Genetic disorders in the Indian community of South Africa

W S Winship, P Beighton

Objectives. To determine the range of genetic disorders in the Indian population of South Africa, assess relevant historical and demographic factors, and discuss the implications for medical and genetic care.

Methods. WSW reviewed the archived data pertaining to patients seen in his paediatric practice in Durban during the past 45 years. Likewise, PB reviewed case details of persons encountered since 1972 in Cape Town, at outreach clinics, and in special institutions for the handicapped throughout South Africa. Additional information was accessed through the Cape Genetic Heritage archive.

Results. In addition to the common ubiquitous worldwide genetic disorders, several rare heritable conditions are present in the Indian community of South Africa. These disorders are the consequence of the founder effect and reflect the biological heritage of the early immigrants. Demographic factors (notably endogamy) are also relevant in this respect. As a result of these processes, thalassaemia is by far the most common and important genetic disorder in the Indian population in the country.

Conclusion. Awareness of the presence of specific genetic conditions in the Indian community of South Africa is important in the diagnostic process. In turn, diagnostic precision facilitates accurate prognostication and optimal medical and genetic management.

S Afr Med J 2011;101:481-484.

Some genetic disorders are ubiquitous, occurring in every ethnic group and in all geographical regions, while others show considerable ethnic and geographical specificity. In turn, the presence or absence of specific genetic disorders in a particular community has important implications for medical diagnosis, management and genetic counselling.

The genetic disorders present in South Africa were first reviewed in 1976.[1] Thereafter, the heritable disorders in individual population groups in this country were recorded. These included the indigenous African population[2-4] and Afrikaner,[5,6] Greek[7] and Jewish communities.[8] However, the genetic status of the Indian community in South Africa remains undocumented. The Indian group recently celebrated the 150th anniversary of their arrival in South Africa, and it is fitting that their genetic heritage should now be recorded. To address this hiatus, we analysed and present our personal experience and case records going back more than four decades.

Historical background

In 1860, the British Colonial Governments of India and the then colony of Natal arranged to transport Indian people as indentured labourers to work in the sugar cane plantations which were being developed in Natal. They were provided with food, clothing, accommodation and a small wage. Each was contracted for 5 years with an option to serve a second period of 5 years after which they could choose to be repatriated to India or to remain in Natal and receive a plot of land. The first ship carrying indentured labourers arrived in Durban on 16 November 1860 and, by 1911, when the scheme was stopped, 384 ships had transported 152 184 indentured labourers to Natal, of whom 62% were men, 25% women and 13% children. More than half of those who completed 10 years as indentured labourers chose to remain in Natal and, by 30 June 1886, 20 877 were free and only 895 were indentured.[9] These individuals were predominantly Bengali Tamils of the Hindu faith from southern India, who came via Calcutta and Madras (now Kolkata and Chennai).

Muslims from Gujarat in the Punjab arrived in South Africa from 1870 onwards on their own initiative, as did Hindus from the Surath coast in present-day Pakistan. Many of them were entrepreneurs and became shopkeepers in the urban environment. By 1911, when indentured emigration ceased, the Indian population of Natal totalled about 152 000.[10]

The Indian immigration into Cape Town which commenced in the closing years of the 19th century was succinctly reviewed by Worden *et al*.:[11] 'By July 1899 there were 600 Indians in the Cape Peninsula; already in the 1880s Indian corner stores had made their appearance. The Indians were by no means homogeneous: while the majority were Muslims, Pathans from the north-west frontier formed a small minority. Gujarati-speaking Hindus came mainly from Broach and Surat; their number also included Tamils from the Madras Presidency and Bengali-speakers from eastern India.'

There are currently about a million persons of Indian ancestry in South Africa, most of whom are domiciled in Durban, with smaller communities in Johannesburg, Cape Town and other centres. Many persons in these three distinct founder populations have retained their cultural and genetic identity.

Genetic disorders in the Indian community

During the past 50 years, WSW has been involved in paediatrics and medical genetics among the Indian community of Natal. Together with Namitha Chabilal, a genetic nurse practitioner, he has reviewed case records of patients whom they encountered; the diagnoses which were established are listed in Table I.

