

Case Report

Renal hypoplasia without optic coloboma associated with PAX2 gene deletion

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Introduction

PAX2 gene encodes a transcription factor that belongs to the paired-box family of homeotic genes and is widely expressed during the development of both ductal and mesenchymal components of the urogenital system.

Human PAX2 gene maps on chromosome 10q24-q25 and comprises 12 exons. Exons 1–4 encode the paired box domain, which is essential for DNA-binding activity. At early stages, the gene is expressed in neural tube cells. Later on, its expression is detected in the developing urogenital system as well as in the ear, eye and central nervous system (CNS). In the urogenital system, PAX2 is expressed in the induced nephrogenic mesenchyme, during the mesenchymal-to-epithelial transition that preludes to glomerulus formation. Its expression is also detected in the branching ureteric bud, in collecting duct epithelia and in uterus, oviduct, vas deferent and epididymis. PAX2 is thought to orchestrate the pattern of gene expression, including that of other PAX family members, also during other organ development.

In humans, PAX2 heterozygous mutations, arising *de novo* or inherited in an autosomal dominant fashion, have been associated with renal coloboma syndrome (RCS) (OMIM 120330). Phenotypic features of the syndrome have been related to PAX2 haploinsufficiency. Haploinsufficiency deals with the notion that level of protein is critical to its correct function.

RCS hallmarks are bilateral optic nerve coloboma and renal hypoplasia. The term coloboma includes developmental abnormalities of the optic nerve (ranging from mild optic disc dysplasia to optic nerve aplasia), retina, choroid and iris [1]. Renal hypoplasia is the most common renal abnormality (60% of patients). Oligomeganephronia, renal dysplasia or multicystic dysplastic kidney have also been reported [2–4]. Additional congenital anomalies may occur with variable penetrance and include: vesicoureteric reflux, which is detected in approximately 25% of patients, even though its frequency may be underestimated as it naturally improves with age; auditory anomalies, namely sensorineural deafness; skin and joint abnormalities, which occur in <20% of patients, and CNS anomalies. A significant degree of phenotypic variation may be observed, even between family members who share the same mutation [5]. Clinical features in humans strongly resemble those observed in PAX2 heterozygous mutant mice.

The effects of PAX2 mutations have been studied through the development of three different PAX2 mutant mouse models: Krd, PAX2^{1NEU} and PAX2-knockout mice. Homozygous carriers of the three different strains of PAX2 mutant mice died in embryonic stages (Krd), at birth or soon after (PAX2^{1Neu} and PAX2-knockout). Irrespective of the type of mutation, heterozygous mutant mice exhibited a broad range of renal phenotypes, from renal agenesis to mild affected or nearly normal urinary tract. They also showed retinal and optic nerve colobomatous changes, while genital tract was normal and CNS and ear might be unaffected.

PAX2 mutations have also been reported in patients with renal hypodysplasia without eye anomalies [4,6,7]. No PAX2 gene complete deletion has yet been reported in the literature.

Herein we describe a 6-year-old girl with an interstitial deletion of the long arm of chromosome 10, involving the entire PAX-2 locus.

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Case report

The girl was referred to our hospital at the age of 5 months because of mild chronic renal failure since the first days of life and a severe renal impairment on imaging investigations.

She had a remarkable past medical history, as she was delivered at 35 weeks of gestation (WG) after an oligohydramnios-complicated pregnancy, with difficult kidneys and bladder ultrasonographic visualization since the 20th WG. Her birth weight was 2500 g. During the first weeks of life, she presented poor weight gain, hypotonia and feeding difficulties. Physical examination was remarkable for Potter-like facial features. Laboratory studies at age 13 days showed a serum creatinine level of 133 $\mu\text{mol/l}$. Family history was non-contributory.

