Violent Death Associated with Specific HLA Haplotypes: A Preliminary Survey of Deceased American Organ Donors

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Importance of the Problem

- Most animal species, including mammals and primates, can identify individuals by their unique scent, which contains HLA.
- Antagonistic interactions in most species rely upon differentiable scent.
- Women tend to prefer men who are heterozygous for HLA alleles.
- Men tend to prefer associations with other men who are homozygous for HLA.
- Do such differences relate to human aggression?

Eggert et al. (1999). Genetica 104:265-73.

Thornhill & Gangestad (1999). Evolution and Human Behavior 20:175-201.

Wedekind & Furi (1997). Proc. Royal Soc London, Biol. Sci. 264:1471-79.

The HLA Locus

- Human Leukocyte Antigen, or
- Major Histocompatibility Complex
- Human Chromosome 6 – 6p21.3
- >224 gene loci; 4.6 megabases
- Largest human multigene complex
- Most polymorphic region of genome

Horton et al. (2004). *Nature Reviews Genetics, 5*, 889-899.

Three Primary HLA Regions

- MHC Class I Genes - glycoproteins which present endogenous antigens to CD8+ T lymphocytes.

  HLA-A, -B, -C, -D, -E, -F, and –G loci
- MHC Class II Genes - glycoproteins which present exogenous antigens to CD4+ T lymphocytes.

  DPA1, DPB1, DQA1/B1, DRA, DRB1/DRB3
- MHC Class III Genes - Inflammation

Horton et al. (2004). *Nature Reviews Genetics, 5*, 889-899.

Specific HLA Role

- Maintain “Self” versus “Non-self”
- Reside on cell surfaces and interact with White Blood Cells to identify one’s own cells from foreign invaders (bacteria, viruses, etc.)
- An identification system unique to each person.

Burnett, F.M. (1959). *The clonal selection theory of acquired immunity.* London: Cambridge University Press.

Horton et al. (2004). *Nature Reviews Genetics, 5*, 889-899.

Medical Applications

- Medical transplant specialists seek to find as close a match as possible between the HLA “haplotypes” of a person needing an organ transplant and the HLA haplotypes of potential organ donors. The closer the HLA match, the better the chance that the organ transplant will succeed.

HLA and Human Diversity

- **HLA-A genetic locus > 30 alleles**
- **HLA-B locus > 63 alleles**
- **HLA-CW locus > 19 alleles**
- **HLA-DR locus > 21 alleles**
- **HLA-DQ locus > 10 alleles**
- **HLA-DP locus > 7 alleles**
- **Every person has 2 alleles per locus**
- **Therefore, the number of possible combinations = $2^{30} \times 2^{63} \times 2^{19} \times 2^{21} \times 2^{10} \times 2^{7} = 2^{150}$**

Mapping Human History

- This extensive human HLA variation has been used to map human migrations.
- It has also been used to identify numerous autoimmune and related HLA-associated diseases.

LL Cavalli-Sforza (2000). Genes, Peoples, and Languages. U. California Pr.

Cavalli-Sforza, Menozzi, Piazza (1994). The History and Geography of Human Genes. Princeton U. Pr.

Flores-Villanueva et al. (2001). PNAS 98:5140-45.

Lin et al. (2001). Cancer Epidemiology, Biomarkers & Prevention 10:1037-45.

Ackerman et al. (2003). Genes and Immunity 4:476-486.

Animal Studies

- HLA plays a central role in animal communication via scent.
- Mating, territoriality, and aggression.

Piertney & Oliver (2006). Heredity 96:7-21.
Scordato & Drea (2007). Animal Behaviour 73:301-14.
Wedekind & Dustin (2000). Nephrology Dialysis Transplantation 15:1269-71.
Zavazava & Eggert (1997). Immunology Today 18:8-10.
Wobst et al. (1999). Genetica 104:275-283.

Primary Question

- Are HLA haplotypes associated with human aggression (e.g., violence)?
- Issues:

  Mating, associated behaviors solidly established

  No previous studies on human HLA and aggression – ethical issues
- This study – exploratory, not "causal"

Data Source

- United Network for Organ Sharing (UNOS, Richmond, Virginia).
- De-identified dataset of n = 182,447 deceased American organ donors from the late 1990's through 2006 (OPTN data as of March 16, 2006).
- Extensive HLA haplotype information and the cause of death for each individual.
- UNOS Data Sharing Agreement
- UNC IRB Exemption.