Outreach genetic clinics and surveys of institutional facilities for persons with various forms of handicap have been undertaken since 1970 in many centres in South Africa by PB. The diagnoses of genetic, cytogenetic and multifactorial disorders in persons of Indian ancestry that were encountered are also in the table. If case details of specific conditions have been published, the relevant references are indicated by numerical superscript.

Department of Paediatric and Child Health, Faculty of Health Sciences, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Durban
W S Winship, *GCOB*, MB ChB, MMed (Paed)

Division of Human Genetics, Faculty of Health Sciences, University of Cape Town
P Beighton, *OMB*, MD, PhD, FRCP, FRSSA

Corresponding author: *P Beighton (Peter.Beighton@uct.ac.za)*

Table I. Diagnoses of genetic, cytogenetic and multifactorial disorders in persons of Indian ancestry

Autosomal dominant	
Achondroplasia	Neurofibromatosis[12-14]
Apert syndrome	Osteogenesis imperfecta type I
Congenital contractural arachnodactyly[15]	Osteogenesis imperfecta type II
Crouzon syndrome	Renal tubular acidosis type I[16]
Ehlers-Danlos syndrome type 1	Robinow syndrome
Ehlers-Danlos syndrome type 2	Spondylo-epiphyseal dysplasia
Familial adenomatous polyposis	Spondylo-metaphyseal dysplasia
Hypochondroplasia	Treacher Collins syndrome
Larsen syndrome	Waardenberg syndrome type I
Marfan syndrome	Waardenberg syndrome type II
Microtia facial palsy and deafness[17]	
Autosomal recessive	
Albinism	Osteogenesis imperfecta type III
Bardet-Biedl syndrome	Osteoporosis-pseudoglioma syndrome[18,19]
Cystic fibrosis (not delta 508)	Pendred syndrome
Dyggve-Melchior-Clausen syndrome[20]	Sanfilippo syndrome (MPS III)
Ellis-van Creveld syndrome	Seckel syndrome
Epidermolysis bullosa dystrophica	Sialidosis[21]
Escobar syndrome	Sickle cell disease
Glycogenosis type II[22]	Spinal muscular atrophy
Hepatolenticular degeneration	TAR syndrome
Hurler syndrome (MPS I)	Thalassaemias (several types)
Morquio syndrome (MPS IV)	Xeroderma pigmentosa
X-linked recessive	
Androgen insensitivity syndrome (XY female)	Haemophilia A
Becker muscular dystrophy	Hunter syndrome (MPS II)
Duchenne muscular dystrophy	
X-linked dominant	
Goltz syndrome	
Hypophosphataemic rickets	
Incontinentia pigmenti	
Multifactorial	
Cleft lip and palate, including Robin sequence	
Neural tube defects – hydrocephalus, encephalocele and meningomyelocele	
Chromosomal disorders	
Complex chromosomal rearrangement 5,8,12[23]	
Fragile X syndrome[24]	
Prader-Willi syndrome 15 q 11	
Trisomy 21, 18 and 13	
Velo-cardio-facial syndrome 22 q 11	
Williams syndrome 7 q 11	
Y chromosome inversion in males from Gujurat, of no clinical significance[25,26]	

Genetic conditions in the Indian community that are of special clinical or academic interest are summarised below. For the sake of completeness, cytogenetic and important multifactorial conditions have also been addressed.

Thalassaemia in Natal

The Indian people who came to Natal originated in regions of the Indian subcontinent where malaria was endemic, and many were heterozygous for a thalassaemia trait that protected them from malaria. It is not surprising that thalassaemia is the most common single gene disorder found in their descendents in Natal, where malaria was also endemic during the 19th and early 20th centuries.

Currently, there are 12 patients with homozygous beta thalassaemia major and one with heterozygous HbE/beta thalassaemia, all under the age of 13 years, being treated in the Paediatric Haematology Clinic in Durban. In addition, 18 affected individuals older than 14 years attend the adult clinic. They all require blood transfusions every 3 - 4 weeks, together with daily oral iron chelation. Several have developed iron overload, and some also have endocrine problems – mostly short stature, delayed puberty and diabetes.

