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# Genetic Monitoring of the Human Population from High-Level Natural Radiation Areas of Kerala on the Southwest Coast of India. II. Incidence of Numerical and Structural Chromosomal Aberrations in the Lymphocytes of Newborns[1]

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**Cytogenetic studies using cord blood samples from newborns from high-level natural radiation areas of the Kerala coast in Southwest India have been in progress since 1986. A total of 963,940 metaphases from 10,230 newborns have been screened for various types of chromosomal aberrations. Comparison of 8,493 newborns (804,212 cells) from high-level natural radiation areas (dose rate >1.5 mGy/year) and 1,737 newborns (159,728 cells) from normal-level natural radiation areas (≤1.5 mGy/year) did not show any significant difference in the frequency of dicentrics, translocations, inversions or other types of aberrations known to be associated with radiation exposure. The cytogenetic studies were continued for constitutional anomalies using karyotype analysis, and scoring of 16,169 newborns has been completed. The overall frequency of constitutional anomalies was 4.95 ± 0.55 per 1,000 newborns, which is comparable to the incidence reported in the literature. Within the limitations of sample size, the frequencies of total autosomal and sex aneuploids as well as structural anomalies were comparable between the high-level and normal-level natural radiation areas. A striking observation was the presence of rogue cells, the rarely occurring metaphases with a high level of chromosomal damage, which have not been reported previously among newborns.** 

## INTRODUCTION

The coastal areas of Kerala state in Southwest India, which have deposits of radioactive monazite-bearing sand, provide unique opportunities to investigate the effect(s) of high-level natural radiation on various forms of life. This area is densely populated and has been inhabited for over 1,000 years. The radiation levels are high, varying from 1.0 to over 35.0 mGy/year in different areas. Radiation exposure is due to thorium and its decay products emitting α- and β-particle and γ radiation and occurs both externally and internally by inhalation and ingestion (*1–3*). Studies dealing with genetic effects in plants, rodents and humans have been reported (see ref. *4*). Cytogenetic studies were initiated in 1986 to establish the frequency of chromosomal aberrations including constitutional anomalies in the newborn population from high-level natural radiation areas, and the results are reported in this communication.

## MATERIALS AND METHODS

Cord blood samples were collected in sterile heparinized vials from consecutive births at the hospital units in the study areas and were transported to the project laboratory in refrigerated conditions, and cultures were set up the following day. In each culture tube, 0.4 ml of cord blood was grown in 4 ml of Ham's F-10 nutrient mixture supplemented with 5% 200 m*M* L-glutamine. To this, 10% fetal calf serum and 2% phytohemagglutinin were added, and the cells were grown as whole blood cultures (*5*). The cultures were terminated at 48 h by adding 0.04 μg/ml Colcemid to obtain metaphase spreads in the first mitotic division. The coded slides stained with Giemsa (G-banded wherever necessary) were analyzed by a group of five or six cytogeneticists. A total of 10,230 newborns were screened for chromosomal aberrations. An average of 100 cells were analyzed for each sample except in a very few cases. When stability in the frequencies of various types of chromosomal aberrations was reached, the studies were continued to determine the frequency of constitutional anomalies by karyotyping 20 cells per sample. So far, karyotype analysis of 16,169 newborns (including the 10,230 screened for chromosomal aberrations) has been completed. All chromosomal aberrations and constitutional abnormalities were confirmed by at least three cytogeneticists before being recorded. Radiation measurements were taken from all four sides of the households using a radiation meter. The present radiation measurements are in conformity with the detailed dosimetry studies carried out earlier (*1, 2, 6*). The areas up to a dose rate of ≤1.50 mGy/year (average 1.15 mGy/year) were considered as normal-level natural radiation areas and those above 1.50 mGy/year as high-level natural radiation areas (see also ref. *4*).

