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Brief Communication

Incidence of Friedreich Ataxia in Italy Estimated from Consanguineous Marriages

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SUMMARY

The frequency of consanguineous marriages up to second-cousin degree has been carefully established in the past for each of the 95 Italian provinces using the Archive of about 500,000 dispensations given by the Catholic church for such marriages over a 55-year period. It has therefore been possible to compare the frequency of consanguineous marriages observed among 83 couples of parents of Friedreich patients with the frequency of consanguineous marriages of the same degree in the different Italian provinces during the same years.

From these data, an estimate of the incidence of the disease has been obtained for the whole nation (between 1/22,000 and 1/25,000). In Southern Italy, where 16 out of the 18 consanguineous marriages among Friedreich parents are concentrated, the incidence of the disease is similar (between 1/25,000 and 1/28,000).

This study indicates that the Archive of consanguinity existing in Italy allows a reliable comparison of the frequency of consanguineous marriages among parents of patients with that of the general population. The same method can therefore be applied to the study of incidence of other autosomal recessive disorders in Italy.

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INTRODUCTION

The frequency of consanguineous marriages (C') expected among parents of children homozygous for a given allele is known to depend on that observed in the general population (C) and on the frequency (q) of the allele [1]. For first-cousin marriages, the value of C' can be calculated using Dahlberg's formula [1]: $C' = [C\ (1 + 15q)]/(C + 16q - Cq)$. According to the relationship just described, an increase of consanguineous marriages among parents of affected children (C') over that observed in the general population is expected for rare autosomal recessive disorders: that is, the rarer the disorder, the higher the proportion of consanguineous marriages. If both C' and C are determined accurately for a given type of consanguineous marriage (e.g., among first cousins), one can estimate the frequency of the allele (q), and therefore of the disease (q^2), according to the following formula [2], derived from [1]: $q = [C(1 - C')]/[C(1 - C') + 16(C' - C)]$. A more general formula, based on the same principle, has been also published in the past [3] and makes use of the estimate of the variance of the inbreeding coefficient: $q = [(\Sigma Ci\ Fi^2 - \alpha^2)/(\alpha' - \alpha)] - \alpha$, where α = average inbreeding coefficient for the general population (defined as $\alpha = \Sigma Ci\ Fi$), C = frequency of consanguineous marriages in the general population, i = degree of consanguinity, F = coefficient of consanguinity, and α' = coefficient of inbreeding in the population of parents of patients (defined as: $\Sigma C'i\ Fi$).

In Italy, the frequency of consanguineous marriages in the general population, up to the second-cousin degree, has been carefully established for 5-year periods and for each of the 95 provinces using dispensations given by the Catholic church, collected in the Archive of consanguineous marriages that lists about 500,000 dispensations according to the alphabetical order of the names of husband and wife [4]. These data cover a 55-year span from 1910 to 1964, and for some regions, even later periods [5]. Since consanguinity varies in space and time, such a fine subdivision of consanguinity data allows an accurate match of the general population with samples of parents of patients originating from different regions of the country. It was therefore possible in this study to assess accurately the ratio C'/C and the gene frequency for Friedreich ataxia in Italy, using data collected from families of patients affected with this autosomal recessive neurological disorder.

Although the molecular defect of Friedreich ataxia is still unknown and no laboratory test can unequivocally confirm the clinical diagnosis, this can be quite reliable if strict criteria are defined for discriminating the disease from other autosomal dominant or recessive spinocerebellar ataxias [6]. We have therefore adopted the criteria reported by Geoffroy et al. [7], described in detail under PATIENTS AND METHODS, in choosing 83 Friedreich patients and have compared the frequency of consanguineous marriages among their parents with that of the general population, divided by year and province of marriage, in order to estimate the incidence of the disease in Italy.

