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Immunoglobulin Haplotypes – Markers of Reproductive Success

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Immunoglobulin Haplotypes: Markers of Reproductive Success?

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Abstract Immunoglobulin haplotypes are highly polymorphic and are useful for analyses of both macro- and microdifferentiation of populations. The origins of this diversity are not known, but recent reports suggest strong selection at this locus. Increased rates of first-trimester spontaneous abortions have been reported when parents share GM phenotypes. Reduced fertility has been observed in mixed European descent white and Hutterite populations when both parents share immunoglobulin haplotypes. Population samples with completed family information and GM haplotype data are rare; the objective here is to provide this information on another sample. A sample of 242 Mennonite couples with mothers older than 40 years was divided into 3 groups of matings based on how many haplotypes were shared: 0, 1, or 2. The distribution of mean completed family sizes for the three groups were 3.35 ± 1.85 ($n = 23$), 3.47 ± 1.69 ($n = 128$), and 3.37 ± 1.60 ($n = 91$), respectively; these values were not significantly different ($F = 0.145$, $p = 0.865$). The log-rank test was used to compare the time-to-next-birth curves. The intervals between first and later births (2–4 births) were not significantly different for the three subgroups either. There is also only limited evidence for segregation distortion in another sample of 923 offspring (in which at least one parent is heterozygous).

Inherited differences in human immunoglobulins known as allotypes or allotypic markers are found on IgG H chains (GM markers), IgA H chains (AM markers), and k-type L chains (KM markers, formerly called Inv) (Schanfield 1978). Each allotypic determinant is normally restricted to

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one of the IgG or IgA subclasses and thus far are found on only the constant regions of the IgG and IgA H chains. Different combinations of allotypic markers are inherited as closely linked units known as haplotypes. Populations are readily distinguished by this system because there are many haplotypes that can serve as unique population markers (Johnson et al. 1977; Ropartz et al. 1963, 1964; Schanfield 1978, 1980; Steinberg 1969; Steinberg and Cook 1981). Widely separated populations are readily differentiated by this system, but one can also distinguish populations in closer proximity because of conspicuous differences in haplotype frequencies.

The origins of this diversity are not yet understood, but recent reports suggest strong selection at the GM loci (Ober et al. 1986; Weitkamp 1986; Weitkamp et al. 1986). Reduced fertility has been reported in mixed white and Hutterite populations when both parents share immunoglobulin haplotypes (Ober et al. 1986; Weitkamp 1986; Weitkamp et al. 1986). There are also increased rates of first-trimester spontaneous abortions when parents share GM phenotypes (Weitkamp et al. 1986). Population samples with both completed family information and GM haplotype data are rare. The objective here is to corroborate Weitkamp and colleagues' findings with data on another population.

The association of shared HLA antigens and reduced reproductive performance has already been documented in Hutterite couples (Ober et al. 1983, 1985; Ober, Elias, O'Brien et al. 1988; Ober, Elias, Hauck et al. 1988) and in couples having habitual abortions [reviewed by Gill (1983b)]. In Hutterite couples, where large families are the rule, intervals between births are larger when couples share one or more HLA antigens, and this effect is more apparent with increasing parity (Ober et al. 1983, 1985; Ober, Elias, O'Brien et al. 1988; Ober, Elias, Hauck et al. 1988).

Reduced fertility resulting from shared antigens has also been reported for the GM system. In preliminary studies a significant reduction in family size was observed by Weitkamp et al. (1986) in a sample of 437 white couples with 2 or more children (selected originally over 15 years for family studies of various diseases and for linkage analysis) when the couples shared the same GM phenotype (3.10 ± 0.16 for like couples versus 3.55 ± 0.13 for unlike couples). The effect was also observed in the 282 couples with mothers older than 40 years (3.59 ± 0.22 for like couples versus 4.90 ± 0.17 for unlike couples). This difference was also apparent in 68 Hutterite couples (4.42 ± 0.68 versus 6.71 ± 0.57) and was even more dramatic among the 33 Hutterite couples with mothers older than 40 years (6.00 ± 1.21 versus 9.16 ± 0.17).