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**TABLE 1**
**Chromosomal Aberrations in the Lymphocytes of Newborns from High-Level Natural Radiation Areas of the Kerala Coast**

| Types of aberrations | Total | | High-level natural radiation area[a] | | Normal-level natural radiation area[b] | | |
|---|---|---|---|---|---|---|---|
| | No.[d] | Frequency[e] | No. | Frequency | No. | Frequency | RF (95% CI)[c] |
| Dicentrics | 180 | 1.87 ± 0.14 | 150 | 1.87 ± 0.15 | 30 | 1.88 ± 0.34 | 0.99 (0.67–1.47) |
| Translocations | 316 | 3.28 ± 0.18 | 269 | 3.34 ± 0.20 | 47 | 2.94 ± 0.43 | 1.14 (0.83–1.55) |
| Inversions | 14 | 0.15 ± 0.04 | 9 | 0.11 ± 0.04 | 5 | 0.31 ± 0.14 | 0.36 (0.12–1.07) |
| Centric fragments | 17 | 0.18 ± 0.04 | 16 | 0.20 ± 0.05 | 1 | 0.06 ± 0.06 | 3.18 (0.42–23.96) |
| Acentric fragments | 171 | 1.77 ± 0.14 | 133 | 1.65 ± 0.14 | 38 | 2.38 ± 0.39 | 0.70[f] (0.48–1.00) |
| Minutes | 42 | 0.44 ± 0.07 | 35 | 0.44 ± 0.07 | 7 | 0.44 ± 0.17 | 0.99 (0.44–2.24) |
| Multiple aberrations | 15 | 0.16 ± 0.04 | 14 | 0.17 ± 0.05 | 1 | 0.06 ± 0.06 | 2.78 (0.37–21.15) |
| Chromosome breaks | 1,388 | 14.40 ± 0.39 | 1,124 | 13.98 ± 0.42 | 264 | 16.53 ± 1.02 | 0.85[f] (0.74–0.97) |
| Chromosome gaps | 106 | 1.10 ± 0.11 | 82 | 1.02 ± 0.11 | 24 | 1.50 ± 0.31 | 0.68 (0.43–1.07) |
| Chromatid breaks | 471 | 4.89 ± 0.23 | 385 | 4.79 ± 0.24 | 86 | 5.38 ± 0.58 | 0.89 (0.70–1.12) |
| Chromatid gaps | 487 | 5.05 ± 0.23 | 393 | 4.89 ± 0.25 | 94 | 5.89 ± 0.61 | 0.83 (0.66–1.04) |
| Polyploids | 618 | 6.41 ± 0.26 | 525 | 6.53 ± 0.28 | 93 | 5.82 ± 0.60 | 1.12 (0.90–1.40) |
| Endoreduplications | 59 | 0.61 ± 0.08 | 48 | 0.60 ± 0.09 | 11 | 0.69 ± 0.21 | 0.87 (0.45–1.67) |
| Samples (cells analyzed) | 10,230 (963,940) | | 8,493 (804,212) | | 1,737 (159,728) | | |

[a] Overall mean radiation level 4.5 mGy/year (range 1.50 to 37.6 mGy/year).
[b] Mean radiation level 1.15 mGy/year (range 0.87 to 1.42 mGy/year).
[c] RF is statistically significant if CI does not include 1.
[d] Number of events.
[e] Frequency per 10,000 cells; ±SE, assuming Poisson distribution.
[f] Statistically significant at 5%.

For statistical analysis, Poisson distribution was assumed, as chromosomal aberrations are very rare. The relative frequency (RF) with 95% confidence intervals (CI) was used to estimate the statistical significance when comparing chromosomal anomalies (*7*). The relative frequency was considered significant if the CI did not include the value 1, i.e. RF under the null hypothesis of no difference. Stratified analysis was also carried out to determine the influence of possible confounding factors.

