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Original Article

Nineteen novel *NPHS1* mutations in a worldwide cohort of patients with congenital nephrotic syndrome (CNS)

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Abstract

Background. Recessive mutations in the *NPHS1* gene encoding nephrin account for ~40% of infants with congenital nephrotic syndrome (CNS). CNS is defined as steroid-resistant nephrotic syndrome (SRNS) within the first 90 days of life. Currently, more than 119 different mutations of *NPHS1* have been published affecting most exons.

Methods. We here performed mutational analysis of *NPHS1* in a worldwide cohort of 67 children from 62 different families with CNS.

Results. We found bi-allelic mutations in 36 of the 62 families (58%) confirming in a worldwide cohort that about one-half of CNS is caused by *NPHS1* mutations. In 26 families, mutations were homozygous, and in 10, they were compound heterozygous. In an additional nine patients from eight families, only one heterozygous mutation was detected. We detected 37 different mutations. Nineteen of the 37 were novel mutations (~51.4%), including 11 missense mutations, 4 splice-site mutations, 3 nonsense mutations and 1 small deletion. In an additional patient with later manifestation, we discovered two further novel mutations, including the first one affecting a glycosylation site of nephrin.

Conclusions. Our data hereby expand the spectrum of known mutations by 17.6%. Surprisingly, out of the two siblings with the homozygous novel mutation L587R in *NPHS1*, only one developed nephrotic syndrome before the age of 90 days, while the other one did not manifest until the age of 2 years. Both siblings also unexpectedly experienced an episode of partial remission upon steroid treatment.

Keywords: mutation analysis; nephrotic syndrome; *NPHS1*

Introduction

The protein nephrin [1] is an essential component of the renal glomerular slit diaphragm [2], which is formed by adjacent glomerular epithelial cells (podocytes). The zipper-like structure of the glomerular slit membrane consists of complexes that contain the molecules neph1 and nephrin, which interact between neighbouring podocyte foot processes [3]. Nephrin contains eight immunoglobulin-like domains, a fibronectin type III-like domain, a transmembranous domain and a short intracellular domain [1]