About 40 years ago, a technologist, Ms Uni Anderson, commenced compiling a database of Natal families with the thalassaemia trait. The Department of Haematology at the Inkosi Luthuli Hospital now has between 4 000 and 5 000 gene carriers recorded, the majority of whom have beta thalassaemia. Other haemoglobinopathies, notably HBED, have also been recorded as has G6PD deficiency.

The gap between diagnosis in childhood and marriage in early adulthood results in many heterozygous couples being unaware of the risk of having children with thalassaemia major. To date, no patients have been referred for prenatal screening and counselling, which is available in Durban.

Familial deafness

In 1987, a diagnostic survey was undertaken in the VN Naik School in Durban for profoundly deaf children from the Indian community. Of the 212 deaf scholars, 48% were of Tamil stock, 29% had antecedents in Surath, and 11% were Gujaratis.[27]

Familial profound hearing loss without any additional manifestations (undifferentiated deafness) that was suggestive of autosomal dominant (AD), autosomal recessive (AR) and X-linked (XL) modes of genetic transmission was recognised. An excess of AR deafness which was present in Gujarati kindreds might reflect the prevalence of parental consanguinity in this group. Molecular investigations could be informative in these forms of familial deafness, but no such studies have been undertaken in the affected families.

Other well-known genetic deafness syndromes which were diagnosed in the deaf scholars include the Waardenburg, Pendred, Treacher Collins and Alport syndromes.

Conductive deafness due to stapedial abnormalities, associated with external ear malformations and congenital facial palsy (Sellars syndrome), is inherited as an AD disorder in a Cape Town family of Indian stock.[17] Three generations are affected and the disorder has proved to be penetrant but variable in phenotypic expression. We are not aware of documentation of the disorder elsewhere, and it appears to be a private syndrome.

Multifactorial disorders: diabetes mellitus, hypercholesterolaemia and hypertension

Almost 50 years ago, the pedigree of a very extensive Cape Town Tamil family with diabetes was documented by Jackson.[28] There is a high frequency of diabetes mellitus in the Indian community of South Africa as a whole, and the interaction of genetic and environmental factors has been explored.[29] Hypercholesterolaemia is also frequent.[30,31] Hypertension is common; in 1976, Seedat and Reddy reported finding a family history in 40% of 500 Indian families investigated in Durban.[32]

Chromosomal disorders

The Fragile X mental disability syndrome has been confirmed cytogenetically in a large Cape Town kindred of predominantly Indian stock; 7 male cousins were severely affected and 4 female cousins were intellectually compromised to a lesser extent.[24] By 2010, another generation had been born and diagnostic confirmation by molecular techniques had become a routine procedure. A large affected Indian family in Durban was also identified; the extensive pedigree compiled by Namitha Chabilal was presented with WSW at the 1999 South African Genetic Society Congress.

An innocuous cytogenetic condition in which the Y chromosome is inverted is present in the Gujarati community of South Africa.[25] A single origin for this anomaly has been demonstrated.[26]

A balanced reciprocal translocation involving chromosomes 5, 8 and 12 has been identified by WSW and his colleagues in 13 individuals in 3 generations of an extensive Indian family in Natal. In the first generation studied, there were 12 pregnancies of which 3 were aborted spontaneously and 4 offspring died in the neonatal period. Of the survivors, only 1 male had a normal karyotype while 2 males and 2 females had the balanced reciprocal translocation. Thereafter, another 9 members of the family were identified with the reciprocal translocation. Three children with an unbalanced translocation resulting in partial Trisomy 8 and partial Monosomy 12 survived in this family, and all had dysmorphic features and severe intellectual handicap.[23]

Trisomy 21, 18 and 13 occur as frequently in Indian families in South Africa as in other populations.

Discussion

Although largely based upon experience in Natal, the genetic disorders outlined here are probably broadly representative of the Indian community in South Africa as a whole. Nevertheless, this community is derived from three distinct populations from different geographical regions of India, each of which brought their ancestral genes to this country. Therefore, we can expect that, as information accumulates, analysis will reveal further discrepancies in the relative frequencies of some of the genetic conditions in these population subgroups.