Of the 304 mixed white couples who had been both HLA and GM typed, virtually all the differences in family size "as a function of sharing

GM phenotypes was limited to the couples who also shared one or more HLA–A or HLA–B antigens" (Weitkamp et al. 1986, p. 33). Weitkamp et al. then compared couples who had first-trimester spontaneous abortions (and at least three pregnancies) with control couples who had three or more offspring, according to whether or not they shared HLA–A or HLA–B antigens. Spontaneous abortions increased significantly in couples who share GM haplotypes when compared to control couples ($\chi^2 = 7.2$ with Yates correction, $p < 0.01$). Weitkamp et al. believe that this represents an interaction "between HLA and GM in susceptibility to spontaneous abortion and in fecundity" (1986, p. 34).

Thus there is some evidence for an association between reduced completed family size and sharing of immunoglobulin markers in population samples representing larger families. In this study we present data from a Mennonite sample not chosen for family size. A segregation analysis was performed to test whether a fetus identical with the mother for both GM haplotypes is at a selective disadvantage compared to a fetus that shares only one haplotype with the mother.

Methods and Materials

The populations studied consisted of one sample of Mennonite couples with mothers older than 40 years (women born before 1941) and a sample of mixed Caucasian matings and offspring. The 242 Mennonite couples represent the communities of Goessel and Meridian, Kansas, and Henderson, Nebraska, and were recruited during an interdisciplinary aging study (Crawford and Rogers 1982). There are no significant differences among the communities for completed family size (Stevenson et al. 1989). The second sample consisted of 923 matings (in which at least one parent is heterozygous) ascertained from 268 paternity studies and 221 family studies of various diseases (not selected for family size). The offspring of the Mennonite couples had not been allotyped and were not included in the segregation analysis. All samples were tested minimally for G1M (A, F, and X) and G3M (B0, B1, B3, B5, G) using previously described methods (Schanfield et al. 1975). The nomenclature used for immunoglobulin allotypes is consistent with the recommendations of Shows et al. (1987).

The Mennonite sample was divided into three groups of matings based on how many haplotypes were shared. There are three GM haplotypes common to European Caucasians: *IGHG1*A G3*G*, *IGHG1*A,X G3*G*, and *IGHG1*F G3*B* (Steinberg and Cook 1981). Each person carries two haplotypes. Thus "zero haplotypes shared" means that the

parents do not share any one of the three haplotypes, and "one (two) haplotypes shared" means that they share one (two) of the three haplotypes.

Weitkamp and colleagues (Ober et al. 1986; Weitkamp 1986; Weitkamp et al. 1986) recognized two subdivisions for GM matings: "like" versus "unlike." Their category of like matings corresponds to two haplotypes shared, because all other matings are phenotypically unlike. The distinctions used here are more consistent with the recent HLA studies in which subdivisions of matings are based on 0, 1, or 2+ antigens shared (Ober et al. 1985; Ober, Elias, O'Brien et al. 1988; Ober, Elias, Hauck et al. 1988).

Distributions of completed family sizes were checked for skewness and kurtosis, and an analysis of variance was performed.

Life table analyses provide another means of comparing the effects of shared haplotypes on mean completed family size (Anderson et al. 1980, pp. 199–234; Cox 1972). Reproductive outcome was assessed indirectly by estimates of the length of the interval from first birth to each successive birth. Time from year of first birth was used rather than from date of marriage because there was no information on the date of marriage for the women of the Meridian and Goessel congregations. Couples were considered to be at risk from the time of the first birth through the time of menopause (or the surgically induced end of the fertility period). The log-rank test was used to compare the time-to-next-birth curves.

The distribution of offspring from various kinds of matings formed the basis of a segregation analysis. Ratios based on Mendelian inheritance were used to predict expected frequencies of offspring; these ratios were then compared in a chi-square analysis to actual distributions of phenotypes in the offspring.

