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Intelligence and genetic markers in Chilean children

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Genetic markers and total intelligence quotient (IQ) assessed by WISC (Wechsler Intelligence Scale for Children) were studied in children of both sexes from Santiago, Chile. Heterozygous boys for phosphoglucomutase 1 (PGM) and heterozygous girls for haptoglobin (Hp) had lower IQ than homozygotes. For ABO system, B girls had lower and B boys had higher IQ than children with other ABO phenotypes. These differences were highly significant with the two tailed t'-test (Student's t-test with the Welch-Satterthwaite correction for degrees of freedom), and most of them remained significant after the correction for multiple comparisons. Girls had greater variance of IQ than boys. Relationships between homozygotes and heterozygotes were found in two independent studies. Thus, the genetic relationship found here seems likely to be a true biotic effect.

***Key terms**: genetic markers, heritability, intelligence, non-linear interactions*

INTRODUCTION

Intelligence is a neuropsychic multifactorial quantitative phenotype assessed by psychological tests. One of these test is the WAIS (Wechsler Adult Intelligence Scale) (Mascie-Taylor *et al*, 1985), from which the WISC (Wechsler Intelligence Scale for children) (Plomin *et al*, 1994) was adapted. As any phenotype, its genetic determination can be conceived for the character considered individually or for its population variability. As an individual phenotype, intelligence is determined mostly genetically by the necessary metabolic or neuropsychic structures or functions of the nervous system, whose impairment leads to severe or discrete pathologies with mental retardation: Down syndrome; X-fragile syndrome; amino acid, lipid, organic acid, nucleotide metabolism enzymopathies; other chromosome disorders; dementias; neurodermal syndromes; etc (Caviness, 1994). These monogenic, polygenic or chromosome syndromes occur in low frequency in humans and do not reach the polymorphic level. In normal people, intelligence shows variability produced by environmental or genetic factors within a normal range. The contribution of these factors is assessed by heritability, a population dependent linear variable. The heritability of intelligence has been found to be near 60% (Turner, 1996; Plomin *et al*, 1995), it has increased since the early studies (Plomin, 1989), probably due to improvements and homogenization of the environment. Mascie-Taylor *et al* (1985) found significant associations of IQ with Haptoglobin (Hp) and Kell systems. Heterozygous females for Hp showed lower IQ than homozygous ones. Ashton (1986)

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found higher scores for homozygotes in the Rh, P, Kidd, Hp, group specific component (GC) and phosphoglucomutase (PGM). In both studies several markers were used and complex analyses were performed. Results were considered mostly due to chance, because of multiple comparisons. Plomin *et al* (1994), using a high *vs* low IQ design with many genetic markers, found significant associations with HLA and brain-expressed triplet repeat markers. In 1976, we determined IQ and genetic markers in children who participated in a follow up longitudinal study (Avendaño & Valenzuela, 1988). These data were available in our files and offered an opportunity to analyze their consistence with those previous findings. Also, we can perform new analyses giving more importance to biotic than to statistical designs, so as to decrease epistemic restrictions (Valenzuela, 1994), due to correction for multiple comparisons, or when using linear models to fit non-linear problems (heterozygous *vs* homozygous, males *vs* females). Our data were not taken to study IQ and genetic markers association. IQ was measured to find out the possible cause of school difficulties. Genetic markers were used to estimate ethnic admixture and association with physical developmental patterns. Some ethno-historical and cultural features of the Chilean population are necessary to place this sample into the socioeconomic stratification and environmental *vs* genetic factors IQ debate (Valenzuela, 1988). Chilean people originated mostly from the mixture of European Caucasian males and Amerindian females. Amerindians are Mongolians which separated from Caucasians 45000 years ago (1500 generations). Both branches met again in Chile since 1541, and remained together for near 15 generations. This asymmetric mating yielded: chromosome Y mostly Caucasian; mitochondrial DNA mostly Amerindian; autosome inheritance according to percentages of admixture; and chromosome X more Amerindian than autosomes (Valenzuela, 1975). In 15 generations recurrent crossovers have transformed autosomes and X chromosome in a Caucasian - Amerindian mosaic. Since the origin, a sociogenetic cline was settled, high socioeconomic strata with little or none Amerindian admixture and low strata with 30% or more Amerindian component (Valenzuela, 1984, 1988; Valenzuela *et al*, 1987). This sociogenetic cline is clearly evident for ABO and Rh systems. The A, B (ABO) and d [Rh(-)] alleles were introduced by Europeans. Amerindians have a very low frequency of A and B or lacked of them at all, and they did not have the d allele. Thus, the frequency of A, B and d is higher in the upper socioeconomic strata. In English blood donors, Beardmore and Karimi-Booshehri (1983) found a higher frequency of the A allele in the upper socioeconomic strata, while that of the O allele was higher in the lower strata. Valenzuela and Harb (1977) and Valenzuela *et al* (1987) found the same result in Santiago (Chile). The English authors proposed that the A allele could be related with intellectual abilities and the O allele with manual ones. Valenzuela (1988), in a study that included the present sample of children, showed that the Rh and ABO sociogenetic cline of Chile was partly due to historical and cultural factors, but gene factors should be present to yield a residual non cultural effect for the differential access to strata. However, it was difficult to attribute the heterogeneous gene distribution among socioeconomic strata to different IQ. The present analysis is also an opportunity to test the relationship between some intellectual abilities and the ABO or Rh phenotypes.

