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LETTER TO THE EDITORS

X-linked agammaglobulinemia with hearing impairment, dystonia-parkinsonism, and progressive neurodegeneration

Aloysius Domingo · Thomas G. P. M. Schmidt · Ela Barcelon · Marissa Lukban · Ana Westenberger · Christine Klein

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Dear Sirs,

X-linked agammaglobulinemia (XLA; OMIM#300755) is characterized by defects in B-cell maturity, predisposing to severe and fatal CNS infections [1]. Intravenous immunoglobulin (IVIg) therapy allows children with XLA to survive into adulthood. Interestingly, there are reports of progressive neurodegeneration occurring in IVIg-treated primary immunodeficiency patients, including those with no history of severe or chronic infections [2–4].

XLA is caused by mutations in the *BTK* gene [5–8], which encodes a tyrosine kinase that participates in B-lymphocyte differentiation. Notably, patients exhibiting an atypical course of XLA, complicated with sensorineural deafness and dystonia (i.e., resembling Mohr–Tranebjaerg syndrome), have been found to carry deletions spanning *BTK* and adjacent *TIMM8A* [6]. In this case report, we describe the clinical and genetic features of a chronically IVIg-treated Filipino XLA patient with childhood-onset hearing impairment, adult-onset dystonia, and progressive neurodegeneration.

The index patient was the only surviving XLA-affected offspring (Fig. 1a), and was receiving IVIg treatments at an average dose of 300–400 mg/kg since being diagnosed with XLA at 3 years of age. Mild hearing impairment was noted early (2 years old), however, language development was at par with age and thus, no formal audiometric evaluation was done. There were no instances of hospitalization for enteric or neurologic infections. At the age of 19 years, the patient started to have dysarthria and gait imbalance, associated with cognitive changes characterized as echolalia, palilalia, and perseveration. Within the year, the behavioral changes increased; the patient had become disinhibited and irritable, necessitating cessation of schooling. Neurologic examination at this time revealed limited horizontal gaze, dystonia in both hands, choreiform movements, postural tremor, and inability to perform tandem gait. Neuroimaging showed atrophy of the caudate nuclei (Fig. 1b). Electroencephalography was unremarkable. Brainstem evoked potentials displayed delayed latencies bilaterally, consistent with central hearing loss. Motor function and cognition further declined, rendering the patient bedbound, incontinent, akinetic mute with generalized hypertonia and spasticity, and dependent for all activities of daily living at 21 years of age. Cerebrospinal fluid parameters did not indicate an infection.

Due to the co-occurrence of XLA, dystonia, and hearing loss, we sequenced the entire coding regions of *BTK* and *TIMM8A*, which revealed a hemizygous c.1751G>A substitution in *BTK* (Fig. 1c), but no mutations in *TIMM8A*. As this transition affects the first nucleotide of exon 18 and potentially altering mRNA splicing, we proceeded to amplify exons 9–19 in cDNA. Sequencing revealed no splicing alterations, indicating that the consequence is

A. Domingo · T. G. P. M. Schmidt · A. Westenberger · C. Klein (✉)
Institute of Neurogenetics, University of Lübeck, Lübeck, Germany
e-mail: christine.klein@neuro.uni-luebeck.de

A. Domingo
Graduate School for Computing in Medicine and Life Sciences, University of Lübeck, Lübeck, Germany

E. Barcelon
Department of Neurosciences, Philippine General Hospital, University of the Philippines-Manila, Manila, Philippines

M. Lukban
Department of Pediatrics, Philippine General Hospital, University of the Philippines-Manila, Manila, Philippines