A minor adjustment was made for phenotype GM A,X G. The phenotype GM A,X G consists of two genotypes (*IGHG1*A G3*G/G1*A,X G3*G* and *IGHG1*A,X G3*G/G1*A,X G3*G*). Therefore the transmission likelihood for the *IGHG1*A,X G3*G* allele will be greater than 0.5. The estimate of the transmission likelihood can be calculated using the expected values from the Hardy-Weinberg equation. The formula for the calculation of the probability of transmission for ambiguous situations is

$$t = [(^*A, XGHt/^*A, XGT) \times 0.5] + [(^*A, XGHm/^*A, XGT) \times 1.0], \quad (1)$$

where $^*A, XGHt$ is the Hardy-Weinberg estimate of the frequency of heterozygous $^*A, XG$, $^*A, XGHm$ is the Hardy-Weinberg estimate of the frequency of homozygous $^*A, XG$, and $^*A, XGT$ is the sum of het-

Table 1. **Summary Statistics for Completed Family Size**

Completed Family Size	*Number of Halotypes Shared*						*Totals*	
	0	*%*	*1*	*%*	*2*	*%*		
0	3	0.130	9	0.070	6	0.066	18	0.074
1	0	0	5	0.039	4	0.044	9	0.037
2	4	0.174	12	0.094	11	0.121	27	0.112
3	5	0.217	38	0.297	26	0.286	69	0.285
4	4	0.174	39	0.305	30	0.330	73	0.302
5	4	0.174	16	0.125	5	0.055	25	0.103
6	3	0.130	4	0.031	6	0.066	13	0.054
7	0	0	1	0.008	2	0.022	3	0.012
8	0	0	2	0.016	1	0.011	3	0.012
9	0	0	2	0.016	0	0	2	0.008
N	23	0.999	128	1.001	31	1.001	242	0.999
Mean number of offspring	3.348 ± 1.849		3.469 ± 1.688		3.374 ± 1.596		3.421 ± 1.664	
Median number of offspring	3		3.5		3		3	
Modal number of offspring	3		4		4		4	
Skewness	−0.374 ± 0.481		0.339 ± 0.214		0.051 ± 0.253		0.160 ± 0.156	
Kurtosis	−0.549 ± 0.935		1.678 ± 0.425		0.690 ± 0.500		1.057 ± 0.312	

erozygous and homozygous frequencies. The probability of transmission estimated using US white frequencies (Dykes 1982) is 0.5995.

Results

The distribution of completed family sizes for the total Mennonite sample and for the three subgroups of the Mennonite sample are presented in Table 1. Completed family sizes for the total sample range from 0 to 9 with a mean of 3.42 ($\pm\sigma$, $\sigma = 1.66$), a median of 3, and a mode of 4 children. The distribution is leptokurtic. The three subgroups consist of 23, 128, and 91 families for 0, 1, and 2 haplotypes shared, respectively, with corresponding mean completed family sizes of 3.35 ± 1.85, 3.47 ± 1.69, and 3.37 ± 1.60. The variances of the three subgroups are not significantly different (Bartlett's Box $F = 0.361$, $p = 0.697$; Cochrane's $C = 0.380$, $p \cong 0.414$).

Analysis of variance was performed to determine the effects of shared haplotypes on completed family size, and the results are presented in Table 2. The low F value (0.145) shows that mean completed family size does not vary significantly ($p = 0.865$) among the subgroups.

The results of the birth interval analyses are presented in Table 3.

Table 2. **Analysis of Variance: Completed Family Size by Haplotype Subgroup**

Source	*Sum of Squares*	*Degrees of Freedom*	*Mean Squares*	*F Ratio*	*F Probability*
Total	664.847	241			
Between groups	0.806	2	0.403	0.145	0.865
Within groups	664.041	239	2.778		

Table 3. **Intervals (Years) from First Birth to Successive Births (Upper Quartile)**[a]

Parity	*Haplotype Subgroups* 0	1	2	*Chi-Square Value*	*Degrees of Freedom*	*Probability*
2	4.08	4.03	3.67	0.465	2	$0.75 < p < 0.90$
3	8.25	8.05	8.50	0.929	2	$0.75 < p < 0.90$
4	11.75	12.20	13.25	0.093	2	$0.95 < p < 0.975$

a. Upper quartiles: 75% of couples completed the interval from first birth to this birth within the time period (number of years). Upper quartiles are estimated from time-to-birth curves generated from survival analysis; *P* values (two-tailed) are based on the log-rank test and compare the full time-to-birth curves for each parity.

