Haptoglobin Genotype and Outcomes in Subarachnoid Hemorrhage And Intracranial Hemorrhage

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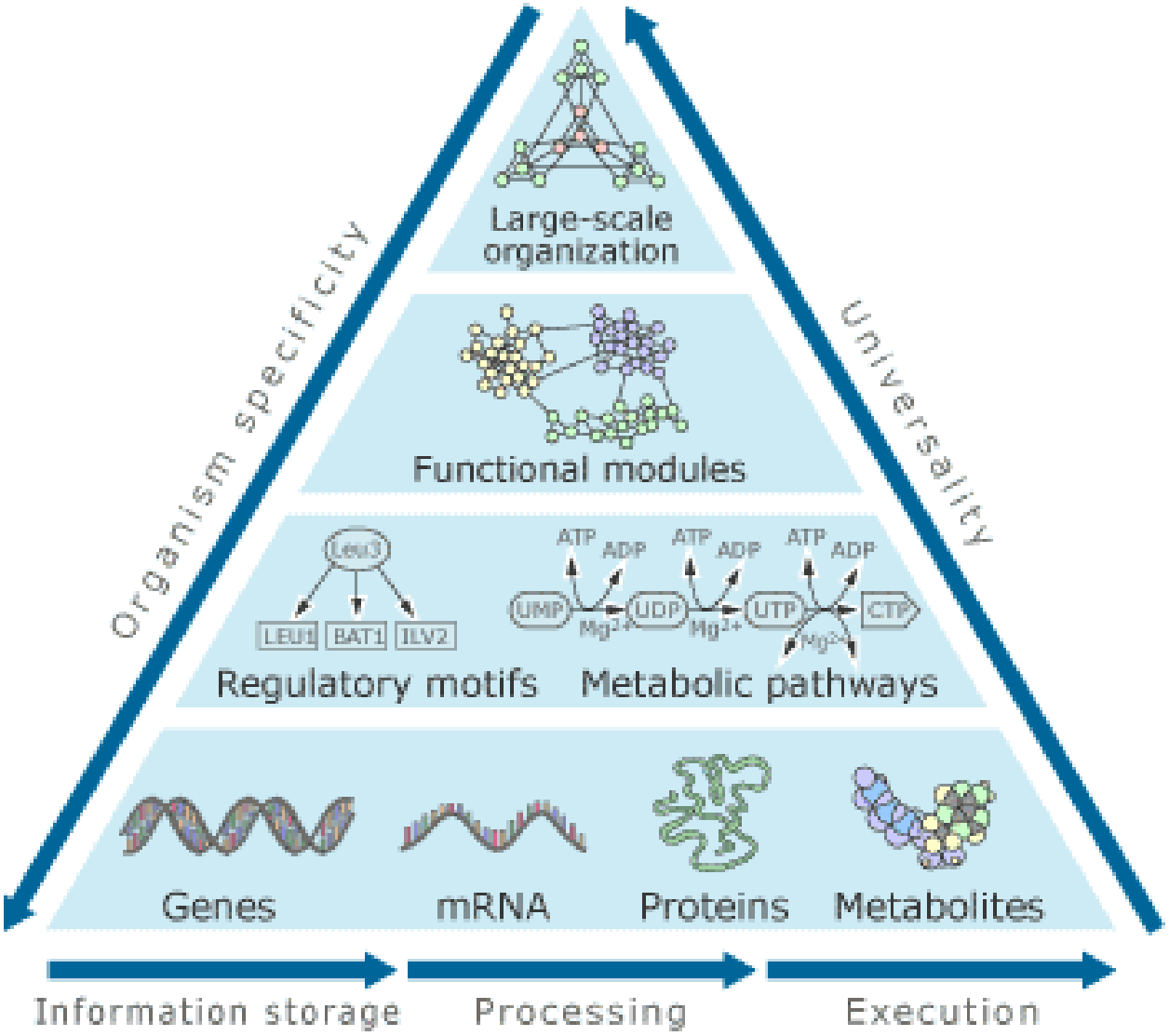
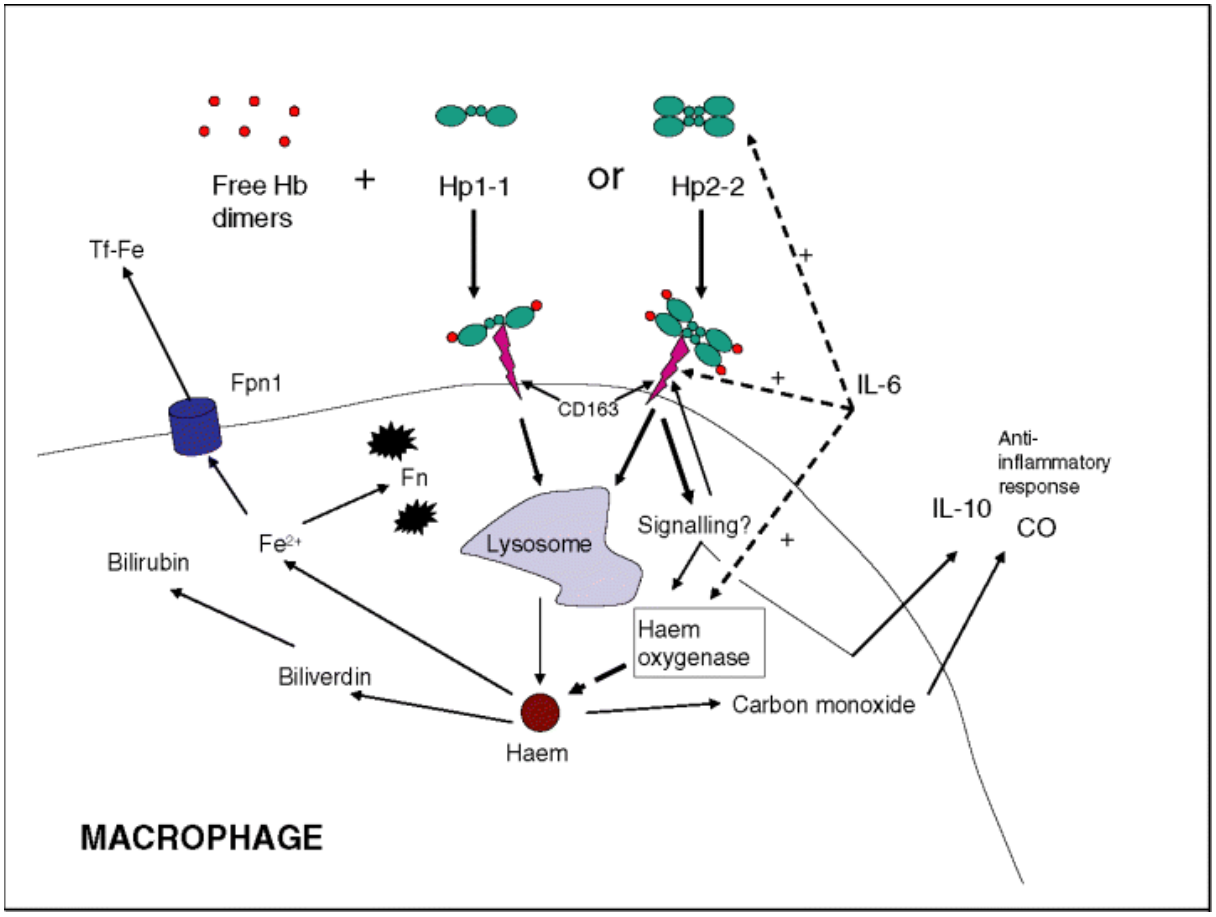
In collaboration with BIOS

