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Down's syndrome and related abnormalities in an area of high background radiation in coastal Kerala

BOTH point mutations and structural aberrations of chromosomes are induced by ionising radiations, causing genetic variation and abnormalities in man and other organisms. The mutagenic effects are dose dependent and in *Drosophila* a linear relationship between dose and mutation rate has been shown for doses up to 5 R (ref. 1). Although man accumulates approximately 5 R of radiation from the environment in 30 yr of reproductive life, it is not known whether this is of any radiobiological consequence[2]. Nor is it known whether in man there is a threshold phenomenon at low doses (several hundred or thousand mr. per year), although there is greater repair of mutational or pre-mutational damage after low-dose irradiation[3]. In a coastal area of Kerala, South India, the background radiation is 1,500–3,000 mr. yr^{-1} due to the presence of thorium-containing monazite mineral in the soil[4–7] (Fig.1). A survey of the rat population in this area with respect to several measurable and non-measurable traits and of humans with regard to dermatoglyphics and demographic data such as fertility index, sex ratio and infant mortality rate revealed no mutational effects[4,7,8]. During an epidemiological study of nodular lesions of the thyroid in this area[9], we noticed an apparently high prevalence of Down's syndrome and other forms of severe mental retardation[10]. We therefore made a house-to-house survey of developmental abnormalities in this area and in a comparable control area without high background radiation[7] (Fig. 1). We also determined the frequency of chromosome aberrations in a sample of the normal population living in the study and control areas. The observations we report here support the view that radiation-induced genetic anomalies occur with above average frequency in the population living

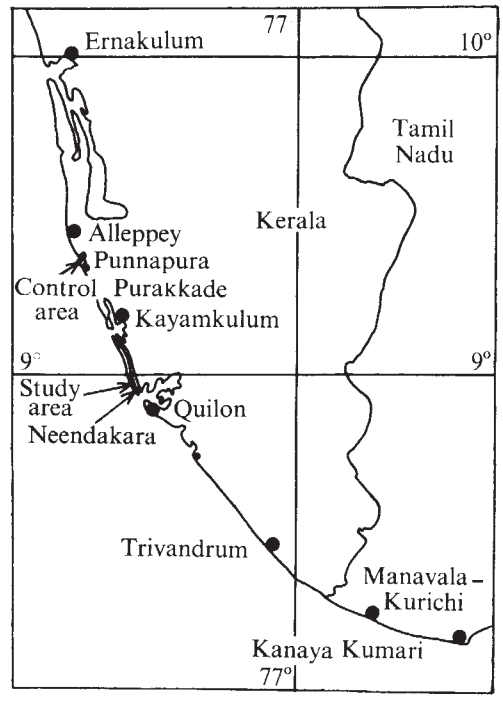

Fig. 1 Map showing the study and control areas.

in the area with high background radiation. The area surveyed was the southernmost one-fifth of the Chavara-Neendakara strip (Fig. 1). In the thatched huts which constitute 75% of all households, the exposure risk is 1,500–3,000 mr. yr^{-1}, and personal exposure, as measured by calcium fluoride dosimeters, closely parallels the exposure risk in the households. The control area consisted of the Purakkade–Punnapura villages, with a background radiation of approximately 100 mr. yr^{-1} (ref. 7). Households were visited repeatedly to ensure examination of all members. Only gross abnormalities evident on clinical examination were recorded. Cytogenetic abnormalities were scored blind on slides prepared from 64-h micro-blood cultures[11].

Demographic and epidemiological details are reported elsewhere[9]. Briefly, the study and control populations were similar in age and sex structure, ethnic composition, living and diet habits, social customs, economic status and occupation. The mean age of all women was 30.3 ± 7.09 yr and 30.12 ± 7.04 yr in the study and control populations, respectively. The frequency distribution by age of women at the birth of the last child was similar in the two populations. The mean family size was 6.2 in the study and 6.4 in the control population. Rate of consanguinity was 12% in the study population and 15% in the control. Abortion rate per 1,000 pregnancies was 109 and 64.5, respectively, in study and control populations ($P > 0.05$), based on a random survey of 57 couples in the study area and 68 couples in the control area.

Table 1 Prevalence of severe mental retardation*

Type	Study population (12,918)		Control population (5,938)	
	Total	Per 1,000	Total	Per 1,000
Genetic				
Down's syndrome	12	0.93	0	0
SMR with physical abnormalities	12	0.93	1	0.17
Idiopathic	11	0.90	3	0.50
Acquired (Perinatal and postnatal)	6	0.46	3	0.50
TOTAL	41	3.1	7	1.16

The definition of severe mental retardation (SMR) is according to the WHO Classification of 1968. Figures in parentheses indicate the total number of persons surveyed.

