S-D8

WT1 사구체병증 소아환자에서 유전자형 및 표현형 분석

서울대학교 어린이병원 소아청소년과[1], 양산부산대학교 어린이병원 소아청소년과[2]
삼성서울병원 소아청소년과[3], 세브란스 어린이병원 소아청소년과[4]
울산의대 서울아산병원 소아청소년병원 소아청소년과[5], 건국대학교병원 소아청소년과[6]

안요한[1], 강희경[1], 김성헌[2], 조희연[3], 신재일[4], 이주훈[5], 박영서[5], 김교순[6], 하일수[1], 정해일[1]

Genotype-phenotype Analysis in Pediatric Patients with WT1 Glomerulopathy

Yo Han Ahn[1], Hee Gyung Kang[1], Seong Heon Kim[2], Hee Yeon Cho[3], Jae Il Shin[4]
Joo Hoon Lee[5], Young Seo Park[5], Kyo Sun Kim[6], Il-Soo Ha[1], Hae Il Cheong[1]

Department of Pediatrics[1], Seoul National University Children's Hospital
Department of Pediatrics[2], Pusan National University Children's Hospital
Department of Pediatrics[3], Severance Children's Hospital
Department of Pediatrics[4], Samsung Medical Center
Department of Pediatrics[5], Asan Medical Center
Department of Pediatrics[6], Konkuk University Hospital

Objectives: WT1 gene mutation is important cause of congenital/infantile nephrotic syndrome typically showing diffuse mesangial sclerosis, often found in Deny-Drash syndrome (DDS). WT1 also causes focal segmental glomerulosclerosis (FSGS), comprising Frasier syndrome (FS). Mutations in exon 8 or 9 of WT1 result in DDS, characterized by infantile nephrotic syndrome (NS), ambiguous genitalia, and high incidence of Wilms tumor. Intronic mutation of donor splice-site at intron 9 causes FS, with FSGS, XY sex reversal, and high incidence of gonadoblastoma. In this study we investigate genotype-phenotype correlation in Korean pediatric patients with WT1 gene mutations.

Methods: Pediatric patients with steroid resistant NS (SRNS) were screened for WT1 gene mutations. In four patients, WT1 mutations were found unexpectedly during investigating genetic cause of CKD without known etiology. Medical records were reviewed for a total of 24 patients with WT1 gene mutations.

Results: The initial manifestations of the patients were infantile NS (n=9), isolated SRNS (n=8), Wilms tumor (n=3), and end-stage renal disease (ESRD) of unknown etiology (n=4, all phenotype female). Median onset age of SRNS was 1.25 (0.03-12.3) years for 18 patients (M:F 4:14, phenotype) who presented with SRNS. Sixteen patients attained ESRD at median age of 1.13 (0.07-20.4) years. Six patients developed Wilms tumor (n=4), gonadoblastoma (n=1), and lymphoma after kidney transplantation (n=1). Nine patients were phenotypically females with karyotype 46, XY. Three patients had diaphragmatic hernia, and 11 patients had genital abnormalities. Genetic analysis revealed intronic mutations in 12 patients and exonic mutations in 12 patients. Patients with intronic mutations presented as isolated SRNS at a significantly older age and with a slower progression to ESRD, compared with patients with missense mutations. Renal histopathology revealed diffuse mesangial sclerosis in 6 (100%) patients with exonic mutations and FSGS in 7 (87.5%) patients with intronic mutations.

Conclusions: WT1 mutations constitute an important genetic cause of SRNS, with a wide spectrum of renal and extrarenal phenotypes. The genetic diagnosis appears important for WT1 disease in view of risk of cancers. We suggest that pediatric patients with SRNS and female patients with chronic kidney disease of unknown origin need WT1 gene screening.

Key Words: 신증후군, WT1 유전자 돌연변이, 말기신부전
Nephrotic syndrome, WT1 gene mutation, End-stage renal disease