## RESULTS

A total of 963,940 metaphases from 10,230 newborns were analyzed for various types of chromosomal aberrations, with 8,493 newborns (804,212 cells) from high-level natural radiation areas (average dose rate 4.5 mGy/year) and 1,737 newborns (159,728 cells) from normal-level natural radiation areas (average dose rate 1.15 mGy/year). Unstable chromosomal aberrations such as dicentrics (with and without fragments), rings, fragments and breaks as well as stable configurations including translocations and inversions were scored from coded slides. The frequency of aberrations per 10,000 cells is reported here. The frequency of dicentrics in the lymphocytes of newborns from the high-level areas was 1.87 ± 0.15 compared to 1.88 ± 0.34 in the normal-level areas (RF 0.99, 95% CI 0.67–1.47), with an overall (pooled) frequency of 1.87 ± 0.14. Only four ring chromosomes were observed, which is a frequency of 0.04 ± 0.02. Stable aberrations had a frequency of 3.46 ± 0.21 in high-level areas and 3.26 ± 0.45 in normal-level areas (RF 1.06, 95% CI 0.79–1.43). The frequency of fragments (centrics, acentrics and minutes) was 2.29 ± 0.17 and 2.88 ± 0.42 in high-level and normal-level areas, respectively. Total chromosome-type aberrations, which included dicentrics, rings, fragments and stable aberrations, were 7.61 ± 0.31 in high-level areas and 8.01 ± 0.71 in normal-level areas (RF 0.95, 95% CI 0.78–1.15). There was no significant difference in aberrations between newborns from high-level and normal-level areas except for chromosomal breaks and acentric fragments considered independently. Other aberrations like gaps, polyploids and endoreduplicated cells also were not significantly different between the two groups (Table 1). The frequencies of dicentrics, stable aberrations and total chromosome-type aberrations were computed for the population groups living in areas with different dose-rate levels (Table 2). No radiation-associated increase, as denoted by the relative frequency, was observed in any of the aberration types among various dose-rate groups compared to the newborns from normal-level natural radiation areas. None of the three categories of aberrations showed any gender-based difference.

An interesting observation was the presence of cells with multiple aberrations, i.e. cells with more than two different exchange-type aberrations. These cells with varying degrees of complex chromosomal rearrangements were seen among 15 newborns, with one cell in each individual, and had a frequency of 1 in 64,263 cells or 1 among 682 newborns. Of these, 11 cells conformed to the classical description of rogue cells, i.e. cells with 5 or more exchange aberrations (*8*). The presence of excess acentrics in the form of double minutes was additional evidence for these cells (*9*). The chromosomal aberrations in the multiple aberrant

**TABLE 2**
**Chromosomal Aberrations in the Lymphocytes of Newborns from Different High-Level Natural Radiation Areas of Kerala Coast**

| Background radiation (mGy/year) | | Samples | Dicentrics[a] | | | Stable aberrations[b] | | | Total chromosomal aberrations[c] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Dose | Mean | (cells) | No. | Frequency | RF (95% CI) | No. | Frequency | RF (95% CI) | No. | Frequency | RF (95% CI) |
| ≤1.50 | (1.15) | 1,737 (159,728) | 30 | 1.88 ± 0.34 | | 52 | 3.26 ± 0.45 | | 128 | 8.01 ± 0.71 | |
| 1.51–3.00 | (1.87) | 5,457 (513,311) | 92 | 1.79 ± 0.19 | 0.95 (0.63–1.44) | 181 | 3.53 ± 0.25 | 1.08 (0.80–1.47) | 389 | 7.50 ± 0.38 | 0.95 (0.77–1.15) |
| 3.01–6.00 | (4.07) | 1,897 (179,162) | 42 | 2.34 ± 0.36 | 1.25 (0.78–1.99) | 58 | 3.24 ± 0.43 | 0.99 (0.68–1.45) | 141 | 7.87 ± 0.66 | 0.98 (0.77–1.25) |
| 6.01–12.00 | (7.47) | 352 (34,464) | 3 | 0.87 ± 0.50 | 0.46 (0.14–1.52) | 11 | 3.19 ± 0.96 | 0.98 (0.51–1.88) | 22 | 6.38 ± 1.36 | 0.80 (0.51–1.25) |
| 12.01–24.00 | (19.05) | 585 (56,866) | 9 | 1.58 ± 0.53 | 0.84 (0.40–1.77) | 22 | 3.87 ± 0.82 | 1.19 (0.72–1.96) | 51 | 8.97 ± 1.26 | 1.12 (0.81–1.55) |
| >24.01 | (31.41) | 202 (20,409) | 4 | 1.96 ± 0.98 | 1.04 (0.37–2.96) | 6 | 2.94 ± 1.20 | 0.90 (0.39–2.10) | 13 | 6.37 ± 1.77 | 0.79 (0.45–1.41) |
| Total | (3.91)[d] | 10,230 (963,940) | 180 | 1.87 ± 0.14 | | 330 | 3.42 ± 0.19 | | 744 | 7.72 ± 0.28 | |