SAMPLE AND METHODS

Children were those of the longitudinal study on growth and development performed by Avendaño and Valenzuela (1988). They were near 800 boys and girls from the low and middle-low socioeconomic strata of the Northern Area of Santiago (Chile), taken at random from all children who began their primary school (6 years of age) in 1973. At the third year of study (1976), they and their parents were asked to participate voluntarily in the genetic

markers program and independently into the program that evaluated neuropsychic performance and development.

We used the WISC measurement of IQ normalized for Chilean children to analyze its distribution among sexes and genetic classes. The WISC test allowed us to determine verbal, manual and total IQ's. In this study we shall analyze total IQ and refer to the other components where an important difference was found.

The genetic systems were blood proteins typed by starch gel electrophoresis: **phosphoglucomutase 1** (PGM), with alleles PGM_1^1 and PGM_1^2 and phenotypes 1-1, 1-2, and 2-2; **haptoglobin** (HPG), with alleles Hp^1 and Hp^2 and phenotypes 1-1, 1-2 and 2-2; and **esterase D** (ESD), with alleles *ESD-1*, *ESD-2* and a third one found mostly in Amerindians (W), and phenotypes 1-1, 1-2, 2-2 and W-3 (only heterozygotes); and the **red cell antigenic systems**: **Rh**, **ABO**, **MN** and **Xg**, typed under standardized international procedures. Technical details have been given previously (Valenzuela *et al*, 1982b; Valenzuela *et al*, 1983; Valenzuela *et al*, 1991). Rh was typed with anti-D, anti-C, anti-c, anti-E and anti-e antisera. Eighteen phenotypes are possible. We named them RH1, RH2, RH3, ..., according to published nomenclature (Valenzuela *et al*, 1982a). ABO was typed with anti-A and anti-B; thus phenotypes are AB, A, B and O. MN was typed only with anti-M, which produces phenotypes M(+) and M(-). Xg was typed with anti-Xg^a, yielding phenotypes $Xg^a(+)$ and $Xg^a(-)$.

For ethical reasons, children were free to come for IQ or genetic studies. Then, it is possible that children with scholar problems related to IQ came preferentially to the study, because medical or psychological treatments were given gratuitously. In fact, the IQ of the sample was significantly lower than 100. When children with scholar deficiencies were excluded, the IQ was not different from 100 (Manterola *et al*, 1981). More girls than boys came for blood extraction, and more boys than girls came for neuropsychic examination. At last, 87 boys and 52 girls were studied for IQ and gene markers. These data were recorded in our files and remained there until the present analysis (18 years later).

The unbalanced ANOVA was applied. Since this test is blind for non-linear heterogeneity among sexes or genetic classes, two kinds of two-tailed Student's *t*-tests were applied for comparisons between two independent samples. One of these *t*-tests assumes equal variances and estimates a pooled variance from both samples (it will be denoted ***t***). The other two-tailed *t*-test is for unequal variances, with Welch-Satterthwaite correction for degrees of freedom (***t'***-test in Howell, 1992). The value obtained from *t*-test is exactly equal to that resulting from ANOVA for two samples. The *t'* value is different from the ANOVA value and it may be larger or smaller than the corresponding *t* value. The *t*-test obtains first the pooled variance and then the standard error of the estimate $\{SE^2 = [(s_1^2(n_1-1)+s_2^2(n_2-1))/(n_1+n_2-2)]\ [1/n_1+ 1/n_2]\}$, while the *t'*-test obtains directly the pooled standard error $\{SE^2 = s_1^2/n_1+s_2^2/n_2\}$. It is evident that the *t'*-test inflates significance with small samples, specially when there is only one individual in one of the samples, but the *t*-test decreases significance (power) in the same situation. We first used *t'* probability and then *t* probability when important differences with *t'* were found.

RESULTS

Sample sizes (N), means (M) and standard deviations (SD) of total IQ for boys and girls were (90; 88.5; 13.0) and (53; 83.5; 16.0), respectively. Boys had higher IQ than girls (unbalanced ANOVA or *t* probability: $p_a = p_t = 0.0435$; *t'* probability: $p_{t'} = 0.0566$). Significant interactions for two factors analyses (sex and genetic systems) were found for sex and ABO (ANOVA probability for interaction $p_{aint} = 0.045$), and sex-PGM ($p_{aint} = 0.0426$).

