TRALI) associated with plasma transfusions containing anti-CD36 antibodies has also been reported (91).

Scavenger receptor CD36

CD36 is a multifunctional membrane receptor highly expressed on vascular and hematopoietic cells, including vascular smooth muscle cells, endothelial cells, macrophages, platelets and fetal erythrocytes. The class B scavenger receptor family, binds to many different ligands, including thrombospondin, oxidized phospholipids, oxidized low-density lipoprotein (oxLDL), and long-chain fatty acids. Furthermore, CD36 also mediates the adhesion of *Plasmodium falciparum*, *Staphylococcus*, and *Mycobacterium* to infected erythrocytes. Accordingly, CD36 is involved in diverse physiological and pathological processes, including thrombosis/hemostasis, atherogenesis, the innate immune defense, and diabetes (92-94).

The human *CD36* gene is located on chromosome 7q11.2 and is encoded by 15 exons, but only exons 3 to 14 encode a 472 amino acid peptide [~molecular weight (MW) 50 kDa] (95,96). The protein harbors two transmembrane domains, a large extracellular domain containing ligand-

binding sites and a single short cytoplasmic tail at each terminal (N and C terminal). The extracellular domain includes a hydrophobic region between amino acids 184–204 that may interact with the plasma membrane (Figure 3). The extracellular domain is heavily glycosylated; 9/10 putative N-linked glycosylation sites are glycosylated. Different CD36 molecular weights were reported for CD36 isolated from platelets, epithelial cells, and erythroblasts [relative molecular mass (Mr) ranging from 78 to 88 kDa], indicating cell type-specific glycosylation (92). Phylogenetic studies of the *CD36* gene among vertebrates, including humans, mice, chickens and zebrafish, indicated that the *CD36* gene appeared early in evolution, before the emergency of bony fish more than 500 million years ago. Human and mouse CD36 share high homology (more than 80%), leading to strong similarities in the structure and tissue distribution (97). Accordingly, several monoclonal antibodies (mAbs) against human CD36 showed cross-reactivity with mouse CD36 and *vice versa* (98).

Besides the transmembrane form of CD36, a soluble form of CD36 (sCD36) associated with microparticles was identified. Elevated sCD36 plasma concentration was detected in patients with cardiovascular disease and diabetes (99). However, little is currently known about the function of sCD36. Recent data demonstrated that type I CD36 deficient individuals characterized by the absence of CD36 on platelets and monocytes failed to produce sCD36 in plasma. This allows rapid identification of these subjects

by analyzing plasma samples using a solid-phase sandwich ELISA (100).

Immunodominant epitopes on CD36

The first IgG mAb against CD36, designated as FA6-152, was generated by immunizing with fetal erythrocytes. mAb FA6-152 binds to fetal monocytes, platelets, reticulocytes, but not lymphocytes and granulocytes. Interestingly, this mAb agglutinated fetal, but not adult erythrocytes (101). Shortly after that, several mAbs against CD36 were assigned by the International Workshop of Leukocyte Typing (102). Some anti-CD36 mAb (5F1; IgM) lysed platelets in plasma and some (ES IVC7; IgG) induced platelet aggregation, and most of them inhibited collagen-induced platelet aggregation.

Using human-mouse chimeric expressing cells, Daviet *et al.* could identify two different immunodominant epitopes recognized by mAbs (103). The majority of mAbs, including FA6-152, recognized epitopes within the domain comprising amino acids 155–183. One unique mAb, 13/10, bound another domain that spans amino acids 30–76. MAb against the 155–183 domain is functionally important regarding their capability to inhibit ligand binding, platelet function, and adhesion of *P. falciparum*-infected erythrocytes onto CD36 (103,104).

Further studies showed that all mAbs recognizing the 155–183 domain inhibited the binding of anti-CD36 antibodies in human sera, whereas mAb against the 30–76 domain did not. These observations indicate that the 155–183 amino acid sequence is important for the binding of anti-CD36 antibodies (105). Therefore, detection of anti-CD36 by an antigen-capture assay using mAb as capture antibody (such as MAIPA) frequently leads to false-negative results caused by competitive inhibition between anti-CD36 mAb and human serum (106). Thus, the selection of appropriate capture mAb is important to eliminate the drawback of the antigen-capture assay for the identification of anti-CD36 antibodies in serum samples. This fact, however, could be useful for the development of therapeutic antibodies: modified mAbs against CD36 competing for the same binding site could be used to displace the binding of human anti-CD36 antibodies preventing the pathogenic effects of these antibodies (98).

CD36 deficiency

The existence of CD36 deficient (Nak^a negative) subjects was described for the first time in Japan. Among the Japanese population, around 3–11% of healthy blood donors were

Nak^a negative lacking CD36 expression on the platelet surface (72,107). Further studies analyzing CD36 expression on monocytes showed two different types of CD36 deficiency. Type I individuals are characterized by the absence of CD36 both on platelets and monocytes whereas type II subjects fail to express CD36 on platelets only (108). Two features are unique to the CD36 deficiency. First, the incidence of CD36 deficiency is relatively high as compared with other glycoprotein deficiencies, such as α Ib β 3 in GT and GPIb/IX in Bernard-Soulier syndrome (BSS) patients (109,110), who present with hemostatic problems. Second, CD36 deficient individuals are apparently healthy without evidence of hemostatic abnormalities (72,107,111). However, studies in humans and mice showed defective uptake and utilization of long fatty acids, indicating a causal link between defective myocardial fatty acids uptake and CD36 deficiency (94,112).

Population studies have shown that the incidence of CD36 deficiency varies among different ethnic groups. CD36 deficiency is very rare in Caucasians (<0.3%) and is more common in African and Asian populations (4–8%) (74,75,113). A higher frequency of CD36-deficient individuals (type I and type II) was reported in Japan (6.8%) (113). In China, the frequency of CD36 deficiency on platelets ranges from 1.8% to 3.6% in the largest ethnic group, the Han population (81,114,115). Similar frequency (2.64%) was reported in the Arabian population (116).

More than 30 mutations in the coding region of the CD36 gene responsible for type I CD36 deficiency have been described (115). Three common mutations, C268T, 949insA, and 329–330 delAC, have been identified in Japanese individuals (117). Although the C268T mutation represents the most frequent substitution (>50%), this polymorphism did not lead to the production of anti-CD36 isoantibodies in reported cases (Table S1). In contrast, 329–330 delAC and 1,228–1,239 delATTGTGCCTATT are the most common mutations in Chinese individuals (81). In Thailand, A1163T seems to be the most frequent mutation associated with CD36 deficiency (100). Because of these heterogeneous mutations, a practicable genotyping approach for identifying individuals with CD36 deficiency is difficult to develop.

Anti-CD36 isoantibodies and FNAIT

Shortly after the discovery of anti-CD36 antibodies as a cause of PTR in Japan (72), the first case of FNAIT due to anti-CD36 antibodies was reported in Thailand (89). After that, the clinical relevance of maternal anti-CD36 antibodies was reinforced by other new cases of FNAIT, three from African-American mothers and one from a mother with

Italian ancestry (90). Meanwhile, several FNAIT cases due to anti-CD36 antibodies were identified in China (118). Recently, anti-CD36 associated with FNAIT was found in Arabic populations living in Germany (116). [Table S1](#) provides a synopsis of previously published clinical cases, their diagnostics, and treatments (81,89,90,116,119-124). Serological diagnostics of the CD36 antigen and antibody will be discussed separately in another review chapter.

Pathomechanisms of anti-CD36 mediated FNAIT

Similar to previously known alloantibody-mediated FNAIT cases, the degree of thrombocytopenia caused by anti-CD36 isoantibodies varies widely from moderate to severe. ICH was also reported. Besides thrombocytopenia, fetal anemia frequently accompanies the clinical picture of the fetus.

In contrast to anti-HPA-1a, anti-CD36 antibodies react with platelets and endothelial cells, and also erythrocytes and monocytes of the fetus. Former studies applying mAbs (clones FA6-152 and 5F1) demonstrated the expression of CD36 solely on fetal but not on adult erythrocytes. The CD36 expression was related to the differentiation stage of the erythroid progenitors. It is expressed on mature BFU-E with an antigenic density increasing until day five CFU-E (101). It is well known that antigen-antibody-mediated red cell hemolysis (e.g., against Rhesus D) can cause anemic hydrops fetalis (AHF), leading to widespread soft-tissue edema and/or the accumulation of fluid in the fetal body cavities (125). Several studies reported an association between anti-CD36 antibodies and AHF (119,121,124). Recently, we found AHF caused by anti-CD36 in a case of severe FNAIT. Maternal anti-CD36 antibodies caused a significant reduction of BFU-E/CFU-E formation associated with an increased number of apoptotic CD34⁺ erythroid/myeloid precursor cells (124). This mechanism may be responsible for fetal anemia and consecutive AHF. Nevertheless, intrauterine transfusion with washed red blood cells (RBCs) should be taken into account to prevent fetal anemia and improve fetal survival (121).

CD36 is found on the placental membranes, microvillus, and basal membrane (126). The central role of CD36 (also known as fatty acid translocase) as a high-affinity receptor for fatty acid uptake and lipid metabolism has been well documented (127,128). During the third trimester of pregnancy, the placenta's preferential transport of maternal plasma FA is critical for fetal growth and development (129). Disturbance of placenta vascular development and function could dramatically alter fetal growth development and thereby neonatal survival. In this process, placental

vascularization and angiogenesis play critical roles (130,131). Recently, we found in the mouse FNAIT model a significant reduction of the placental labyrinth area and decreased fetal capillary numbers in immunized *Cd36*^{-/-} mothers compared to the naïve cohort. This phenomenon depends on FcγRIIa (CD32) expressed on placenta microvascular endothelial cells (132). It is conceivable that crosslinking between endothelial and blood cells by anti-CD36 antibodies may enhance the inflammatory response leading to severe FNAIT and even fetal death by affecting placenta angiogenesis (98).

