

## Supplementary Data for:

### Haptoglobin genotype and outcome after aneurysmal subarachnoid haemorrhage

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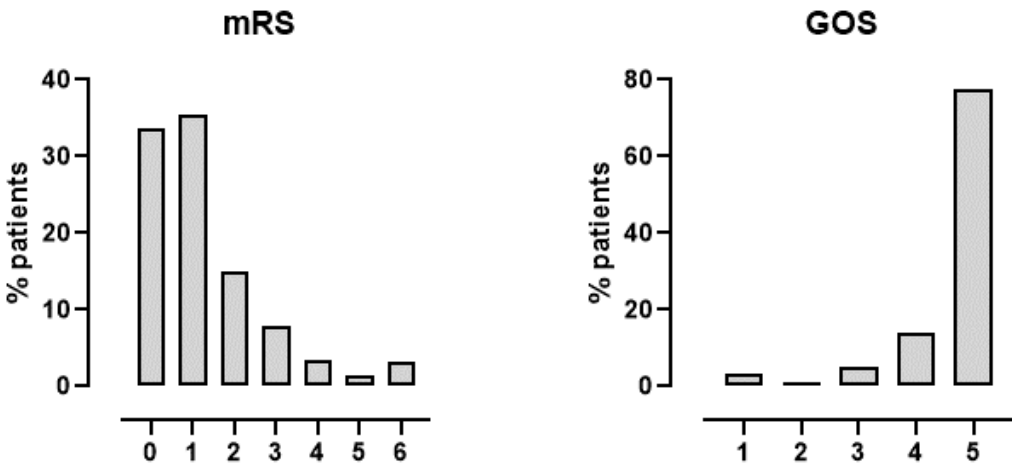
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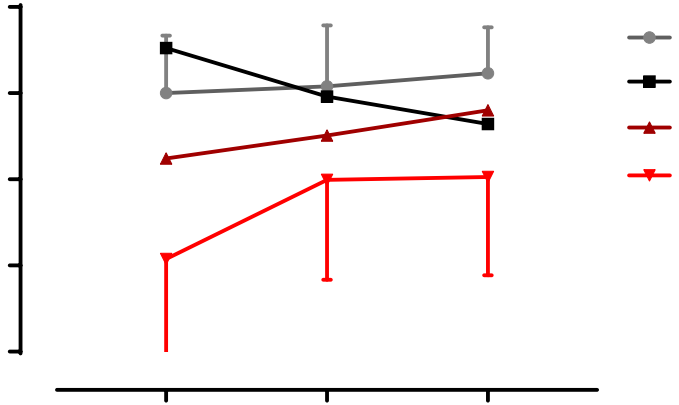
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**Supplementary Figure 1.** mRS and GOS in the analysis population.



**Supplementary Figure 2.** Mean predicted probability of favourable outcome (mRS: 0-1)  $\pm$  standard deviation, by *HP* CNV and undichotomized Fisher grade. Contrasts: (1) At high Fisher:  $p=0.013$ , Odds ratio = 2.69 (95% CI: 1.2-5.9) for HP2-2 *versus* HP1-1; (2) At low Fisher:  $p=0.42$ , Odds ratio = 2.33 (95% CI: 0.30-17.9) for HP2-2 *versus* HP1-1. Error bars are only shown for Fisher I and IV to enhance readability.



**Supplementary Table 1.** Frequencies of *HP* CNV and rs2000999 genotypes in GOSH and ALSPAC cohorts: n (%).

	<b>HP1-1</b>	<b>HP2-1</b>	<b>HP2-2</b>	<b>Total</b>	$\chi^2$ vs GOSH
<b>GOSH</b>	205 16%	612 47%	481 37%	1298 100%	
<b>ALSPAC</b>	137 15%	418 45%	372 40%	927 100%	NS

	<b>rs2000999 AA</b>	<b>rs2000999 AG</b>	<b>rs2000999 GG</b>	<b>Total</b>	$\chi^2$ vs GOSH
<b>GOSH</b>	57 5%	379 29%	854 66%	1290 100%	
<b>ALSPAC</b>	34 4%	229 31%	485 65%	748 100%	NS

**Supplementary Table 2.** Multivariable linear regression of plasma haptoglobin level *versus* the *HP* CNV and rs2000999 in the ALSPAC cohort (n=325). *HP* CNV was considered as the exposure and plasma haptoglobin level as the outcome, with adjustment for covariates rs2000999 and sex (model fit:  $r^2 = 0.23$ ,  $p = 2.2 \times 10^{-16}$ ).