Table I shows the distribution of IQ among Rh, ABO, MN and Xg classes and sexes. Table III presents the *t* and *t'* probabilities for these serological blood systems.

Biol Res 31: 81-92 (1998)

Table I

Total IQ distribution according to sex and Rh, ABO MN and X_g systems

System	Phenotype	Boys			Girls				Total Sample		
		N	M	SD	N	M	SD	$p_{t'}$	N	M	SD
Rh	RH1	1	88.0	0.0	-	-	-	-	1	88.0	0.0
	RH2	-	-	-	1	80.0	0.0	-	1	80.0	0.0
	RH3	27	89.4	15.3	13	88.8	12.6	0.8964	40	89.2	14.3
	RH4	1	82.0	0.0	1	91.0	0.0	-	2	86.5	6.4
	RH5	16	88.8	9.9	14	85.7	22.5	0.6393	30	87.3	16.7
	RH6	21	89.6	13.6	11	78.1	8.7	0.0069	32	85.6	13.1
	RH7	3	84.7	7.1	8	76.3	15.3	0.2441	11	78.5	13.7
	RH8	11	88.9	12.5	1	85.0	-	0.3251	12	88.5	12.0
	RH9	3	90.3	9.0	1	67.0	-	0.0463	4	84.5	13.7
	RH18	4	78.0	6.2	2	83.0	8.5	0.5367	6	79.6	6.6
	p_a		0.8989			0.6553				0.6263	
ABO	AB	5	90.2	9.6	1	102.0	-	0.0515	6	92.1	9.8
	A	33	88.7	14.9	10	85.6	15.2	0.5787	43	87.9	14.8
	B	7	82.4	11.1	4	97.0	9.1	0.0427	11	87.7	14.1
	O	42	89.1	11.4	37	80.2	15.5	0.0054	79	84.9	14.1
	p_a		0.6197			0.1006				0.4815	
MN	MN(+)	75	88.1	11.7	44	83.3	14.9	0.0710	119	86.3	13.1
	M(-)	12	91.1	17.9	8	80.9	20.5	0.2698	20	87.0	19.1
	p_a		0.4573			0.6928				0.8442	
Xg	$Xg^a(+)$	60	88.9	12.9	47	81.6	15.6	0.0112	107	85.7	14.5
	$Xg^a(-)$	27	87.5	12.2	5	95.8	9.4	0.1230	32	88.8	12.0
	p_a		0.6379			0.0521				0.2736	

N = sample size; M = total IQ mean; SD = standard deviation; $p_{t'}$ = two tailed *t'* probability; p_a = unbalanced ANOVA probability

Rh system. The IQ of boys (p_a = 0.90), girls (p_a = 0.66) and the total sample (p_a = 0.63) was distributed homogeneously among phenotypes. RH6 and RH9 boys had higher IQ than RH6 and RH9 girls ($p_{t'}$ = 0.0069 and $p_{t'}$ = 0.0463). The significance of RH6 (t') holds after correcting for 7 possible comparisons (phenotypes). It was evident that RH6 and RH9 showed a bimodal behavior of IQ between sexes; thus, ANOVA is not a valid test.

ABO system. In the total sample (p_a = 0.48), boys (p_a = 0.62) and girls (p_a = 0.10) no significant heterogeneity of IQ was found. The only AB girl had higher IQ than AB boys ($p_{t'}$ = 0.0515). A boys and girls did not differ in IQ ($p_{t'}$ = 0.5787). B girls had higher IQ than boys ($p_{t'}$ = 0.0427) and O boys had higher IQ than girls ($p_{t'}$ = 0.0054). This last result remains significant after multiplying it for 4 (possible comparisons of phenotypes, p = 0.0216).

MN system. No significant heterogeneity of IQ was found in total sample (p_a = 0.84), boys (p_a = 0.46) and girls (p_a = 0.69) samples, nor it was by *t*- or *t'*-tests.

Xg system. No significant ANOVAs were found in total (p_a = 0.27) and boys (p_a = 0.64). Girls showed a weak heterogeneity of IQ (p_a = 0.0521). Xg(+) (hemizygous) boys had higher IQ than Xg(+) (homozygous and heterozygous) girls ($p_{t'}$ =