Natural history of maternal immunization

Prospective studies on FNAIT in Caucasian populations provided information on the natural history of FNAIT. Cumulative data from ten prospective studies (133) show that 9.7% of all HPA-1a (-) negative mothers are immunized during pregnancy. The chance that a HPA-1a (-) mother gives birth to a HPA-1a (+) child is approximately 84%, given a gene frequency of 0.839 for HPA-1a (134). In the large Norwegian study (8), 34.2% of all HPA-1a (+) neonates of immunized mothers were severely thrombocytopenic (platelet counts <50×10⁹/L), whereas 47.2% had normal counts with platelets >150×10⁹/L. In this study the rate of FNAIT cases with ICH (platelet counts <150×10⁹/L) was 2.4%. This rate may be the consequence of the screening and treatment strategy applied by the investigators: as children of all immunized mothers were delivered 2 to 4 weeks prior to term by cesarean section. Furthermore, HPA-1a immunization is strongly correlated with the HLA-DRB3*01:01 class II major histocompatibility antigen (135). In HPA-1a (-) women giving birth to HPA-1a (+) progeny, the risk of immunization is about 25 times higher if the mothers are a carrier of HLA-DRB3*01:01 (136). Accordingly, the outcome of the neonates is associated with the HLA-DRB3*01:01 (137).

Little is known about the natural history of maternal immunization against other platelet alloantigens and isoantigens until today. Therefore, such a study is important to predict the risk of immunization.

Current therapies of FNAIT

Antenatal prophylactic and postnatal therapeutic interventions aim to reduce the risk of ICH and other serious bleeding complications in the fetus and the newborn. Most therapeutic recommendations and guidelines on

prenatal therapy refer to anti-HPA-1a mediated FNAIT. In HPA-1a immunized women with at least one previously affected child, the risk for the next pregnancy depends upon the paternal genotype (HPA-1aa or HPA-1ab). In case of heterozygous father (HPA-1ab) the fetal HPA genotype should be determined, preferably by (noninvasive) typing of cell free fetal DNA in maternal plasma (138-140). The risk of fetal ICH is enhanced, if a previous sibling with FNAIT suffered from ICH (141) and the clinical outcome of the newborn seems to be worse, if the mother carries the DRB3*01:01 antigen (142). For pregnancies at risk, maternal intravenous immunoglobulin (IVIg) therapy (1 g/kg once a week) is considered to be effective in avoiding cerebral bleeding. Due to the lack of randomized studies with a control group, maternal IVIg for preventing fetal ICH in NAIT is used off-label. It is not clear whether additional maternal therapy with corticosteroids is effective (143). In the past, high-risk patients have been subjected to fetal blood sampling and platelet counting followed by intrauterine transfusion of compatible platelets in case of thrombocytopenia. However, owing to the high risk of fetal complications, the non-invasive approach with weekly IVIg infusions is now preferred (143).

Normally, pregnant women in their first pregnancy are not aware of the risk of immunization. Therefore, the screening program for platelet alloimmunization is deliberately performed, but it is still intensively debated. If thrombocytopenic newborns of alloimmunized mothers are at risk of serious bleeding, including ICH, the therapy of choice is the transfusion of antigen-compatible platelets, including maternal platelets (144). However, in urgent situations, platelet concentrates from random donors are usually also effective (144,145). In case platelet concentrates are not available, IVIg may be used (144).

Consensus for standard pre- and postnatal therapies for other antibodies, except HPA-1, is not yet available.

New therapeutic approaches

Although the use of IVIg for the prevention/treatment of FNAIT during pregnancy is increasing, the precise mechanism of IVIg action is still unclear (143). Several mechanisms have been proposed, including decreasing of maternal antibody production by inducing immune tolerance or reduction of placental transfer, and enhancement of maternal IgG catabolism via the FcRn receptor (146-148). However, such strategies may inhibit the transfer of immune-protective maternal IgG, with

potential increased risk of infections by the locally dominant pathogens during pregnancy and during the first weeks after birth. Therefore, more specific and effective antenatal therapies are desirable.

The first concept is the development of FcRn inhibitors. Studies in mouse models demonstrated that anti-FcRn antibodies could decrease miscarriages and improve angiogenesis by inhibiting fetal FcRn (17,131,149-151). FcRn is a pH-dependent Fc γ R that only binds IgG at acidic pH (152). Following pinocytosis into endosomes of endothelial cells, IgG binds to FcRn (due to acidic milieu) and thereby escapes rapid degradation. The FcRn-IgG complex can be translocated back to the cell surface, and IgG can be released after dissociation from FcRn (due to neutral milieu). This recycling process is responsible for the relatively long half-life of IgG. Consequently, inhibition by anti-FcRn leads to rapid IgG degradation and clearance from the circulation (152). This effect reduces anti-platelet antibodies, which has been shown in ITP patients treated with high-dose IVIg (153). Thus, anti-FcRn antibodies may have two modes of action in FNAIT; reduction of maternal antibody concentration and inhibition of FcRn-mediated transfer via the placenta into the fetus (154).

Currently, a clinical trial with the inhibitory anti-FcRn blocking mAb nivalimab (M281) has been initiated for the therapy of hemolytic disease of the fetus and newborn (HDFN). Therefore, it seems warranted to consider this therapy for FNAIT when this approach turns out to be effective for the therapy of HDFN (154).

An attractive alternative strategy would be to administer non-destructive IgG, which shares the allospecificity of maternal antibodies and can inhibit the binding of pathogenic maternal alloantibody to fetal platelets. Such a therapeutic agent should not trigger effector function by inability to interact with fetal Fc γ Rs, but still retain the ability to be transported across the placenta. Ghevaert *et al.* introduced such a strategy by developing human recombinant anti-HPA-1a (termed B2G1 Δ nab) (155). These modified mAb against HPA-1a would be an excellent candidate for treatment of FNAIT if it could be shown in humans that it is able to cross the placenta in sufficient amounts and can displace effectively bound to fetal platelets (155).

In recent years, the therapeutic potential of deglycosylated IgG (deg-IgG) antibodies for treatment of autoimmune disorders has been widely recognized (156). Removal of the N-glycan (linked to asparagine 297), located on the Fc part, leads to a significant reduction of IgG binding with the

Fc γ Rs expressed on macrophages and its ability to activate complement C1q. Interestingly, these deg-IgG antibodies could still be transported from the maternal circulation to the fetus via FcRn (157). Accordingly, our previous *in vivo* study in mice demonstrated that deg-mAb specific for HPA-1a (mAb SZ21) could cross the placenta and prevent the clearance of fetal platelets mediated by maternal anti-HPA-1a antibodies. This observation indicates that the use of epitope-specific antibodies for the antenatal therapy of severe FNAIT is feasible (158).

Recently, we evaluated this treatment strategy in mice model of anti-CD36-mediated FNAIT. By the antenatal administration (5 mg/kg body weight) of deglycosylated mouse mAb 32-106 (deg-32-106), the high frequency of fetal death could be significantly reduced (40% to 2%) However, similar antenatal treatment with IVIG administered in a dose of 1 g/kg body weight on days 10, 15, and 20 after breeding did not increase platelet counts. Furthermore, it did not reduce fetal death rates (40%). Only IVIG administration three days earlier at days 7, 12, and 17 instead at days 10, 15, and 20 reduced fetal death (40% to 13%) (98). Our results indicated that deg-32-106 could prevent placenta angiogenesis caused by maternal antibodies (98). Interestingly, deg-32-106 reacted with human CD36. Thus, the development of humanized deg-32-106 as a drug to prevent severe FNAIT caused by anti-CD36 could be envisaged.

Another strategy to prevent fetal bleeding complications is to reduce the risk of alloimmunization by administering antibodies to eliminate fetal platelets and fetal cellular particles from the maternal circulation. This has been attempted by administration of anti-HPA-1a antibodies (159). It is assumed that anti-D causes rapid clearance of D positive fetal RBCs from the maternal circulation (160). Tiller *et al.* were able to transfer this situation of antibody-mediated immune suppression (AMIS) to a mouse model for FNAIT: they reduced the immunizing effects of human platelet transfusions to $\beta 3^{-/-}$ mice with infusions of human anti-HPA-1a and with infusions of mouse monoclonal anti- $\beta 3$ antibodies (161). First results from a clinical trial show (EudraCT number 2019-003459-12) show that NAITgam is able to reduce the half life of HPA-1a positive platelets transfused to HPA-1a-negative subjects (162). However, more trials are mandatory to show both safety and efficiency of this prophylactic therapy.

Other HPAs

HPA-2 on GPIIb α

Immunization against antigens of the biallelic HPA-2 system residing on platelet GPIIb/IX/V complex can lead to the production of anti-HPA-2a and anti-HPA-2b alloantibodies. The HPA-2 polymorphism, discovered in Caucasians, also exists in other Asian populations (118) and in sub-Saharan African populations (163). The rarer allele, HPA-2b, has a frequency of 0.088 in the Western European population (134). In Han Chinese, the frequency of this antigen is 0.0485 and in Koreans 0.077 (118). In sub-Saharan populations, HPA-2b frequencies vary from 0.224 to 0.393 (163). Alloantibodies against HPA-2b were first discovered in a Dutch patient, who had received blood transfusions (164). Later anti-HPA-2b antibodies were found in a multi-transfused Japanese patient (165). These antibodies have been also found in rare cases of FNAIT (166-168). An atypical case of neonatal amegakaryocytic thrombocytopenia associated with anti-HPA-2b was reported (169).

