



From pharmacogenetics to clinical practice: which SNPs are associated with major long term graft complications of kidney transplantation



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BACKGROUND

In recent years, several studies have identified many single-point gene variants (SNP) involved in the metabolism of immunosuppressive drugs (IS): they are able to predict drug efficacy and side effects, but it is uncertain if they are associated with long-term complications of kidney transplantation (KTx).

Each SNP might be associated with different KTx complications, but the strength of association is usually low.

Aim of this study was to evaluate the association between major SNPs involved in IS metabolism and severe long term complications of KTx.

METHODS

Design and data collection/analysis:

DNA collection: cross sectional

Clinical data collection: prospective

Data analysis: retrospective

Population:

- Ktx recipient (not combined with other organs)
- Living and deceased donors
- First or subsequent KTx (89.9% first KTx)
- Any ethnicity (96.8% Caucasian)

SNPs:

Gene	SNP	WT	Pathway	Mutation Effect
CYP3A5	6986A>G	*3	CNI met	
CYP3A4	rs35599367C>T	CC	CNI met	Slower met. (=more toxicity)
MDR1	3435C>T	CC	Drug met	
MDR1	1236C>T	CC	Drug met	Faster met.
TCF7L2	rs7903146 C>T	CC	Trans. Fact	PT Diab Mell (other?)

RESULTS

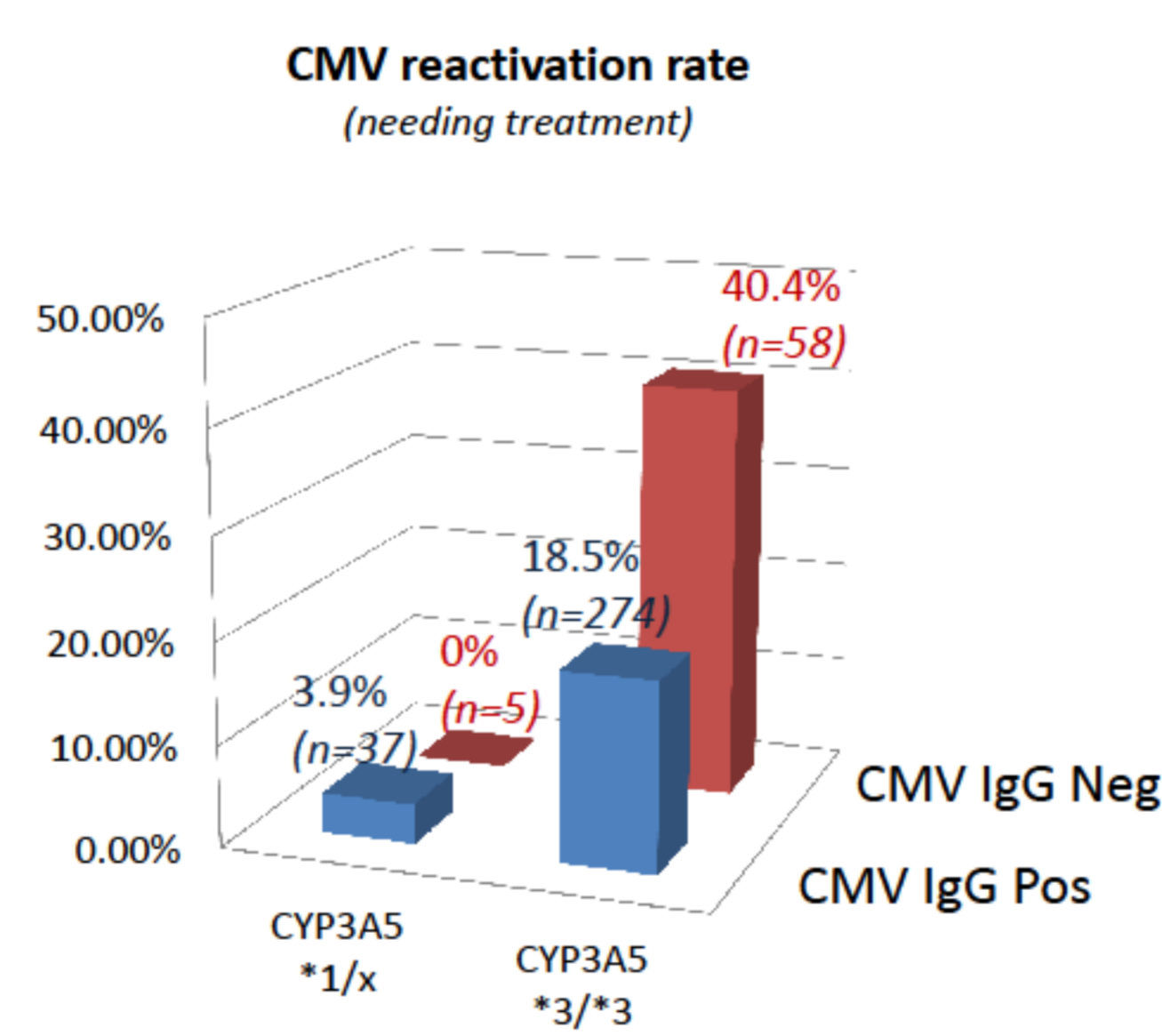
Enrolled population (n=436)	
Male	65,6%
Age at KTx	52,7 ± 12,4
Follow up (years)	4,3 ± 3,7
HLA Mismatch	2,9 ± 1,0
Diabetes (pre-KTx)	5,7%
Weight	66,2 ± 17,4
BMI	24,0 ± 3,5
Delayed Graft F.	25,0%
BP Ac.Rejection	12,8%