Table II

Total IQ distribution according to sex and PGM, Hp and Esterase D systems

System	Phenotype	Boys			Girls				Total Sample		
		N	M	SD	N	M	SD	$p_{t'}$	N	M	SD
PGM	1-1	49	90.9	12.0	19	87.2	14.4	0.4311	68	89.8	12.7
	1-2	26	81.7	9.2	27	81.9	16.2	0.9560	53	81.7	13.1
	2-2	11	93.5	17.2	6	74.2	14.7	0.0290	17	86.7	18.5
	p_a		0.0033			0.1817				0.0068	
Hp	1-1	20	88.4	12.0	13	87.2	18.7	0.8394	33	87.8	14.7
	1-2	45	88.0	13.6	33	80.5	14.7	0.0247	78	84.8	14.4
	2-2	15	87.9	14.4	6	92.3	15.1	0.5547	21	89.1	14.3
	p_a		0.9929			0.1657				0.3698	
ESD	1-1	57	89.5	13.8	33	82.7	15.4	0.0402	90	87.0	14.6
	1-2	22	87.2	11.1	12	79.1	12.1	0.0679	34	84.3	11.9
	2-2	1	78.0	-	1	73.0	-	-	2	75.5	3.5
	W-3	6	84.5	6.9	6	93.7	21.6	0.3587	12	89.0	16.0
	p_a		0.6114			0.2695				0.4738	

N = sample size; M = total IQ mean; SD = standard deviation; $p_{t'}$ = two tailed *t'* probability; p_a = unbalanced ANOVA probability

0.0112), while Xg(-) boys (hemizygous) had lower IQ than Xg(-) (homozygous) girls ($p_{t'}$ = 0.1230).

Tables II and IV show a similar analysis of the IQ distribution among PGM, Hp and ESD phenotypes.

Phosphoglucomutase 1 (PGM) system. The IQ was highly heterogeneous in the total sample (p_a = 0.0068) and in boys (p_a = 0.0033), but not in girls (p_a = 0.1817). The IQ heterogeneity of the total and boys samples remains significant after correction by the seven and fourteen possible ANOVAs, respectively (7 markers, 2 sexes; p = 0.0476 and p = 0.0462). The different IQ distribution in boys and girls was evident. While homozygous boys showed higher IQ than heterozygotes, girls showed a cline 1-1 (87), 1-2 (82), 2-2 (74). The difference between sexes was significant in 2-2 phenotype ($p_{t'}$ = 0.029). The *t'*-test showed higher IQ for 1-1 ($p_{t'}$ = 0.0402) boys. Both unique 2-2 boy and girl showed very low IQ's. Boys deviated from Hardy-Weinberg equilibrium (p < 0.025) due to lack of heterozygotes and excess of homozygotes 2-2, while girls showed a non significant excess of heterozygotes, instead. Also, boys had a higher frequency of PGM_1^1 than girls (0.7209 *vs* 0.6250). The lower IQ of girls in relation to boys is statistically and fully explained by this sex dimorphic PGM1 abnormal distribution. These results show an evident association between total IQ and PGM1 genotypes. This association was less significant in verbal and manual IQ, but with the same sex dimorphism.

Haptoglobin system. No significant IQ heterogeneity was found in the total (p_a = 0.37), boys (p_a = 0.993) and girls (p_a = 0.18). Boys fitted significantly near with the linear model (p_a = 0.0071). There was a significant difference between heterozygous boys and girls ($p_{t'}$ = 0.0247). Girls deviated significantly from the Hardy -Weinberg equilibrium due to heterozygotes excess and lack of both homozygotes (p < 0.04), while boys did not show a significant deviation.

Table III

t' (over diagonal) and *t* (under diagonal) probabilities
for paired comparisons of IQ among serological phenotypes

System	Phenotype							
RH					BOYS			
		RH3	RH5	RH6	RH7	RH8	RH9	RH18
	RH3	--------	0.9018	0.9620	0.3877	0.9176	0.8875	0.0194
	RH5	0.9017	--------	0.8372	0.4310	0.9825	0.8113	0.0235
	RH6	0.9626	0.8439	--------	0.3703	0.8852	0.9125	0.0181
	RH7	0.6075	0.5070	0.5520	--------	0.4700	0.4361	0.2491
	RH8	0.9241	0.9817	0.8880	0.5939	--------	0.8346	0.0423
	RH9	0.9218	0.8107	0.9326	0.4451	0.8607	--------	0.1118
	RH18	0.1564	0.0543	0.1123	0.2397	0.1243	0.0829	--------
					GIRLS			
		RH3	RH5	RH6	RH7	RH8	RH9	RH18
	RH3	--------	0.6604	0.0228	0.0727	0.2982	0.00004	0.4654
	RH5	0.6660	--------	0.2618	0.2582	0.9091	0.0083	0.7589
	RH6	0.0267	0.3019	--------	0.7702	0.0251	0.0017	0.5328
	RH7	0.0558	0.3080	0.7482	--------	0.1518	0.1293	0.4391
	RH8	0.7763	0.9765	0.4651	0.6085	--------	--------	0.7955
	RH9	0.1213	0.4364	0.2499	0.5845	--------	--------	0.2288
	RH18	0.5465	0.8722	0.4782	0.5782	0.8792	0.3672	--------
			BOYS				GIRLS		
ABO		AB	A	B	O	AB	A	B	O
	AB	--------	0.7725	0.2204	0.8205	--------	0.0077	0.3521	0.0000
	A	0.8294	--------	0.2256	0.8989	0.3305	--------	0.1106	0.3367
	B	0.2344	0.2986	--------	0.1790	0.6568	0.1917	--------	0.0181
	O	0.8372	0.8955	0.1552	--------	0.1737	0.3317	0.0410	--------
MN			M(+)	M(—)			M(+)	M(—)	
	M(+)		--------	0.5847			--------	0.5847	
	M(—)		0.4486	--------			0.4486	--------	
Xg			$Xg^a(+)$	$Xg^a(-)$			$Xg^a(+)$	$Xg^a(-)$	
	$Xg^a(+)$		--------	0.6287			--------	0.0208	
	$Xg^a(-)$		0.6353	--------			0.0525	--------	