Common AD genetic disorders such as neurofibromatosis (NF) which are sub-lethal and which have a high mutation rate, have a worldwide distribution. X-linked conditions such as haemophilia and Duchenne dystrophy also have a high mutation rate and, as females with the determinant gene are unaffected, transmission of these potentially lethal disorders is unimpeded. The presence of these conditions in each of the Indian communities in South Africa is in accordance with these mechanisms. Likewise, chromosomal disorders are ubiquitous in their geographical and ethnic distribution.

Sickle cell anaemia (AR), thalassaemia (AR) and G6PD deficiency (XL) typically occur in high frequency in malaria-endemic regions, as asymptomatic or mildly affected carriers of a single copy of the determinant gene have a degree of protection against the malarial parasite. The biological advantage of these genes is largely negated by immigration to non-malarial regions. Nevertheless, this genetic heritage is retained and poses threats to the health of homozygous persons who have inherited a copy of the determinant gene from each of their heterozygous parents.

The demography of the Indian communities in South Africa has relevance for their genetic circumstances. Members of large extended families are scattered throughout the country; the diagnosis of an unusual genetic disorder in one individual may have implications for numerous relatives, both close and distant. Endogamy is also important in some communities; close relatives share a proportion of their genes, and the offspring of consanguineous unions are at an increased risk of receiving the same deleterious recessive gene from each of their parents and developing the disorder in question. This risk could be present throughout a large extended family. Common AR conditions such as the aforementioned genetic blood dyscrasias and rare AR disorders such as undifferentiated congenital deafness, osteogenesis imperfecta type III and spinal muscular atrophy, exemplify this situation.

In medical practice, awareness of the presence of a specific genetic disorder in a particular community is an important aspect of the diagnostic process. It is axiomatic that diagnostic precision promotes optimal therapy and appropriate genetic management.

Authorship. The authors have both made substantial contributions to the concept, design and content of the data. They have jointly drafted the article and approved the final version.

Research ethics. This project was approved by the University of Cape Town Health Sciences Faculty Research Ethics committee (Ref 026/2010).

We gratefully acknowledge the receipt of support from the South African Medical Research Council and the National Research Foundation. We appreciate the input of our colleagues in Durban – Professor Y K Seedat and Dr Rajendra Thejpal, paediatric haematologist, who kindly supplied information concerning thalassaemia in Natal. PB received support from the South African Medical Research Council and the National Research Foundation.

