Online Supplement

Transient and Chronic Childhood Immune Thrombocytopenia Are Distinctly Affected by Fc-Gamma Receptor Polymorphisms

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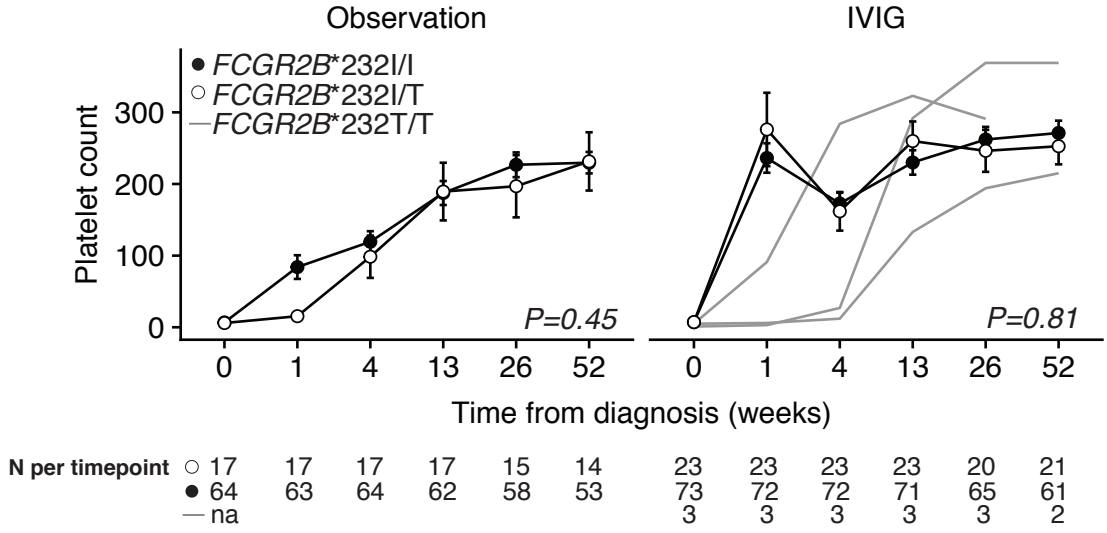
Supplementary Figure 1. Effect of genotypes of *FCGR2B**232I/T variant on longitudinal platelet counts in patients with newly diagnosed ITP. Patients in the observation cohort with the *FCGR2B**232I/I variant showed a predisposition to early recovery at week 1 (see Heitink-Pollé *et al.* Blood 2018). There were no differences in platelet count trajectories seen during follow-up.



Supplemetary Table S1. Systematic search (PubMed and EMBASE) of articles describing genotying of FCGR2/3 variants in childhood ITP.

Pubmed (2018-04-18)

Search	Query
#35	Search (((#34) AND #27) AND #22) AND #19
#34	Search (#33 OR #32 OR #30 OR #29 OR #28)
#33	Search single nucleotide polymorphism
#32	Search variant
#31	Search single nucleotiode polymorphism
#30	Search mutation
#29	Search snp
#28	Search polymorphism
#27	Search (#23 OR #24 OR #25 OR #26)
#26	Search Fc-gamma
#25	Search FCGR*
#24	Search fc gamma receptor
#23	Search fc receptor
#22	Search (#10 OR "Purpura, Thrombocytopenic, Idiopathic"[Mesh])
#19	Search (#16 OR ("Pediatrics"[Mesh]))
#16	Search (#12 or #13 or #14 OR #15)
#15	Search childhood
#14	Search paediatric
#13	Search pediatric
#12	Search child*
#11	Search child
#10	Search (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
#9	Search ((((((ITP) OR immune thrombocytopenia) OR idiopathic thrombocytopenia) OR idiopathic thrombocytopenic purpura) OR idiopathic thrombo*) OR immune thrombo*) OR autoimmune thrombo*
#8	Search ((((((autoimmune thrombo*) AND immune thrombo*) AND idiopathic thrombo*) AND idiopathic thrombocytopenic purpura) AND idiopathic thrombocytopenia) AND immune thrombocytopenia) AND ITP
#7	Search autoimmune thrombo*
#6	Search immune thrombo*
#5	Search idiopathic thrombo*
#4	Search idiopathic thrombocytopenic purpura
#3	Search idiopathic thrombocytopenia
#2	Search immune thrombocytopenia
#1	Search ITP