Esterase D system. No significant differences after applying ANOVAs were found in the total sample ($p_a = 0.47$), boys ($p_a = 0.61$) and girls ($p_a = 0.27$).

The comparison between sexes showed a non-linear, non-Gaussian and heteroscedastic behavior of parameters among subsamples. This violation of assumptions does not allow us to apply a formal ANOVA or its application could lead to unreliable results. The comparisons among phenotypes within systems showed the same critical result on ANOVA assumptions. Tables III and IV show *t*- and *t'*-probabilities for paired comparisons between phenotypes of the systems described in Tables I and II, respectively.

Table IV

t' (over diagonal) and *t* (under diagonal) probabilities
for paired comparisons of IQ among blood protein phenotypes

System	Phenotype	Boys			Girls		
PGM		1-1	1-2	2-2	1-1	1-2	2-2
	1-1	--------	0.00045	0.6426	--------	0.2497	0.0902
	1-2	0.0011	--------	0.0527	0.2593	--------	0.2843
	2-2	0.5526	0.0100	--------	0.0675	0.2936	--------
HAPTOGLOBIN		1-1	1-2	2-2	1-1	1-2	2-2
	1-1	--------	0.9059	0.9139	--------	0.2610	0.5369
	1-2	0.9102	--------	0.9814	0.2046	--------	0.1204
	2-2	0.9115	0.9807	--------	0.5674	0.0797	--------

ESD		1-1	1-2	2-2	W-3	1-1	1-2	2-2	W-3
	1-1	--------	0.4455	0.0000	0.1646	--------	0.4210	0.0010	0.2777
	1-2	0.4870	--------	0.0008	0.4743	0.4693	--------	0.1086	0.1676
	2-2	0.4122	0.4267	--------	0.0691	0.5393	0.6376	--------	0.0658
	W-3	0.3870	0.5787	0.4230	--------	0.1386	0.0814	0.4156	--------

Table III shows 4 *t'* and no *t* significant differences in boys, for Rh phenotypes with more than 2 individuals in total. Among 21 possible comparisons, only one is expected to be significant at the 0.05 level. The *t'*-tests showed that RH18 boys had significantly lower IQ's than all the other phenotypes, with the exception of RH7 and RH9. Thus, *t'*-test showed significant IQ heterogeneity among sexes and Rh phenotypes, that remains after the correction for multiple comparisons. The deviation of *t'* towards significant results and that of *t* towards non significant results were evident. Since probabilities of tests are uniformly distributed in the [0-1] interval, the distribution of any set of independent probabilities can be tested. By excluding those probabilities from RH18 boys, a set of 15 independent probabilities can be obtained. It is expected that 7.5 from the 15 probability values would be over 0.5, and that 7.5 values would be under 0.5. Among the 15 *t'* values, 5 were under and 10 over 0.5, a very probable result ($c^2_1 = 1.67$, $p = 0.1967$); while 14 *t* values were over and only one was under 0.5 ($c^2_1 = 11.267$, $p = 0.00079$). Thus, the probabilities distribution of *t* values was abnormal, while *t'* values were in agreement with the expected distribution. Girls showed significant *t'* values between RH3-RH6, RH6-RH8, RH3-RH9, RH5-RH9, RH6-RH9 paired comparisons, and a significant *t* value only in the RH3-RH6 IQ differences. However, only one girl was found in each of the RH8 and RH9 classes; thus, significance in comparisons where RH8 and RH9 were involved should be taken cautiously. With both tests, the RH3 girls had higher IQ than RH7 girls in the limit of the significance level. Thus, also in girls, significance from *t'*-test could remain after correction for multiple comparisons. Table III also shows that B girls had higher IQ than O (homozygous) girls ($p_{t'} = 0.0181$), while B boys had lower IQ than O boys ($p_{t'} = 0.0179$). The order of IQ was different in boys (AB, O, A and B) and girls (AB, B, A and O). Both differences between sexes and between phenotypes showed that the significant interaction between ABO and sex ($p_{aint} = 0.045$) was underestimated. Paired phenotype comparisons showed a significant higher IQ of $Xg^a(-)$ than that of $Xg^a(+)$ girls, with *t*- and *t'*-tests.

