Segregation Analysis of A Large t(21q22q) Family

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Summary. A large family in which a t(21q22q) chromosome is segregating is described. Segregation analysis using data from this family and previously published families shows the risk to a female carrier of having a child with translocation Down's syndrome to be 0.0684 ± 0.0270 . The risk to a male carrier is probably much smaller with an upper limit of 0.0286. The segregation ratio for phenotypically normal offspring of carrier parents of both sexes is 0.5053 ± 0.0524 .

Familial t(21q22q) Down's syndrome (DS) is the least common type of Robertsonian translocation Down's syndrome (TDS). In the combined data accumulated by Mikkelsen (1971) and Matsunaga and Tonomura (1972/73), 5% of a total of 4330 DS cases had a Robertsonian translocation. The (Dq21q) translocation was slightly the more common, occurring in 55.3% of all TDS cases; of these 45.0% were known to be familial. (Gq21q) translocations were present in 44.7% of the TDS cases, but only 8.2% of these were familial.

Stene (1970) has published a segregation analysis of the offspring of t(21q22q) carriers from the data he was able to accumulate at the time. Information was available from only eight families, some of them small. We have recently investigated a large New Zealand family in which a t(21q22q) chromosome is segregating. We have added the data from this family to those assembled by Stene to produce a more precise segregation analysis.

The Family

The family (Fig. 1) was ascertained through two propositi. A preliminary report is appearing as part of a survey of Down's syndrome in New Zealand (Gardner *et al.*, 1973). The first propositus (V.172) was born in 1964 in Auckland and chromosome analysis was done at seven months of age because of uncertainty of the clinical diagnosis of Down's syndrome. The mother, the maternal grandmother, and a sister were shown to be t(21q22q)

carriers at that time. The second propositus (V.16) was born in 1954, and was karyotyped in 1968 during a survey of all clinically diagnosed cases of Down's syndrome in institutions for the retarded in the Nelson area. Subsequently, it was discovered that a first cousin was recorded in the hospital notes as having Down's syndrome. The mother was shown to be a t(21q22q) carrier at that time.

A full investigation of these 'two' families was begun in 1971. The 82-year-old great-aunt (III.35) of the first propositus, reputed to be a reliable repository of family facts, was interrogated in order to put together a full family tree. She provided the link between the two branches of the family; she knew that her cousin's grandson (the second propositus, V.16) had Down's syndrome, having nursed him several years previously. No one else in either branch of the family had known that Down's syndrome had occurred in the other branch.

The great-great-grandparents (I.1 and I.2) of the propositi had emigrated to New Zealand from Ireland in the middle of last century. Nine of their children (born between 1846 and 1870), and subsequently most of their descendants remained in New Zealand. No further cases of Down's syndrome were found in the two branches of the family initially investigated; and no cases of Down's syndrome were known to several family members interrogated in other branches. Almost all of the living descendants of II.11 were karyotyped. Unfortunately, we were not permitted to approach the near family of the second propositus (V.16). We did, however, arrange for his Down's syndrome cousin (V.3) to be karyotyped; she was shown to have (21q22q) TDS. In the unaffected branches of the family we were able to karyotype one of the offspring of II.3, six of II.8, one of II.12, one of III.1, and two of III.2. All had normal chromosomes.

Especially as no other carrier branch was found, we had to consider the possibility that a common ancestor other than I.1 or I.2 might have been the original translocation carrier. The parents of II.5, and I.1 and I.2,

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FIG. 1. Family pedigree.

came from adjacent counties in southern Ireland. The parents of II.10 came from northern Ireland and Scotland. These six had no surnames in common. Although it would seem that II.4 and II.11 are much more likely than their spouses to have been carriers, we have felt obliged to exclude them from the present analysis. We have accepted without question that III.31 and IV.42 were carriers.

Except for the descendants of III.13 (who are in Australia) all pregnancies proceeding to term in the two affected branches are believed to have been recorded. There were two stillbirths, one perinatal death, and two infant deaths. V.146 was stillborn two weeks post mature. Necropsy examination revealed no congenital malformations. V.167 was stillborn at 32 weeks following a toxæmic episode. V.4 died shortly after birth, apparently from cord compression. IV.114 died in 1929 at 2½ years from pneumonia. His mother states he had been a normal child; nevertheless, we have excluded him from this analysis. V.162 died suddenly at 5 months. Photographs reveal no stigmata of Down's syndrome, and this case has therefore been included as a phenotypically normal individual. V.164 and V.165 are twin girls of very similar appearance and of the same genotype for several blood markers (A, R₂R₂, MM, Ss, P+, Kell-, Fy^{a+b+}, Jk^{a+}, Lu^{a-b+}, Xg^{a+}, Hp 1-1, Gc 1-1, Ph.Glu.Mut. 2-1, Ad. Kinase 1-1). They are therefore taken to be monozygous, and have been treated as one individual.

