

Influence of the Combination and Phase Variation Status of the Haemoglobin Receptors on Meningococcal Virulence

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INTRODUCTION

Neisseria meningitidis can utilize haem, haemoglobin and haemoglobin-haptoglobin complexes as sources of iron via two TonB-dependent phase variable haemoglobin receptors, HmbR and HpuAB. The distribution, expression and tract length of both systems varies between diverse meningococcal isolates. Critically, HmbR was previously reported to be associated with disease isolates (Harrison *et al.*, 2009).

In this study, 214 disease and 305 carriage isolates from 4 separate strain collections were investigated for the presence, poly-C tract lengths and ON-OFF status of both haemoglobin binding systems.

RESULTS

a) Distribution of Haemoglobin Receptors

- Statistical analysis revealed:
- No significant difference in the frequency of the presence of both genes versus that of *hmbR* only in disease isolates.
- Significant selection against the presence of *hpuAB* only in invasive isolates.

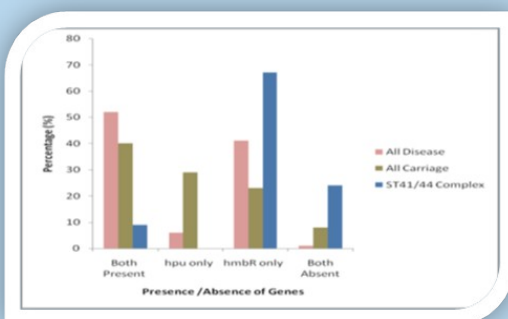


Figure 1: Graphical representation of distribution of haemoglobin receptors in meningococcal isolates.

b) Status of Haemoglobin Receptors

- ON/OFF status indicate that strains harbouring both genes have either "both" or "one" gene ON.
- Most of the isolates with both genes OFF belonged to the carriage group.
- The receptor *hmbR* was in the ON state in the majority of both disease and carriage isolates when present alone but this was true for *hpuAB* alone only in carriage isolates.

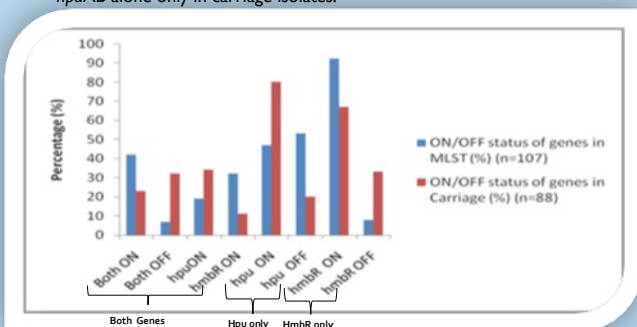


Figure 2: ON-OFF status of haemoglobin receptors in strains of MLST (84% invasive & 16% carriage) and Carriage (2008) group.

CONCLUSION:

- ❖ Data indicates that isolates with only HpuAB are under-represented in invasive isolates and that HpuAB is frequently 'off' in invasive isolates containing both receptors, suggesting that there is selection against expression of HpuAB during invasion. The HmbR receptor is over-represented in invasive isolates and is usually in an 'on' phase variation state.
- ❖ When HpuAB is present in combination with HmbR, there is the potential for phase variation between the expression of both receptors resulting in immune evasion but no loss of the ability to acquire haem/iron from haemoglobin.
- ❖ A number of ST41/44 carriage isolates lacking both systems suggests that acquisition of haemoglobin during carriage is not essential.

c) poly-C Tracts length Distribution among Haemoglobin Receptors

- Variation in repeat tract length was evident with modal repeat numbers of 9 Cs for *hmbR* and 10 Cs for *hpuAB*.
- Analysis also revealed a slight selection for tract lengths longer than the modal numbers as compared to shorter lengths.

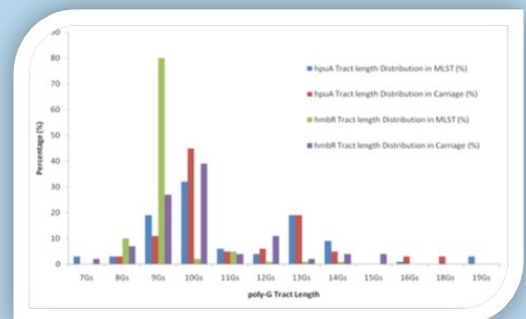


Figure 3: Tract length distribution of *hmbR* and *hpuA* in MLST and Carriage (2008) group.

d) Genetic Analysis of *hpuAB* Locus and Deletion Mechanisms

- An array of repeat elements (REP) of varying lengths was identified.
- Analysis revealed that *hpuAB* was either replaced by an IS element (IS1106A3) or completely deleted.
- IS element was distributed mainly in ST41/44 CC (57%) and ST-18 CC (10%) while the complete deletion was found mainly in ST-32 CC (45%) and ST-269 CC (28%).

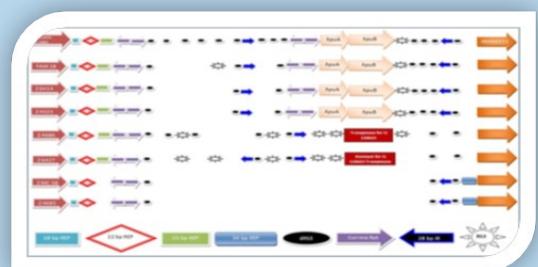


Figure 4: Arrangement of different repetitive elements and illustration of repeat mediated *hpuAB* deletion mechanisms.