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Review Article

Importance of genome-wide sequencing and MLPA techniques in gene diagnosis for nail patella syndrome

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Abstract

Nail patella syndrome (NPS) is a rare autosomal dominant hereditary disease caused by mutations in *LMX1B* gene, which characterized by nail malformations, patellar hypoplasia or absence. The development of technology for gene diagnosis provided conditions for our better understanding its pathogenesis. It is reported that mutation in *LMX1B* gene can cause NPS with an autosomal recessive inheritance. However, according to our experience, it is not rigorous to make such a conclusion without genome-wide sequencing or MLPA. By this article, we hope to make more researchers realize the importance of whole genome sequencing and MLPA technology in the diagnosis of nail patella syndrome, so as to guide genetic counseling and prenatal diagnosis more accurately.

INTRODUCTION

Nail patella syndrome (NPS, OMIM 161200) is a rare hereditary disease with the incidence roughly estimated at 1 in 50, 000 live births [1]. It is characterized by nail malformations, patellar apoplasia or hypoplasia, additional skeletal abnormalities encompassing iliac horns and elbow dysplasia, progressive nephropathy, and primary open angle glaucoma [2-4].

In 1998, Dreyer et al. [5] showed that NPS is caused by mutations in the *LMX1B* gene. The involvement of this gene in NPS was subsequently confirmed by others [6-7]. Mutations within the *LMX1B* gene have been detected in approximately 85% of families with NPS, including missense, nonsense, frameshift, splice-site mutations, and small intragenic insertions/deletions [8]. As we known, NPS is normally associated with autosomal dominant inheritance. However, some studies reported that mutations in *LMX1B* gene can cause NPS with an autosomal recessive inheritance. According to our experience, it is not rigorous to make such a conclusion without further validation.

Argument

In 2008, Bongers et al.[8] first described two entire *LMX1B* gene deletions and one smaller exonic *LMX1B* deletion by multiplex ligation-dependent probe amplification (MLPA) in a series of eight unrelated families with classical features of NPS in whom no pathogenic LMX1B mutation was found by sequence analysis. Their result strongly confirmed that haploinsufficiency is the principal pathogenetic mechanism of NPS.

Similarly, we identified a microdeletion encompasses the entire *LMX1B* gene in a Chinese family with NPS [9]. In this family, no mutation was found in the proband by direct DNA sequence analysis. In contrast, two hemizygous synonymous variants, c.441A>G (p.E147) and c.726G>C (p.S242), were detected in the proband's father. These genetic alterations passed on to the proband's normal elder sister. Notably, these two point mutations were not identified in the proband and his mother by DNA sequencing. These sequence results suggest a haploinsufficiency of *LMX1B* as the father's synonymous variants were not passed on to the proband. This hypothesis was confirmed by MLPA analysis, which showed a single-copy deletion of the entire *LMX1B* in the proband and his father. The determination of the deletion breakpoints by Illumina genome-wide DNA analysis beadchip showed that the heterozygous deletion was located in chromosome 9q33.3 and spanned about 0.66 Mb in size.

The same synonymous mutation, c.726G>C (p.S242) of *LMX1B*, which detected in our research has been also reported in a Korean Family with NPS [10], the author could not demonstrate any segregation of this synonymous mutation with NPS. However, our findings indicate that the synonymous substitutions could be single-nucleotide polymorphisms rather than pathogenic mutations and have no correlation with NPS. Thus, there must be other pathogenic mechanism for the observed phenomenon in this Korean family. It is necessary to carry out MLPA detection or genome-wide sequencing to further find the etiology.

Recently, autosomal recessive inheritance was reported in two unrelated consanguineous Saudi families with NPS caused by missense mutation (c.268C>T p.Leu90Phen) in exon 2 of the *LMX1B* gene [11, 12]. All patients in the families were found the gene mutation which did not exist in healthy family members, so the recessive inheritance was determined. But

the researchers didn't carry out further functional verification, can't prove that this missense mutation could affect *LMX1B* gene function. In addition, the patients didn't perform the whole genome sequencing or MLPA to exclude the possibility of haploinsufficiency of *LMX1B* gene. So we believe that whether the NPS could recessive inheritance needs further verification.

In summary, it doesn't mean that the patients did not have gene defects even if no mutation was detected by direct DNA sequencing. May be some one has haploid deficiency of *LMX1B* gene during these patients. Similarly, not all mutations were pathogenic and they may be innocuous polymorphisms. For this part of patients, MLPA detection or genome-wide sequencing may help them clarify the etiology.

CONCLUSION

Genetic counseling is crucial for any genetic disorder. By this article, we hope to make more researchers realize the deficiency of direct DNA sequence and the importance of genome-wide sequencing and MLPA technology in the diagnosis of nail patella syndrome. We believe that more NPS patients can find the cause by genome-wide sequencing and MLPA , so as to guide genetic counseling and prenatal diagnosis more accurately and decrease the birth of patient

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