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Inbreeding and the incidence of childhood genetic disorders in Karnataka, South India

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SUMMARY Consanguineous marriages are strongly favoured among the populations of South India. In a study conducted on 407 infants and children, a total of 35 genetic diseases was diagnosed in 63 persons: 44 with single gene defects, 12 with polygenic disorders, and seven with Down's syndrome. The coefficient of inbreeding of the total study group, F=0·0414, was significantly higher than that previously calculated for the general population, F=0·0271, and autosomal recessive disorders formed the largest single disease category diagnosed. The results suggest that long term inbreeding may not have resulted in appreciable elimination of recessive lethals and sub-lethals from the gene pool.

Among the Dravidian populations of the four southern states of India, Andhra Pradesh, Karnataka, Kerala, and Tamil Nadu, consanguineous marriages are strongly favoured.[1–4] The actual levels of consanguinity observed vary considerably,[5 6] for example, from 4·5 to 61·3% depending on factors such as religion,[7 8] caste,[9 10] and socioeconomic status,[11 12] but generally inbreeding is most common in the more traditional, rural communities.[4 6] In contrast to some inbreeding isolates reported from other parts of the world, consanguinity in South India does not result from a shortage of potential marital partners. At the last Census of India conducted in 1981, the combined population of the four southern states exceeded 164 millions, and consanguineous marriages are also common in the contiguous portion of Maharashtra.[13]

While inbreeding at this level might reasonably be expected to result in large numbers of infant and childhood disorders due to the expression of rare single lethal and sub-lethal recessives or polygenic combinations of rare recessives, it has been proposed that the long term practice of inbreeding would have led to a marked reduction in the number of deleterious genes in the gene pool.[14] Evidence in support of this hypothesis has been claimed in large scale prospective and retrospective studies on fertility and infant mortality in Tamil Nadu.[15–17] However, contrary conclusions were reached in recent surveys in Karnataka on childhood mortality,[18] and on the incidence of aminoacidopathies in newborns.[19] The aim of the present study was to obtain baseline information on the prevalence of genetic disorders among a group of children under hospital investigation in Karnataka, and to determine the nature(s) of the relationship(s) between the disorders diagnosed and the common preference for consanguineous marriages.

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Subjects

A total of 407 infants and children from the cities of Bangalore and Mysore was studied during the years 1982 and 1984. They represented 394 sibships; the male/female ratio was 1·22 and their ages ranged from 15 days to 14 years (mean 2·89 years). In just over half of the cases (211/407), the patients were referred to the Centre for Biomedical Research with a preliminary diagnosis suggestive of some form of genetic disorder. The remainder (196/407), who were all recruited as hospital inpatients, had no specific symptoms (table 1). The mean size of the families from which the patients were drawn was 2·67 liveborns (SD 1·63) with 2·35 living children (SD 1·43). To put these figures into perspective, the mean total marital fertility for Karnataka in 1978 was 3·7 in rural areas and 3·0 for urban groups.[20] The religious profile of the patients and their coefficients

TABLE 1 *Reasons for referral/investigation.*

	No
Suspected genetic disorder	60
Stunted growth/delayed milestones	36
Convulsions	10
Delayed learning/mental retardation	25
Hearing/speech defect	25
Eye defect	17
Skeletal abnormalities	7
Diplegia/hemiplegia	5
Gastrointestinal symptoms	10
Abnormal hair colour	5
Skin complaints	4
Poor maternal obstetric history	7
'Sick child'	192
Others	4
Total	407

TABLE 2 *Religious profile and consanguinity classes of the study group.*

	Coefficient of inbreeding (F)						
Religion	*0*	*<0·0156*	*0·0156*	*0·0625*	*0·125*	*Unknown*	*Totals*
Hindu	157	11	17	41	88	27	349
Muslim	23	1	1	12	3	3	43
Christian	11	0	0	0	0	1	12
Others	1	0	0	0	0	0	1
Unknown	0	0	0	0	0	2	2
Totals	192	12	18	61	91	33	407

of inbreeding (F) are shown in table 2. The F values refer to consanguinity only in the present generation as, due to a lack of written records, no information was available on inbreeding levels in previous generations.

Methods

All patients were examined clinically on an individual basis and radiological investigations were requested when deemed necessary. Finger prick or toe prick blood samples and random urine specimens were routinely collected. The urines were first examined for evidence of inborn errors of metabolism using basic side room tests.[21] Urinary amino acids, standardised on a creatinine equivalent, were analysed by circular chromatography.[22] Blood amino acids were screened by a semiquantitative thin layer chromatographic technique[23] followed, where appropriate, with quantitative assay on venepuncture samples using an automatic amino acid analyser. Evidence of reducing substances in the urine was further investigated by descending paper chromatography with aniline staining.[24] Excess mucopolysaccharides in the urine were detected with an Alcian blue spot test[25]; in such cases the specific, abnormal constituent(s) was identified via cellulose acetate electrophoresis.[26] Where possible, specific blood product or enzyme assays were employed to confirm diagnoses, for example, in congenital hypothyroidism, glucose-6-phosphate dehydrogenase deficiency, galactosaemia, and Wilson's disease. In a minority of cases, examples being maple syrup urine, tyrosinaemia, and alcaptonuria, the requisite assay methods were unavailable. The clinical diagnoses of Down's syndrome were confirmed by cytogenetic analysis, using phytohaemagglutinin stimulated blood cultures and trypsin banding.

