IgG Fc receptors determine susceptibility for childhood immune thrombocytopenia, recovery and response to intravenous immunoglobulins

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Abstract

Immune thrombocytopenia (ITP) is most frequently caused by platelet specific autoantibodies leading to accelerated platelet clearance by Fc-gamma receptor (FcγR) bearing phagocytes. Single nucleotide polymorphisms (SNP) and copy number variation (CNV) in the *FCGR* gene cluster affect FcγR function through either altered affinity for IgG or altered expression levels, respectively. The high affinity allele *FCGR3A*V158* and *FCGR2C*C-ORF*, encoding for functional FcγRIIc, have previously been associated with ITP. We now evaluated FcγR profiles in children with newly diagnosed ITP also in relation to recovery and response to intravenous immunoglobulins (IVIg), administered in the first week after diagnosis.

We included 138 children aged 3 months to 16 years with newly diagnosed ITP (platelet count below $20*10^9$/L and no severe or life threatening bleeding at presentation), who were participating in the multicenter randomized study: Treatment with or without IVIg in Kids with acute ITP (TIKI). Seventy-nine (57.2%) received a single dose of IVIg (0.8 g/kg body weight) within three days after diagnosis, and 59 (42.8%) patients were assigned to the observation arm. A multiplex ligation-dependent probe amplification (MLPA) assay (MRC Holland, Amsterdam, the Netherlands) was used to determine the genetic variation in the *FCGR* locus.

Our results suggest that only *FCGR2C*C-ORF* is a true risk factor for developing pediatric ITP. Both *FCGR2C*ORF* and the 2B.4 promotor haplotype of *FCGR2B*, which is associated with a high expression of inhibitory FcγRIIb, were found overrepresented in our cohort of cases with pediatric ITP. Those with *2B.4-FCGR2B* and homozygous for *FCGR2B*I232*, thus with high expression and maximal capacity to downmodulate function of activating FcγRIIb function, responded less to IVIg. Taken together, FcγR polymorphisms are correlated with ITP susceptibility, fast recovery and immediate response to IVIg.