The antigenic determinants of HPA-2a and HPA-2b are formed by substitution of threonine into methionine at amino acid position 145 located on the amino terminal domain of GPIIb α subunit (170). The GPIIb α contains a N-terminal ligand binding domain (LBD), an anionic and sulfated region, a macroglycopeptide region and a mechanosensory domain (MSD) (171). This Thr145Met dimorphism resides in the LBD domain within VWF and alters their binding (172). However, little is known about the impact of anti-HPA-2 antibodies on platelet function. Platelet GPIIb α is sensitive for protease cleavage (173). A soluble extracellular fragment of GPIIb α (glycocalicin) containing anti-HPA-2 binding sites is continuously released due to proteolytic cleavage by ADAM17 metalloproteinase (171). This fact may hamper the detection of anti-HPA-2 antibodies and may explain the rarity of these antibodies.

The glycoprotein GPIIb-IX-V complex is expressed exclusively on platelets and megakaryocytes. After integrin α IIb β 3, GPIIb/IX/V complex is the second most abundant receptor on human platelets (171). Early study reported that human endothelial cells in culture also expressed GPIIb/IX/V complex (174). In contrast to $\beta 3$ integrin carrying HPA-1a epitopes (22,175), GPIIb/X/V complex is not found on

trophoblast. One might speculate that this is reason for the rare immunization against HPA-2 system in FNAIT.

HPA-15 on CD109

Immunization against the biallelic HPA-15 system residing on GPI-anchored CD109 glycoprotein can lead to the production of anti-HPA-15a and anti-HPA-15b alloantibodies. These alloantibodies were found in different clinical settings of immune mediated thrombocytopenia including PTR and FNAIT (176-180).

The gene frequencies of HPA-15a and -15b were 0.512 and 0.488 in Caucasians (181), while 0.532 and 0.468 in Asian populations (182,183). Although the gene frequencies of HPA-15a and HPA-15b are similar, anti-HPA-15b was found more frequently than anti-HPA-15a both in PTR and FNAIT cases (51,180,181). The reason for this phenomenon is currently unknown.

Anti-HPA-15 antibodies were originally discovered by radioimmunoprecipitation (176). Meanwhile, anti-HPA-15 can also be detected using antigen capture assay (184). This approach, however, seems to be insensitive when platelets are used for testing due to the low copy number of CD109 on platelets. The use of cell lines stably expressing high CD109 copy number could reduce the rate of false negative result obtained with platelets (185).

CD109 is expressed in fetal and adult CD34 positive bone marrow cell subsets, activated T lymphoblast, activated platelets, endothelium, megakaryoblastic cell leukemia cells, and human tumor cell lines (186-189). Upregulation of CD109 was observed in several tumor cells (190,191). Cuppini and coworkers reported that CD109 positive circulating endothelial cells was associated with increased progression free survival and overall survival suggesting the role CD109 on the mechanism of tumor progression (192).

On platelets, CD109 is not constitutively expressed on the cell surface, but appears as early activation marker. After agonist-induced activation, such as low-dose ADP and epinephrine, CD109 is rapidly displayed on the platelet surface. In resting platelets, CD109 resides in α -granules, co-distributed with P-selectin and within the open canicular system (OPS). Accordingly, only low expression level of CD109 (500–2,000 molecules/platelet) was detectable on the platelet surface (193). In addition, marked inter-individual differences in the copy number of CD109 were observed on platelets (184,194). However, the physiological role of this differential expression is still unknown.

Since CD109 is a platelet activation antigen, it is

remarkable that anti-HPA-15 antibodies, although rare, could also be found in FNAIT cases. Among 213 patients with FNAIT only two (0.94%) were related to anti-HPA-15 antibodies (181). In the same study, HPA-15 antibodies were much more common in sera of transfused patients (27.7%). Interestingly, ICH associated with anti-HPA-15b antibodies has been reported (51,178,184). Currently, little is known about the function of anti-CD109 antibodies. Initial studies demonstrated that CD109 antibodies abrogated responder cell proliferation in a mixed lymphocyte response assay (195). Recently, Ye and coworkers reported that knockdown of CD109 suppressed cell migration resulted in reduction of endothelial tube formation (196). The question whether anti-HPA-15 bound to CD109 on endothelial cells could inhibit cell migration and suppress endothelial tube formation is currently not known.

Conclusions and perspectives

Apart from the well-known platelet alloantibodies, isoantibodies against platelet glycoproteins play an important role in the pathomechanism of FNAIT, particularly anti-CD36 antibodies. Although they seem to be uncommon in the Caucasian population, anti-CD36 isoantibodies are of clinical importance in Asian and other populations. Meanwhile, in the course of world globalization, anti-CD36 mediated FNAIT has been reported in Western countries.

Platelet alloantibodies and isoantibodies not only bind to platelets, as confirmed previously, but also interact with endothelial cells (such as anti-HPA-1a) as well as other blood cells (such as anti-CD36). All these antibody-mediated effects can trigger FNAIT by different mechanisms leading to different clinical pictures and consequently require adapted treatment strategies. For example, the IVIG standard therapy for anti-HPA-1a does not seem effective for anti-CD36, at least in the animal model.

In addition, recent evidence indicated that maternal antibodies are also heterogeneous with respect to their epitopes, and their ratio may differ from one case to other, reflecting the various clinical pictures of FNAIT. Therefore, further improvement on laboratory diagnostics, both on serological and functional analysis of platelet antibodies, is mandatory for the better prediction and management of FNAIT.

To achieve this goal, a further understanding of the nature of the pathogenic antibodies will be necessary.

Concerning anti-CD36 antibodies, visible progress has been made in the last few years. However, there are several open questions, namely, on the incidence, natural history, antibody titer/types, severity/clinical pictures in FNAIT, and the involvement of anti-CD36 in other antibody-mediated platelet disorders and TRALI.

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References

1. Santoso S, Kalb R, Kroll H, et al. A point mutation leads to an unpaired cysteine residue and a molecular weight polymorphism of a functional platelet beta 3 integrin subunit. The Sra alloantigen system of GPIIIa. *J Biol Chem* 1994;269:8439-44.
2. Zhi H, Ahlen MT, Thinn AMM, et al. High-resolution mapping of the polyclonal immune response to the human platelet alloantigen HPA-1a (PLA1). *Blood Adv* 2018;2:3001-11.
3. Santoso S, Wihadmyatami H, Bakchoul T, et al. Antiendothelial $\alpha\beta 3$ Antibodies Are a Major Cause of Intracranial Bleeding in Fetal/Neonatal Alloimmune Thrombocytopenia. *Arterioscler Thromb Vasc Biol* 2016;36:1517-24.
4. Mueller-Eckhardt C, Kiefel V, Grubert A, et al. 348 cases of suspected neonatal alloimmune thrombocytopenia. *Lancet* 1989;1:363-6.
5. Davoren A, Curtis BR, Aster RH, et al. Human platelet antigen-specific alloantibodies implicated in 1162 cases of neonatal alloimmune thrombocytopenia. *Transfusion* 2004;44:1220-5.
6. Curtis BR. Recent progress in understanding the pathogenesis of fetal and neonatal alloimmune thrombocytopenia. *Br J Haematol* 2015;171:671-82.
7. Dale ST, Coleman LT. Neonatal alloimmune thrombocytopenia: antenatal and postnatal imaging findings in the pediatric brain. *AJNR Am J Neuroradiol* 2002;23:1457-65.
8. Kjeldsen-Kragh J, Killie MK, Tomter G, et al. A screening and intervention program aimed to reduce mortality and serious morbidity associated with severe neonatal alloimmune thrombocytopenia. *Blood* 2007;110:833-9.
9. Tan JY, Lian LH, Nadarajan VS. Genetic polymorphisms of human platelet antigens-1 to -6, and -15 in the Malaysian population. *Blood Transfus* 2012;10:368-76.
10. Armawai MI, Yahya NM, Hasan A, et al. The first case of fetal neonatal alloimmune thrombocytopenia caused by anti-HPA-1a antibodies in Asian population. *ISBT Sci Ser* 2015;10:52-6.
11. Winters JL, Jennings CD, Desai NS, et al. Neonatal alloimmune thrombocytopenia due to anti-HPA-