Embase (2018-04-19)

Search	Query
1.	ITP.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
2.	immune thrombocytopenia.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
3.	idiopathic thrombocytopenia.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
4.	idiopathic thrombocytopenic purpura.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
5.	idiopathic thrombo*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
6.	immune thrombo*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
7.	autoimmune thrombo*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
8.	exp *idiopathic thrombocytopenic purpura/
9.	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10.	pediatrics/
11.	exp *pediatrics/
12.	pediatrics.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
13.	paediatrics.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
14.	child*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

15. child.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
16. childhood.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
17. 10 or 11 or 12 or 13 or 14 or 15 or 16
18. fc receptor.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
19. fc gamma receptor.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
20. FCGR*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
21. Fc-gamma.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
22. 18 or 19 or 20 or 21
23. polymorphism.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
24. snp.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
25. mutation.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
26. variant.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
27. single nucleotide polymorphism.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
28. 23 or 24 or 25 or 26 or 27
29. 9 and 17 and 22 and 28

Supplemetary Table S2. Characeristics of studies included in meta analysis for the association of FCGR2/3 polymorphisms and susceptibility to childhood ITP.

Study and year	Controls (N)	Childhood ITP (N)	Age (mean)	Age (sd)	Female (proportion)	Chronic ITP (proportion)	Setting	Ethnicity	Country	Genotyping method
Carcao 2003	130	98	7,1	5,1	0,52	0,72	Academic	No	Canada	RFLP
Amorim 2012	78	39	12,5	3,9	0,54	0,85	Academic	No	Brazil	RFLP
Papagianni 2013	45	53	5,9	3,9	0,51	0,4	Academic	No	Greece	RFLP
Bruin 2004	154	60	7,2	NA	0,55	0,27	Academic	No	Netherlands	MLPA
Breunis 2008	100	72	NA	NA	NA	NA	Academic	No	Netherlands	MLPA
TIKI	199	180	4.1*	2.6 - 7.7*	0,47	0,1	Peripheral	Yes	Netherlands	MLPA
Foster 2001	219	37	NA	NA	NA	NA	NA	Caucasian	USA	Oligohybridization
Eyada 2012	90	92	8,3	4,5	0,52	0,87	Academic	NA	Egypt	RFLP
Rajantie 2004	6	16	6,1	4	0,5	1	Academic	NA	Finland	RFLP

* Median (IQR) is given

Supplementary Table S3. Sensitivity analysis for distribution of polymorphisms for susceptibility to childhood immune thrombocytopenia

	Newly diagnosed ITP (N=180)					Newly diagnosed ITP, caucasian (N=123)				
	0	1	2	3	4	0	1	2	3	4
Copy number variation										
CNR1	0 (0)	12 (7)	152 (84)	16 (9)	0 (0)	0 (0)	7 (6)	106 (86)	10 (8)	0 (0)
CNR2	0 (0)	0 (0)	173 (96)	7 (4)	0 (0)	0 (0)	0 (0)	119 (97)	4 (3)	0 (0)
CNR3	0 (0)	0 (0)	180 (100)	0 (0)	0 (0)	0 (0)	0 (0)	123 (100)	0 (0)	0 (0)
Alleles										
FCGR2A*27W	127 (71)	49 (27)	4 (2)	0 (0)	0 (0)	90 (73)	30 (24)	3 (2)	0 (0)	0 (0)
FCGR2A*131H	39 (22)	95 (53)	46 (26)	0 (0)	0 (0)	25 (20)	67 (55)	31 (25)	0 (0)	0 (0)
FCGR2B*232T	137 (76)	40 (22)	3 (2)	0 (0)	0 (0)	99 (81)	21 (17)	3 (2)	0 (0)	0 (0)
FCGR2C*ORF	122 (68)	56 (31)	2 (1)	0 (0)	0 (0)	85 (69)	36 (29)	2 (2)	0 (0)	0 (0)
FCGR2C*ncORF	170 (94)	3 (2)	7 (4)	0 (0)	0 (0)	115 (94)	2 (2)	6 (5)	0 (0)	0 (0)
FCGR3A*158V	62 (34)	85 (47)	33 (18)	0 (0)	0 (0)	47 (38)	52 (42)	24 (20)	0 (0)	0 (0)
FCGR3B*NA2	20 (11)	83 (46)	77 (43)	0 (0)	0 (0)	15 (12)	56 (46)	52 (43)	0 (0)	0 (0)
FCGR3B*SH	172 (96)	8 (4)	0 (0)	0 (0)	0 (0)	116 (94)	7 (6)	0 (0)	0 (0)	0 (0)
FCGR2 promoter 2B.4	134 (74)	46 (26)	0 (0)	0 (0)	0 (0)	92 (75)	31 (25)	0 (0)	0 (0)	0 (0)