Immunosuppressive Therapy	
rATG	10,3%
Basiliximab	82,3%
FK	90,6%
MMF	93,1%
mTORi	7,0%
St withdrawal	20,4%
days to w/drawal	825 ± 810

CYP3A5

	CYP 1/x (n=52)	CYP 3/3 (n=384)	p
Male	59,6%	66,4%	0,334
Age	52,1±12,0	52,8±12,5	0,720
Caucasian	86,5%	98,2%	0,001
BK nephrop.	5,8%	1,0%	0,011
CMV react.	1,9%	18,8%	0,002
BPARreject	15,3%	12,5%	0,345
Virus-assoc. malign	0/52 (0%)	32/384 (8,3%)	0,03

Renal function, other malignancies, CV Events and other major infections were not associated with this SNP.



TCF7L2

	TCF7L2 CC (n=156)	TCF7L2 CT or TT (n=274)	RR	p
Male	65,4%	65,3%	n/a	0,991
Age	52,0 ± 13,2	53,1 ± 11,9	n/a	0,371
Pre-KTx Diabetes	7,1%	5,1%	n/a	0,409
BMI	24,0 ± 3,3	24,1 ± 3,6	n/a	0,617
PT-Diabetes	5,8%	16,4% (see Poster FP814)	2.83	0,001
Acute Myoc. Inf.	0,6%	4,7%	7.83	0,022
Atheroscl. CV Ev.	1,9%	9,1%	4.80	0,004
Total CV Ev	12,8%	25,2%	1.97	0,003

No other significant association

Post Transplant Lymphoproliferative Disorders

on CNI	PTLD (n=8)	Other (n=407)	P
Male	75,0%	66,1%	0,56
Age	57,9 ± 11,7	52,9 ± 12,4	0,13
EBV SeroNeg	12,5%	2,9%	0,09
CYP3A5 3/3	100%	80,1%	0,16
CYP3A4 CC	100%	80,3%	0,16
MDR1236 TT	75%	26,0%	<0,01
MDR3435 CC	50%	22,1%	0,06
TCF7L2 TT	37,5%	12,8%	0,04
MMF	87,5%	96,5%	0,17
ATG	12,5%	11,7%	0,95

Preval.	Risk	EBV	MDR1 1236	TCF7L2	CYP3A5
3-5%	High (15%)	Any	TT	TT	Any
35-40%	Medium (4-8%)	Neg	Any	Any	Any
		Pos	TT in either one	WT	
55-60%	Low risk (<1%)	Pos	Cx	Cx	Any
		Pos	TT in either one	1/3	

DISCUSSION

The evaluation of the CYP3A5 *1, MDR1 1236C>T and TCF7L2 rs7903146C>T SNPs is able to greatly improve the risk stratification of post-transplant viral-associated diseases, CVEs and PTLD. Particularly they are associated with:

Gene	SNP	Genotype	KTx complication	OR
CYP3A5	6986A>G	*1/x (Heteroz)	CMV reactivation	0.08
			Virus-rel. Malign.	<0.21
MDR1	1236C>T	TT	PTLD	8.5
TCF7L2	rs7903146 C>T	T/x (Heteroz)	CV Event	2.3
			Atheroscl. Event	4.8
		TT	PTLD	4.1
		per T allele	PT Diabetes Mellitus	1.7

Future developments/Clinical use: interestingly these SNPs may be known before surgery, so that specific prevention strategies might be adopted in high-risk patients.

More studies are needed to include these SNPs in risk models of the main transplant complications.

Specific intervention (screening or more aggressive prophylaxis) should be evaluated in high-risk patients.

Costs should also be evaluated, but are likely low (a panel of SNPs costs less than a standard hemodialysis session in Italy)