- 1b (PLA2)(Zwb). A case report and review. *Vox Sang* 1998;74:256-9.
12. Thinn AMM, Wang Z, Zhou D, et al. Autonomous conformational regulation of $\beta 3$ integrin and the conformation-dependent property of HPA-1a alloantibodies. *Proc Natl Acad Sci U S A* 2018;115:E9105-14.
 13. Holzwarth ST, Bayat B, Zhu J, et al. Naturally occurring point mutation Cys460Trp located in the I-EGF1 domain of integrin $\beta 3$ alters the binding of some anti-HPA-1a antibodies. *Transfusion* 2020;60:2097-107.
 14. Fiore M, Bayat B, Phuangtham R, et al. Immunization against α IIb $\beta 3$ and $\alpha v \beta 3$ in Glanzmann thrombasthenia patients carrying the French Gypsy mutation. *J Thromb Haemost* 2021;19:255-61.
 15. Bayat B, Traum A, Berghöfer H, et al. Current Anti-HPA-1a Standard Antibodies React with the $\beta 3$ Integrin Subunit but not with α IIb $\beta 3$ and $\alpha v \beta 3$ Complexes. *Thromb Haemost* 2019;119:1807-15.
 16. Kroll H, Penke G, Santoso S. Functional heterogeneity of alloantibodies against the human platelet antigen (HPA)-1a. *Thromb Haemost* 2005;94:1224-9.
 17. Chen ZY, Oswald BE, Sullivan JA, et al. Platelet physiology and immunology: pathogenesis and treatment of classical and non-classical fetal and neonatal alloimmune thrombocytopenia. *Ann Blood* 2019;4:29.
 18. Yougbaré I, Lang S, Yang H, et al. Maternal anti-platelet $\beta 3$ integrins impair angiogenesis and cause intracranial hemorrhage. *J Clin Invest* 2015;125:1545-56.
 19. Liu ZJ, Bussel JB, Lakkaraja M, et al. Suppression of in vitro megakaryopoiesis by maternal sera containing anti-HPA-1a antibodies. *Blood* 2015;126:1234-6.
 20. Zeng DF, Chen F, Wang S, et al. Autoantibody against integrin $\alpha v \beta 3$ contributes to thrombocytopenia by blocking the migration and adhesion of megakaryocytes. *J Thromb Haemost* 2018;16:1843-56.
 21. Vanderpuye OA, Labarrere CA, McIntyre JA. A vitronectin-receptor-related molecule in human placental brush border membranes. *Biochem J* 1991;280:9-17.
 22. Kumpel BM, Sibley K, Jackson DJ, et al. Ultrastructural localization of glycoprotein IIIa (GPIIIa, beta 3 integrin) on placental syncytiotrophoblast microvilli: implications for platelet alloimmunization during pregnancy. *Transfusion* 2008;48:2077-86.
 23. Huppertz B, Kingdom J, Caniggia I, et al. Hypoxia favours necrotic versus apoptotic shedding of placental syncytiotrophoblast into the maternal circulation. *Placenta* 2003;24:181-90.
 24. Ohto H, Miura S, Ariga H, et al. The natural history of maternal immunization against foetal platelet alloantigens. *Transfus Med* 2004;14:399-408.
 25. Morel-Kopp MC, Blanchard B, Kiefel V, et al. Anti-HPA-4b (anti-Yuk(a)) neonatal alloimmune thrombocytopenia: first report in a Caucasian family. *Transfus Med* 1992;2:273-6.
 26. Puig N, Muñiz-Diaz E, Monteagudo E, et al. A second case of neonatal alloimmune thrombocytopenia by anti-HPA-4b (anti-Yuka) in a Caucasian family. *Transfus Med* 1993;3:164-5.
 27. Wiwanitkit V. Gene frequencies of the human platelet antigen-3 in different populations. *Clin Appl Thromb Hemost* 2005;11:89-93.
 28. Harrison CR, Curtis BR, McFarland JG, et al. Severe neonatal alloimmune thrombocytopenia caused by antibodies to human platelet antigen 3a (Baka) detectable only in whole platelet assays. *Transfusion* 2003;43:1398-402.
 29. Lin M, Shieh SH, Liang DC, et al. Neonatal alloimmune thrombocytopenia in Taiwan due to an antibody against a labile component of HPA-3a (Baka). *Vox Sang* 1995;69:336-40.
 30. Boehlen F, Kaplan C, de Moerloose P. Severe neonatal alloimmune thrombocytopenia due to anti-HPA-3a. *Vox Sang* 1998;74:201-4.
 31. Glade-Bender J, McFarland JG, Kaplan C, et al. Anti-HPA-3A induces severe neonatal alloimmune thrombocytopenia. *J Pediatr* 2001;138:862-7.
 32. Kataoka S, Kobayashi H, Chiba K, et al. Neonatal alloimmune thrombocytopenia due to an antibody against a labile component of human platelet antigen-3b (Bak b). *Transfus Med* 2004;14:419-23.
 33. Socher I, Zwengel C, Santoso S, et al. Heterogeneity of HPA-3 alloantibodies: consequences for the diagnosis of alloimmune thrombocytopenic syndromes. *Transfusion* 2008;48:463-72.
 34. Lyman S, Aster RH, Visentin GP, et al. Polymorphism of human platelet membrane glycoprotein IIb associated with the Baka/Bakb alloantigen system. *Blood* 1990;75:2343-8.
 35. Calvete JJ, Muñiz-Diaz E. Localization of an O-glycosylation site in the alpha-subunit of the human platelet integrin GPIIb/IIIa involved in Baka (HPA-3a) alloantigen expression. *FEBS Lett* 1993;328:30-4.
 36. Take H, Tomiyama Y, Shibata Y, et al. Demonstration of the heterogeneity of epitopes of the platelet-specific alloantigen, Baka. *Br J Haematol* 1990;76:395-400.
 37. Djaffar I, Vilette D, Pidard D, et al. Human platelet antigen 3 (HPA-3): localization of the determinant of the alloantibody Lek(a) (HPA-3a) to the C-terminus of platelet

- glycoprotein IIb heavy chain and contribution of O-linked carbohydrates. *Thromb Haemost* 1993;69:485-9.
38. Barba P, Pallarés P, Nogués N, et al. Post-transfusion purpura caused by anti-HPA-3a antibodies that are only detectable using whole platelets in the platelet immunofluorescence test. *Transfus Med* 2010;20:200-2.
 39. Noris P, Simsek S, de Bruijne-Admiraal LG, et al. Max(a), a new low-frequency platelet-specific antigen localized on glycoprotein IIb, is associated with neonatal alloimmune thrombocytopenia. *Blood* 1995;86:1019-26.
 40. Wihadmyatami H, Heidinger K, Röder L, et al. Alloantibody against new platelet alloantigen (Lap(a)) on glycoprotein IIb is responsible for a case of fetal and neonatal alloimmune thrombocytopenia. *Transfusion* 2015;55:2920-9.
 41. Zhang N, Santoso S, Aster RH, et al. Bioengineered iPSC-derived megakaryocytes for the detection of platelet-specific patient alloantibodies. *Blood* 2019;134:e1-8.
 42. Fitzgerald LA, Poncz M, Steiner B, et al. Comparison of cDNA-derived protein sequences of the human fibronectin and vitronectin receptor alpha-subunits and platelet glycoprotein IIb. *Biochemistry* 1987;26:8158-65.
 43. Kieffer N, Phillips DR. Platelet membrane glycoproteins: functions in cellular interactions. *Annu Rev Cell Biol* 1990;6:329-57.
 44. Giltay JC, Leeksa OC, von dem Borne AE, et al. Alloantigenic composition of the endothelial vitronectin receptor. *Blood* 1988;72:230-3.
 45. Calvete JJ, Schäfer W, Henschen A, et al. Characterization of the beta-chain N-terminus heterogeneity and the alpha-chain C-terminus of human platelet GPIIb. Posttranslational cleavage sites. *FEBS Lett* 1990;272:37-40.
 46. Rout UK, Wang J, Paria BC, et al. Alpha5beta1, alphaVbeta3 and the platelet-associated integrin alphaIIb beta3 coordinately regulate adhesion and migration of differentiating mouse trophoblast cells. *Dev Biol* 2004;268:135-51.
 47. Vadasz B. Pathogenesis of Anti-integrin α IIb-mediated Fetal and Neonatal Alloimmune Thrombocytopenia: Establishment of Novel Murine Models in α IIb Deficient and Human α IIb Transgenic Mice. Master Thesis. Department of Laboratory Medicine and Pathobiology University of Toronto, 2015. Available online: https://tspace.library.utoronto.ca/bitstream/1807/69706/1/Vadasz_Brian_201506_MSc_thesis.pdf
 48. Kiefel V, Santoso S, Katzmann B, et al. A new platelet-specific alloantigen Bra. Report of 4 cases with neonatal alloimmune thrombocytopenia. *Vox Sang* 1988;54:101-6.
 49. Santoso S, Kiefel V, Mueller-Eckhardt C. Immunochemical characterization of the new platelet alloantigen system Bra/Brb. *Br J Haematol* 1989;72:191-8.
 50. Kroll H, Kiefel V, Santoso S. Clinical aspects and typing of platelet alloantigens. *Vox Sang* 1998;74 Suppl 2:345-54.
 51. Ghevaert C, Campbell K, Walton J, et al. Management and outcome of 200 cases of fetomaternal alloimmune thrombocytopenia. *Transfusion* 2007;47:901-10.
 52. Schnaidt M, Wernet D. Platelet-specific antibodies in female blood donors after pregnancy. *Transfus Med* 2000;10:77-80.
 53. Twilfert M, Sumnig A, Bakchoul T, et al. Abstract IMH-V14: Prevalence of platelet alloantibodies in female blood donors with previous pregnancies. *Transfusion Med Hemother* 2014;41:29.
 54. Panzer S, Auerbach L, Cechova E, et al. Maternal alloimmunization against fetal platelet antigens: a prospective study. *Br J Haematol* 1995;90:655-60.
 55. Kaplan C, Morel-Kopp MC, Kroll H, et al. HPA-5b (Br(a)) neonatal alloimmune thrombocytopenia: clinical and immunological analysis of 39 cases. *Br J Haematol* 1991;78:425-9.
 56. Tiller H, Kamphuis MM, Flodmark O, et al. Fetal intracranial haemorrhages caused by fetal and neonatal alloimmune thrombocytopenia: an observational cohort study of 43 cases from an international multicentre registry. *BMJ Open* 2013;3:002490.
 57. Kiefel V, Shechter Y, Atias D, et al. Neonatal alloimmune thrombocytopenia due to anti-Brb (HPA-5a). Report of three cases in two families. *Vox Sang* 1991;60:244-5.
 58. Arber C, Bertrand G, Halter J, et al. Platelet refractoriness due to combined anti-HLA and anti-HPA-5a alloantibodies: clinical management during myeloablative allogeneic HSCT and development of a quantitative MAIPA assay. *Br J Haematol* 2007;139:159-61.
 59. Madamanchi A, Santoro SA, Zutter MM. α 2 β 1 Integrin. *Adv Exp Med Biol* 2014;819:41-60.
 60. Takada Y, Hemler ME. The primary structure of the VLA-2/collagen receptor alpha 2 subunit (platelet GPIa): homology to other integrins and the presence of a possible collagen-binding domain. *J Cell Biol* 1989;109:397-407.
 61. Kehrel B, Kokott R, Balleisen L, et al. Selective staining of platelet glycoproteins using two-dimensional O'Farrell gel electrophoresis and avidin-biotin-conjugated lectins. *Thromb Haemost* 1987;58:960-3.
 62. Kritzik M, Savage B, Nugent DJ, et al. Nucleotide polymorphisms in the alpha2 gene define multiple alleles that are associated with differences in platelet alpha2 beta1