PATIENTS AND METHODS

Each of the 83 probands diagnosed by the different centers that participated in this study was considered affected with "typical" Friedreich ataxia if the diagnosis met the following

criteria [7]: (1) age of onset of ataxia during the first or second decade of life, and not later than 20 years of age; (2) progression without remission of ataxia; (3) dysarthria; (4) areflexia; (5) deep sensory loss; (6) muscle weakness; (7) pes cavus; (8) Babinski sign; (9) cardiomyopathy; and (10) kyphoscoliosis.

Whereas criteria (1)–(6) were required for all patients, (7)–(10) could occasionally be absent. However, since dysarthria and muscle weakness, although very frequent, may develop rather late during the course of the disease [8], these symptoms were not considered indispensable for the diagnosis. In most patients, sensory conduction velocity was studied, and the amplitude of sensory orthodromically evoked responses was found to be severely reduced [9].

The information regarding date and place of marriage of each set of parents was collected through interview of at least one parent on questionnaires distributed to the centers. For 17 probands whose families were not available for interview, the same kind of information was obtained from Municipal Census Offices, and the possibility of parental consanguinity was checked in the Archive. In all cases, the answers given through interviews always corresponded with the information contained in the Archive. In particular, no discrepancies were found between the degree of consanguinity given on questionnaires and that reported in the Archive, nor was consanguinity found for those couples who had considered themselves as nonconsanguineous. Each marriage (either consanguineous or nonconsanguineous) was assigned to a given province for a given 5-year period. Using the corresponding frequencies of consanguineous marriages that had already been calculated for the 95 Italian provinces (G. Zei and A. Moroni, unpublished data, 1982), it was possible to build a control population that matched quite accurately, with respect to time and space, the population of parents of patients. The control frequency computed as a weighted average of consanguinity rates in the general population was obtained according to the following formula: $C = (\Sigma Cij\ Mij)/\Sigma Mij$, where Cij = the frequency of consanguineous marriages of a given degree for each province (i) and for each 5-year period (j); Mij = the number of marriages among parents of patients in the province i for each 5-year period; and ΣMij = total number of marriages among parents of patients. Using the same questionnaires, information regarding the sibs of the probands, both affected and nonaffected, were also collected and used for the analysis of segregation of the disease as reported in the APPENDIX. Since a diagnosis of Friedreich ataxia is rarely made before age 10, at least in Italy, only sibs older than 10 were taken into consideration for segregation analysis.

RESULTS

The marriages of the 83 couples of parents of Friedreich patients were assigned to their corresponding provinces of birth when both parents originated from the same province, which occurred in 73 out of 83 couples (88%). When the birthplaces of the parents were located in different provinces, their marriage was assigned to the province that corresponded to the proband's birthplace. This corresponded for four probands (or about 5% of the total) to the mother's birthplace and for two other probands to the father's birthplace. Only in four cases did the proband's birthplace differ from those of origin of either parent. This system of assignment of marriages allows the use of a control weighted average of consanguineous marriages calculated for 5-year periods from data obtained from the Archive of consanguinity, as described under PATIENTS AND METHODS. Among 83 couples, the frequency of first-cousin marriages was 14.5% (see value of C' in table 1), and the corresponding weighted national average for the same degree of consanguineous marriages was 1.62%. These results show an increase of about ninefold in consanguinity among parents of Friedreich patients with respect to the general population. Using the first equation given in the INTRODUCTION for first-cousin marriages, the incidence of the disease in Italy (q^2) can be calculated as 1/22,206.