Systems Biology



Haptoglobin: a review of the major allele frequencies worldwide and their association with diseases



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Haptoglobin Mechanism

- The essential role of Hp in removing free haemoglobin from the circulation
- Two Main types of Haptoglobin Hp1 and Hp2 with three main phenotypes Hp 1-1, Hp 2-1, Hp 2-2
  - The macrophage CD163 receptor has an approximately eight times greater affinity for Hp2-2 than Hp1-1
  - Studies in cultured CHO cells transfected with CD163 demonstrated more rapid uptake of the Hp(1-1)–Hb complex
  - Rates of breakdown of Hb within the cell were similar
- All three factors indicate that Hp1-1 will be the more effective molecule in preventing oxidative damage by free Hb

Presence of haptoglobin-2 allele is associated with worse functional outcomes after spontaneous intracerebral hemorrhage

Murthy SB, Levy AP, Duckworth J, Schneider EB, Shalom H, Hanley DF, Tamargo RJ, Nyquist PA. World Neurosurg. 2015 Apr;83(4):583-7. doi: 10.1016/j.wneu.2014.12.013. Epub 2014 Dec 17. PMID: 25527876

Methods

- We prospectively studied consecutive patients admitted with a diagnosis of ICH to the Neurosciences critical care unit at Johns Hopkins Medical Institutions, Baltimore, MD between January 2008, and July 2013.
- The inclusion criteria were: 1) age > 18 years 2) non-traumatic ICH 3) presentation within 24 hours post ICH. Exclusion criteria were death on arrival, and surgical evacuation of the ICH.
- The main outcomes of the study were modified Rankin score (mRS) of 0-2 at 30 days (favorable outcome) and in-hospital mortality.
- Pearson's Chi-square test and Kruskall Wallis tests were used for categorical and continuous variables respectively Logistic regression models were constructed to assess the effect of Hp phenotype on ICH outcomes.

Supplemental Table I: Baseline characteristics of patients admitted with intracerebral hemorrhage.

GCS: Glasgow Coma Scale, ICH: Intracerebral hemorrhage, IVH: Intraventricular Hemorrhage, mRS: modified Rankin Score, SD: Standard Deviation.

* p<0.05

Variables	Haptoglobin 1-1 n=12 (%)	Haptoglobin 2-1 n= 46 (%)	Haptoglobin 2-2 n= 36 (%)	p value
Age (SD)	50.0 (±16.2)	58.87 (±13.9)	63.47 (±20.5)	0.062
Sex Males Females	 5 (41.7) 7 (58.3)	 25 (54.3) 21 (45.7)	 20 (55.6) 16 (44.4)	0.689
Race White Black Others	 3 (25.0) 8 (66.7) 1 (8.3)	 16 (34.8) 26 (56.5) 4 (8.7)	 21 (58.3) 11 (30.6) 4 (11.1)	0.106
Hypertension	11 (91.7)	35 (76.1)	24 (66.7)	0.214
Diabetes Mellitus	1 (8.3)	10 (21.7)	9 (25.0)	0.471
Hyperlipidemia	2 (16.7)	4 (8.7)	4 (11.1)	0.723
Smoking	3 (25.0)	13 (28.3)	10 (27.8)	0.975
Antiplatelet Use	2 (16.7)	9 (19.6)	10 (27.8)	0.594
Anticoagulant Use	0	2 (4.3)	6 (16.7)	0.074
Mean GCS (SD)	12.3 (±3.6)	10.5 (±4.4)	11.28 (±3.7)	0.489
Mean Hematoma Volume (SD)	30.7 (±10.5)	34.3 (±6.5)	27.9 (±4.7)	0.704
IVH	2 (18.2)	25 (54.3)	17 (47.2)	0.097
Mean sICH Score (SD)	1.18 (±1.4)	1.83 (±1.5)	1.69 (±1.4)	0.205
mRS 0-1	4 (33.4)	2 (4.3)	4 (11.1)	0.015*
Mortality	1 (8.3)	8 (17.4)	9 (25)	0.408

Table 1: Univariate analysis of outcomes in patients with ICH.