- density. *Blood* 1998;92:2382-8.
63. Santoso S, Kalb R, Walka M, et al. The human platelet alloantigens Br(a) and Brb are associated with a single amino acid polymorphism on glycoprotein Ia (integrin subunit alpha 2). *J Clin Invest* 1993;92:2427-32.
 64. Kunicki TJ, Williams SA, Diaz D, et al. Platelet adhesion to decorin but not collagen I correlates with the integrin $\alpha 2$ dimorphism E534K, the basis of the human platelet alloantigen (HPA)-5 system. *Haematologica* 2012;97:692-5.
 65. Botero JP, Lee K, Branchford BR, et al. Glanzmann thrombasthenia: genetic basis and clinical correlates. *Haematologica* 2020;105:888-94.
 66. Kiefel V, Meyer E, Greinacher A, et al. Neonatal isoimmune thrombocytopenia by anti-GP IIb/IIIa. *Beitr Infusionsther* 1992;30:450-3.
 67. Léticée N, Kaplan C, Lémery D. Pregnancy in mother with Glanzmann's thrombasthenia and isoantibody against GPIIb-IIIa: Is there a foetal risk? *Eur J Obstet Gynecol Reprod Biol* 2005;121:139-42.
 68. Wijemanne A, Watt-Coote I, Austin S. Glanzmann thrombasthenia in pregnancy: Optimising maternal and fetal outcomes. *Obstet Med* 2016;9:169-70.
 69. Barg AA, Hauschner H, Luboshitz J, et al. From thrombasthenia to next generation thrombocytopenia: Neonatal alloimmune thrombocytopenia induced by maternal Glanzmann thrombasthenia. *Pediatr Blood Cancer* 2018;65:e27376.
 70. Siddiq S, Clark A, Mumford A. A systematic review of the management and outcomes of pregnancy in Glanzmann thrombasthenia. *Haemophilia* 2011;17:e858-69.
 71. Jacquelin B, Tuleja E, Kunicki TJ, et al. Analysis of platelet membrane glycoprotein polymorphisms in Glanzmann thrombasthenia showed the French gypsy mutation in the alphaIIb gene to be strongly linked to the HPA-1b polymorphism in beta3. *J Thromb Haemost* 2003;1:573-5.
 72. Ikeda H, Mitani T, Ohnuma M, et al. A new platelet-specific antigen, Naka, involved in the refractoriness of HLA-matched platelet transfusion. *Vox Sang* 1989;57:213-7.
 73. Tomiyama Y, Take H, Ikeda H, et al. Identification of the platelet-specific alloantigen, Naka, on platelet membrane glycoprotein IV. *Blood* 1990;75:684-7.
 74. Curtis BR, Aster RH. Incidence of the Nak(a)-negative platelet phenotype in African Americans is similar to that of Asians. *Transfusion* 1996;36:331-4.
 75. Lee K, Godeau B, Fromont P, et al. CD36 deficiency is frequent and can cause platelet immunization in Africans. *Transfusion* 1999;39:873-9.
 76. Fujino H, Ohta K, Taniue J, et al. Primary refractoriness to platelet transfusion caused by Nak(a) antibody alone. *Vox Sang* 2001;81:42-4.
 77. Ogata T, Ohto H, Yasuda H, et al. CD36 (Naka) sensitization with platelet-transfusion refractoriness in a liver transplant recipient. *Transplantation* 2005;79:620.
 78. Flesch B, Miller J, Repp R, et al. Successful autologous hematopoietic progenitor cell transplantation in a patient with an isoantibody against CD36 (glycoprotein IV, Naka). *Bone Marrow Transplant* 2008;42:489-91.
 79. Saw CL, Szykoluk H, Curtis BR, et al. Two cases of platelet transfusion refractoriness associated with anti-CD36. *Transfusion* 2010;50:2638-42.
 80. Yin XL, Shen WD, Chen YS, et al. Refractory platelet transfusion in a patient with CD36 deficiency due to pseudothrombocytopenia. *Platelets* 2011;22:237-40.
 81. Xu X, Ye X, Xia W, et al. Studies on CD36 deficiency in South China: Two cases demonstrating the clinical impact of anti-CD36 antibodies. *Thromb Haemost* 2013;110:1199-206.
 82. Tandon NN, Rock G, Jamieson GA. Anti-CD36 antibodies in thrombotic thrombocytopenic purpura. *Br J Haematol* 1994;88:816-25.
 83. Rock G, Chauhan K, Jamieson GA, et al. Anti-CD36 antibodies in patients with lupus anticoagulant and thrombotic complications. *Br J Haematol* 1994;88:878-80.
 84. Schultz DR, Arnold PI, Jy W, et al. Anti-CD36 autoantibodies in thrombotic thrombocytopenic purpura and other thrombotic disorders: identification of an 85 kD form of CD36 as a target antigen. *Br J Haematol* 1998;103:849-57.
 85. Rock G, Clark W, Sternbach M, et al. Haemolytic uraemic syndrome is an immune-mediated disease: role of anti-CD36 antibodies. *Br J Haematol* 2005;131:247-52.
 86. Wakamoto S, Fujihara M, Urushibara N, et al. Heterogeneity of platelet responsiveness to anti-CD36 in plasma associated with adverse transfusion reactions. *Vox Sang* 2005;88:41-51.
 87. Morishita K, Wakamoto S, Miyazaki T, et al. Life-threatening adverse reaction followed by thrombocytopenia after passive transfusion of fresh frozen plasma containing anti-CD36 (Nak) isoantibody. *Transfusion* 2005;45:803-6.
 88. Bierling P, Godeau B, Fromont P, et al. Posttransfusion purpura-like syndrome associated with CD36 (Naka) isoimmunization. *Transfusion* 1995;35:777-82.
 89. Kankirawatana S, Kupatawintu P, Juji T, et al. Neonatal alloimmune thrombocytopenia due to anti-Nak(a).

