Understanding the genetic diversity of South Africa's peoples

The diverse nature of the peoples living in South Africa (SA) and their history has offered unique opportunities over the years to its researchers, particularly those working in the field of human and medical genetics. Many genetic conditions and/or genetic causative mutations have been demonstrated to have interesting population-specific distributions. This is well demonstrated by two articles in this issue of the *SAMJ*.[1,2] Apart from research opportunities, this diversity of genetic disease has major relevance when offering diagnostic testing. Frequencies of disease may differ between groups, and the mutational basis may be different. Unless clinicians and laboratories are aware of these differences, and offer testing appropriate to the origins of patients, inappropriate testing may be performed and important diagnoses may be missed. Different mutation-specific therapies may also be required in the future.

The trinucleotide or dynamic repeat disorders, as a group, illustrate many of these points very clearly. They are a group of disorders, first described in the early 1990s, with a similar underlying mutation mechanism. The majority of the conditions have some neurological or neurodegenerative manifestations, but in many cases other systems are involved. Although only approximately 20 of these conditions have been identified, they include some of the commoner genetic conditions, such as fragile X mental retardation syndrome, myotonic dystrophy, Huntington disease (HD) and a number of the spinocerebellar ataxias. All these conditions are characterised by similar mutations – an area within or close to the gene where there is a repetitive DNA sequence, usually three base pairs. These repeat areas occur in everyone, but the number of repeat units is critical. Less than a defined threshold and the number of repeat units is inherited unchanged, like any other genetic material. Greater than a threshold and they are unstable and the repeat number changes from one generation to the next, hence dynamic. Typically they expand, but contractions also occur. Greater numbers of repeats are associated with increased severity, earlier age of onset and in some cases different disease manifestations. These diseases are therefore characterised by marked clinical variability within and between families. The origins of these mutations are uncertain, with a combination of 'tip-over' from the normal range and underlying genetic background appearing important.

Fragile X mental retardation syndrome is the commonest cause of intellectual disability in all the local SA populations,[3] as it is worldwide. It was previously thought to be rare in blacks, but this was due to under-ascertainment.[4] Although the disease frequencies are uncertain, the diagnosis should be considered in individuals of either gender with intellectual disability, developmental delay or autism, especially if they have physical or behavioural characteristics of fragile X syndrome and/or a family history of undiagnosed intellectual disability. Mutations can also result in premature ovarian insufficiency and a late-onset ataxia, fragile X-associated tremor/ataxia syndrome. Importantly, these individuals may be at risk of having children and grandchildren with severe intellectual disability. Further, the condition is X-linked but has some unusual features. The familial nature therefore needs to be recognised and the implications for other family members conveyed once an expansion is identified in an individual.

On the other hand, there are a number of trinucleotide dynamic repeat disorders that show population differences at some level. At least two of the common conditions, myotonic dystrophy and HD, are said to occur at higher frequency in the Afrikaans-speaking population, owing to founder mutations.[5,6] The Afrikaner population of SA has many features of a founder population. They originated from a small number of individuals, German, Dutch and Huguenot settlers who immigrated to the Cape Colony in the 1600s and then underwent a period of rapid growth. Genetic mutation frequencies in the new population may differ significantly from those in the original population. There are many diseases for which such founder mutations have been described in the Afrikaner population, including porphyria variegata, familial hypercholesterolaemia, Fanconi's anaemia, Gaucher disease and autosomal recessive polycystic kidney disease.[7-11] In this issue, Schutte *et al.*[1] report a rare dynamic repeat disorder, oculopharyngeal muscular dystrophy (OPMD), for the first time in a family with Afrikaner ancestry. Preliminary evidence, not surprisingly, suggests a founder effect. It remains to be seen whether other families will be recognised, and awareness of the possibility of the condition is therefore important.

Myotonic dystrophy is the commonest adult neuromuscular disorder, but affected individuals may also present with cataracts, cardiac conduction defects or neonatal hypotonia. It is an autosomal dominant condition and therefore has significant implications for family members. Further, its diverse presentation means that different family members may be treated by different specialists, and the familial nature of the condition may not be recognised.

Similarly, some interesting population-specific findings among people of African ancestry in SA have been reported for the trinucleotide repeat disorders – myotonic dystrophy, Friedreich's ataxia, HD and spinocerebellar ataxia type 7. Neither myotonic dystrophy nor Friedreich's ataxia has ever been reported in a black patient in South Africa[12] (and Jacquie Greenberg, personal communication, 2015). Its absence is ascribed to the absence of a predisposing chromosomal background (haplotype) and possibly fewer large repeats close to the critical expansion threshold.

Further, HD, a progressive autosomal dominant neurodegenerative disorder characterised by abnormal movements, cognitive decline and psychiatric symptoms, shows some unique features in black individuals. This condition was previously thought to be rare in this ethnic group, and the few cases described were reported to be due to admixture.[13,14] Although the frequency of HD remains uncertain, many cases have now been documented. HD in people of African ancestry has been shown to be genetically heterogeneous. HD due to mutations in the *HTT* gene occurs, but on African-specific haplotypes that differ from those in white patients.[15] In addition, a second HD gene (*JPH3*) has been implicated in African patients with an HD-like phenotype (HDL2), who do not have an expansion in the *HTT* gene. Individuals with HDL2 share many clinical features with individuals with HD and are clinically indistinguishable in many individual cases, although the average age of onset and diagnosis in HDL2 is approximately 5 years later than HD and individual clinical features may be more prominent.[16] While mutations at

the *HTT* locus account for all confirmed HD diagnoses in white patients, about two-thirds of patients with African ancestry have mutations in *HTT* and one-third mutations in *JPH3*. Genetic testing in black African patients with an HD phenotype, and in those with African origins, even if distant, should therefore include routine testing of both *HTT* and *JPH3* to avoid false-negative diagnoses.