The length of the interval from the first to the fourth birth does increase slightly, as seen in Figure 1. However, the length of the intervals from first birth to second, first to third, and first to fourth were not significantly different for any of the three subgroups.

The results of the segregation analyses are presented in Table 4. There are two statistically significant deviations from Mendelian expectations. Mothers with phenotype GM F B mated to fathers with phenotype GM A,X G have a slight excess of GM A,F,X,Z B,G and slight deficiency of GM A,F B,G phenotypes in the offspring. This is most likely an artifact of the fact that the GM A,X G phenotype is a combination of two genotypes, *IGHG1*A, X G3*G/G1*A G3*G* and *IGHG1*A, X G3*G/G1*A, X G3*G*; neither can be distinguished without further pedigree analysis. In addition, mothers with phenotype GM A G mated to fathers with GM A,F B,G produce a slight excess of GM A,F B,G phenotypes and a slight deficiency of GM A G phenotypes in the offspring. Small sample size (28) may account for this discrepancy. This last deviation from Mendelian expectations, if biologically real, would represent low-level selection against the homozygous *IGHG1*A G3*G/G1*A G3*G* genotype. In the 64 matings of mothers with phenotype GM A,F,X B,G with fathers with GM A,F B,G, the results are not statistically significant given four outcomes of equal probability. The chi-square value could also be calculated as a 1:3 ratio of GM

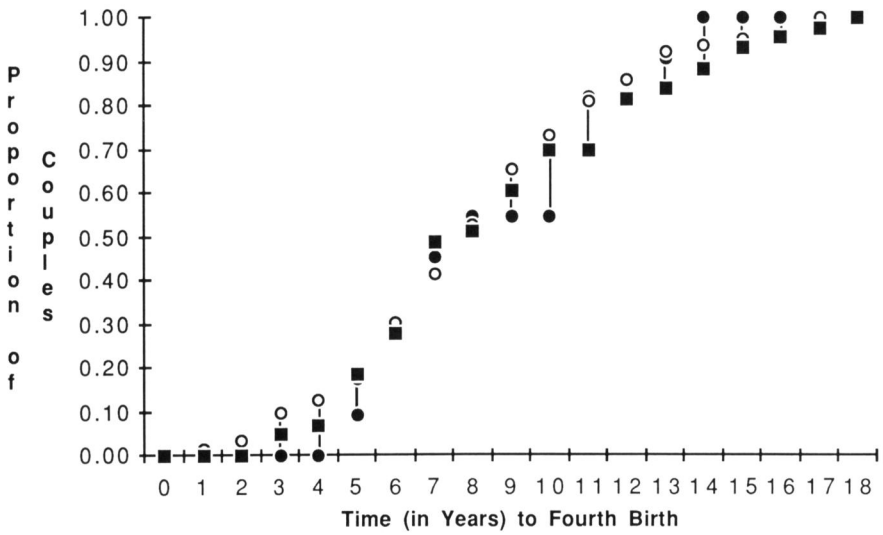

Figure 1. Time to third child by haplotype subgroup. Filled circles, 0 shared haplotypes; open circles, 1 shared haplotype; squares, 2 shared haplotypes.

F B versus the other three phenotypes. Observed (to expected values) of 24 (16):40 (48) result in a chi-square value of 5.33, which for 1 degree of freedom is now significant ($0.2 < p < 0.5$). Thus there is a slight excess of GM F B phenotypes, or in other words, evidence for low-level selection in favor of the *IGHG1*F G3*B/G1*F G3*B* homozygotes.

Discussion and Conclusions

It is HLA or GM compatibility (rather than incompatibility) that is correlated by Weitkamp and colleagues with a reduction in fertility in couples not selected for excessive abortions (Ober et al. 1983, 1986; Weitkamp 1986; Weitkamp et al. 1986) and in couples with abortions (Gill 1983b). It is likely that both immunologic and genetic mechanisms are operating (Gill 1983a; Gill and Repetti 1979; Gill, MacPherson et al. 1987; Hedrick 1988; Hedrick and Thomson 1988; Schacter et al. 1984; Weitkamp et al. 1986). There is growing evidence that histoincompatible fetuses elicit a maternal response to paternal antigens that increases the frequency of successful implantation and may prevent rejection of the implanted ovum (Gill, MacPherson et al. 1987). It is likely that an unidentified class 1 antigen is the primary stimulus in eliciting the immune response to the conceptus, and in humans the antigen is coded by