N(% of cohort).

Supplementary Table S4. Susceptibility to transient, self-limiting/IVIg-responsive childhood immune thrombocytopenia

	Healthy controls (N=180)					Transient ITP (Self-limiting or IVIg-responsive) TIKI (N=131)					
	0	1	2	3	4	0	1	2	3	4	**P**
Copy number variation											
CNR1	0 (0)	12 (7)	155 (86)	12 (7)	1 (1)	0 (0)	4 (3)	118 (90)	9 (7)	0 (0)	0.44
CNR2	0 (0)	1 (1)	168 (93)	11 (6)	0 (0)	0 (0)	0 (0)	126 (96)	5 (4)	0 (0)	0.51
CNR3	0 (0)	0 (0)	180 (100)	0 (0)	0 (0)	0 (0)	0 (0)	131 (100)	0 (0)	0 (0)	ND
Alleles											
FCGR2A*27W	146 (81)	29 (16)	5 (3)	0 (0)	0 (0)	88 (67)	39 (30)	4 (3)	0 (0)	0 (0)	**0.013**
FCGR2A*131H	38 (21)	87 (48)	55 (31)	0 (0)	0 (0)	27 (21)	68 (52)	36 (27)	0 (0)	0 (0)	0.82
FCGR2B*232T	143 (79)	31 (17)	6 (3)	0 (0)	0 (0)	98 (75)	30 (23)	3 (2)	0 (0)	0 (0)	0.41
FCGR2C*ORF	143 (79)	32 (18)	5 (3)	0 (0)	0 (0)	81 (62)	48 (37)	2 (2)	0 (0)	0 (0)	**<0.001**
FCGR2C*ncORF	173 (96)	3 (2)	4 (2)	0 (0)	0 (0)	125 (95)	3 (2)	3 (2)	0 (0)	0 (0)	0.91
FCGR3A*158V	79 (44)	78 (43)	23 (13)	0 (0)	0 (0)	46 (35)	63 (48)	22 (17)	0 (0)	0 (0)	0.27
FCGR3B*NA2	31 (17)	79 (44)	68 (38)	2 (1)	0 (0)	11 (8)	66 (50)	54 (42)	0 (0)	0 (0)	0.07
FCGR3B*SH	173 (96)	7 (4)	0 (0)	0 (0)	0 (0)	128 (98)	3 (2)	0 (0)	0 (0)	0 (0)	0.53
FCGR2 promoter 2B.4	145 (81)	31 (17)	4 (2)	0 (0)	0 (0)	92 (70)	39 (30)	0 (0)	0 (0)	0 (0)	**0.007**

N(% of cohort). Frequency P-value by Fisher's exact test. ND, not performed.

Transient ITP was defined as spontaenous recovery or a favorable response to IVIg 3 months after diagnosis.

