A novel CYBB mutation with the first genetically confirmed case of chronic granulomatous disease in South Africa

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Chronic granulomatous disease (CGD) is a rare primary immunodeficiency disease of phagocytic cells, resulting from impaired function of one of five essential subunits of the reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme complex within neutrophils, eosinophils, monocytes, and macrophages. This enzyme complex mediates intracellular killing of phagocytosed micro-organisms. The NADPH oxidase complex is composed of membrane-bound glycoproteins gp91phox and p22phox, and cytosolic subunits p47 phox, p67 phox, and p40 phox. A case of a child with chronic granulomatous disease (CGD) presenting with recurrent mycobacterial infections and invasive Aspergillus fumigatus disease is described. Genetic analysis confirmed X-linked CGD with a novel mutation in exon 10 of the CYBB gene – the first South African report of genetically confirmed CGD.

A case of a child with chronic granulomatous disease (CGD) presenting with recurrent mycobacterial and fungal infections is described. Genetic analysis confirmed X-linked CGD with a novel mutation in exon 10 of the CYBB gene – the first South African report of genetically confirmed CGD.

Although there was no reported family history of primary immunodeficiencies, 2 maternal uncles and 1 maternal male cousin died in infancy of unknown causes that suggested an X-linked inheritance pattern (Fig. 1). Sequencing of the CYBB gene on peripheral blood samples was completed by the University of...
Hong Kong: 13 exon fragments were amplified using HotStarTaq Plus PCR system (Qiagen GmbH, Germany). Homology analysis of the sequenced data with CYBB genomic DNA was performed through the NCBI database (http://www.ncbi.nlm.nih.gov/BLAST) and the Ensembl SNPs database (http://www.ensembl.org). Analysis of the CYBB gene of the patient revealed a novel insertion-deletion mutation in exon 10, while his mother was found to be a heterozygous carrier of the mutation (Fig. 2).

Discussion
We describe a patient with CGD and a novel mutation in the CYBB gene. If the South African incidence is similar to international prevalence, 4 - 5 new cases of CGD should be identified in the country per year, which suggests that many children with CGD are not being diagnosed, most probably owing to failure to recognise the clinical manifestations.

Three mycobacterial infections and invasive aspergillosis in our patient is consistent with CGD. Acute bacterial infections with Staphylococcus aureus, Burkholderia cepacia, Serratia marcescens and Nocardia sp, predominate, while Aspergillus – the most frequently associated fungal infection – is the leading cause of morbidity and mortality.2 Several CGD patients with Bacille-Calmette-Guérin (BCG) disease and TB have been described in regions endemic for tuberculosis.5 Other CYBB mutations not related to CGD have also been associated with X-linked recessive mendelian susceptibility to mycobacteria.7 Other primary immunodeficiency diseases (PIDs) that cause recurrent mycobacterial infections include X-linked hyper-IgM syndrome, severe combined immunodeficiency syndrome and deficiencies of the IL-12/23-IFN-γ axis.1,2 Several CGD patients with Bacille-Calmette-Guérin (BCG) disease and TB have been described in regions endemic for tuberculosis.4 Other CYBB mutations not related to CGD have also been associated with X-linked recessive mendelian susceptibility to mycobacteria.5 Other primary immunodeficiency diseases (PIDs) that cause recurrent mycobacterial infections include X-linked hyper-IgM syndrome, severe combined immunodeficiency syndrome and deficiencies of the IL-12/23-IFN-γ axis.1,2 Sequencing of the CYBB gene documented a novel insertion-deletion mutation in exon 10 which resulted in amino acid alterations at positions 388 and 389. Over 400 different mutations of the CYBB gene have been described.6 While mutational analysis is important for definitive diagnosis, it is not routinely available, however, and immunological evaluation with neutrophil burst testing is sufficient to make a diagnosis and initiate treatment. Prophylactic antibiotic therapy with cotrimoxazole has been effective in reducing serious bacterial infections, while prophylactic itraconazole has substantially decreased the number of Aspergillus infections.1,2 Interferon-gamma has also been shown to be a highly effective prophylactic therapy, but the cost remains prohibitive in resource-limited settings.1

Improved recognition of CGD and early diagnosis is the cornerstone in reducing morbidity and mortality, so that prophylaxis may be initiated early, infections may be treated promptly and possibly curative haematopoietic stem cell transplantation considered.

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References

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