Nail-Patella Syndrome: evidence for genetic heterogeneity

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INTRODUCTION

Nail patella syndrome (NPS) is a hereditary osteo-onychodysplasia with autosomal dominant inheritance. Prevalence is estimated at 1/50,000. This affection comprises characteristic skeletal anomalies (nail dysplasia, hypoplastic or absent patella, elbow dysplasia, iliac horns. See Figure 1.) Frequently associated with ocular or renal involvement. NPS results from mutations in the LMX1B gene, localized in 9q34 and spanning approximately 95 kb. This gene encodes a transcription factor belonging to the LIM homeodomain protein family. This protein plays a crucial role in the dorso-ventral polarisation of the limbs.

Mutations responsible for haploinsufficiency of LMX1B are identified in 85-90% of patients. In about 10-15% of patients, no mutation is identified in LMX1B. To our knowledge, the hypothesis of a genetic heterogeneity has never been studied in this disease.

We study 4 families affected with typical NPS for whom routine screening did not identify a mutation in LMX1B (exons and flanking introns sequencing, MLPA). We performed NGS for the whole LMX1B gene, revealing no mutation in coding or non-coding sequence. In one family, results provide clues for non-linkage at 9q34, confirming the likelihood of a genetic heterogeneity.

RESULTS

Number of variants identified by whole LMX1B sequencing in 5 NPS patients (single nucleotide variations and indels). Results after successive filtering (1/ allele frequency between 20-80%; 2/ variants identified in controls; 3/ dSNP135, rs frequency<5%) and number of remaining variants validated by Sanger sequencing, segregating with the phenotype in the family and absent in 100 control chromosomes.

<table>
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<th>Patient</th>
<th>Number of variants</th>
<th>20-80%</th>
<th>85-90%</th>
<th>Exon</th>
<th>Intron</th>
<th>Validated by Sanger sequencing</th>
<th>Controls</th>
<th>Exon-intron boundaries</th>
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For one family (Patients 1 and 2), SNPs segregation analysis show no linkage in LMX1B locus (9q34), suggesting that this gene is not directly implicated in the phenotype.

DISCUSSION

LMX1B is the major gene responsible for Nail-Patella syndrome, 85 to 90% of patients harboring a mutation responsible for haploinsufficiency. We studied 4 families affected with NPS for whom routine screening did not identify a mutation in LMX1B. We performed whole LMX1B next generation sequencing in 5 patients and found 2 intronic single nucleotide variants in 2 families. These variants lie between the large intron 2, at long-distance from the exon-intron boundaries, thus suggesting that an consequence on its splicing is unlikely. Additionally, the regions concerned are not evolutionary conserved, and no binding-site for transcription factors are predicted in silico. Assuming these data, these are likely to be rare non-pathogenic variants. Furthermore, segregation of SNPs in one of the families (patients 1 and 2) shows no linkage in 9q34, suggesting a genetic heterogeneity. LMX1B transcript expression studies and whole exome sequencing are in progress to further understand the molecular mechanisms involved in these families affected with Nail Patella Syndrome.

The authors declare no conflict of interest.