Severe mental retardation was the commonest developmental abnormality encountered in the study area (Table 1). Clinically, 85% of the abnormalities detected in the study population were "genetic" in origin[10], compared with the 56% in the control population. The frequency of acquired retardation was comparable in the two populations. Prevalence of Down's syndrome was 0.93 per 1,000 in the study population, accounting for a third of the genetic retardations observed, whereas no cases were detected in the control population.

Chromatid and chromosome aberrations were scored in 1,705 metaphases from 46 subjects and in 1,547 metaphases from 39 individuals in the study and control areas, respectively. The mean frequency of aberrations was higher in the study area (chromatid, 3.0 ± 4.6 compared with 1.2 ± 1.9; chromosome, 1.9 ± 3.1 compared with 0.2 ± 0.6). Considering the high variance of mean aberration number, a χ^2 test was applied by grouping the data as shown in Table 2. This revealed no significant difference in chromatid aberrations between the two groups

Table 2 Frequency of cytogenetic aberrations

% Aberrations	Chromatid		Chromosome	
	Study	Control	Study	Control
0	20	23	24	36
1–3	12	11	13	3
>3	14	5	9	0
	$P > 0.05$		$P < 0.01$	

Figures in columns 2–5 give numbers of individuals.
*These were mostly deletions (acentric fragments and minutiae), with few rings and dicentrics.

($P > 0.05$), while the difference in the chromosome aberrations was significant ($P < 0.01$).

The observed frequency of Down's syndrome in the study population (1:1,076) was higher than in the control population ($P < 0.05$), and was significant for the following reasons. (1) Although no data are available on the population frequency of Down's syndrome in India, there are figures for the Eastern counties of England, 1:10,000; London, 1:3,000; Germany, 1:7,000; Denmark, 1:4,000; Australia, 1:2,083, and North-east Scotland, 1:2,000[12,13]. The frequency in Kerala is higher than in any of those (except the Shetland islands, for which the value

Table 3 Frequency of Down's syndrome distributed by maternal age at conception in study area

Maternal age (yr)	No. of females	% of all females	No. of cases	Frequency
20–29	862	13.6	1	1:862
30–39	729	11.5	9	1:81
40–49	532	8.4	2	1:266

Comparative figures for the distribution of females in the control population were: 20–29-yr group, 478 (16.5%); 30–39-yr group, 369 (12.7%); 40–49-yr group, 264 (9.1%). There was no case of Down's syndrome in this population.

is 1:714)[13] although infant mortality is four to five times greater than in these areas. (2) The frequency of Down's syndrome among births in India as a whole is 1:1,215 (ref. 14). In Madras, South India where the people are ethnically closer to those in Kerala, the incidence is lower (1:3,833). The frequency in the general population is expected to be lower than this because of the higher mortality among patients with Down's syndrome[15] while in Kerala the frequency is higher. (3) Most striking is the higher frequency of cases of Down's syndrome born to mothers aged 30–39 yr (Table 3). This figure of 1:81 can be compared with 1:880 and 1:290 for maternal ages of 30–34 yr and 35–39 yr, respectively, calculated by Penrose and Smith[12]. (4) The increase is also evident in a comparison of the proportion of cases of Down's syndrome born to mothers more than 30 yr old in the study area (91%) with that among 615 cases documented in India (51%)[16].

Epidemiological and experimental evidence is accumulating which suggests an association between low dose irradiation of older mothers and non-disjunctional disorders in the offspring[17–19]. The maternal age-dependence suggests that the damaging event accelerates oocyte ageing and causes primary trisomy rather than translocation trisomy which is known to be independent of maternal age[17]. These observations agree remarkably well with our results. In 11 of 12 cases of Down's syndrome maternal age was greater than 30 yr and six of the cases who were successfully karyotyped had trisomy 21. The higher prevalence of chromosome aberrations in apparently normal subjects from the radiation area also supports the view that environmental radiation may be the cause of the genetic damage in the population. Similar cytogenetic findings have been reported from a Brazilian population living in an area of high natural radioactivity[20].

The prevalence of severe mental retardation of genetic origin was four times higher in the study than in the control population, whereas that due to acquired perinatal and postnatal causes is comparable. The nature of the genetic defect remains undetermined in most of these patients, except in the group with Down's syndrome, where trisomy 21 was demonstrated by karyotyping. Mental retardation was associated with different physical abnormalities in 12 patients in the study area. Although karyotyping was not done in these patients, chromosome imbalance is now recognised to be important in the genesis of such syndromes[21,22]. Kirman suggested that a grade of genetic defect intermediate between, on one hand, gross and visible chromosome errors, and, on the other hand, point mutations involving structural changes in the chromosomes, such as inversions and crossovers, may cause idiopathic mental retardation[23]. In view of these possibilities, radiation-induced genetic damage seems likely to be responsible for the high prevalence of mental retardation in the area we studied.

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