- Transfusion 2001;41:375-7.
90. Curtis BR, Ali S, Glazier AM, et al. Isoimmunization against CD36 (glycoprotein IV): description of four cases of neonatal isoimmune thrombocytopenia and brief review of the literature. *Transfusion* 2002;42:1173-9.
 91. Nakajima F, Nishimura M, Hashimoto S, et al. Role of anti-Nak(a) antibody, monocytes and platelets in the development of transfusion-related acute lung injury. *Vox Sang* 2008;95:318-23.
 92. Greenwalt DE, Lipsky RH, Ockenhouse CF, et al. Membrane glycoprotein CD36: a review of its roles in adherence, signal transduction, and transfusion medicine. *Blood* 1992;80:1105-15.
 93. Febbraio M, Hajjar DP, Silverstein RL. CD36: a class B scavenger receptor involved in angiogenesis, atherosclerosis, inflammation, and lipid metabolism. *J Clin Invest* 2001;108:785-91.
 94. Pepino MY, Kuda O, Samovski D, et al. Structure-function of CD36 and importance of fatty acid signal transduction in fat metabolism. *Annu Rev Nutr* 2014;34:281-303.
 95. Armesilla AL, Vega MA. Structural organization of the gene for human CD36 glycoprotein. *J Biol Chem* 1994;269:18985-91.
 96. Abumrad NA, el-Maghrabi MR, Amri EZ, et al. Cloning of a rat adipocyte membrane protein implicated in binding or transport of long-chain fatty acids that is induced during preadipocyte differentiation. Homology with human CD36. *J Biol Chem* 1993;268:17665-8.
 97. Holmes RS. Comparative Studies of Vertebrate Platelet Glycoprotein 4 (CD36). *Biomolecules* 2012;2:389-414.
 98. Xu X, Chen D, Ye X, et al. Successful prenatal therapy for anti-CD36-mediated severe FNAIT by deglycosylated antibodies in a novel murine model. *Blood* 2021;138:1757-67.
 99. Little KM, Smalley DM, Harthun NL, et al. The plasma microparticle proteome. *Semin Thromb Hemost* 2010;36:845-56.
 100. Phuangtham R, Santoso S, Leelayuwat C, et al. Frequency of CD36 deficiency in Thais analyzed by quantification of CD36 on cell surfaces and in plasma. *Transfusion* 2020;60:847-54.
 101. Edelman P, Vinci G, Villeval JL, et al. A monoclonal antibody against an erythrocyte ontogenic antigen identifies fetal and adult erythroid progenitors. *Blood* 1986;67:56-63.
 102. Von dem Borne AEGK, Modderman P. Cluster Report: CD36. In: Knapp W, Dörken B, Gilks WR, et al. editors. *Leukocyte Typing IV. White cell differentiation antigens*. Oxford: Oxford University Press, 1989:996.
 103. Daviet L, Buckland R, Puente Navazo MD, et al. Identification of an immunodominant functional domain on human CD36 antigen using human-mouse chimaeric proteins and homologue-replacement mutagenesis. *Biochem J* 1995;305:221-4.
 104. Daviet L, Craig AG, McGregor L, et al. Characterization of two vaccinia CD36 recombinant-virus-generated monoclonal antibodies (10/5, 13/10): effects on malarial cytoadherence and platelet functions. *Eur J Biochem* 1997;243:344-9.
 105. Daviet L, Morel-Kopp MC, Kaplan C, et al. A structural/functional domain on human CD36 is involved in the binding of anti-Nak(a) antibodies. *Thromb Haemost* 1995;73:543-5.
 106. Morel-Kopp MC, Daviet L, McGregor J, et al. Drawbacks of the MAIPA technique in characterising human antiplatelet antibodies. *Blood Coagul Fibrinolysis* 1996;7:144-6.
 107. Shibata Y, Kim N, Morita S, et al. Monoclonal antibody OKM5 and platelet alloantibody anti-Naka have the same specificity. *Proc Japan Acad* 1990;66:41-2.
 108. Yamamoto N, Akamatsu N, Sakuraba H, et al. Platelet glycoprotein IV (CD36) deficiency is associated with the absence (type I) or the presence (type II) of glycoprotein IV on monocytes. *Blood* 1994;83:392-7.
 109. Nurden AT. Glanzmann thrombasthenia. *Orphanet J Rare Dis* 2006;1:10.
 110. Savoia A, Kunishima S, De Rocco D, et al. Spectrum of the mutations in Bernard-Soulier syndrome. *Hum Mutat* 2014;35:1033-45.
 111. Yamamoto N, Akamatsu N, Yamazaki H, et al. Normal aggregations of glycoprotein IV (CD36)-deficient platelets from seven healthy Japanese donors. *Br J Haematol* 1992;81:86-92.
 112. Coburn CT, Knapp FF Jr, Febbraio M, et al. Defective uptake and utilization of long chain fatty acids in muscle and adipose tissues of CD36 knockout mice. *J Biol Chem* 2000;275:32523-9.
 113. Yanai H, Chiba H, Fujiwara H, et al. Phenotype-genotype correlation in CD36 deficiency types I and II. *Thromb Haemost* 2000;84:436-41.
 114. Xu X, Liu Y, Hong X, et al. Variants of CD36 gene and their association with CD36 protein expression in platelets. *Blood Transfus* 2014;12:557-64.
 115. Li R, Qiao Z, Ling B, et al. Incidence and molecular basis of CD36 deficiency in Shanghai population. *Transfusion* 2015;55:666-73.

116. Flesch BK, Scherer V, Opitz A, et al. Platelet CD36 deficiency is present in 2.6% of Arabian individuals and can cause NAIT and platelet refractoriness. *Transfusion* 2021;61:1932-42.
117. Kashiwagi H, Tomiyama Y, Nozaki S, et al. Analyses of genetic abnormalities in type I CD36 deficiency in Japan: identification and cell biological characterization of two novel mutations that cause CD36 deficiency in man. *Hum Genet* 2001;108:459-66.
118. Wu G, Zhou Y, Li L, et al. Platelet Immunology in China: Research and Clinical Applications. *Transfus Med Rev* 2017;31:118-25.
119. Okajima S, Cho K, Chiba H, et al. Two sibling cases of hydrops fetalis due to alloimmune anti-CD36 (Nak a) antibody. *Thromb Haemost* 2006;95:267-71.
120. Taketani T, Ito K, Mishima S, et al. Neonatal isoimmune thrombocytopenia caused by type I CD36 deficiency having novel splicing isoforms of the CD36 gene. *Eur J Haematol* 2008;81:70-4.
121. Xu X, Li L, Xia W, et al. Successful management of a hydropic fetus with severe anemia and thrombocytopenia caused by anti-CD36 antibody. *Int J Hematol* 2018;107:251-6.
122. Lin M, Xu X, Lee HL, et al. Fetal/neonatal alloimmune thrombocytopenia due to anti-CD36 antibodies: antibody evaluations by CD36-transfected cell lines. *Transfusion* 2018;58:189-95.
123. Bertrand G, Renac V, Lefaix MC, et al. Neonatal intracranial hemorrhage with a dramatic outcome due to maternal anti CD36 antibodies. *Reports* 2019;27:7.
124. Wu Y, Chen D, Xu X, et al. Hydrops fetalis associated with anti-CD36 antibodies in fetal and neonatal alloimmune thrombocytopenia: Possible underlying mechanism. *Transfus Med* 2020;30:361-8.
125. de Haan TR, Oepkes D, Beersma MFC, et al. Aetiology, diagnosis and treatment of hydrops fetalis. *Curr Pediatr Rev* 2005;1:63-72.
126. Duttaroy AK. Transport of fatty acids across the human placenta: a review. *Prog Lipid Res* 2009;48:52-61.
127. Abumrad NA, Davidson NO. Role of the gut in lipid homeostasis. *Physiol Rev* 2012;92:1061-85.
128. Podrez EA, Byzova TV, Febbraio M, et al. Platelet CD36 links hyperlipidemia, oxidant stress and a prothrombotic phenotype. *Nat Med* 2007;13:1086-95.
129. Duttaroy AK, Basak S. Maternal dietary fatty acids and their roles in human placental development. *Prostaglandins Leukot Essent Fatty Acids* 2020;155:102080.
130. Reynolds LP, Redmer DA. Angiogenesis in the placenta. *Biol Reprod* 2001;64:1033-40.
131. Yougbaré I, Tai WS, Zdravic D, et al. Activated NK cells cause placental dysfunction and miscarriages in fetal alloimmune thrombocytopenia. *Nat Commun* 2017;8:224.
132. Gröger M, Sarmay G, Fiebiger E, et al. Dermal microvascular endothelial cells express CD32 receptors in vivo and in vitro. *J Immunol* 1996;156:1549-56.
133. Kamphuis MM, Paridaans N, Porcelijn L, et al. Screening in pregnancy for fetal or neonatal alloimmune thrombocytopenia: systematic review. *BJOG* 2010;117:1335-43.
134. Vorholt SM, Hamker N, Sparka H, et al. High-Throughput Screening of Blood Donors for Twelve Human Platelet Antigen Systems Using Next-Generation Sequencing Reveals Detection of Rare Polymorphisms and Two Novel Protein-Changing Variants. *Transfus Med Hemother* 2020;47:33-44.
135. Valentin N, Vergracht A, Bignon JD, et al. HLA-DRw52a is involved in alloimmunization against PL-A1 antigen. *Hum Immunol* 1990;27:73-9.
136. Kjeldsen-Kragh J, Olsen KJ. Risk of HPA-1a-immunization in HPA-1a-negative women after giving birth to an HPA-1a-positive child. *Transfusion* 2019;59:1344-52.
137. Kjeldsen-Kragh J, Titze TL, Lie BA, et al. HLA-DRB3*01:01 exhibits a dose-dependent impact on HPA-1a antibody levels in HPA-1a-immunized women. *Blood Adv* 2019;3:945-51.
138. Wienzek-Lischka S, Krautwurst A, Fröhner V, et al. Noninvasive fetal genotyping of human platelet antigen-1a using targeted massively parallel sequencing. *Transfusion* 2015;55:1538-44.
139. Nogués N. Recent advances in non-invasive fetal HPA-1a typing. *Transfus Apher Sci* 2020;59:102708.
140. Ouzegdouh Mammasse Y, Chenet C, Drubay D, et al. A new efficient tool for non-invasive diagnosis of fetomaternal platelet antigen incompatibility. *Br J Haematol* 2020;190:787-98.
141. Radder CM, Brand A, Kanhai HH. Will it ever be possible to balance the risk of intracranial haemorrhage in fetal or neonatal alloimmune thrombocytopenia against the risk of treatment strategies to prevent it? *Vox Sang* 2003;84:318-25.
142. Kjeldsen-Kragh J, Ahlen MT. Foetal and neonatal alloimmune thrombocytopenia - The role of the HLA-DRB3*01:01 allele for HPA-1a-immunisation and foetal/neonatal outcome. *Transfus Apher Sci* 2020;59:102707.
143. Winkelhorst D, Murphy MF, Greinacher A, et al. Antenatal management in fetal and neonatal alloimmune thrombocytopenia: a systematic review. *Blood* 2017;129:1538-47.