	<b>Coefficient</b>	<b>SE</b>	<b>Lower 95% CI</b>	<b>Upper 95% CI</b>	<b>p value</b>
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<b><i>HP</i> CNV</b>	-0.2641	0.0354	-0.334	-0.195	$8.46 \times 10^{-13}$
<b>rs2000999</b>	-0.1356	0.041	-0.217	-0.054	0.00124
<b>Sex (reference male)</b>	-0.136	0.046	-0.227	-0.045	0.0037

**Supplementary Table 3.** Demographics and clinical characteristics of the CSF cohorts. Mean & SD<sup>a</sup>, number and %<sup>b</sup>.

	<b>High Fisher grade</b>	<b>Low Fisher grade</b>
<b>Collection</b>	Prospective	Retrospective
<b>Number</b>	44	8
<b>Age (years)<sup>a</sup></b>	59.8 ± 12.3	52.8 ± 9.0
<b>Sex<sup>b</sup></b> male female	15 (34%) 29 (66%)	2 (25%) 6 (75%)
<b>Hypertension<sup>b</sup></b> Yes No	23 (52.3%) 21 (47.7%)	1 (12.5%) 7 (87.5%)
<b>WFNS<sup>b</sup></b> 1 2 3 4 5	5 (11.4%) 10 (18%) 6 (13.6%) 15 (29.5%) 8 (13.6%)	7 (87.5%) 1 (12.5%)
<b>Fisher grade<sup>b</sup></b> 1 2 3 4		7 (87.5%) 1 (12.5%)
<b>Aneurysmal management<sup>b</sup></b> Coiled Clipped Supportive	32 (72.7%) 5 (11.4%) 6 (13.6%)	3 (37.5%) 4 (50%) 1 (12.5%)

**Supplementary Table 4.** Analysis after imputation of missing values. Eight variables had missing values (range 0.7-7.4%). The findings were similar to the complete case analysis, namely (1) an interaction between *HP* and Fisher; (2) a protective effect of HP2-2 at high but not low Fisher grade; (3) a poor prognostic effect of a high Fisher category was present in HP1-1 but not HP2-2 patients.

	Imputation number										Pooled imputation	
	1		2		3		4		5			
	OR	<i>p</i>	OR	<i>p</i>	OR	<i>p</i>	OR	<i>p</i>	OR	<i>p</i>	OR	<i>p</i>
<b>Fisher x <i>HP</i></b>		0.008		0.052		0.014		0.032		0.003		
<b>Fisher at HP1-1</b>	3.9 (1.6-9.6)	0.003	3.4 (1.4-8.1)	0.005	4.7 (1.8-12.2)	0.001	3.1 (1.3-7.3)	0.008	3.7 (1.5-9.2)	0.004	3.7 (1.4-9.7)	0.007
<b>Fisher at HP2-2</b>	0.9 (0.5-1.5)	0.685	1.0 (0.6-1.8)	0.89	1.0 (0.6-1.7)	0.987	0.9 (0.5-1.6)	0.781	0.8 (0.5-1.6)	0.411	0.9 (0.5-1.6)	0.799
<b><i>HP</i></b>		0.011		0.046		0.043		0.012		0.025		
<b>HP2-2 vs HP1-1 at low Fisher grade</b>	0.5 (0.2-1.3)	0.151	0.6 (0.3-1.4)	0.255	0.4 (0.2-1.1)	0.077	0.7 (0.3-1.6)	0.373	0.4 (0.2-1.1)	0.073	0.5 (0.2-1.4)	0.194
<b>HP2-2 vs HP1-1 at high Fisher grade</b>	2.3 (1.3-4.0)	0.003	2.0 (1.2-3.5)	0.013	2.0 (1.2-3.5)	0.012	2.3 (1.3-4.0)	0.003	2.1 (1.2-3.6)	0.009	2.1 (1.2-3.8)	0.01