Segregation Analysis

The statistical analysis of the data from our family and from the literature has been carried out using methods devised by Stene (1969/1970a and b). These are small sample procedures based on different types of binomial and hypergeometric distributions. Certain assumptions about the mode of ascertainment of the material are made—in particular, it is assumed that the probability model is effectively the same as if we had complete selection. Estimation procedures are performed after two sets of hypotheses have been tested, one relating to the risk of a carrier producing offspring with Down's syndrome and the second to the chance of a phenotypically normal child of a carrier being himself a carrier. Each procedure is halted if a hypothesis is rejected. For the segregation into Down's syndrome offspring and phenotypically normal individuals the hypotheses are: (1) The segregation ratio is the same for all carrier parents of the same sex in the same generation of each family. (2) The segregation ratio is the same for carrier parents of the same sex in all generations of each family. (3) The segregation ratio is the same for carrier parents of the same sex in all families. (4) The segregation ratio is the same for carrier males and females.

Significance levels are set so that the overall level

of significance for the four tests is 0.05. Stene has chosen 0.01 for the first three hypotheses, and 0.02 for the fourth.

The data to be analysed are set out in Tables I and II, and the results in Tables III and IV. These tables correspond to those in Stene (1970). In Tables I and II we have listed only the totals for the families analysed by Stene. It can be seen that there is no heterogeneity within our family for the offspring of female carriers and no heterogeneity between families. The offspring of male carriers cannot be tested as all the Down's syndrome cases have been propositi. A significant difference in the segregation ratio between the sexes cannot be detected in the present data. We estimate the segregation ratio in the offspring of female carriers to be 0.0684 (SE = 0.0270). No estimate for male carriers is possible, but an upper limit may be set at 2/70 or 0.0286 (the number of Down's syndrome offspring over the total number of offspring).

The analysis for the segregation into carriers and karyotypically normal among the phenotypically normal offspring is carried out in an analogous manner. The hypotheses to be tested are as follows: (1) Equal segregation ratio for carriers of the one sex in the one family. (2) Equal segregation ratio for carriers of the one sex in all families. (3) Equal segregation ratio for male and female carriers. (4) The overall segregation ratio is equal to 0.5.

The results are set out in Tables V and VI. The levels of significance are 0.05 overall and 0.01 for hypotheses 2, 3, and 4. There is no heterogeneity detected within our family or between all the families. Neither is there a significant difference in the segregation ratios for males and females, although the probability level is nearer the chosen level of significance. The chance of a phenotypically normal child of a carrier parent being himself a carrier is estimated to be 0.5053 (SE = 0.0524). This does not differ significantly from the predicted value of 0.5.

Discussion

From the point of view of the genetic counsellor, the most useful information we have derived concerns the risk to a t(21q22q) carrier parent of having a child with Down's syndrome. Our results, as presently interpreted, do not show a significant difference between male and female carriers. They are, however, close to the chosen level of significance, and closer than Stene's. Further data may well demonstrate the difference to be significant. Drawing on what is known of t(Dq21q) carriers, one would predict that this will indeed be the case.

TABLE I
THE OFFSPRING OF FEMALE CARRIERS

References*	Generation and Number	M	PN	T	KN	MP	TP
Jackson and Ashford (1967)	Total	2	4	1	3	1	0
Mikkelsen and Niebuhr (1970)	Total	0	6	5	1	0	0
Pfeiffer (1963)	Total	1	2	1	1	1	0
Scheibenreiter <i>et al</i> (1969)	Total	1	1	1	0	1	0
Shaw (1962)	Total	1	3	3	0	1	0
Yang and Rosenberg (1969)	Total	2	19	12	4	1	1
Yunis <i>et al</i> (1965)	Total	2	2	1	1	1	1
Present series and Gardner <i>et al</i> (1973)	III.32	0	4	2	2	0	0
	III.36	0	2	2	0	0	1
	IV.42	1	6	0	0	0	0
	IV.45	1	5	0	0	1	0
	IV.104	0	4	1	1	0	0
	IV.115	0	1	0	1	0	0
	IV.116	0	4	1	2	0	0
	IV.128	1	2	1	1	1	0
	Total	3	28	7	7	2	1
Grand total		12	65	31	17	8	3

* These papers are all cited in Stene (1970).