Table IV shows that boys with the PGM 1-1 phenotype had higher IQ than 1-2 ones (p_t = 0.0011 and $p_{t'}$ = 0.00045, see Table IV). This significance remains after the correction for 2x3x7 = 42 possible paired comparisons (p = 0.0462 and p = 0.0189 respectively). Girls did not show significant *t* or *t'* values. The comparison of the IQ between homozygous and heterozygous boys was highly significant (p_t = 0.0009 and $p_{t'}$ = 0.0002). This result could not be explained by multiple comparisons. The haptoglobin system did not show significant paired comparisons among phenotypes, and the esterase D system did for *t'* in those comparisons with 2-2 phenotypes in both sexes, probably due to the presence of one 2-2 boy and one 2-2 girl.

Unequal variances. The girls/boys variance ratio was $F = (16/13)^2 = 1.515$, with 52 and 89 degrees of freedom (p = 0.05). Thus, girls showed a larger variance of IQ than boys. As phenotypes are independent one from another, their variance differences can be studied by the sign test. Tables I and II show 21 classes with more than 1 child. There were 16 variances of girls larger than those of boys ($c^2_1 = 5.762$, $p < 0.025$). None of the larger variances of boys was significant; while significant larger variances of girls were found for RH5 ($p < 0.005$), M(+) ($p < 0.05$), PGM 1-2 ($p < 0.005$), Hp 1-1 ($p < 0.05$) and ESD W-3 ($p < 0.01$).

Two factor ANOVA interactions for genetic systems. Significant interactions in the total sample were found for ABO and XG (p_{aint} = 0.0174), and MN and PGM (p_{aint} = 0.0052). The structure of these significant two genetic factors-IQ interactions, according to the sex of the child, is presented in Table V. Sex had given a significant interaction with ABO and PGM

PGM-MN-Sex interactions were mainly due to: i- M(+) girls had a cline in IQ for PGM classes (1-1 > 1-2 > 2-2), but not a lower IQ in heterozygotes as the other three M(+) groups had; ii- M(-) individuals showed an increased difference in IQ between homozygotes and heterozygotes for PGM; iii- M(+), 2-2 girls had a very low IQ with a small variance. The IQ difference between [M(+), 2-2] boys and girls was highly significant ($p_{t'}$ = 0.0069). Within M(+) boys, the significant difference between 1-1 and 1-2 increased ($p_{t'}$ = 0.0016). M(+) 1-1 girls had significant higher IQ than M(+) 2-2 girls ($p_{t'}$ = 0.0037; p_t = 0.0103; they were 0.0902 and 0.0675, respectively, for the total sample of girls, see Table 4). Similarly, M(+) 1-2 girls showed higher IQ than M(+) 2-2 ones ($p_{t'}$ = 0.0217 and p_t = 0.0573 vs 0.2843 and 0.2936 for the total sample). M(+) 2-2 girls had very lower IQ than the unique M(-) 2-2 one ($p_{t'}$ = 0.002, p_t = 0.043). M(-) PGM 2-2 children had higher IQ than M(+) PGM 2-2 ones ($p_{t'}$ = 0.0856, p_t = 0.0272). There was a similar situation in ABO-Xg interactions. The significant interaction was mainly due to: i- very low IQ of Xg(+) O girls; ii- relative high IQ of Xg(+) B girls; iii- high IQ of Xg(-) AB boys and girls; iv- very low IQ of the unique Xg(-) B boy. Among the most significant differences for paired comparisons, we found: Xg(+) O boys had higher IQ than Xg(+) O girls ($p_{t'}$ = 0.0077); Xg(+) B boys had higher IQ than the unique Xg(-) B boy ($p_{t'}$ = 0.0004; p_t = 0.0254); and in the whole sample B Xg(+) individuals had higher IQ than the only B Xg(-) one ($p_{t'}$ = 0.0000054; p_t = 0.0185). However, the most significant disagreement in significance between ANOVA and *t'* or *t* tests was found among ABO phenotypes of the Xg(-) total sample, where the ANOVA probability was weakly significant (p_a = 0.0183). However, all but two of the differences for six paired comparisons were significant: AB-A ($p_{t'}$ = 0.00074; p_t = 0.0228); AB-B ($p_{t'}$ = 0.0331; p_t = 0.0573); AB-O ($p_{t'}$ = 0.0330; p_t = 0.3665); A-B ($p_{t'}$ = 0.000003; p_t = 0.0231); A-O ($p_{t'}$ = 0.0586; p_t = 0.0856); B-O ($p_{t'} < 10^{-7}$; p_t = 0.0294).

