【Symposium 8-3】

Autosomal recessive renal tubular dysgenesis: From Bedside to Bench

Min-Hua Tseng

Division of Nephrology, Department of Pediatrics, Chang Gung Memorial Hospital and Chang Gung University

Autosomal recessive renal tubular dysgenesis (ARRTD) is an inherited disorder characterized by the absence or poor-differentiation of proximal convoluted tubules, profound arterial hypotension, pulmonary hypoplasia, and anuria with a very high mortality. Nearly all patients die either in utero or within the first few postnatal days secondary to refractory hypotension and/or pulmonary hypoplasia. Due to its extreme rarity, its exact prevalence is unknown. In 2005, Gribouval et al described mutations in four different genes encoding proteins of the renin-angiotensin system (RAS) resulting in ARRTD.10 These mutations were identified as either AGT encoding angiotensinogen, REN encoding renin, ACE encoding angiotensin converting enzyme (ACE), or AGTR encoding angiotensin II (Ang II) receptor. RAS is critical in maintenance of blood pressure and blood perfusion of vital organs including kidneys during fetal life and also a key regulator of kidney development. A defect in RAS has been proposed to be responsible for the development of renal tubular dysgenesis and ARRTD via compromised renal perfusion14,15 and defective metanephritic kidney development. Without a clear understanding of how mutations affecting the RAS can contribute to the pathogenesis of this disease, specific therapeutic strategies cannot be developed.

We have identified six patients with ARRTD from ten unrelated Taiwanese families in the past 7 years. All affected neonates of ARRTD in Taiwan were caused by identical homozygous large deletion of AGT gene. Further study showed the prevalence of AGT heterozygosity of healthy Taiwanese is 1%, which point this disease is not rare in Taiwan. The identified AGT mutation was demonstrated to attenuate the interaction of the truncated AGT protein with renin. By creating conditional knockout mice, we examined the potential rescue therapy recently.