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Genetic aspects of hearing loss in the Limpopo Province of South Africa.

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ABSTRACT

The aetiological diagnosis of recessive non-syndromic hearing loss poses a challenge owing to marked heterogeneity and the lack of identifying clinical features. The finding that up to 50% of recessive non-syndromal genetic hearing loss among Caucasians was due to mutations in *GJB2*, the gene encoding Connexin 26 (Cx26) was a breakthrough, whose value as a diagnostic tool has been limited by the significant variation in the prevalence of deafness genes and loci among population groups. The significant association of the *GJB6*-D13S1830 deletion among individuals with one mutant *GJB2* allele highlighted the need to explore population specific genetic mutations for NSHL. Although data from Sub-Saharan Africa is limited, reported studies found a high prevalence of R143W *GJB2* mutation among Ghanaian, the 35delG mutation in 5 out of 139 Sudanese and a low prevalence of *GJB2* variations among 385 Kenyan deaf children. The mutation spectrum of Waardenburg Syndrome (WS) in Africans has not been documented.

During a visit to a School for the Deaf in the Limpopo Province of South Africa in 1997, it was noted that a high number of students came from Nzhelele sub-district. All had childhood onset hearing loss with no associated anomalies or disorders. The question arose as to whether there was a high-risk area for deafness in the Limpopo Province and what the aetiology of this hearing loss was.The main aim of this study was to investigate the role of *GJB2*, the *GJB6*-D13S1830 deletion, and the four common mitochondrial mutations, A1555G, A3243G, A7511C and A7445G, in the African hearing-impaired population of Limpopo province in South Africa, and to identify the mutation spectrum of the deafness genes found. The type and degree of hearing loss in this hearing impaired population would also be assessed. Secondly, this study sought to identify the mutations in a sibling pair with

clinical WS and to use the findings in a future study to establish the mutation spectrum of WS in the African population of the Limpopo province and of South Africa in general.

The study was designed as a two phase study, in which phase 1 was used for hypothesis formulation and phase 2 was for hypothesis testing. While phase 1 was a descriptive retrospective case study, phase 2 was a combination of sample survey and prospective descriptive case study. In phase 1, demographic data of 361 students in two schools of the deaf in the Limpopo province was analyzed for evidence of areas of high risk populations for deafness in the province. In phase 2, a group of 182 individuals with genetic non-syndromic hearing loss (NSHL) and two siblings with clinical WS from two schools for the Deaf in the Limpopo Province of South Africa were investigated. A thorough clinical examination, audiological evaluation and urinalysis were done. Mutational screening was carried out in all 184 subjects using genomic DNA using single-strand conformation polymorphism (SSCP), multiplex polymerase chain reaction (PCR), and direct sequencing for *GJB2,* and Restriction Fragment-Length Polymorphism (PCR–*RFLP) analysis for GJB6, and* SSCP, hetero-duplex analysis, and direct sequencing of the first 8 exons of *PAX3* and all of *MITF* for Waarenburg syndrome. Data analysis was by geographical mapping, frequency tables, tests of association with calculation of odds ratios, and binary logistic regression analysis using STATA and GIS mapping systems.

The results indicate that there seem to be areas of genuine populations at risk for hearing loss in the Limpopo province of South Africa, namely Mutale and parts of Makhado and Thulamela municipalities. In Thulamela (NP343) wards 11-15, 26-30 and 31-35, and in Mutale (NP 344) wards 6-10, together accounted for 67 (18%) of participants in phase 1, and 33 (18%) of the participants in phase 2 of the study. Mutale municipality in the Vhembe

district gave with a projected prevalence of at least 13.14 deaf children per 100,000 African population attending the local school for the deaf.