Key to Tables I and II

M = The known total number of DS individuals in the sibship.

PN = The total number of phenotypically normal individuals and individuals who are not diagnosed as DS, in the sibship.

T = Total number of cytogenetically investigated, phenotypically normal translocation carriers in the sibship.

KN = Number of cytogenetically investigated karyotypically normal individuals in the sibship.

MP = Number of DS propositi in the sibship.

TP = Number of translocation carrier propositi in the sibship.

TABLE II
THE OFFSPRING OF MALE CARRIERS

References*	Generation and Number	M	PN	T	KN	MP	TP
Jackson and Ashford (1967)	Total	0	5	2	2	0	1
Mikkelsen and Niebuhr (1970)	Total	1	18	6	10	1	1
Pfeiffer (1963)	Total	0	7	2	1	0	1
Shaw (1962)	Total	1	13	5	7	1	2
Yang and Rosenberg (1969)	Total	0	4	3	1	0	0
Present series	III.16	0	4	1	0	0	1
	III.31	0	13	4	8	0	0
	IV.105	0	3	2	1	0	0
	IV.127	0	1	1	0	0	0
	Total	0	21	8	9	0	1
Grand total		2	68	26	30	2	6

* These papers are all cited in Stene (1970).

TABLE III
TEST RESULTS FOR SEGREGATION OF DS
INDIVIDUALS IN OUR FAMILY

	No. of Sibships	Probability of Heterogeneity	
		Within Last Generation	Between the Last Two Generations
Probability for females	6	1.0000	0.7647

TABLE IV
SEGREGATION OF DS INDIVIDUALS IN ALL
FAMILIES

Hypothesis to be Tested	Test Statistic (Z_0)	$P(Z \geq Z_0)$	Result
Equal segregation ratio in all families in the offspring of female carriers	8.9228	0.2608	Non-rejection
Equal segregation ratio in the offspring of female carriers and of male carriers	—	0.0567	Non-rejection

TABLE V
ANALYSIS OF THE SEGREGATION INTO CARRIERS
AND NORMAL WITHIN OUR FAMILY

Sex of Carrier Parent	Z_0	$P(Z \geq Z_0)^*$
Female	2.2698	0.9580
Male	1.7778	0.7033

* Probability of this degree of heterogeneity or more.

TABLE VI
ANALYSIS OF SEGREGATION INTO CARRIERS AND
NORMAL IN ALL FAMILIES

Hypothesis to be Tested	Z_0	$P(Z \geq Z_0)$	Result
Equal segregation in all families in the offspring of female carriers	9.9137	0.17	Non-rejection
Equal segregation in all families in the offspring of male carriers	2.9688	0.75	Non-rejection
Equal segregation in the offspring of male and female carriers	4.6789	0.04	Non-rejection

On this basis, it is reasonable to consider the risk figures derived for each sex separately to be valid. In the case of females, we have somewhat lowered the figure derived by Stene, and have narrowed the confidence limits. Stene's figure was 0.0887 ± 0.0402 ; ours is 0.0684 ± 0.0270 . This risk is slightly (but not significantly) less than in the case of female t(Dq21q) carriers (Stene, 1970/1971). Except for two probands, none of the 70 children of carrier fathers had Down's syndrome; the risk may therefore be taken to be small, with an upper limit of 0.0286.

The combined data confirm that of the phenotypically normal offspring of both male and female carriers, half will themselves be carriers, and half

will have normal chromosomes. This is the same as with t(Dq21q) carriers (Stene, 1970/1971).

Addendum

Since submitting this paper, two more family members have had their chromosomes analysed. V.145 is a balanced translocation carrier and V.147 has a normal karyotype.

The first proband was examined by Dr D. M. O. Becroft of the Princess Mary Hospital for Children, Auckland, and the second by Mrs Jennifer R. Eiby of Nelson Hospital. Chromosomal analyses on other family members were done by Dr P. H. Fitzgerald of Christchurch Hospital, Mr H. E. Hutchings of Palmerston North Hospital, Dr Helen R. McCreanor of Wellington Hospital, Mr M. I. Parslow of the Human Genetics Research Unit, Dunedin, Mr R. L. Shaw of the Princess Mary Hospital for Children, Auckland, Miss S. E. Whyte of the Memorial Hospital, Hastings, and Dr Jennifer Wong of the Waikato Hospital, Hamilton.

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