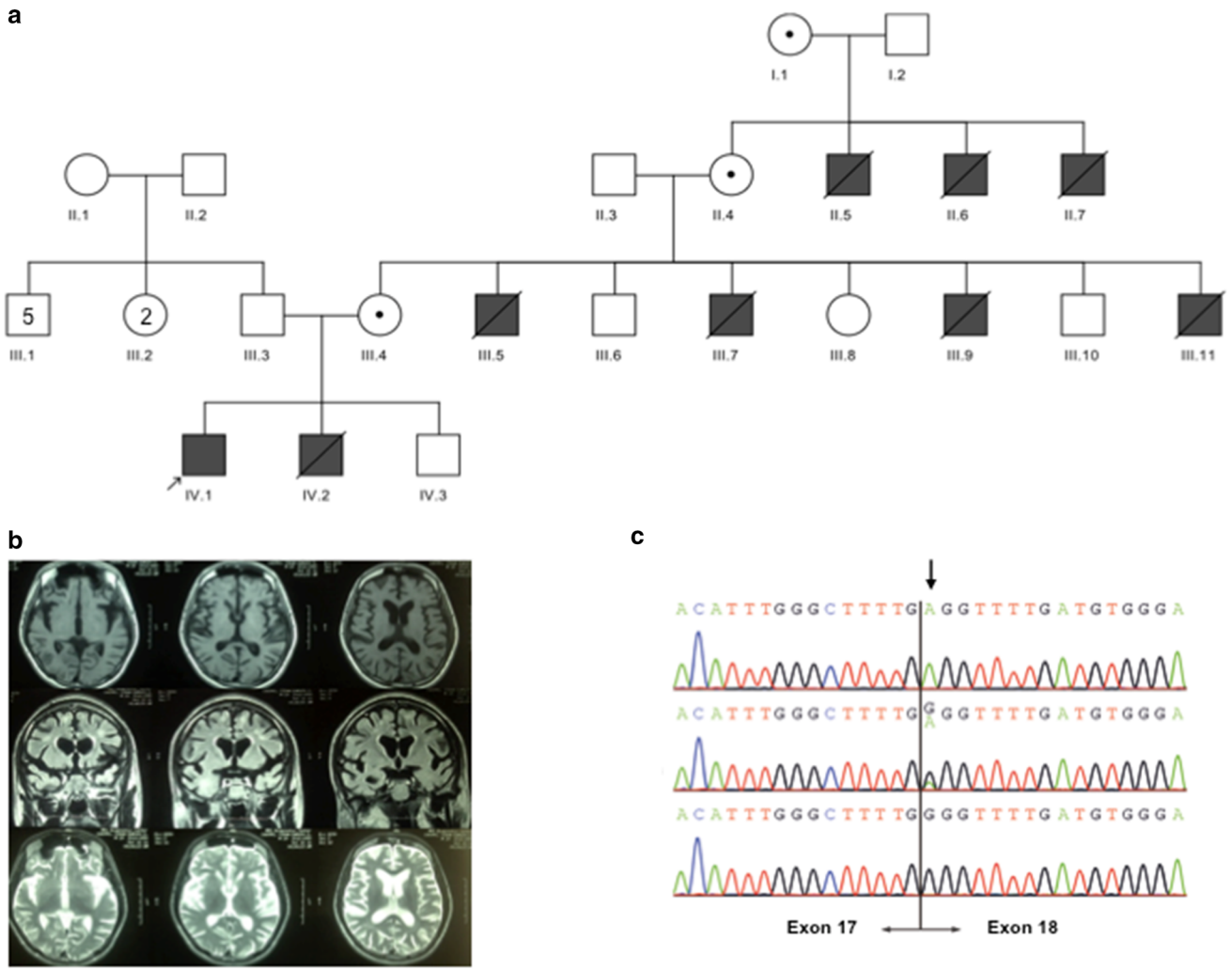

Fig. 1 Clinical and genetic features of a patient with XLA and neurodegeneration. **a** Pedigree showing a clear X-linked pattern of inheritance. **b** T1 and T2-weighted MRI revealing atrophy of the heads of the caudate nuclei. **c** Mutational analysis revealed a c.1751G>A change in the index patient (hemizygous, *first row*) and in his mother (III.4 in **a**; heterozygous, *second row*), affecting the first nucleotide of exon 18 of *BTK*. *Last row* is wildtype

rather a missense mutation (p.Gly584Glu). This mutation was already described in two XLA patients [7]; unfortunately, no clinical information was given in the report. In addition, a different transition at the same locus (c.1751G>C, p.Gly584Arg) was previously found in a European individual [8].

The etiology of neurodegeneration in this and other previously reported patients with agammaglobulinemia is currently unclear, although a relationship with chronic IVIg use has been suggested [2, 9]. Interestingly, the other reported IVIg-treated XLA patient presenting with dystonia-parkinsonism carried a c.1969G>C (p.Glu657Gln) substitution in exon 19 [4]. This mutation and the mutation we detected are both situated in highly conserved regions at the C-terminus of the BTK protein. The p.Gly584Glu change lies within the tyrosine kinase domain, and the p.Glu657Gln change is directly adjacent. Of note, *BTK* is highly expressed in the CNS and has been found to be important in neuronal differentiation [10]. Thus, although the number of patients is small, we hypothesize that the terminal tyrosine kinase domain plays a role in the function of BTK in the CNS, and that mutations in this region contribute to the neurologic phenotype. In future studies it will be important to investigate this potential genotype–phenotype correlation in a larger number of IVIg-treated XLA patients with and without neurodegeneration.

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Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical standard A consent for examination and genetic testing was obtained from the index patient's parents prior to the conduct of the study. This study was approved by the local ethics committee.

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