[a] With and without fragments.
[b] Translocations, inversions.
[c] Dicentrics, translocations, inversions, fragments and minutes.
[d] The average radiation dose rate for the population including high and normal radiation areas was 3.91 mGy per year.

cells included quadricentrics, tricentrics, dicentrics, rings, translocations, inversions, fragments and double minutes. In 5 cases of rogue cells, all the chromosome groups appeared to be involved in the formation of abnormal configurations.

Of the 16,169 samples karyotyped for screening constitutional anomalies, 12,496 were from high-level areas and 3,673 from normal-level areas. Eighty newborns with constitutional chromosome anomalies were identified (frequency: 4.95 ± 0.55 per 1,000 newborns), of which 41 were numerical and 39 structural chromosomal variants (Table 3). The numerical variants included 13 cases of Down syndrome, two Patau's syndrome, two Edwards' syndrome, one double aneuploid, four triple X, six Klinefelter's syndrome, three Turner's syndrome, six XYY, and four with additional centric fragments, with an overall frequency of 2.54 ± 0.40 per 1,000 newborns. Structural anomalies (2.41 ± 0.39 per 1,000) included six deletions, eight inversions, eight Robertsonian translocations, and 17 with other translocations. There was no significant difference between high-level and normal-level natural radiation areas in the incidence of constitutional anomalies. Chromosomal polymorphism was observed in 340 cases, which included prominent short arm and satellites in the acrocentric chromosomes and variations in the length of the "q" arm of the Y chromosome, with a frequency of 21.03 ± 1.14 per 1,000 newborns.

## DISCUSSION

There is paucity of information on chromosome aberrations among newborns. An earlier study based on 15,403 cells reported no dicentrics in the newborns (*10*). The present data based on nearly 1,000,000 cells should represent the baseline frequency of various chromosomal aberrations. The frequency of the dicentrics among adults has been reported to range from 4 to 28 per 10,000 cells (*11*). An age-dependent higher frequency of dicentrics has been reported in the population from high-level natural radiation areas of China (*11*). Those authors also found a significant increase in the production of dicentrics as a function of cumulative exposure to high background radiation (*12*). Surprisingly, in the control areas, the frequency of dicentrics did not increase as a function of age, which ranged from 9 to 62 years. Our studies have clearly shown an increase in the frequency of dicentrics as a function of age, ranging from 2 among newborns (present study) to 8–10 among adults (20–40 years) to 18–20 dicentrics per 10,000 cells in the elderly (60–80 years) (unpublished observations). However, an age-dependent increase in unstable chromosomal aberrations was also reported from both high- and normal-level radiation areas in China (*13*). Similar to the present studies, cytogenetic analysis of children born to parents exposed to radiation in Hiroshima and Nagasaki also have not shown an excess of chromosomal aberrations, including balanced structural rearrangements (*14*). Comparison of unstable and stable aberrations among Russians exposed to radioactive fallout from the Chernobyl accident and a Ukrainian population receiving little or no increased radiation also did not show any significant differences (*15*). During our studies, no association was observed between the incidence of chromosomal aberrations and the radiation levels, which range from 1.0 to over 35.0 mGy per year. Thus, although the average dose rate increased over 25-fold in the highest

**TABLE 3**
**Constitutional Chromosomal Abnormalities among Newborns from High-Level Natural Radiation Areas of the Kerala Coast**

