ASSOCIATION OF TOLL-LIKE RECEPTOR 2 GENE POLYMORPHISM WITH THE INCIDENCE OF BACTERIAL INFECTIONS IN SICKLE CELL DISEASE

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Karina Tozatto-Maio[1, 2, 3], Robert Girot[4], Christina Mariaselvam[5,6], Meriem Bennabi[5,6], Annalisa Ruggeri[1,3], Barbara Cappelli[1, 3], Rajagopal Krishnamoorty[5], Belinda Pinto Simões[2], Ibrahima Diagne[7], Eliane Gluckman[1], Ryad Tamouza[5,6]
[1]Eurocord, Université Paris 7, Paris, France, [2]Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil, [3]Monacord, International Observatory on Sickle Cell Disease, Centre Scientifique de Monaco, Monaco, Monaco, [4]Hôpital Tenon, [5]Inserm U1160, Université Paris 7, Paris, [6]Hôpital Henri Mondor, Créteil, France, [7]Pediatrics Unit, Centre Hospitalier National d'Enfants Albert Royer, Dakar, Senegal
karina.tozatto-maio-ext@aphp.fr

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BACKGROUND

Despite antimicrobial prophylaxis and immunization, bacterial infection remains a leading cause of morbidity and mortality in sickle cell disease (SCD) patients. Functional hyposplenia/asplenia partially explains their susceptibility, since even young SCD children with functional spleen are at raised infectious risk. Toll-like receptors (TLR), that recognize pathogen molecular patterns, are at the forefront of immune protection. The interaction between TLR and infectious diseases in SCD patients has never been explored.

OBJECTIVES

This study aims to evaluate if functional polymorphisms (SNPs) in TLR confer susceptibility/resistance to infections in SCD.

MATERIALS & METHODS

One hundred-sixty SCD patients followed either in France (n=104) or Senegal (n=56) with recorded history of infections were tested for SNPs in TLR-1, TLR-2, TLR-4, TLR-6 and TLR-10 by TaqMan 5'-nuclease assay for their association with infectious history. All patients had vaccinations against *Streptococcus pneumoniae* and *Haemophilus influenza B,* and patients under 10 years had received penicillin prophylaxis. Comparisons between groups were evaluated by x^2 or Fisher exact T-test with Bonferroni corrections of P-value (Pc); associations were measured by odds ratio (OR).

	No infected (n=84) (%)	Infected (n=76) (%)	P-value
Gender	n=82	n=76	
Male	34 (41)	36 (47)	0.45
Female	48 (59)	40 (53)	
Sickle cell genotype	n=84	n=75	
SS/SB/SD	69 (82)	70 (93)	0.053
SC	15 (18)	5 (7)	
Age (median)	23	25	0.24

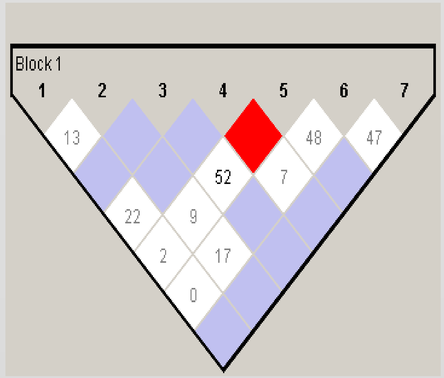
RESULTS

Site of infection	N=76 (%)
Respiratory	24 (32)
Bone and joints	21 (28)
Blood stream	17 (22)
Urinary tract	11 (14)
CNS	8 (11)
Abdominal	5 (6)
Etiological agent	**N=58 (%)**
Encapsulated bacteria	35 (61)
Mycobacterium tuberculosis	11 (19)
Mycoplasma spp	6 (10)
Others	6 (10)

Eleven patients had more than one episode of infection.

	SNP	genotype	infected (%) x others (%)	cP-value	OR	95%CI
infected (n=76) vs	rs4696480	T/A	68 (45%) x	**<0.01**	0.02	0.01-0.09
not infected (n=84)			164 (98%)			
encapsulated (n=35)	rs4696480	T/A	18 (51%) x	**<0.01**	0.19	0.08-0.44
vs others (n=107)			91 (85%)			

Group (n)	Infected (76)	Controls (84)	Infected by EB (35)	Others (107)	All patients (160)
MAF (A)	0.39	0.5	0.44	47.2	0.45
HWE (p)	0.57	0	0.94	0	0



Linkage disequilibirum plot for SNPs in TLR-1, TLR-2, TLR-6 and TLR-10

The red block represents significant complete LD (D'=1). Blue blocks represent not significant complete LD. White blocks represent incomplete LD.

SNPs:
1: rs4696480
2: rs3804099
3: rs5743699
4: rs11466653
5: rs11096957
6: rs5743618
7: rs5743810

SUMMARY

The *rs*4696480 TA genotype apparently confers protection against infections especially for encapsulated bacteria. Given the previously demonstrated association of AA genotype with exacerbated expression of inflammatory cytokines as well as association of T allele with lower expression of cytokines it is tempting to postulate that TA genotype can be considered as a compromise between deleterious effects of over inflammatory response (TLR-2 AA genotype) and under response (TLR-2 TT genotype) to infectious agents. Such balanced selection effect is probably reflected by the observed deviation from Hardy-Weinberg equilibrium.

CONCLUSIONS

TA genotype of rs4696480 is strongly associated with less occurrence of bacterial infections in sickle cell disease patients, likely meaning a protective effect against such infections.

REFERENCES

Eder W et al. Toll-like receptor 2 as a major gene for asthma in children of European farmers. **J Allergy Clin Immunology.** 2004 Mar;113(3):482-8.

Ntoufa S et al. Toll-like receptors signaling: A complex network for NF-kB activation in B-cell lymphoid malignancies. **Semin Cancer Biol** 2016 Jul 9. pii: S1044-579X(16)30024-4.

Oh DY et al. Association of the toll-like receptor 2 A16934T promoter polymorphism with severe atopic dermatitis. **Allergy**. 2009 Nov;64(11):1608-15.

Stuart MJ, Nagel RL. Sickle cell disease. **Lancet** 2004; 364: 1343–6