On admission to our Department, serum creatinine level was 102 $\mu\text{mol/l}$ and blood urea nitrogen was 18.2 $\mu\text{mol/l}$, while remaining laboratory findings were not noteworthy. Renal ultrasonography revealed a left hypoplastic kidney and a contralateral one displaying diffusely increased echogenicity and diminished cortico-medullary differentiation. No vesicoureteric reflux was observed on contrast-voiding cystography. By the age of 2 years, her somatic growth was satisfactory, but psychomotor development was inadequate. Mild facial dysmorphic features and joint laxity were also evident on physical examination. Ophthalmological examination at 5 years of age excluded the presence of optic nerve coloboma. No sensorineural hearing loss was present. No anomalies to other organs were found in further investigations. On recent investigations conducted at 6 years of age, serum creatinine and blood urea nitrogen level were 292 $\mu\text{mol/l}$ and 20.1 $\mu\text{mol/dl}$, respectively.

A high resolution cytogenetic analysis detected an interstitial deletion of the long arm of chromosome 10. The girl's karyotype was: 46,XX,del(10)(q23.2q24.3). Further molecular analysis by CGH-array demonstrated that the deletion spanned 7.9 Mb between 95.2 e 103.1 Mb. About 90 genes were identified in the deleted region. Among these genes, PAX2 drew our attention for its important role in nephrogenesis and in renal developmental disorders. Therefore, a quantitative analysis by Real Time PCR on patient blood DNA was performed and confirmed the lack of one copy of PAX2 gene.

Discussion

Several different PAX2 mutations, including frameshift, missense and nonsense mutations, have been identified in patients with RCS. A single case of translocation with a breakpoint on chromosome 10q24.3 was also reported (PAX2 allelic variant database-<http://pax2.hgu.mrc.ac.uk>). Most frequently, the reported mutations involve exon 2 (N-terminal

portion of the paired box domain) and lead to a truncated protein that lacks the ability to bind DNA. Mutations not affecting the paired box domain probably lead to a PAX2 protein that should still be able to bind DNA, but it may lack the ability to regulate the expression of target genes [8]. Whether PAX2 disease-causing mutations may result in a complete or partial loss of the protein function, i.e. PAX2 haploinsufficiency, or in a mutated protein that may act in a dominant negative effect, is still to be elucidated.

In the present report, we describe a girl with a deletion in chromosome 10 involving the entire PAX2 locus and thus resulting in PAX2 complete haploinsufficiency. To our knowledge, this is the first case of heterozygous PAX2 gene deletion with renal abnormalities, but not optic coloboma in humans. The homologue murine deletion, obtained in the Krd mouse, resulted in PAX2 haploinsufficiency with a renal phenotype of hypoplasia, cysts or agenesis and ocular anomalies.

In the literature, four patients with renal abnormalities associated with PAX2 mutations but without ocular anomalies were reported [4,6,7]. Indeed Nishimoto described a novel PAX2 mutation, affecting exon 9, in a child with renal hypoplasia but no optic nerve coloboma [6]. Moreover, two novel mutations localized in exon 2 have been reported in patients with renal hypodysplasia but no optic nerve coloboma [4]. In a recent study, a novel PAX2 mutation in exon 8 was detected in a RCS family, one member of which had no detectable eye defects [7].

In eye embryonic development, PAX2 is thought to take part in the so-called coloboma gene network (CGN), a complex network of transcriptional factors, cell cycle regulators and signalling molecules, which act in concert to form different ocular compartments, regulate cell proliferation or apoptosis and specify cell identities [9]. There are two master control genes, SHH and PAX6, that underpin the CGN, acting as transcriptional regulators of many other genes involved in the network.

In patients with coloboma but no renal anomalies, PAX2 mutations have never been detected [1,10]. Our patient carries a complete PAX2 haploinsufficiency, but does not display optic coloboma. It is, therefore, possible that the lack of coloboma in our patient could be explained by the absence of the mutated protein due to complete gene deletion. This suggests that eye anomalies in RCS may be due to a dominant negative effect of the mutated protein rather than to PAX2 haploinsufficiency.

Conclusion

To our knowledge, this is the first reported case of human PAX2 gene deletion. The PAX2 mutation studies to date have focused on identifying mutations in patients who have both ocular and renal anomalies.

It is, therefore, possible that there is a population of patients with isolated renal hypodysplasia who carry PAX2 deletions.

Conflict of interest statement. None declared.

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