| | Total | | High-level natural radiation area | | Normal-level natural radiation area | |
|---|---|---|---|---|---|---|
| Abnormality | No.[a] | Frequency[b] | No. | Frequency | No. | Frequency |
| Numerical | | | | | | |
| Autosomal trisomies | 17 | 1.05 ± 0.26[c] | 12 | 0.96 ± 0.28 | 5 | 1.36 ± 0.61 |
| 48,XXY + 21 | 1 | 0.06 ± 0.06 | 1 | 0.08 ± 0.08 | — | — |
| +Centric fragments | 4 (2 mosaics) | 0.25 ± 0.12 | 3 (1 mosaic) | 0.24 ± 0.14 | 1 (mosaic) | 0.27 ± 0.27 |
| Sex chromosomal | 19 (8 mosaics) | 1.18 ± 0.27 | 16 (6 mosaics) | 1.28 ± 0.32 | 3 (2 mosaics) | 0.82 ± 0.47 |
| Total numerical | 41 | 2.54 ± 0.40 | 32 | 2.56 ± 0.45 | 9 | 2.45 ± 0.82 |
| Structural | | | | | | |
| Deletions | 6 | 0.37 ± 0.15 | 3 | 0.24 ± 0.14 | 3 | 0.82 ± 0.47 |
| Inversions | 8 | 0.49 ± 0.17 | 7 | 0.56 ± 0.21 | 1 | 0.27 ± 0.27 |
| Robertsonian translocations | 8 | 0.49 ± 0.17 | 7 | 0.56 ± 0.21 | 1 | 0.27 ± 0.27 |
| Other translocations | 17 | 1.05 ± 0.26 | 13 | 1.04 ± 0.29 | 4 | 1.09 ± 0.54 |
| Total structural | 39 | 2.41 ± 0.39 | 30 | 2.40 ± 0.44 | 9 | 2.45 ± 0.82 |
| Overall | 80 | 4.95 ± 0.55 | 62 | 4.96 ± 0.63 | 18 | 4.90 ± 0.16 |
| Newborns analyzed | 16,169 | | 12,496 | | 3,673 | |

[a] Newborns with constitutional anomalies.
[b] Per 1,000 newborns.
[c] SE, assuming Poisson distribution.

exposure group (average 31.41 mGy/year) compared to normal-level areas (average 1.15 mGy/year), there was no significant increase in chromosomal aberrations between the two groups of newborns (Table 2).

To our knowledge, the presence of cells with multiple aberrations/rogue cells among newborns has not been reported previously. However, in recent years rogue cells have been reported in cultured lymphocytes from different adult populations (*8, 9*). Though all types of chromosomal rearrangements are encountered in rogue cells, the number of double minutes present in the cell has been considered as an indicator of the degree of damage (*8, 9*). In our studies, there were also cells with extensive heavy cytogenetic damage, even though the number of double minutes was not high and only one rogue cell was encountered in an individual. The lack of any association of rogue cells with geographical location, ethnicity, maternal age, gender of the newborn, and radiation levels indicated their random occurrence (details to be published). The possible explanation proposed by Neel *et al. (8, 9, 15)* relating to viral etiology through the activation of transposon-retroposon sequences appears to be gaining support.

Almost all types of constitutional chromosomal abnormalities reported in the literature were observed among the newborns in this study. The classical syndromes involving autosomes were typical trisomies, with no mosaic being recorded. However, mosaics were observed in sex chromosomal anomalies in addition to trisomies, except in the cases of Turner's syndrome, where no true monosomy could be observed. All 13 Down syndrome cases were primary trisomy 21. The overall incidence of Down syndrome, one in 1,250 births (0.80 per 1000 births), represents the study population, where 90% of the deliveries took place below the age of 30 years, and is compatible with younger maternal age (*16, 17*). There were no significant differences among newborns from high- and normal-level radiation areas with respect to Down syndrome and other autosomal or sex aneuploids. These observations based on cytogenetic analysis of newborns are in contrast to an earlier report of higher Down syndrome cases in high-level natural radiation areas reported on the basis of a population survey (*18*). However, at present, the sample size is too small to draw any definite conclusions about Down syndrome or other individual constitutional anomalies. A few cases of structural constitutional anomalies were found to be familial. Likewise, though the overall incidence of constitutional chromosomal anomalies (4.95 ± 0.55 per 1,000 newborns) is compatible with published data (*19*), the sample size is not adequate to examine a dose–response relationship. In conclusion, no significant differences in the frequency of chromosomal aberrations in the newborns from high-level and normal-level areas were observed. Within the limitations of sample size, the overall incidence of constitutional

chromosomal anomalies in high-level and normal-level natural radiation areas was also found to be comparable.

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