TABLE 1

REGIONS OF ASSIGNMENT OF MARRIAGES AND NO. CONSANGUINEOUS MARRIAGES

	TOTAL MARRIAGES							CONSANGUINEOUS MARRIAGES		
(a) REGION	(b) No.	(c) Mean yr (± SEM)	(d)	(e)	(f)	(g)	(h)	First cousins	Second cousins	First cousins once removed
Campania	46	1948.1 ± 1.50	46	45	44	2	...	7	3	2
Puglia	8	1943 ± 4.26	6	3	...	8	...	2	...	...
Sicilia	6	1956 ± 5.69	5	3	...	6*	...	2	...	...
Calabria	1	1915	1	1	...	1	...	...	...	...
Southern Italy (total)	61	1947.7† ± 1.51	58	52	44	17*	...	11	3	2
Abruzzo	2	1946.5 ± 12.49	...	1	...	...	2	...	...	...
Umbria	1	1918	1	1	...	...	1	...	...	...
Marche	2	1939 ± 15.99	2	2	2	...	...	1	...	...
Central Italy (total)	5	1937.8 ± 8.28	3	4	2	...	3	1	...	...
Lombardia	6	1957.8 ± 4.00	6	6	6	...	...	...	1	...
Piemonte	3	1958.7 ± 2.18	3	3	...	...	3	...	...	...
Liguria	1	1961	1	...	...	...	1	...	...	...
Veneto	3	1952 ± 1.73	1	1	...	...	3	...	...	...
Emilia	4	1946.3 ± 6.60	4	4	3	...	1	...	...	...
Northern Italy (total)	17	1954.4† ± 2.45	15	14	9	...	8	...	1	...
Total	83	1948 ± 1.45	76	70	55	17	11	12	4	2

NOTE: (a) Regions to which marriages were assigned. Each of 20 Italian regions includes, on average, five provinces; (b) total number of marriages assigned to each region according to criteria described under RESULTS; (c) average yr of celebration ± SEM; (d) total no. patients born in the same region of column (a); (e) total no. patients living in the same region of column (a); (f) total no. patients diagnosed in the same region of column (a); (g) total no. patients from the South diagnosed in the North; (h) total no. patients *not* from the South diagnosed in other regions.

Incidence calculated from first-cousin marriages: $C' = 12/83 = 14.5\%$; $C = 1.62\%$; $C'/C = 8.9$; $q^2 = 1/22206$.

Incidence calculated from all consanguineous marriages: $\alpha = 0.00118$; $\alpha' = 0.00979$; $q^2 = 1/25034$.

Incidence for Southern Italy only: $C' = 11/61 = 18.03\%$; $C = 1.98\%$; $C'/C = 9.1$; $q^2 = 1/25449$; $\alpha = 0.00142$; $\alpha' = 0.01203$; $q^2 = 1/28392$.

* One of the six patients from Sicily was diagnosed in Campania.

† The difference between the average yrs of celebration of Southern and Northern Italy is significant (t test = 2.13 with 76 df; $P < .05$).

A similar result is obtained if the more general formula proposed by Barrai et al. [3] is used (table 1). These estimates refer to the whole national territory but do not change significantly if only the 61 marriages assigned to Southern Italy are taken into consideration (table 1). On the other hand, the incidence of the disease in the Northern and Central regions cannot be estimated because of the few marriages assigned to these regions.

The proportion of diagnoses of Friedreich ataxia made in Northern Italy (30 out of 83 or 36%) is higher than the proportion of patients born (14.5%) or the proportion of marriages assigned (16.9%) to the same part of Italy (table 1). Also, all the patients whose parents had been married in Northern Italy were diagnosed in the North, while 16 of the 61 patients from the South (26.2%) were diagnosed in Northern Italy (column (g) of table 1). This can be due, in part, to migration of the families of patients from the South to the North as shown by the comparison of columns (b) and (e) of table 1, which indicates that nine out of 61 patients from the South (14.8%) live now in the North. The remaining seven of the 16 Southern patients (column (g) of table 1) might have been diagnosed in the North for other reasons.

The analysis of segregation performed on the data shown in the APPENDIX yields values of p under single and truncate selection in agreement with autosomal recessive inheritance.