DISCUSSION

Ashton (1986) found significant differences between homozygotes and heterozygotes for Rh specificities C and E in Caucasians or Japanese people. We did not. This could be because our Chilean population is a

Table V

Structures of significant two genetic factors - IQ interactions

System	Phenotype	Boys N	Boys M	Boys SD	Girls N	Girls M	Girls SD	$p_{t'}$	Total Sample N	Total Sample M	Total Sample SD
					PGM1 - MN - Sex interactions						
PGM					M(+)						
	1-1	44	91.0	12.1	15	88.7	14.1	0.5780	59	90.4	12.5
	1-2	23	82.1	9.5	24	82.9	14.7	0.8250	47	82.5	12.3
	2-2	7	88.6	10.9	5	69.2	9.3	0.0069	12	80.5	14.0
	p_a		0.0124			0.0352				0.0021	
					M(—)						
	1-1	5	90.0	12.7	4	81.8	16.5	0.4399	9	86.3	14.2
	1-2	3	78.0	7.5	3	73.7	28.5	0.8241	6	75.8	18.8
	2-2	4	102.3	24.3	1	99.0	0.0	0.8035	5	101.6	21.1
	p_a		0.2175			0.6348				0.0768	
					ABO - Xg - Sex interactions						
ABO					Xg^a(+)						
	AB	4	88.3	9.8	-	-	-	--------	4	88.3	9.8
	A	23	90.9	16.7	9	85.0	16.0	0.3681	32	89.2	16.5
	B	6	85.8	7.0	4	97.0	9.1	0.0822	10	90.3	9.4
	O	27	88.1	10.8	34	78.9	15.2	0.0077	61	82.9	14.1
	p_a		0.8123			0.0648				0.1586	
					Xg^a(—)						
	AB	1	98.0	0.0	1	102.0	0.0	--------	2	100.0	2.8
	A	10	83.7	8.1	1	91.0	0.0	0.0191	11	84.4	8.0
	B	1	62.0	0.0	-	-	-	--------	1	62.0	0.0
	O	15	91.1	12.6	3	95.3	12.1	0.6237	18	91.8	12.2
	p_a		0.0510			0.8249				0.0183	

N = sample size; M = total IQ mean; SD = standard deviation; p_a = ANOVA probability; $p_{t'}$ = two tailed *t'* probability.

Caucasian-Amerindian mixture. Thus, if the whole chromosome 1 (where Rh locus is located) rather than the Rh locus is related to IQ, Chilean homozygotes for Rh are highly heterozygous for other chromosome 1 loci. The d, A and B frequencies were higher in boys than in girls, and the O frequency was higher in girls. Thus, the significantly higher Amerindian admixture proportion of girls remains unexplained. In 1980, we proposed selective genetic interactions or consociated chromosome segregation (Valenzuela *et al*, 1980). We assumed that the Y chromosome, mostly from Caucasian origin, could segregate preferentially with other chromosomes from Caucasian origin (9 for ABO and 1 for Rh) at the first meiotic division. The finding by Beardmore and Karimi-Booshehri (1983) of a higher frequency of the A and a lower one of the O alleles in the upper socioeconomic strata, led them to propose a relationship between A and intellectual abilities, and between O and manual abilities. Our children come from the lower socioeconomic strata and showed an interactive sex dimorphism between ABO

and IQ. O boys had higher IQ than O girls while B children showed the reverse relation. Both O boys and girls were not different in IQ from A children. These complex, non-linear associations do not agree with Beardmore and Karimi-Booshehri (1983) proposition on intellectual and manual abilities and ABO phenotypes. Furthermore, our present results make that hypothesis still more difficult, because O boys had a relative high IQ and A girls a relative low IQ. If some genes for IQ are located in the X (Turner, 1996) and Y chromosomes, these associations could be explained. Yet, more interesting, the sociogenetic cline was evident in men but not in women, and the B allele had a random behaviour in Chile and England. The socioeconomic stratum is determined according to power, prestige, occupation, income, source of income, educational level, life style, and other complex variables which are not necessarily related to intelligence. Thus, it is very probable that other psychic factors such as aggressiveness, autonomy, early maturation, power or money need, associated to ABO or Rh could be involved in the maintenance of the cline. Also, we found that B girls had higher IQ than B boys. This is not an isolated sociogenetic or biotic relationship. The B allele showed this dimorphic or irregular behaviour among socioeconomic strata (Beardmore & Karimi-Booshehri, 1983; Valenzuela, 1988). Besides that, among children of the same area and strata, B girls were protected to typhoid fever while B boys showed susceptibility to this disease (Valenzuela & Herrera, 1993). It may be possible that the very low IQ of the B $Xg^a(-)$ boy was due to a sequel of brain infectious disease or high fever episodes (for example, meningitis).

