Leber congenital amaurosis (LCA; OMIM 204000) is the most severe form of inherited retinal dystrophy that presents in infancy [1-6]. The currently recognized criteria for a diagnosis of LCA are: onset of blindness or poor vision (appearing early in the first year of life, before 6 months of age), sluggish pupillary reactions, roving eye movements/nystagmus, oculo-digital signs (eye-poking, eye-rubbing, etc.), extinguished or severely reduced scotopic and photopic electroretinogram (ERG), absent or abnormal visually evoked potentials, variable fundus (normal, marbled, albinotic with pigmentation).

LCA is generally inherited in an autosomal recessive manner, although some autosomal dominant families have been described [7-9]. Non syndromic LCA has been associated with mutations in 11 genes: AIPL1 [10], CEP290 [11], CRB1 [12], CRX [13], GUCY2D [3], IMPDH1 [14], LRAT [15], RPE65 [16], RPGRIP1 [17], RDH12 [18], and TULP1 [19].

Mutations in the CEP290 (OMIM 610142) gene have been shown to account for Joubert and Senior-Loken syndromes and to represent a frequent cause of non-syndromic LCA. The aim of the present study was to establish the prevalence of CEP290 c.2991_1655A>G in non-syndromic Spanish patients having LCA or early-onset retinitis pigmentosa (RP).

The aim of the present study was to establish the prevalence of CEP290 c.2991_1655A>G in non-syndromic Spanish patients having LCA or early-onset retinitis pigmentosa (RP).

METHODS

A total of 175 Spanish patients with retinal dystrophy were studied for the c.2991_1655A>G mutation. Informed consent was obtained from all study participants or from their legal guardians in accordance with the tenets of the Declaration of Helsinki (Edinburgh, 2000). Of these 175 non-syndromic patients, two different cohorts were investigated individually: 49 families affected with LCA and 126 affected with early-onset RP. We also recruited 50 unrelated Spanish healthy individuals. These results were compared to other populations.

The frequencies of mutated alleles were 6% in LCA cases and 0% in early-onset RP and healthy individual controls. These results were compared to other populations.

Conclusions: The CEP290 c.2991_1655A>G mutation frequency in Spanish non-syndromic LCA families is lower than that of other countries.
The study of the CEP290 c.2991_1655A>G mutation was performed on genomic DNA with Taq DNA polymerase and 1.5 mM MgCl2 under standard PCR conditions through use of primers designed to flank the mutation (Table 1) and used at 60 °C annealing temp. Products were further sequenced using the dRhodamine Terminator Cycle Sequencing Kit (ABI Prism, Applied Biosystems, Foster City, CA) on a 3100 automated sequencer (Figure 1).

RESULTS

We screened a total of 98 alleles in patients diagnosed with LCA and 252 alleles in patients diagnosed with early onset RP, respectively. The c.2991_1655A>G mutation was found only in the LCA group: two homozygous families and two heterozygous families. In total, we detected six alleles with the c.2991_1655A>G sequence change (6% of all the alleles). The mutation was not detected in the early-onset RP patients and the control group.

DISCUSSION

The results obtained in the Spanish population tested here (6% of mutated alleles, 6 out of 98) were different from other populations as den Hollander [22] and Perrault [23] indicated that the c.2991_1655A>G mutation may explain up to 21% of LCA cases because this mutation was detected in 16 (21%) of 76 unrelated patients with LCA. Also Perrault [23] noted the high frequency of CEP290 mutations in their series of LCA families from around the world (22%).

den Hollander and Perrault [22,23] suggested that the mutation led to aberrant splicing, but a small amount of correctly spliced product is present, which suggests that this may be sufficient for normal cerebellar and renal function but not for correct function of the photoreceptors. Complete loss of function of both CEP290 alleles leads to Joubert syndrome, whereas the retinal-restricted phenotype in LCA patient could be due to a residual CEP290 activity. In this study, the patients with the c.2991_1655A>G mutation had typical phenotypes of LCA.

These results indicate that the CEP290 c.2991_1655A>G mutation may not have a major causative role in Spanish LCA patients. Other studies with Spanish populations show that the frequencies of different genes present in retinal dystrophies are variable compared to other countries [24-26].

ACKNOWLEDGEMENTS

The authors thank everyone at the Genetics Service of Fundación Jiménez Díaz. We thank all the patients for their participation in this study. Elena Vallespín García is supported by Fundación Conchita Rábago de Jiménez Díaz. This research was supported by Ciberer CB06/07/0036, FIS PI040193, and EVI-GENORET LSHG-CT-2005-512036.

REFERENCES