Table 4. **Segregation Analysis**

	GM Phenotypes of Parents (at least one parent heterozygous)		*GM Phenotypes of Offspring: Observed (Expected)*					
Offspring	*Mother*	*Father*	*F B*	*A,F B,G*	*A,F,X B,G*	*A G*	*A,X G*	χ^2
28	A G	A,F B,G	0	20 (14)	0	8 (14)	0	5.1429*
3	A G	A,F,X B,G	0	1	0	0	2	ID
4	A G	A,X G	0	0	0	2	2	ID
10	A,F B,G	A G	0	4	0	6	0	ID
128	A,F B,G	A,F B,G	33 (32)	65 (64)	0	30 (32)	0	0.1719
21	A,F B,G	A,F,X, B,G	5	9	6	0	1	ID
22	A,F B,G	A,X G	0	7	4	4	7	ID
152	A,F B,G	F B	79 (76)	73 (76)	0	0	0	0.2368
2	A,F,X B,G	A G	0	0	0	0	2	ID
64	A,F,X B,G	A,F B,G	24 (16)	14 (16)	13 (16)	0	13 (16)	5.3750
42	A,F,X B,G	A,F,X B,G	10 (10.5)	0	24 (21)	0	8 (10.5)	1.0476
17	A,F,X B,G	A,X G	2 (4.25)	0	8 (4.25)	0	7 (8.5)	4.7647
102	A,F,X B,G	F B	49 (51)	53 (51)	0	0	0	0.1569
6	A,X G	A G	0	0	0	4	2	ID
16	A,X G	A,F B,G	0	5	6	2	3	ID
16	A,X G	A,F,X B,G	0	4	4	0	8	ID
6	A,X G	A,X G	0	0	0	3	3	ID
40	A,X G	F B	0	16 (16.02)	24 (23.98)	0	0	0.0000
123	F B	A,F B,G	68 (61.5)	55 (61.5)	0	0	0	1.3740
68	F B	A,F,X B,G	30 (34)	0	38 (34)	0	0	0.9412
53	F B	A,X G	0	13 (21.2265)	40 (31.7735)	0	0	5.3182*
923			300	339	167	59	58	

ID = Insufficient data.
* $0.02 < P < 0.05$.

gene(s) in the HLA A,B,C region of the major histocompatibility complex (MHC) [Gill 1983b; see also Faulk and McIntyre (1981), Hedrick and Thomson (1988), McIntyre and Faulk (1979, 1982), Ober et al. (1985), Ober, Elias, O'Brien et al. (1988), and Ober, Elias, Hauck et al. (1988)]. In addition, there may be lethal recessive genes (such as the t haplotypes in the mouse and the grc in the rat) epistatically linked to the HLA loci that may come together more frequently in homozygous matings, resulting in increased frequencies of spontaneous abortions (Gill et al. 1983; Gill, Wegmann et al. 1987; Hedrick 1988; Schacter et al. 1984).

Whatever the mechanism(s), there is little evidence here for reduced fertility in matings homozygous for GM haplotypes. Statistically significant differences were not demonstrated among the three subgroups of this study for mean completed family sizes or mean times from first to second, first to third, and first to fourth births. The segregation analysis provided little evidence for statistically significant deviations from Mendelian expectations.

Low-level selection is not ruled out. Birth histories collected from Mennonite women reveal that miscarriages and stillbirths were reported for 22.7%, 20.9%, and 25.3% of women who share 0, 1, and 2 haplotypes, respectively, with their husbands. Plus, the trend to increasing intervals between first and fourth births as the number of haplotypes shared increases, although not statistically significant, is suggestive. Future research should include more information on birth and marriage. More sensitive detection of fetal loss would also be helpful [see Ober, Elias, Hauck et al. (1988)]. Finally, detection may be possible only in large samples or samples consisting primarily of couples who are maximizing family size (e.g., Hutterites).

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