Methodology

- Independent Variable:

  Each Individual locus Specific Haplotype vs. Remainder of Sample (non-Haplotype)
- Dependent Variable:

  Violent vs. Non-violent circumstance of death
- Analyses:

  Repeating Non-parametric Chi-Square and Odds Ratio for all possible Haplotypes

Methodology

- Power: 0.80 to detect a small effect size difference (0.1 SD units).
- Bonferroni Adjustment of $\alpha = 0.001$ due to multiplicity of comparisons.
- SPSS, Version 15.0

Violent Death

- Operational Definition:

  Coroner's report of suicide, homicide, or child abuse in "Circumstances of Death."

World Health Organization (2002). World report on violence and health. Geneva.

Limitations

- Small cell sizes for many haplotypes
- Small vs. Large group comparisons
- No linkages to census data for varying violent crime rates by region
- Associational study, not causal, since causal would require HLA haplotypes of perpertrators
- *Correlation (or lack thereof) does not necessarily imply causation (or lack thereof)!*

Results: Demographics

- N = 182,447 cases
- n = 155,624 cases with death circumstances
- j = 92,722 complete HLA information
- k = 16,839 violent deaths (10.8% of n)
- Gender

  37.1% Female

  54.8% Male

  8.1% Not Reported

Results*: HLA-A

Haplotype		%Violent	%Non	p	OR	LowerCI	UpperCI
A2	A30	2.4	1.9	.000	1.303	1.141	1.488
A2	A68	1.6	1.2	.000	1.332	1.134	1.563
A2	A74	0.5	0.3	.000	2.098	1.572	2.800
A23	A33	0.5	0.2	.000	1.919	1.402	2.626
A23	-	0.4	0.2	.000	2.098	1.502	2.929
A28	A30	0.4	0.3	.001	1.632	1.190	2.237
A28	A33	0.3	0.1	.001	1.917	1.266	2.902
A29	A68	0.3	0.2	.000	1.947	1.328	2.854
A30	A33	0.5	0.3	.001	1.624	1.200	2.198
A30	A68	0.5	0.3	.000	1.937	1.436	2.613
A30	A74	0.3	0.1	.000	2.901	1.918	4.387
A30	-	0.6	0.3	.000	1.841	1.400	2.420
A33	-	0.3	0.2	.001	1.857	1.254	2.751

*Significant at p < .001; .95 Confidence Intervals

Results*: HLA-B

Haplotype		%Violent	%Non	p	OR	LowerCI	UpperCI
B7	B53	0.5	0.3	.001	1.641	1.222	2.203
B8	B53	0.3	0.2	.000	1.943	1.325	2.848
B35	B39	0.8	0.5	.000	1.646	1.306	2.073
B35	B42	0.3	0.1	.000	2.552	1.730	3.765
B35	B53	0.6	0.3	.000	1.894	1.439	2.492
B35	B70	0.4	0.2	.000	2.592	1.848	3.637
B42	B53	0.3	0.1	.000	2.372	1.622	3.467
B44	B53	0.5	0.3	.001	1.632	1.209	2.203
B44	B72	0.2	0.1	.001	2.648	1.549	4.528
B45	B58	0.2	0.1	.000	2.416	1.526	3.825
B45	B70	0.2	0.1	.000	2.634	1.604	4.327
B49	B53	0.2	0.1	.000	2.796	1.652	4.729

*Significant at p < .001; .95 Confidence Intervals

Results*: HLA-B (continued)

Haplotype		%Violent	%Non	p	OR	LowerCI	UpperCI
B53	B57	0.3	0.1	.000	2.187	1.476	3.241
B53	B58	0.4	0.2	.000	2.020	1.443	2.829
B53	B70	0.3	0.2	.000	1.942	1.332	2.831
B62	B65	0.2	0.1	.001	2.186	1.388	3.443
*Significant at p < .001; .95 Confidence Intervals							

Results*: HLA-BW Epitope

Epitope		%Violent	%Non	p	OR	LowerCI	UpperCI
4	4	11.8	9.2	.000	1.327	1.244	1.417
6	6	32.1	24.1	.000	1.486	1.421	1.554
4	6	6.0	13.7	.000	.398	.365	.433
*Significant at p < .001; .95 Confidence Intervals							