The observed hearing loss is a genetic, non-syndromic form, which is mainly severe and severe to profound, although without any clear defining configuration or shape. It is a stable, non-progressive and prelingual form of hearing loss, implying that this may be a recessive form of deafness. No identifiable environmental confounding factors or associations were identified. The deafness is not linked the common known auditory gene mutations in *GJB2*, the *GJB6*-D13S1830 deletion, or the common mitochondrial mutations A1555G, A3243G, A7511C and A7445G. Severe and profound levels of hearing loss were found in 22.8% and 75% of the cohort respectively, with the majority exhibiting flat (70.1%) or sloping (23.4%) audiograms that were commonly symmetrical (81.5%). However, as indicated, there was no clear pattern in the audiological findings overall.

None of the 184 hearing impaired individuals exhibited any of the reported disease causing mutations of *GJB2*, including 35delG. There was, however, a high prevalence of two variants, the C>T variant at position g.3318-15 and the C>T variant at position g.3318-34, occurring in 21.4% and 46.2% of the deaf cohort respectively. The same variants were found to occur in 35% and 42.6% of a normal hearing control group (n = 63) respectively, indicating that these variations are polymorphisms. In three subjects (1.63% of the cohort), a T>A homozygous variation at position g.3318-6 was detected. Its significance in the causation of NSSNHL is yet to be determined. The *GJB6*-D13S1830 deletion was not detected in any of the participants. None of the four mitochondrial mutations screened for were found.

These results indicate that *GJB2* is not a significant deafness gene in the African population of the Limpopo Province of South Africa and that significant genes for non-syndromic recessive hearing loss in this population are yet to be found. The geographical clustering of deafness found in this study, combined with the lack of identifiable common associated clinical features among the subjects of this study (excluding the WS sibling pair), suggests that these subjects have a genetic recessive non-syndromal type of hearing loss. In the context of historical and cultural evidence of consanguinity in this population, a founder effect cannot be ruled out.

A rare mutation, R223X, previously identified only once out of 470 WS patients, was identified in the *PAX3* gene among the WS sibling pair. A novel silent change GGG>GGT at amino acid 293, was also identified. These identical findings document, for the first time, a molecular defect in WS in an African sibling pair, and confirm WS Type I in this family, which could be found in other WS type I South Africans in the Limpopo Province of South Africa.

The current study demonstrated that parents of genetically hearing impaired children in these areas are able to detect hearing loss at an early age, with over 60% suspecting their children's hearing loss below 6 months of age. A child-centered management model encompassing all the areas relevant to childhood deafness/hearing impairment, which takes into consideration the prevailing logistical and financial constraints of the available healthcare system, is proposed. The implementation of this model requires a paradigm shift from the current fragmented model of service delivery to a cohesive patient-centered approach, based on concrete data from appropriate community based research, in which all the relevant parties communicate and share resources.

It would achieve the goals of early detection and intervention, as well as inclusive education for all. The relevant health and education policies are already in place and the posts funded. Equitable implementation of these policies would require appropriate community based research, as well as improved communication and consultation between the various stakeholders to ensure an efficient and affordable quality healthcare service for all hearing impaired South Africans.

Key words

Recessive, non-syndromic hearing loss, Connexin 26 (Cx26), Sub-Saharan Africa, *GJB2*, *GJB6*-D13S1830 deletion, Waardenburg Syndrome (WS) type I, mitochondrial mutations A1555G, A3243G, A7511C and A7445G, Limpopo Province of South Africa, *PAX3* R223X mutation, *PAX3* silent change GGG>GGT at amino acid 293, prevalence, high-risk area for deafness, single strand conformation polymorphism (SSCP) assay, direct sequencing for *GJB2*, Restriction Fragment-Length Polymorphism (PCR–*RFLP) analysis,* hetero-duplex analysis, direct sequencing, enzyme digest, congruent choropleth maps, computer-generated cluster-display map, populations-at-risk, geographical displays, consanguinity, risk factors for hearing loss, audiogram configuration, polymorphisms, congenital hearing loss, childhood hearing loss, Universal Neonatal Hearing Screening, EDHI, early detection of hearing impairement programmes