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Research Article

Novel Mutations in *NPHS1* are a Rare Cause of Congenital Nephrotic Syndrome

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Abstract

Congenital Nephrotic Syndrome (CNS) is an autosomal recessive disorder most commonly caused by mutations in *NPHS1* which encodes the nephrin protein. It is characterized by massive proteinuria, hypoalbuminemia and gross edema in the neonatal period. This report describes two male siblings of mixed Filipino and German descent who both presented in the neonatal period with CNS. Sequencing of *NPHS1* demonstrated a previously unreported novel heterozygous mutation in exon 11 denoted c.1437C>G (p.Y479X). This mutation creates a premature stop codon which is very likely to result in a truncated protein or loss of protein production, and it is therefore likely disease-causing. Additionally a previously unreported novel heterozygous large deletion encompassing exons 25, 26, 27, 28 and 29 of the *NPHS1* gene was detected by qPCR. This mutation is very likely to result in loss of protein production, and it is therefore likely disease-causing. We note that long deletions are particularly rare in CNS [4,5], and this could be due to the lack of clinically available testing for deletions in *NPHS1* – at this time deletion/duplication analysis is not clinically available in the US. In summary, this report describes two siblings affected with previously undescribed mutations in *NPHS1* which are a cause of CNS.

Keywords: Congenital Nephrotic syndrome; NPHS1; c.1437C>G; Exons 25, 26, 27, 28 and 29

Abbreviations

CNS – Congenital Nephrotic Syndrome; FSGS - Focal Segmental Glomerulosclerosis; AFP – Alpha Fetal Protein; MoM – Multiples of Median

Introduction

Congenital Nephrotic Syndrome (CNS) is an autosomal recessive disorder most commonly caused by mutations in *NPHS1* which encodes the nephrin protein. It is characterized by massive proteinuria, hypoalbuminemia and gross edema in the neonatal period. Kidney biopsy may demonstrate non-specific findings such as minimal change disease, focal segmental glomerulosclerosis (FSGS) or diffuse mesangial proliferation [1,2,3]. Due to the high incidence in the Finnish population it also known as Finnish Congenital Nephrosis. In general kidney transplant is considered the only effective therapy as immunosuppressive therapy is ineffective and medication such as ACE inhibitors and diuretics are non-curative. End-stage renal failure will occur in childhood without treatment. Recurrence after transplant is well documented and antinephrin antibodies likely have a role in pathogenesis of recurrence [1].

Case Presentation

This report describes two male siblings of mixed Filipino and German descent who both presented in the neonatal period. The first was born at 36 weeks to a 25 year old G1P1 mother after an uncomplicated pregnancy with no prenatal screening. Birth weight was 2.18kg and he was discharged a day of life 3 after treatment for neonatal jaundice. He presented at 3 weeks of age with massive edema and ultimately required a living related donor kidney transplant from his father at 9 months of age. Molecular sequencing of NPHS1 during this time revealed a novel heterozygous mutation, c.1437C>G, however failed to identify the second mutation.

The second sibling had a positive prenatal screen and the pregnancy was closely followed, it which was notable for an elevated MS-AFP of 24.16 multiples of median (MoM) and an extremely elevated amniotic fluid AFP (AF-AFP) of 79.06 MoMs which virtually confirmed the diagnosis of CNS. Karyotype was performed prenatally which was normal 46, XY male and a fetal echocardiogram was normal. The parents had already been informed of a 25% recurrence risk in this pregnancy.The patient was born at 29+5 weeks gestation via C-section secondary to non-reassuring fetal heart notes to a now 28 year old G2P2 mother and 29 year old father and weighed 1.76kg, was 42cm in length and head circumference of 40cm. Apgars were 1 and 7 at one and five minutes respectively. Ultimately this sibling expired in the neonatal period due to overwhelming medical problems including anuria with renal failure.

Materials & Methods

Sequencing and deletion/duplication analysis of *NPHS1* was sent to a commercial laboratory in Europe given deletion/duplication analysis was unavailable in the US.

Summary of Results

Sequencing of *NPHS1* demonstrated a previously unreported novel heterozygous mutation in exon 11 denoted c.1437C>G (p.Y479X). This mutation creates a premature stop codon which is very likely to result in a truncated protein or loss of protein production, and it is therefore likely disease-causing. A second

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mutation was not found on sequencing therefore deletion testing was sent to ascertain the second mutation causing CNS in the siblings. Deletion testing reported a previously unreported novel heterozygous large deletion encompassing exons 25, 26, 27, 28 and 29 of the *NPHS1* gene was detected by qPCR. This mutation is very likely to result in loss of protein production, and it is therefore likely disease-causing. Parental testing confirmed the mutations were inherited in *trans*; the sibling's father carried the c.1437C>G mutation and the mother carried the deletion encompassing exons 25, 26, 27, 28 and 29.

Discussion

Nephrin is necessary for the proper functioning of renal filtration and acts as a glomerular filtration barrier protein. It is located in glomerular podocytes at the slit diaphragm. CNS is a genetically and clinically heterogeneous disorder with mutations in both *NPHS1* and *NPHS2* known to be disease causing. In particular, patients with *NPHS1* mutations appear to have a more severe phenotype which generally presents at less than 1 month of age. The most commons mutations in *NPHS1* are the Fin_{Major}(c.121delCT; p.L41fs) and Fin_{Minor}(c.3325C>T; p.R1109X) deletions which account for over 90% of mutations in the Finnish population. Outside of the Finnish population they account for roughly 50% of cases. There are over 140 other mutations that have been described which fall into categories of either missense, non-sense, splice-site or small deletions. There is only one other report of large deletion mutations as a cause of CNS. Whilst this maybe a true representation of the mutation spectrum we feel more likely there is ascertainment bias as large deletions are not commonly tested for – at this time deletion/duplication analysis is not clinically available in the US. In addition we note that a molecular diagnosis is only found in around 80% of cases of CNS and therefore postulate lack of testing of long deletions as a possible cause of this. This limits the ability to confirm a molecular diagnosis and subsequent prenatal options. Indeed in our case, due to the lack of deletion testing in the United States, only sequencing was sent initially which only revealed one mutation; we were left without clear molecular confirmation of the diagnosis until deletion testing was able to be sent thus delaying the final molecular diagnosis and options for family planning in subsequent pregnancies. In summary, this report describes two siblings affected with previously undescribed mutations, including a novel large deletion, in *NPHS1* which are a cause of CNS.

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