Spinocerebellar ataxias are also differently distributed in SA populations, with SCA1 being most common in individuals of mixed ancestry and whites, and SCA7 and SCA2 being most common in blacks.[17] SCA7 has only been reported in black patients in SA.[18]

As genetic testing expands with the introduction of new technologies, the number of examples of population- or regional-specific disease and/or mutation distributions is likely to increase. These findings should be incorporated so that appropriate diagnostic testing is offered to South Africans and Africans, and all patients are given the best available information to make a diagnosis and to guide treatment, genetic counselling and reproductive decisions.

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1. Schutte CM, Dorfling CM, van Coller R, Honey EM, van Rensburg EJ. A South African family with oculopharyngeal muscular dystrophy: Clinical and molecular genetic characteristics. S Afr Med J 2015;105(7):540-543. [http://dx.doi.org/10.7196/SAMJnew.7880]
2. Watson CM, Crinnion LA, Gleghorn L, et al. Identification of a mutation in the ubiquitin-fold modifier 1-specific peptidase 2 gene, UFSP2, in an extended South African family with Beukes hip dysplasia. S Afr Med J 2015;105(7):558-563. [http://dx.doi.org/10.7196/SAMJnew.7917]
3. Essop F, Krause A. Diagnostic, carrier and prenatal genetic testing for Fragile X syndrome in Johannesburg, South Africa: A 20-year review. S Afr Med J 2013;103(12, Suppl 1): 994-998. [http://dx.doi.org/10.7196/SAMJ.7144]
4. Goldman A, Krause A, Jenkins T. Fragile X syndrome occurs in the South African black population. S Afr Med J 1997;87(4):418-420.
5. Hayden MR, Hopkins HC, Macrae M, et al. The origin of Huntington's chorea in the Afrikaner population of South Africa. S Afr Med J 1980;58(5):197-200.
6. Goldman A, Krause A, Ramsay M, et al. Founder effect and the prevalence of myotonic dystrophy in South Africans: Molecular studies. Am J Hum Genet 1996;59(2):445-452.
7. Meissner P, Dailey TA, Hift RJ, et al. A R59W mutation in human protoporphyrinogen oxidase results in decreased enzyme activity and is prevalent in South Africans with variegate porphyria. Nat Genet 1996;13(1):95-97.
8. Callis M, Jansen S, Thiart R, et al. Mutation analysis in familial hypercholesterolaemia patients of different ancestries: Identification of three novel LDLR gene mutations. Mol Cell Probes 1996;12(3):149-152.
9. Tipping AJ, Pearson T, Morgan NV, et al. Molecular and genealogical evidence for a founder effect in Fanconi anaemia families of the Afrikaner population of South Africa. Proc Natl Acad Sci USA 2001;98(10): 5734-5739.
10. Morar B, Lane AB. The molecular characterization of Gaucher disease in South Africa. Clin Genet 1996;50(2):78-84.
11. Lambie L, Amin R, Essop F, et al. Clinical and genetic characterization of a founder PKHD1 mutation in Afrikaners with ARPKD. Pediatr Nephrol 2015;30(2):273-279. [http://dx.doi.org/10.1007/s00467-014-2917-1]
12. Goldman A, Ramsay M, Jenkins T. Ethnicity and myotonic dystrophy: A possible explanation for its absence in sub-Saharan Africa. Ann Hum Genet 1996;60(1):57-65.
13. Hayden MR, MacGregor JM, Beighton PH, et al. The prevalence of Huntington's chorea in South Africa. S Afr Med J 1980;58(5):193-196.
14. Harper PS. The epidemiology of Huntington's disease. Hum Genet 1992;89(4):365-376.
15. Baine FK, Kay C, Ketelaar ME, et al. Huntington disease in the South African population occurs on diverse and ethnically distinct genetic haplotypes. Eur J Hum Genet 2013;21(10):1120-1127. [http://dx.doi.org/10.1038/ejhg.2013.2]
16. Krause A, Mitchell CL, Essop F, et al. Junctophilin 3 (*JPH3*) expansion mutations causing Huntington disease like 2 (HDL2) are common in South African patients with African ancestry and a Huntington disease phenotype. Am J Med Genet 2015 (in press).
17. Smith DC, Bryer A, Watson LM, et al. Inherited polyglutamine spinocerebellar ataxias in South Africa. S Afr Med J 2012;102(8):683-686. [http://dx.doi.org/10.7196/SAMJ.5521]
18. Greenberg J, Solomon GAE, Vorster AA, et al. Origin of the *SCA7* gene mutation in South Africa and implications for molecular diagnostics in the South African indigenous black population. Clin Genet 2006;70(5):415-417. [http://dx.doi.org/10.1111/j.1399-0004.2006.00680.x]

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