ICH: Intracerebral hemorrhage, mRS: modified Rankin Score.
* p<0.05

Variables	Favorable Outcome (mRS 0-1)		Mortality	
	OR (95% CI)	p value	OR (95% CI)	p value
Haptoglobin type (1-1 vs. 2-1, 2-2)	0.16 (0.04-0.68)	0.013*	2.88 (0.37-23.8)	0.328
Age (<50 vs. >=50)	0.06 (0.01-0.33)	0.001*	3.47 (0.74-16.35)	0.115
Sex (Male vs. Female)	0.73 (0.19- 2.79)	0.649	2.05 (0.72-5.85)	0.181
Glasgow Coma Scale (>8 vs.<=8)	0.22 (0.03- 1.84)	0.163	6.9 (2.29-21.25)	0.001*
Hematoma Volume (<30 cc vs. >=30 cc)	0.59 (0.14- 2.43)	0.464	7.44 (2.21-25.04)	0.001*
Intraventricular Hemorrhage	0.29 (0.06- 1.46)	0.132	13.429 (2.87-62.81)	0.001*
Antiplatelet/anticoagulant Use	0. 63 (0.12- 3.16)	0.570	1.91 (0.65- 5.63)	0.241
ICH Score (<=2 vs. >2)	0.25 (0.05-1.25)	0.091	38.15 (7.80-186.52)	<0.001*

Table 2: Multivariate analysis of outcomes based on Haptoglobin phenotypes, adjusted for sex, race, hypertension, intracerebral hemorrhage score, anticoagulant/antiplatelet use. mRS: modified Rankin Score.
* p<0.05

Variables	Favorable Outcome (mRS 0-1)		Mortality	
	OR (95% CI)	p value	OR (95% CI)	p value
Model 1				
Haptoglobin (1-1 vs. 2-1, 2-2)	0.13 (0.03-0.71)	0.018*	1.70 (0.15-19.1)	0.667
Model 2				
Haptoglobin 1-1	Reference		Reference	
Haptoglobin 2-1	0.05 (0.01- 0.468)	0.008*	1.46 (0.12- 17.7)	0.763
Haptoglobin 2-2	0.14 (0.02- 0.96)	0.045*	4.02 (0.31- 52.99)	0.290

Results

- A total of 94 ICH patients with Hp phenotype were included in the study
- Analysis of the demographics and comorbidities otherwise showed no significant differences in the in the three groups
- Favorable outcome was achieved in a total of 10 patients with the distribution of mRS 0-2
  - 4 (33.4%) in Hp 1-1
  - 2 (4.3%) in Hp 2-1
  - 4 (11.1%) in Hp 2-2 (p=0.015)
- There were 18 deaths in the ICH cohort, which included
  - 1 (8.3%) in Hp 1-1
  - 8 (17.4%)in Hp 2-1
  - 9 (25.0%) in Hp 2-2 (p=0.408)

Conclusions

- Hp 1-1 genotype was independently associated with better functional outcomes in patients with ICH
- There was a non-significant trend towards lower mortality with Hp 1-1
- Further evaluation of this association with a larger sample size would aid in risk stratification and prognostication of ICH patients

Haptoglobin 2-2 Genotype Is Associated With Cerebral Salt Wasting Syndrome in Aneurysmal Subarachnoid Hemorrhage

Murthy SB, Caplan J, Levy AP, Pradilla G, Moradiya Y, Schneider EB, Shalom H, Ziai WC, Tamargo RJ, Nyquist PA.
Neurosurgery. 2015 Sep 4. [Epub ahead of print]

Hypothesis

- We hypothesized that Hp genotype could potentially play a role in determining CSW and subsequently vasospasm in SAH patients

Methods

- Hp genotypic determination was done for patients admitted with a diagnosis of SAH
- Outcome measures included CSW, delayed cerebral infarction (DCI) and Glasgow Outcome score (GOS) of 4-5 at 30 days
- Criteria for CSW included hyponatremia <135 mEq/L, and urine output > 4 liters in 12 hours with urine sodium > 40 mEq/L.