144. Lieberman L, Greinacher A, Murphy MF, et al. Fetal and neonatal alloimmune thrombocytopenia: recommendations for evidence-based practice, an international approach. *Br J Haematol* 2019;185:549-62.
145. Kiefel V, Bassler D, Kroll H, et al. Antigen-positive platelet transfusion in neonatal alloimmune thrombocytopenia (NAIT). *Blood* 2006;107:3761-3.
146. Liu P, Li L, Fan P, et al. High-dose of intravenous immunoglobulin modulates immune tolerance in premature infants. *BMC Pediatr* 2018;18:74.
147. Wabnitz H, Khan R, Lazarus AH. The use of IVIg in fetal and neonatal alloimmune thrombocytopenia- Principles and mechanisms. *Transfus Apher Sci* 2020;59:102710.
148. Hansen RJ, Balthasar JP. Intravenous immunoglobulin mediates an increase in anti-platelet antibody clearance via the FcRn receptor. *Thromb Haemost* 2002;88:898-9.
149. Zdravic D, Yougbare I, Vadasz B, et al. Fetal and neonatal alloimmune thrombocytopenia. *Semin Fetal Neonatal Med* 2016;21:19-27.
150. Chen P, Li C, Lang S, et al. Animal model of fetal and neonatal immune thrombocytopenia: role of neonatal Fc receptor in the pathogenesis and therapy. *Blood* 2010;116:3660-8.
151. Li C, Piran S, Chen P, et al. The maternal immune response to fetal platelet GPIIb/IIIa causes frequent miscarriage in mice that can be prevented by intravenous IgG and anti-FcRn therapies. *J Clin Invest* 2011;121:4537-47.
152. Roopenian DC, Akilesh S. FcRn: the neonatal Fc receptor comes of age. *Nat Rev Immunol* 2007;7:715-25.
153. Ling LE, Hillson JL, Tiessen RG, et al. M281, an Anti-FcRn Antibody: Pharmacodynamics, Pharmacokinetics, and Safety Across the Full Range of IgG Reduction in a First-in-Human Study. *Clin Pharmacol Ther* 2019;105:1031-9.
154. Bussel JB, Vander Haar EL, Berkowitz RL. New developments in fetal and neonatal alloimmune thrombocytopenia. *Am J Obstet Gynecol* 2021;225:120-7.
155. Ghevaert C, Herbert N, Hawkins L, et al. Recombinant HPA-1a antibody therapy for treatment of fetomaternal alloimmune thrombocytopenia: proof of principle in human volunteers. *Blood* 2013;122:313-20.
156. Crispin M. Therapeutic potential of deglycosylated antibodies. *Proc Natl Acad Sci U S A* 2013;110:10059-60.
157. Nimmerjahn F, Ravetch JV. Fcγ receptors as regulators of immune responses. *Nat Rev Immunol* 2008;8:34-47.
158. Bakchoul T, Greinacher A, Sachs UJ, et al. Inhibition of HPA-1a alloantibody-mediated platelet destruction by a deglycosylated anti-HPA-1a monoclonal antibody in mice: toward targeted treatment of fetal-alloimmune thrombocytopenia. *Blood* 2013;122:321-7.
159. Bowman J. Thirty-five years of Rh prophylaxis. *Transfusion* 2003;43:1661-6.
160. Kumpel BM. On the immunologic basis of Rh immune globulin (anti-D) prophylaxis. *Transfusion* 2006;46:1652-6.
161. Tiller H, Killie MK, Chen P, et al. Toward a prophylaxis against fetal and neonatal alloimmune thrombocytopenia: induction of antibody-mediated immune suppression and prevention of severe clinical complications in a murine model. *Transfusion* 2012;52:1446-57.
162. Geisen C, Fleck E, Schäfer SMG, et al. Rapid and complete clearance of HPA-1a mismatched platelets in a human model of fetal and neonatal alloimmune thrombocytopenia by a hyperimmune plasma derived polyclonal anti HPA-1a antibody. *Res Pract Thromb Haemost* 2021;5:abstr PB0969.
163. Halle L, Bigot A, Mullen-Imandy G, et al. HPA polymorphism in sub-Saharan African populations: Beninese, Cameroonians, Congolese, and Pygmies. *Tissue Antigens* 2005;65:295-8.
164. Van Der Weerd CM, Veenhoven-Vonriesz LE, Nijenhuis LE, et al. The Zw Blood Group System in Platelets. *Vox Sang* 1963;8:513-30.
165. Saji H, Maruya E, Fujii H, et al. New platelet antigen, Siba, involved in platelet transfusion refractoriness in a Japanese man. *Vox Sang* 1989;56:283-7.
166. Grenet P, Dausset J, Dugas M, et al. Neonatal thrombopenic purpura with anti-Ko-a fetomaternal isoimmunization. *Arch Fr Pediatr* 1965;22:1165-74.
167. Esquirol A, Canals C, Ibáñez M, et al. Foetal-neonatal alloimmune thrombocytopenia due to anti-HPA-2b antibodies present in the serum of a mother initially mistyped as HPA-1a negative. *Blood Transfus* 2012;10:390-2.
168. Goldman M, Trudel E, Richard L, et al. Neonatal alloimmune thrombocytopenia due to anti-HPA-2b (anti-Koa). *Immuno-hematology* 2003;19:43-6.
169. Bizzaro N, Dianese G. Neonatal alloimmune amegakaryocytosis. Case report. *Vox Sang* 1988;54:112-4.
170. Kuijpers RW, Faber NM, Cuypers HT, et al. NH2-terminal globular domain of human platelet glycoprotein Ib alpha has a methionine 145/threonine145 amino acid polymorphism, which is associated with the HPA-2 (Ko) alloantigens. *J Clin Invest* 1992;89:381-4.
171. Quach ME, Li R. Structure-function of platelet glycoprotein Ib-IX. *J Thromb Haemost* 2020;18:3131-41.
172. Ulrichs H, Vanhoorelbeke K, Cauwenberghs S, et al.

- von Willebrand factor but not alpha-thrombin binding to platelet glycoprotein Ibalpha is influenced by the HPA-2 polymorphism. *Arterioscler Thromb Vasc Biol* 2003;23:1302-7.
173. Clemetson KJ, Clemetson JM. Platelet GPIb-V-IX complex. Structure, function, physiology, and pathology. *Semin Thromb Hemost* 1995;21:130-6.
174. Wu G, Essex DW, Meloni FJ, et al. Human endothelial cells in culture and in vivo express on their surface all four components of the glycoprotein Ib/IX/V complex. *Blood* 1997;90:2660-9.
175. Eksteen M, Heide G, Tiller H, et al. Anti-human platelet antigen (HPA)-1a antibodies may affect trophoblast functions crucial for placental development: a laboratory study using an in vitro model. *Reprod Biol Endocrinol* 2017;15:28.
176. Kelton JG, Smith JW, Horsewood P, et al. Gova/b alloantigen system on human platelets. *Blood* 1990;75:2172-6.
177. Smith JW, Hayward CP, Horsewood P, et al. Characterization and localization of the Gova/b alloantigens to the glycosylphosphatidylinositol-anchored protein CDw109 on human platelets. *Blood* 1995;86:2807-14.
178. Bordin JO, Kelton JG, Warner MN, et al. Maternal immunization to Gov system alloantigens on human platelets. *Transfusion* 1997;37:823-8.
179. Moncharmont P, Courvoisier S, Pagnier A, et al. Severe HPA-15b related neonatal alloimmune thrombocytopenia. *Acta Paediatr* 2007;96:1701-3.
180. Matsushashi M, Tsuno NH, Sone S, et al. The role of alloantibodies against human platelet antigen-15 in multiply platelet transfused patients. *Transfusion* 2014;54:1093-9.
181. Ertel K, Al-Tawil M, Santoso S, et al. Relevance of the HPA-15 (Gov) polymorphism on CD109 in alloimmune thrombocytopenic syndromes. *Transfusion* 2005;45:366-73.
182. Feng ML, Liu DZ, Shen W, et al. Establishment of an HPA-1- to -16-typed platelet donor registry in China. *Transfus Med* 2006;16:369-74.
183. Phuangtham R, Romphruk A, Puapairoj C, et al. Human platelet antigens in Burmese, Karen and north-eastern Thais. *Transfus Med* 2017;27:60-5.
184. Berry JE, Murphy CM, Smith GA, et al. Detection of Gov system antibodies by MAIPA reveals an immunogenicity similar to the HPA-5 alloantigens. *Br J Haematol* 2000;110:735-42.
185. Koh Y, Nishimiya H, Inoue H, et al. A novel simple assay system for the detection of human platelet antigen 15 (HPA-15) alloantibodies based on three techniques: an HPA-15 expressing cell line, a monoclonal antibody-specific antigen-capture method and mixed-passive haemagglutination. *Vox Sang* 2020;115:202-6.
186. Brashem-Stein C, Nugent D, Bernstein ID. Characterization of an antigen expressed on activated human T cells and platelets. *J Immunol* 1988;140:2330-3.
187. Haregewoin A, Solomon K, Hom RC, et al. Cellular expression of a GPI-linked T cell activation protein. *Cell Immunol* 1994;156:357-70.
188. Murray LJ, Bruno E, Uchida N, et al. CD109 is expressed on a subpopulation of CD34+ cells enriched in hematopoietic stem and progenitor cells. *Exp Hematol* 1999;27:1282-94.
189. Giesert C, Marxer A, Sutherland DR, et al. Antibody W7C5 defines a CD109 epitope expressed on CD34+ and CD34- hematopoietic and mesenchymal stem cell subsets. *Ann N Y Acad Sci* 2003;996:227-30.
190. Hashimoto M, Ichihara M, Watanabe T, et al. Expression of CD109 in human cancer. *Oncogene* 2004;23:3716-20.
191. Zhang JM, Hashimoto M, Kawai K, et al. CD109 expression in squamous cell carcinoma of the uterine cervix. *Pathol Int* 2005;55:165-9.
192. Cuppini L, Calleri A, Bruzzone MG, et al. Prognostic value of CD109+ circulating endothelial cells in recurrent glioblastomas treated with bevacizumab and irinotecan. *PLoS One* 2013;8:e74345.
193. Prosper JYA. Characterization of CD109. PhD Thesis. Department of Medical Biophysics. University of Toronto. Available online: https://tspace.library.utoronto.ca/bitstream/1807/29842/1/Prosper_Joseph_Y_201106_PhD_thesis.pdf
194. Mašlanka K, Michur H, Guz K, et al. The relevance of HPA-15 antigen expression for anti-HPA-15 antibody detection. *Int J Lab Hematol* 2012;34:65-9.
195. Suci-Foca N, Reed E, Rubinstein P, et al. A late-differentiation antigen associated with the helper inducer function of human T cells. *Nature* 1985;318:465-7.
196. Ye BG, Sun HC, Zhu XD, et al. Reduced expression of CD109 in tumor-associated endothelial cells promotes tumor progression by paracrine interleukin-8 in hepatocellular carcinoma. *Oncotarget* 2016;7:29333-45.

