Most “Sporadic” Cases of X-linked Ichthyosis are not De Novo Mutations

S. A. CUEVAS-COVARRUBIAS1, M. VALDES-FLORES1, E. OROZCO OROZCO2, J. C. DÍAZ-ZAGOYA2 and S. H. KOFMAN-ALFARO1
1Department of Genetics, General Hospital of Mexico, 2Department of Biochemistry, School of Medicine, UNAM and 3Department of Experimental Pathology, CINVESTAV, IPN, Mexico DF, Mexico

INTRODUCTION

X-linked ichthyosis (XLI) is an inherited disease caused by a metabolic defect in the steroid sulphatase (STS) enzyme (1). The gene encoding STS is on Xp22.3 (2) and a complete deletion of the STS gene is present in most XLI cases (3). XLI patients present dark, regular and adherent skin scales as clinical characteristics (4). The extremities, trunk and neck are the major areas affected (5). Cryptorchidism in patients, delayed labour in carriers and corneal opacities in both patients and carriers are features frequently associated with the condition (6–8). Ichthyosis vulgaris shares many clinical features with XLI and a differential diagnosis must be made among both entities (9, 10). XLI diagnosis is possible by determining the STS activity in leukocytes or other cell lines (11–13). In the same way, XLI carriers can be identified through STS enzyme assay as their STS activity is lower than in normal controls (14, 15). In a previous report, 4 mothers of 5 unrelated sporadic Mexican cases of XLI showed an STS activity compatible with a carrier state, indicating that they presented the primary gene defect (16). In another report, the XLI carrier state was demonstrated in the mother of a patient classified as a de novo mutation (17). The aim of the present study was to corroborate in a larger group of XLI sporadic cases that most of them do not correspond to de novo mutations.

RESULTS AND DISCUSSION

We analysed 42 sporadic cases of XLI in a sample of Mexican patients. None of them presented an STS activity (0.00 pmol/mg protein/h) when compared with normal controls (0.84 ± 0.20 pmol/mg protein/h). The DNA from the 42 XLI patients showed no amplification of the 5’ and 3’ ends of the STS gene, corroborating the XLI diagnosis. These results allowed them to be classified as XLI patients. Increased blood cholesterol sulphate and electrophoretic mobility of low-density lipoprotein are two alternative methods of diagnosing XLI patients (21). Nevertheless, these procedures are not reli-

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able for carrier assessment, as the values observed in XLI carriers are similar to those found in normal controls. STS activity assay in leukocytes allows identification of XLI patients and carriers (14, 15). To confirm the validity of the STS assay to discard the XLI carrier state, 24 obligated carriers were included in this study. All showed an STS activity similar to that expected for XLI carriers as reported in previous studies (14, 15). When the STS assay was performed in the mothers of the 42 XLI patients, 36 presented an STS activity compatible with an XLI carrier state (0.20 ± 0.12 versus 0.84 ± 0.20 pmol/mg protein/h). The STS assay was performed twice in all XLI carriers. This data allows us to classify 85% of the sporadic cases as inherited cases and not as de novo mutations, thus corroborating our previous findings. These results seem to indicate that de novo mutation is not a common condition in XLI.

We could only analyse 3 maternal grandmothers of the XLI sporadic cases and found normal STS activity in all of them. We also found in 7 families normal STS activity in all sisters of the XLI individual carriers, supporting the fact that the patients’ mothers suffered the primary gene defect. In a previous report, an XLI individual case was analysed and the authors state that the gene defect of STS arose on an allele inherited from the pro-band’s clinically normal maternal grandfather (17). It would be interesting to determine in more cases whether the maternal or paternal X-chromosome with the gene defect is transmitted to the XLI carrier mother. This data could inform us whether the recombination events that produce the STS gene deletion occur during male or female meiosis.

We conclude that in our sample, 36 of 42 mothers of XLI “sporadic” cases were carriers of the gene defect, excluding the assignment of these patients as de novo mutations. It is necessary to perform similar analyses in other geographic areas to identify whether the transmission pattern observed in this study is a common condition in XLI. In addition, it is important to include the STS assay as a routine test for all potential XLI carriers in order to offer adequate genetic counselling.

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REFERENCES