J Pediatr (Rio J). 2014;90(1):58–64

Jornal de Pediatria
www.jped.com.br

ORIGINAL ARTICLE

Study of the association between the BMP4 gene and congenital anomalies of the kidney and urinary tract☆

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Received 8 March 2013; accepted 4 June 2013
Available online 13 October 2013

KEYWORDS
Association study;
BMP4;
Congenital anomalies of the kidney and urinary tract;
CAKUT

Abstract
Objective: to determine the frequency of different phenotypes for congenital anomalies of the kidney and urinary tract (CAKUT) in a Brazilian sample, and to evaluate the association between the CAKUT phenotypes and the BMP4 gene.
Methods: in this study, 457 Brazilian individuals were analyzed in an attempt to establish the association between the BMP4 gene and the CAKUT diagnosis. A case-control sample was genotyped for three BMP4 gene polymorphisms.
Results: association data was established with CAKUT sample as a whole and with the three most important CAKUT phenotypes: multicystic dysplastic kidney disease (MDK), ureteropelvic junction obstruction (UPJO) and vesicoureteral reflux (VUR). When the sample was segregated in these three phenotypes, associations between the BMP4 gene were observed with UPJO and with MDK. Conversely, VUR was not associated to the polymorphisms of the BMP4 gene.
Conclusions: the present data suggest that Brazilian individuals with polymorphisms of the BMP4 gene have a higher risk to develop CAKUT, especially the malformations related to nephrogenesis and initial branching such as MDK and UPJO. Conversely, VUR appeared not to be related to BMP4 gene.

☆ Please cite this article as: Reis GS, Simões e Silva AC, Freitas IS, Heilbuth TR, Marco LA, Oliveira EA, et al. Study of the association between the BMP4 gene and congenital anomalies of the kidney and urinary tract. J Pediatr (Rio J). 2014;90:58–64.

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0021-7557
http://dx.doi.org/10.1016/j.jped.2013.06.004

PALAVRAS-CHAVE
Estudo de associação;
BMP-4;
Anomalias congênitas do rim e do trato urinário;
CAKUT

Estudo da associação entre o gene BMP-4 e anomalias congênitas do rim e trato urinário

Resumo

Objetivo: determinar a frequência de diferentes fenótipos de anomalias congênitas do rim e trato urinário (CAKUT) em uma amostra brasileira e avaliar a associação entre os CAKUT e o gene BMP-4.

Métodos: neste estudo, analisamos 457 indivíduos brasileiros em uma tentativa de estabelecer a associação entre o gene BMP-4 e o diagnóstico de CAKUT. As amostras de caso e de controle foram genotipadas em busca de três polimorfismos do gene BMP-4.

Resultados: os dados de associação foram estabelecidos com a amostra de CAKUT como um todo e com os três fenótipos de CAKUT mais importantes: rim displásico multicístico (RDM), obstrução da junção ureteropélvica (UPJO) e refluxo vesico-ureteral (VUR). Quando a amostra foi separada nesses três fenótipos, encontramos associações entre o gene BMP-4 com UPJO e com RDM. Por outro lado, o VUR não foi associado aos polimorfismos do gene BMP-4.

Conclusões: esses dados sugerem que os indivíduos brasileiros com polimorfismos do gene BMP-4 apresentam maior risco de desenvolver CAKUT, principalmente as malformações relacionadas a nefrogênese e ramificação inicial, como RDM e UPJO. Por outro lado, o VUR parece não estar relacionado ao gene BMP-4.

Introduction

Congenital anomalies of the kidney and urinary tract (CAKUT) occur in 0.5% to 6% of all pregnancies,[1,2] and are common causes of end stage renal disease in children.[3] CAKUT are polygenic traits and might be the result of multifactorial conditions such as *de novo* mutations, teratogenic substances, and maternal diet.[3] Several candidate genes, including some that are expressed during nephrogenesis, have been associated with CAKUT.

Bone morphogenetic proteins (BMPs) are involved in the organogenesis of almost all vertebrates, regulating many aspects of development, including those of the urinary tract. The BMP4 gene, located in chromosome 14q22.2, is a member of the transforming growth factor-beta (TGF-β) superfamily.[4] During urogenital development, BMP4 controls nephrogenesis and ureter branching and outgrowth,[5,6] as well as the activity of the metanephric mesenchyma, ensuring that the ureteric bud is formed adjacent to the metanephron mesenchyme.[7] Recent data from Chi et al. demonstrated that BMP4 also reduces the expression of important genes related to nephrogenesis process, such as glial cell line-derived neurotrophic factor gene (GDNF), paired box 2 gene (PAX2) and wingless-type MMTV integration site family, member 11 gene (WNT11).[8,9]

Functional studies showed that the BMP4 mutated gene generates an alternative protein complex with functional impairment.[10] Miyazaki et al. demonstrated that mice with reduced expression of BMP4 ($BMP4^{+/-}$). The authors demonstrated three different patterns of malformations: hydronephrosis with hypo/dysplastic kidneys, hydronephrosis due to ureterovesical junction obstruction, and duplex kidney with bifid ureter.[9] In mice $BMP4^{+/-}$, 60% coursed with hypo/dysplastic kidneys, 32% with ureterovesical junction obstruction, and 8% with bifid ureter.[9] In 2008, Weber et al. identified three missense mutations in five CAKUT patients, presenting kidney aplasia or hypoplasia and dysplasia.[11] From a mice model, it is known that only some $BMP4^{+/-}$ mice present CAKUT, which leads to the assumption that BMP4 is a fine-tuning protein that modulates the amount of functional nephrons and the ureteric branching.[9,11,12] Based on these previous findings, the authors hypothesized that the BMP4 gene would be associated with CAKUT in a Brazilian sample. In this study, the association between three SNPs (rs17563, rs2071047, and rs762642) and CAKUT in general were evaluated, as well as the association to specific phenotypes in a Brazilian CAKUT sample. Since the Brazilian population presents a diverse genetic background,[13] this study aimed to evaluate the role of the BMP4 gene in a case/control Brazilian sample.

Methods

Case and control groups

The study followed the ethics guidelines of the Declaration of Helsinki, and was approved by the local ethics committee. An informed consent was obtained from all subjects.

Cases

At the Division of Fetal Medicine, all fetuses underwent a detailed ultrasound (US) scan aimed at detecting renal abnormalities and other malformations as previously detailed.[14–16] Postnatally, infants who presented fetal renal pelvic dilatation or other renal alterations underwent systematic investigation for urinary tract anomalies, and were prospectively followed up at the Pediatric Nephrology Unit according to a systematic protocol, as previously described.[14,16] Renal pelvic dilatation in fetal US was considered to be present if the maximum anteroposterior diameter of the renal pelvis was $\geq$ 5 mm on prenatal US after 28 weeks' gestation.[16] Associated hydronephrosis was defined as dilatation of other segments of the urinary tract, in