Results

A total of 35 different genetic diseases was identified in 63 persons. The numbers and types of each disorder diagnosed in the study group are shown in table 3 and the specific disease classifications, based on Stanbury *et al*[27] and McKusick,[28] are presented in tables 4 and 5. For a number of disorders the absence of written records or inadequate pedigree data or both made determination of the precise mode of inheritance impossible. In addition to the single gene and polygenic disorders listed in tables 4 and 5, seven chromosomal anomalies were diagnosed, all being cases of Down's syndrome.

The role of inbreeding in the aetiology of the genetic disorders is clearly shown in table 6. The coefficient of inbreeding of the study group (F= 0·0414) was significantly greater than that previously determined for the population as a whole (F= 0·0271).[18] The further rise in the coefficients of inbreeding of all single gene defects (F=0·0513) and those with an autosomal recessive mode of inheritance only (F=0·0625) confirm the deleterious effect of consanguinity. If the 44 subjects with single gene defects (F=0·0513) and the 12 with polygenic disorders (F=0·0638) are excluded from the study group, the coefficient of inbreeding for the remaining patients is F=0·0397. Since this is significantly higher than the value for the general population

TABLE 3 *Genetic disorders diagnosed in the study population.*

Type	*Number*	*Percentage of total*
Single gene defects		
Autosomal dominant	11	2·7
Autosomal recessive	24	5·9
X linked	5	1·2
Uncertain	4	1·0
Chromosomal anomalies	7	1·7
Polygenic disorders	12	2·9
Total	63	15·5

TABLE 4 *Single gene defects.*

	Mode of inheritance	*No of cases*
Disorders of metabolism		
Amino acids		
Phenylketonuria	AR	1
Tyrosinaemia	AR	2
Histidinaemia	AR	3
Branched chain aminoacidaemia	AR	3
Congenital hypothyroidism	AR	1
Alkaptonuria	AR	1
Carbohydrate		
Galactosaemia	AR	1
Glycogen storage, type 1	AR	1
Purine and pyrimidine		
Lesch-Nyhan syndrome	X	1
Porphyrin and haem		
Acute intermittent porphyria	AD	3
Blood		
Glucose-6-phosphate dehydrogenase deficiency	X	1
Metal		
Wilson's disease	AR	2
Lysosomal enzymes		
Mucopolysaccharidoses:		
Type III Sanfilippo	AR	1
Type IV Morquio	AR	3
Connective tissue and muscle		
Marfan syndrome	AD	2
Duchenne muscular dystrophy	X	1
Transport		
Familial hypophosphataemic rickets	X	2
Vitamin D dependent rickets	AR	1
Indicanuria	AR	1
Renal glycosuria	AR	1
Miscellaneous		
Retinitis pigmentosa	?	4
Klippel-Feil syndrome	AD	1
Bardet-Biedl syndrome	AR	1
Congenital biliary atresia	AR	1
Syndactyly	?	1
Polydactyly	?	1
Deaf-mutism	?	3
Total		44

TABLE 5 *Polygenic disorders.*

Type	*No of cases*
Congenital heart defects	3
Microcephaly	3
Hydrocephalus	1
Multiple skeletal abnormalities, hip dislocation, cleft lip and palate	1
Cleft lip±palate	2
Congenital posturethral valves	1
Juvenile onset diabetes	1
Total	12

TABLE 6 *Inbreeding levels of the study population.*

	Percentage inbreeding	*Coefficient of inbreeding (F)*
Total study population	48·7	0·0414
Single gene disorders only	45·2	0·0513
Autosomal recessive disorders only	60·9	0·0625
General newborn population	32·2	0·0271

(F=0·0271), it is strongly suggestive of a sizeable recessive gene contribution to the symptoms of many of the patients in whom no diagnosis was possible.

Discussion

The overwhelming majority of childhood referrals in South India remains infectious or nutritional in origin. Against the background of this large environmental burden, it may be impossible to detect statistically significant consanguinity related effects, for example, on infantile mortality[15 16] or mental retardation.[29] This has encouraged belief in the unproven but widely held assumption that high rates of inbreeding over multiple generations necessarily would have resulted in appreciable elimination of deleterious recessive genes.[14] The theoretical and practical limitations associated with this hypothesis have recently been reviewed[18] and the results of the present survey, in conjunction with other reports from different parts of southern India,[30–32] indicate the continued existence in the gene pool of a wide range of lethal and sub-lethal genes.

Unfortunately, extrapolation from the current study to provide estimates for the incidence of specific genetic disorders in the total population is not feasible as, besides the relatively small number of subjects investigated, their symptoms and referral patterns were notably heterogeneous (table 1). In addition, the testing protocol was strongly biased towards the detection of disorders with recognisable biochemical abnormalities, resulting in a deficit of other types of cases, for example, chromosomal anomalies, which would have been referred to an alternative local centre. As malaria has been and, to a varying extent, is still endemic in South India, haemoglobinopathies could be predicted to be prevalent; their absence from table 4 reflects the limited range of laboratory tests currently available, rather than the probable incidence of these conditions in the population.

Nevertheless, the study confirms that many genetic disorders do exist in the Karnatakan population. Therefore, the conclusion which must be drawn is that as environmental causes of childhood morbidity and mortality decline in the region, so the proportion of diseases with an exclusive or partial genetic aetiology will increase, a phenomenon previously described in the United Kingdom.[33 34]

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