



Identification of *Plasmodium falciparum* parasite virulence markers

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Objectives

To explore two hypothesis:

- 1) some specific *P. falciparum* genotypes are more likely than others to induce cerebral malaria,
- 2) *P. falciparum* gene(s) associated with severity of cerebral malaria segregate with the *Pf-msp1* gene.



Methods (1)

- **Multicenter** (Mali, Cameroon, Gabon) **case - control study**, 2007-2008
- **Cases : Cerebral malaria (CM) or prostration** according to WHO (2000) criteria
- **Controls : Uncomplicated malaria (UM)** according to WHO (2000) criteria
- *P. falciparum* isolates collected on FTA®-Elute filter papers



Methods (2)

- ***m*sp1 block 2** (chr.9) & ***m*sp2** (chr.2) AFLP genotyping
- ***Pf*crt** (codon 76), ***Pf*dhfr** (codon 108, 51 & 59) & ***Pf*hdps** (codon 437 & 540) SNPs genotyping
- Analysis :
 - MOI estimated by *m*sp1 & *m*sp2 genotyping
 - **Comparison of allele frequencies according to clinical status**



Results (1)

	Mali	Cameroon	Gabon
UM			
n	106	102	24
Age (y) : mean (SD)	4.6 (2.9)	13.8 (16.9)	5.9 (3.1)
Parasite density/ μ L : geo. mean (95%CI)	20580 (14910-28407)	3191 (2205-4617)	18485 (9157-37313)
Mean multiplicity (95%CI)	2.21 (1.96-2.46)	1.98 (1.7-2.26)	2.88 (2.34-3.41)
CM or prostration			
n	178	103	3
Age (y) : mean (SD)	4.1 (3.1)	10.9 (14.3)	1 (1)
Parasite density/ μ L : geo. mean (95%CI)	11053 (8139-15010)	6424 (4200-9823)	13873 (2773-69400)
Mean multiplicity (95%CI)	2.15 (1.96-2.33)	2.34 (2.04-2.64)	2



Results (2)

Risk of severe malaria (CM or prostration) vs. UM according to the detected *msp1* allelic families of *P. falciparum*

	Mali (n=277)		Cameroon (n=184)	
	OR (IC95%)	p-value	OR (IC95%)	p-value
<i>msp1</i> allelic families				
K1	0.98 (0.56-1.7)	0.944	1.16 (0.55-2.44)	0.704
Mad20	0.72 (0.43-1.2)	0.211	1.97 (1.06-3.66)	0.031
Ro33	1.66 (1.01-2.72)	0.045	0.77 (0.43-1.38)	0.373

OR: Odds ratio, 95%IC: 95% confidence interval

No association with *msp2*, *Pfcr*, *Pfdhfr* & *Pfhdps* genotypes



Discussion & Conclusions

- Significant association of malaria severity (cerebral malaria & prostration) with *msp1* block2 genotype (chr. 9)
- Association already found in French Guyana, Ghana, Gabon & India
- ➔ *msp1* segregates with gene(s) strongly associated with severe neurological presentations of the disease
- No association with *msp2* (chr. 2), *Pfcrt* (chr. 7), *Pfdhfr* (chr. 4) & *Pfhdps* (chr. 8) genotypes



Future perspectives

- Ongoing whole genome genotyping using Affymetrix™ DNA microarray
 - ➔ extensive linkage disequilibrium screening & gene mapping
- New insight in pathophysiology, genetics, diagnosis, prevention, treatment and molecular epidemiology of severe *P. falciparum* malaria