References

1. Beighton P. Genetic disorders in Southern Africa. S Afr Med J 1976;50:1125-1128.
2. Beighton P, Botha MC. Inherited disorders in the black population of Southern Africa: Part I. Historical and demographic background;genetic haematological conditions. S Afr Med J 1986; 69:247-249.
3. Beighton P, Botha MC. Inherited disorders in the black population of Southern Africa: Part II. Gene disorders. S Afr Med J 1986;69:293-296.
4. Beighton P, Botha MC. Inherited disorders in the black population of Southern Africa: Part III. Multifactorial, chromosomal and congenital conditions. S Afr Med J 1986;69:375-378.
5. Botha MC, Beighton P. Inherited disorders in the Afrikaner population of Southern Africa. Part I. S Afr Med J 1983;64:609-612.
6. Botha MC, Beighton P. Inherited disorders in the Afrikaner population of Southern Africa. Part II. S Afr Med J 1983;64:664-667.
7. Bonafede RP, Botha MC, Beighton P. Inherited anaemias in the Greek community of Cape Town. J Med Genet 1979;16(3):197-200.
8. Lane AB, Dunn DS, Jenkins T. A genetic profile of the South African Ashkenazi Jewish population. S Afr Med J 1985;68:935-939.
9. Dhupelia-Mesthrie U. From Canefields to Freedom. Goodwood, South Africa: National Book Printers, 2000.
10. Bhana S, Brain JB. Movements of Indians in South Africa 1860-1911. SA Historical Society Conference Papers, 1985.
11. Worden N, van Heyningen E, Bickford-Smith V. The Making of a City. Cape Town: David Philip Publishers, 1998:212-213.
12. Beighton P, Goldblatt J, Wallis G. Genetic disease in South Africa. A molecular approach. S Afr Med J 1987;72:766-769.
13. Wallis CE, Slater CP. Neurofibromatosis in the South African Indian community – further evidence for heterogeneity ? S Afr Med J 1987;72:478-480.
14. Mathew CGP, Thorpe K, Easton DF, et al. Linkage analysis of British and Indian families with Von Recklinghausen neurofibromatosis. J Med Genet 1987;24:524-526.
15. Viljoen D, Ramesar R, Behari D. Beals syndrome: clinical and molecular investigations in a kindred of Indian descent. Clin Genet 1991;39:181-188.
16. Seedat YK. Some observations of renal tubular acidosis – a family study. S Afr Med J 1963;38:600-610.
17. Sellars S, Beighton P. Autosomal dominant inheritance of conductive deafness due to stapedial anomalies, external ear malformations and congenital facial palsy. Clin Genet 1983;23:376-379.
18. Gong Y, Vikkula M, Boon L, et al. Osteoporosis-pseudoglioma syndrome, a disorder affecting skeletal strength, is assigned to chromosome region 11q12-13. Am J Hum Genet 1996;59:146-151.
19. Beighton P, Winship I, Behari D. The ocular form of osteogenesis imperfecta: a new autosomal recessive syndrome. Clin Genet 1985;28:69-75.
20. Winship WS, Rubin DL. The Dyggve-Melchior-Clausen syndrome in Indian siblings. Clin Genet 1992;42:240-245.
21. Bhigjee AI, Seebaran AR, Petersen EM, Bill PLA. Sialidosis type I:first report in the Indian population. Clin Neurol Neurosurg 1991;93(2):115-118.
22. Van der Ploeg AT, Hoefsloot LH, Hoogeveen-Westerveld M, Petersen EM, Reuser JJ. Glycogenosis Type II: Protein and DNA analysis in five South African families from various ethnic origins. Am J Hum Genet 1989;44:787-793.
23. Winship WS, Govender L, Chabilal N, Kavonic S. Complex chromosome rearrangement: a problem of counselling, ethics and responsibility. Proceedings of the 11th Biennial Congress of the South African Society of Human Genetics, 2005.
24. Gardner RJM, Smart RD, Cornell JM, Merckel LM, Beighton P. The fragile X chromosome in a large Indian kindred. Clin Genet 1983;23:311-317.
25. Bernstein R, Wadee A, Rosendorff J, Wessels A, Jenkins T. Inverted Y chromosome polymorphism in the Gujerati Muslim Indian population of South Africa. Hum Genet 1986;74:223-229.
26. Spurdle A, Jenkins T. The inverted Y chromosome polymorphism in the Gujerati Muslim Indian Population of South African has a single origin. Human Heredity 1992;42:330-332.
27. Beighton P, Sellars SL, Goldblatt J, Viljoen DL, Beighton G. Childhood deafness in the Indian population of Natal. S Afr Med J 1987;72:209-211.
28. Jackson WPU, Van Mieghem W, Marine N, Keller P, Edelstein I. Diabetes among the Tamil Indian community in Cape Town: Re-examination after five years. S Afr Med J 1974;48:1839-1843.
29. Conn V, Ramsay M, Jenkins T. Non-insulin-dependent diabetes mellitus and the 5' hypervariable region of the insulin gene in two South African Indian families. S Afr Med J 1987;71:174-178.
30. Langenhoven E, Warnich L, Thiart R, et al. Two novel point mutations causing receptor-negative familial hypercholesterolemia in a South African Indian homozygote. Atherosclerosis 1996;125:111-119.
31. Kotze MJ, Loubser O, Thiart R, et al. CpG hotspot mutations at the LDL receptor locus are a frequent cause of familial hypercholesterolemia among South African Indians. Clin Genet 1997;51:394-398.
32. Seedat YK, Reddy J. The clinical pattern of hypertension in the South African Black population. A study of 1000 patients. Afr J Med Sci 1976;5:1-7.

Accepted 29 November 2010.