DISCUSSION

The estimate reported in the present study should be considered as a value of incidence at birth of Friedreich ataxia because of the very nature of the method used. This method yields an estimate of gene frequency in the population, independent of the partial ascertainment of patients due to missed diagnoses, which usually cause an underestimate of the prevalence in epidemiological studies of rare diseases. Our estimate of incidence of the disease in Southern Italy is only slightly lower than that obtained for the whole country in spite of the fact that most consanguineous marriages are concentrated in the South (table 1). In fact, the frequency of consanguineous marriages among first cousins (C') increases from 14.5% in the whole sample of Friedreich parents to 18% in the subgroup of parents from the South (table 1). However, the weighted average for first-cousin marriages (C) restricted to the general population of Southern regions is higher than the corresponding national value (1.98% in the South against 1.62% for the whole country). This depends, in general, on the higher frequency of first-cousin marriages in the South and also, in our sample, on the relatively earlier marriages among Friedreich parents (see t test in table 1). The evolution of consanguineous marriages with time is an important source of variation in studies based on consanguinity and, in Italy, there has been a continuous trend toward lower frequencies since World War II [4].

Consanguinity data can also be used to discuss the possible genetic heterogeneity of Friedreich ataxia. This has recently been done using data from Great Britain [10]. In fact, if mutations responsible for Friedreich ataxia occur in more than one gene (or cistron), one would observe more consanguineous marriages among Friedreich parents than those expected from prevalence estimates. In Great Britain

TABLE 2

EXPECTED FREQUENCY OF FIRST-COUSIN MARRIAGES (C') AMONG FRIEDREICH PARENTS FROM SOUTHERN ITALY (CALCULATED FROM DAHLBERG'S FORMULA [1]) BASED ON BIRTH INCIDENCE (DERIVED FROM ESTIMATES OF PREVALENCE) AND COMPARED WITH THE OBSERVED FREQUENCY

a) Prevalence [11]	1.1×10^{-5}
b) Birth incidence (prevalence × 70/30)	2.56×10^{-5}
c) Weighted average for first-cousin marriages for Southern Italy (from table 1)	0.0198
d) Expected frequency of first-cousin marriages among Friedreich parents (from Dahlberg's formula, using values derived from b and c)	0.212
e) Observed frequency of first-cousin marriages among Friedreich parents (from table 1)	0.180

this was the case, with the number of consanguineous marriages observed among Friedreich parents double the number expected. This result would be compatible with the hypothesis of genetic heterogeneity of the disease. The prevalence of the disease has been estimated as 1.1×10^{-5} in the Campania region of Southern Italy [11]. Given a life expectancy of 70 years for the general population and of 30 years for Friedreich patients [6], the estimates of incidence at birth can be approximated as equal to prevalence × 70/30 [10]. The birth incidence thus obtained, together with the weighted average of first-cousin marriages in Southern Italy, has been used to solve Dahlberg's equation and to compute the expected frequency of consanguineous marriages among Friedreich parents (table 2). For Southern Italy, the proportion of consanguineous marriages observed among Friedreich parents (0.180) is slightly lower than the computed C' (0.212). This last observation does not support the hypothesis of genetic heterogeneity of Friedreich ataxia based on the occurrence of mutations in different cistrons that has been proposed [10].

In conclusion, the results of our study confirm that estimates of incidence for autosomal recessive diseases can be obtained in Italy using frequencies of consanguineous marriages, as already done for cystic fibrosis [2] and classic phenylketonuria (G. Romeo et al., manuscript in preparation). This method can therefore yield useful information about the order of magnitude of the incidence of autosomal recessive diseases in Italy, provided that these are single gene Mendelian disorders caused by mutations occurring in the same cistron.

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APPENDIX

SEGREGATION ANALYSIS OF FRIEDREICH ATAXIA IN 71 FAMILIES FOR WHICH RELIABLE INFORMATION ON AFFECTED AND UNAFFECTED CHILDREN WERE AVAILABLE

	r				
s	1	2	3	4	TOTAL
1	7	...	...	...	7
2	11	4	...	...	15
3	16	5	1	...	22
4	8	1	1	...	10
5	4	2	1	...	7
6	1	2	...	...	3
7	1	...	2	...	3
8	2	1	...	...	3
9	...	...	...	...	...
10	...	...	...	1	1
Total	50	15	5	1	71

NOTE: Only sibs older than 10 were taken into consideration (see PATIENTS AND METHODS). The p values were calculated [12] from the data above. p value under single selection = .156 ± .037; p value under truncate selection = .247 ± .04.