Results*: HLA-CW Haplotype

Haplotype		%Violent	%Non	p	OR	LowerCI	UpperCI
CW2	CW4	1.8	1.4	.001	1.344	1.119	1.615
CW4	CW7	5.9	5.0	.000	1.205	1.086	1.336
CW4	CW8	1.0	0.7	.001	1.480	1.160	1.887
CW4	CW17	0.3	0.1	.000	2.707	1.683	4.353
*Significant at p < .001; .95 Confidence Intervals							

Results*: HLA-DR Haplotype

Haplotype		%Violent	%Non	p	OR	LowerCI	UpperCI
DR4	DR8	1.7	1.3	.001	1.305	1.114	1.527
DR4	DR13	3.4	2.7	.000	1.251	1.119	1.399
DR4	DR17	2.2	1.8	.001	1.238	1.078	1.421
DR7	DR15	3.1	2.4	.000	1.268	1.128	1.426
DR7	DR17	1.6	1.2	.000	1.345	1.146	1.579
DR8	DR12	0.3	0.2	.000	1.954	1.368	2.792
DR9	DR12	0.2	0.1	.001	2.373	1.470	3.829
DR10	DR15	0.4	0.2	.000	2.123	1.501	3.002
DR11	DR13	2.4	1.9	.001	1.246	1.092	1.422
DR11	DR14	0.7	0.4	.000	1.560	1.207	2.015
DR11	DR15	2.5	1.9	.000	1.303	1.143	1.485
DR11	DR18	0.3	0.1	.000	2.341	1.584	3.459

*Significant at p < .001; .95 Confidence Intervals

Results*: HLA-DR (continued)

Haplotype		%Violent	%Non	p	OR	LowerCI	UpperCI
DR13	DR14	0.6	0.4	.000	1.583	1.223	2.049
DR13	DR15	2.9	2.4	.000	1.245	1.104	1.405
DR13	DR16	0.4	0.2	.000	2.041	1.468	2.837
DR13	DR17	1.6	1.1	.000	1.428	1.213	1.680
DR13	DR18	0.4	0.2	.000	2.271	1.595	3.233
DR15	DR17	2.0	1.5	.000	1.377	1.190	1.594
DR15	DR18	0.3	0.2	.001	1.779	1.237	2.558
*Significant at p < .001; .95 Confidence Intervals							

Summary

- For HLA-A, 17 heterozygotes were significantly associated with increased incidence of violent death, with clustering for A2, A30, A68, and A74 alleles.
- For HLA-B, 23 heterozygotes were significant, with clustering for B35, B45, and B53 alleles.
- For HLA-BW, homozygotes had significantly increased odds ratios for violent death, whereas heterozygotes had significantly reduced ratios.

Summary

- For HLA-DR, 44 heterozygotes were significant, with clustering for increased risk with DR4, DR11, DR13, and DR15 alleles.
- There were no apparent patterns for HLA-CW.

Conclusions

- There are significant associations between certain HLA heterozygous haplotypes at multiple MHC I-II loci and the occurrence of violent death.
- Even with a stringent Bonferroni adjustment, some correlations may be spurious, so caution is strongly recommended for all interpretations at this point in time.
- This is the first known study of this type with humans, so much more work is needed.

Possible Explanations

- If there are causal relationships between specific HLA haplotypes and the occurrence of violent death, which is yet to be determined, the most likely explanation would involve olfaction.
- HLA markers are demonstrated inter-individual, detectable chemical markers.
- The human vomeronasal organ is likely to be be functional, although there is debate.

Monti-Bloch et al. (1998). Ann NY Acad Sci 855:373-89.
Liman & Innan (2003). PNAS 100:3328-32.

Future Research

- Ideal study would involve adolescent or workplace bullying, but there would be difficulties with experimental design and ethical/IRB issues.
- U.S. Army pursues an HLA-based odortype detection program, with RFAs for research projects.

Disclaimer

- The data reported here have been supplied by the United Network for Organ Sharing as the contractor for the Organ Procurement and Transplantation Network. The interpretation and reporting of these data are the responsibility of the author and in no way should be seen as an official policy of or interpretation by the OPTN or the U.S. Government.

Thank You!

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