Supplementary Table S5. Recovery rate of patients in observation and IVIg groups stratified by *FCGR2C**ORF haplotype

	Recovery in Observation		**Recovery in IVIG**	
	ORF (N=27)	STOP (N=54)	ORF (N=31)	STOP (N=68)
Week 1, n/N	*27*	*53*	*31*	*67*
CR	8 (30)	7 (13)	26 (84)	41 (61)
PR	5 (19)	9 (17)	2 (6)	7 (10)
NR	14 (52)	37 (70)	3 (10)	19 (28)
Month 1, n/N	*27*	*54*	*31*	*67*
CR	13 (48)	20 (37)	25 (81)	37 (55)
PR	5 (19)	12 (22)	4 (13)	14 (21)
NR	9 (33)	22 (41)	2 (6)	16 (24)
Month 3, n/N	*27*	*52*	*31*	*66*
CR	20 (74)	31 (60)	29 (94)	47 (71)
PR	4 (15)	7 (13)	2 (6)	6 (9)
NR	3 (11)	14 (27)	-	13 (20)
Month 6, n/N	*25*	*48*	*30*	*58*
CR	22 (88)	34 (71)	29 (97)	43 (74)
PR	1 (4)	5 (10)	1 (3)	7 (12)
NR	2 (8)	9 (19)	-	8 (14)
Month 12, n/N	*23*	*44*	*25*	*59*
CR	22 (96)	34 (77)	25 (100)	49 (83)
PR	-	6 (14)	-	6 (10)
NR	1 (4)	4 (9)	-	4 (7)

Data are presented as n (column %). n/N, response data available for n patients of N.

CR, PR, NR - complete, partial and no recovery; based on platelet count (Rodeghiero Blood 2009)

Supplementary Table S6. Subgroup analysis for differences between transient and chronic childhood ITP stratified by treatment group

	Copies	Chronic ITP	Transient ITP (Observation group)	IVIg responsive ITP (IVIG group)
n		43	51	80
CNR1 (%)	1	**7 (16.3)**	**1 (2.0)**	**3 (3.8)**
	2	33 (76.7)	47 (92.2)	71 (88.8)
	3	3 (7.0)	3 (5.9)	6 (7.5)
CNR2 (%)	1	1 (2.3)	0 (0.0)	0 (0.0)
	2	42 (97.7)	47 (92.2)	79 (98.8)
	3	0 (0.0)	4 (7.8)	1 (1.2)
CNR3 (%)	2	43 (100.0)	51 (100.0)	80 (100.0)
FCGR2A*27W (%)	0	**37 (86.0)**	**37 (72.5)**	**51 (63.7)**
	1	5 (11.6)	12 (23.5)	27 (33.8)
	2	1 (2.3)	2 (3.9)	2 (2.5)
FCGR2A*131H (%)	0	11 (25.6)	14 (27.5)	13 (16.2)
	1	18 (41.9)	27 (52.9)	41 (51.2)
	2	14 (32.6)	10 (19.6)	26 (32.5)
FCGR2B*232T (%)	0	31 (72.1)	41 (80.4)	57 (71.2)
	1	10 (23.3)	10 (19.6)	20 (25.0)
	2	2 (4.7)	0 (0.0)	3 (3.8)
FGR2C*ORF (%)	0	**38 (88.4)**	**31 (60.8)**	**50 (62.5)**
	1	5 (11.6)	19 (37.3)	29 (36.2)
	2	0 (0.0)	1 (2.0)	1 (1.2)
FGR2C*ncORF (%)	0	38 (88.4)	49 (96.1)	76 (95.0)
	1	2 (4.7)	1 (2.0)	2 (2.5)
	2	3 (7.0)	1 (2.0)	2 (2.5)
FCGR3A*158V (%)	0	13 (30.2)	17 (33.3)	29 (36.2)
	1	22 (51.2)	21 (41.2)	42 (52.5)
	2	8 (18.6)	13 (25.5)	9 (11.2)
FCGR3B*NA2 (%)	0	9 (20.9)	2 (3.9)	9 (11.2)
	1	18 (41.9)	24 (47.1)	42 (52.5)
	2	16 (37.2)	25 (49.0)	29 (36.2)
FCGR3B*SH (%)	0	39 (90.7)	50 (98.0)	78 (97.5)
	1	4 (9.3)	1 (2.0)	2 (2.5)
2B.4 (%)	0	37 (86.0)	32 (62.7)	60 (75.0)
	1	**6 (14.0)**	**19 (37.3)**	**20 (25.0)**

Bold lines for variables that were different between chronic ITP and transient ITP at $P < 0.05$ (Table 4).