Results

- A total of 133 patients were studied
- The distribution of Hp genotype was-
  - Hp 1-1: 29 (21.8%)
  - Hp 2-1: 57 (42.9%)
  - Hp 2-2: 47 (35.3%)
- The three Hp subgroups did not differ in terms of baseline characteristics. CSW occurred in
  - 1 patient (3.4%) with Hp 1-1
  - 8 (14.0%) patients with Hp 2-1
  - 15 (31.9%) patients with Hp 2-2 (p=0.004)
- In the multivariate regression model, Hp 2-2 was associated with CSW (OR: 4.94 CI: 1.78-17.43, p=0.013)
- Hp 2-1 was not (OR: 2.92, CI: 0.56-4.95, p=0.150) compared with Hp 1-1.
- There were no associations between Hp genotypes and functional outcome or DCI
- CSW strongly correlated with DCI (OR: 7.46, 95% CI: 2.54-21.9, p<0.001)

Table 2: Univariate analysis of outcomes in patients with aneurysmal Subarachnoid Hemorrhage. DCI: Delayed Cerebral Ischemia, GCS: Glasgow Coma Scale, GOS: Glasgow Outcome Scale, Hp: Haptoglobin, NA: Not Applicable, WFNS: World Federation of Neurologic Surgeons

Admission Variables	Cerebral Salt Wasting			Functional Outcome at 30 days			DCI		
	Yes	No	p value	GOS 1-3	GOS 4-5	p value	Infarction	No infarction	p value
Hp 1-1 Hp 2-1 Hp 2-2	1 (3.4) 8 (14.0) 15 (31.9)	28 (96.6) 49 (86.0) 32 (68.1)	0.004	8 (27.6) 16 (28.1) 14 (29.8)	21 (72.4) 41 (71.9) 33 (70.2)	0.973	5 (17.2) 14 (24.6) 14 (29.8)	24 (82.8) 43 (75.4) 33 (70.2)	0.468
Hp allele1 (1-1, 2-1) Hp allele 2 only (2-2)	9 (10.5) 15 (31.9)	77 (89.5) 32 (68.1)	0.005	24 (27.9) 14 (29.8)	62 (72.1) 33 (70.2)	0.977	19 (22.1) 14 (29.8)	67 (77.9) 33 (70.2)	0.440
Age, mean (SD)	48.0 (16.3)	55.1 (12.9)	0.022	50.2 (12.2)	62.7 (13.5)	<0.001	51.1 (14.4)	54.7 (13.5)	0.201
GCS, median (range 3-15)	15	14	0.089	8	15	<0.001	13	14	0.416
Hunt Hess Grade, median (range 1-5)	2	3	0.452	3	2	<0.001	3	3	0.507
WFNS Grade, median (range 1-5)	1	2	0.150	4	1	<0.001	2	2	0.456
Hydrocephalus Present Absent	13 (54.2) 11 (45.8)	61 (56.0) 48 (44.0)	0.873	27 (71.1) 11 (28.9)	47 (49.5) 48 (50.5)	0.024	18 (54.5) 15 (45.5)	56 (56.0) 44 (44.0)	0.884

Table 4: Multivariable analysis of Haptoglobin-2 allele patients (2-1 and 2-2) showing predictors of clinical outcomes in aneurysmal subarachnoid hemorrhage.
DCI: Delayed Cerebral Ischemia**,** GOS: Glasgow Outcome Scale, Hp: Haptoglobin

Variables	Cerebral Salt Wasting		GOS 4-5 at 30 days		DCI	
	OR (95% CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value
Diabetes Mellitus	0.78 (0.22-2.76)	0.694	0.32 (0.11-0.93)	0.037	1.59 (0.50-5.04)	0.431
Age	0.96 (0.92-1.01)	0.059	0.94 (0.89-0.98)	0.011	0.98 (0.94-1.03)	0.453
Poor Grade Hunt Hess	0.96 (0.26-3.54)	0.952	0.29 (0.09-0.98)	0.046	4.07 (1.15-14.45)	0.030
Hydrocephalus	1.11 (0.41-3.02)	0.845	0.64 (0.21-1.96)	0.433	0.52 (0.18-1.55)	0.242

Vision: Next Steps

- We would like to preform a prospective study of aSAH, haptoglobin
- CSW, vasospasm, and DIND
- D/C, 30days, and 90 days
- Bulters Diederik Bullers, UNIVERSITY HOSPITAL SOUTHAMPTON NHS FOUNDATION TRUST
- Over 100 cases with data and Haptoglobin for DIND and Vasospasm
- Subgroup to do CSW