ANOVA or regression analyses: i- are linear, ii- do not consider the structure of data, iii- assume continuity, Gaussianity and homoscedasticity, and iv- include the effects of factors in parameter estimates. They have small epistemic power (Valenzuela, 1994) for uncovering biotic, non-linear, heteroscedastic, non-Gaussian, structured relationships. This low epistemic power was evidenced by the simultaneous *t*- and *t'*-tests of paired subsamples from the total sample upon which the ANOVA was applied (Tables III and IV). Any random division of a sample leads to a reduction in the sample size of subsamples. This reduction increases the standard error of the estimates, which leads to a reduction of the power of tests applied to subsamples. Thus, significance is expected to be decreased when applying tests to subsamples randomly obtained by partitioning the total sample. Tables I and II show the reverse situation. The subdivision in sexes yielded lower ANOVA probabilities in boys or girls for all, but Rh, genetic markers. This is a strong indication of a true interaction between sexes and genetic systems on IQ. This interaction is demonstrated with the *t*- and *t'*-tests. Several significant results with both tests hold even after the correction for multiple comparisons. It is important to remark that the Student's *t*-test is identical to the ANOVA for two samples. The *t'*-test is less sensitive to heteroscedasticity and non-Gaussianity. In our study ANOVA and *t*-tests were applied to the IQ, which was clearly a non-linear, heteroscedastic and non-Gaussian variable (several subsamples showed bimodal behavior between sexes or genetic markers). This mostly explains the different significance obtained after applying ANOVA, *t*- or *t'*-tests. Naturally, cases where *t'* gave significant differences with only one individual in a subsample must be considered cautiously; but, differences continued to be significant without including these cases. Moreover, *t'* probabilities seem to be distributed more "normally" than *t* probabilities, at least for Rh paired comparisons in boys.

We found that children heterozygous for PGM (differences highly significant in boys and total sample) and Hp (differences non significant in girls and total sample) systems had lower IQ than homozygous children. Similar results were found by Mascie-Taylor *et al* (1985) for IQ performance in women, as by Ashton (1986). Our study (Avendaño & Valenzuela, 1988) was initiated previously (1976) than those of Mascie-Taylor *et al* (1985) and Ashton (1986); then, these coincidences

can not be due to chance in multiple comparisons. Moreover, in both systems there are 4 IQ mean structures for homozygotes and heterozygotes, thus, the probability of finding the same structure of IQ in 3 studies and in 2 genetic systems is $(1/4)^6$ or 0.00024. Even though we had found no significant ANOVA or *t* probabilities, this simple coincidence should strongly indicate a true biotic relationship between PGM or Hp and IQ. The hypothesis of a higher IQ in homozygotes seems valid for Xg and chromosome X. These results can be hardly compatible with the hypothesis of genes with linear action for IQ on the X chromosome, as proposed by Turner (1996).

We conclude that there is a true biotic association between these genetic markers and IQ. In summary: i- a highly significant non-linear interactions among sexes and heterozygous or homozygous individuals for PGM1 and Hp loci; ii- a sexual dimorphic behaviour of ABO phenotypes, specially O and B, for IQ; iii- a strong non-linear interaction between PGM1 and MN systems, and between ABO and Xg systems. Such a heterogeneous set of genetic markers-IQ associations does not allow any theoretical interpretation, nor a simple mechanistic explanation. For example, a model based on heterozygote disadvantage should be valid only for males but not for females or *vice-versa*, and depending on the genetic marker.

The above analysis also shows that common ANOVA used with grouped data has a low epistemic and statistical power, because: i- most assumptions such as Gaussianity, independence of classes, homoscedasticity and linearity are violated; ii- the structure of the IQ distribution among classes cannot be taken into account, being one of the main effects of biotic factors. Moreover, our significant differences continued to be so with the correction for multiple comparisons. Furthermore, the random division of the total sample, by sexes or phenotypes, should vanish the significance, because smaller groups are produced. We found the reverse result instead. The last analysis of IQ according to ABO phenotypes with the total Xg(-) sample is conclusive. This finding is practically impossible to be produced by non biotic factors.

Thus, intelligence -as assessed by the WISC- appears mainly determined and influenced by genes, but in a complex non-linear interactive ontogenetic process. It is not possible to assign components of IQ variability either to Caucasians or Amerindians, because all the Chilean chromosomes are ethnic mosaics and contradictory behaviour could be observed with the alleles most frequently found in either group. Nor it is possible to calculate linear heritability. This estimate should be different in males and females and depending on the genetic system. However, the large non-linear genetic determination of intelligence is evident, because standard deviations were 13 (boys) and 16 (girls) and differences in means reached 10 points of IQ, between sexes or phenotypes. Since some heterozygotes had lower IQ and they could associate with better fitness, the population IQ could develop in a balanced polymorphism, and no tendency towards lower or higher IQ could be produced in human evolution. Thus, intelligence appears as a very complex, non-linearly interactive and integrated adaptive multifactorial phenotype, that is also dependent on indirect genetic determination. To take intelligence away from evolutionary and ethno-cultural contexts seems -in our opinion- a misconception and could lead to mistakes or dangerous ideologically biased positions.

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