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Table S1 Clinical profiles of patients with FNAIT caused by anti-CD36 antibodies

Case	Year	Clinical description	CD36 mutations	Serological testing	Treatment	Reference
1	2001	A full-term female newborn (birth weight: 2,940 g; Apgar score: 9 and 10) with generalized petechiae hemorrhage at birth. Her mother was in good health with no history of transfusion. At 7 hours of life, the infant developed upper gastrointestinal hemorrhage. She was moderately anemic and had severe thrombocytopenia (Hb, 11.9 g/dL; Ht, 37%; platelet, 15,000/dL)	Unknown	MPHA: anti-CD36	A single dose of hydrocortisone (10 mg/kg) and IVIG (400 mg/kg). Two doses of maternal irradiated platelets and WBC-reduced RBCs	Kankirawatana <i>et al.</i> , 2001, (89)
2	2002	A newborn with a platelet count of 40,000/ μ L. The mother was a 37-year-old para 1, gravida 1 non-transfused Nigerian woman	Homozygous T1264G	PakPlus: anti-CD36, anti-HLA class I; PSIFT: pos; MACE: anti-CD36	No treatment	Curtis <i>et al.</i> , 2002, (90)
3	2002	A newborn with a platelet count of 60,000/ μ L. The mother was a non-transfused 32-year-old para 2, gravida 1 white woman of Italian descent. She had a history of moderate thrombocytopenia (platelets: 60–90,000/ μ L) during her first pregnancy 4 years earlier. Mild thrombocytopenia (platelets: 90,000–110,000/ μ L) recurred during the second pregnancy	Homozygous; exons 1–3 deletion	PakPlus: anti-CD36 and anti-HLA class I; PSIFT: pos; MACE: anti-CD36	A single dose of IVIG 1.0 g/kg 10 days before delivery	Curtis <i>et al.</i> , 2002, (90)
4	2002	Twin male newborns had widespread petechial hemorrhages on the first day of life and were found to be profoundly thrombocytopenic (platelets <10,000/ μ L). The mother was a non-transfused 28-year-old para 2, gravida 1 African-American woman	Homozygous T1264G	PakPlus: anti-CD36; PSIFT: pos; MACE: anti-CD36	5–6 random donor platelets during the first week of life. 400 mg/kg IVIG on 4 successive days and washed maternal platelets	Curtis <i>et al.</i> , 2002, (90)
5	2002	A female newborn was found to have a platelet count of 50,000/ μ L at birth without bleeding symptoms. Her mother was a non-transfused 21-year-old para 2, gravida 1 African-American woman	Unknown	PakPlus: anti-CD36; PSIFT: pos; MACE: anti-CD36	No treatment	Curtis <i>et al.</i> , 2002, (90)
6	2006	A female fetus had ascites at 18 weeks of gestational age by ultrasonography. Also, fetal anemia (Hb 3.2 g/dL) and hypoproteinemia (<1.0 g/dL) were revealed from umbilical cord centesis. This infant (birth weight: 2,420 g) was delivered by emergent caesarian section at 30 weeks and 3 days of gestational age (RBC: 1200,000/ μ L; Hb 4.5 g/dL; Ht 13.4%; platelets: 47,000/ μ L). Her mother was a non-transfused 27-year-old Japanese woman	C1156T; 1,228–1,239 delATTGTGCCTATT	PSIFT: pos	Intraperitoneal RBC transfusion and albumin replacement after delivery, and several bloodlettings	Okajima <i>et al.</i> , 2006, (119)
7	2006	A female fetus had ascites (ultrasonography) at 25 weeks of gestational age. She (birth weight: 1,920 g) was delivered by emergent caesarian section at a gestational age of 29 weeks (RBC: 990,000/ μ L; Hb 3.9 g/dL; Ht, 13.6%; platelets: 108,000/ μ L). Her mother was a non-transfused 28-year-old Japanese woman	C1156T; 1,228–1,239 delATTGTGCCTATT	PSIFT: pos	A single-volume exchange with 200 mL RBC	Okajima <i>et al.</i> , 2006, (119)
8	2008	A female baby (birth weight: 2,406 g; Apgar score: 9) was born at a gestational age of 37 weeks. Her mother suffered from antiphospholipid antibody syndrome and had experienced two spontaneous abortions. The infant had cephalohematoma at birth and gradually increased after 3 days. The platelet count of this baby was low (106,000/ μ L) and fell to 18,000/ μ L 6 days after birth	Exon 4 skipping Exon 9 skipping	PakPlus: anti-CD36	The baby was given 400 mg/kg/day IVIG on 3 successive days from days 6 to 8 post birth	Taketani <i>et al.</i> , 2008, (120)
9	2013	A 30-year-old Chinese mother experienced four abortions. No history of blood transfusion and or transplantation. The last pregnancy ceased with fetal death at 27 weeks of gestation. Autopsy of the fetus showed edema of fetal skin with bleeding spots in the lower extremities, severe ICH, and hydrops fetalis	C380T; 429+4insg	PakPlus: anti-CD36; PSIFT: pos; MACE: anti-CD36 Coombs: neg	No treatment	Xu <i>et al.</i> , 2013, (81)
10	2018	A 36-year-old Chinese woman had a history of abortion at the first pregnancy, and intrauterine fetal deaths with fetal hydrops occurred during 6–8 months in the following five pregnancies. Ascites, pericardial effusion, cardiomegaly, and hydropic placenta were found by ultrasound at 26weeks of gestational age. At 27weeks of gestational age, umbilical cord centesis showed severe fetal anemia (Hb, 48g/L; Ht, 16.6%) and thrombocytopenia (platelets: 16,000/ μ L)	Homozygous 329–330delAC	PakPlus: anti-CD36; PSIFT: pos; Coombs: neg	Four intrauterine transfusions with RBC; two times leuko-depleted, non-irradiated CD36null platelets; prednisone for 11 days (10 mg, bid)	Xu <i>et al.</i> , 2018, (121)
11	2018	The neonate (birth weight: 3,500 g) developed thrombocytopenia (platelets: 36,000/ μ L) at 4 days of age. The mother was a non-transfused 26-year-old para 2, gravida 1 Taiwanese woman	329–330del AC; 1,254+6–1,254+11delTATTTG	FACS with transfected cells: anti-CD36; ACA: anti-CD36	Intravenous IVIG 1 g/kg at 8 days of ag	Lin <i>et al.</i> , 2018, (122)
12	2019	A 41-year-old para 4, gravida 1 Canadian woman originated from Africa, who delivered a male dead newborn at 39 weeks of gestation. The platelet count of the newborn was not defined, but ICH was identified	Homozygous T975G	PakLx: anti-CD36	No treatment	Bertrand <i>et al.</i> , 2019, (123)
13	2020	A fetus was found to increase the middle cerebral artery peak systolic velocity at 24 weeks of gestational age by ultrasonography. Analysis of umbilical cord blood showed fetal anemia (Hb, 96 g/L; Ht, 28%) at an early gestational age (23–24 weeks) and deteriorated slightly (Hb, 87 g/L; Ht, 25.2%), and the platelet count remained low (89,000/ μ L). Pericardial effusion and scant ascites were detected by ultrasonography. The Chinese mother had a history of recurrent spontaneous abortions	Homozygous 329–330delAC	PakPlus: anti-CD36; PSIFT: pos; Coombs: neg	Two times intrauterine transfusions with washed RBCs to improve the fetal anemia	Wu <i>et al.</i> , 2020, (124)
14	2021	A neonate of Arabian origin was born with a low platelet count (27,000/ μ L) without signs of bleeding. A random platelet apheresis concentrate was given, and the platelet count rose to 47,000/ μ L but dropped again to 23,000 on day 2. Second random platelet apheresis was successfully given on day 2, and the platelet count remained stable at 50,000/ μ L during the next days	C220CT (Gln74Stop); T1079G (Leu360Stop)	PakLx: anti-CD36	Two times random platelet transfusions	Flesch <i>et al.</i> , 2021, (116)

FNAIT, fetal neonatal and alloimmune thrombocytopenia; Hb, hemoglobin; Ht, hematocrit; RBC, red blood cell; ICH, intracranial hemorrhage; IVIG, intravenous immunoglobulin.