Published in final edited form as:

Pediatr Nephrol. 2010 February ; 25(2): 261–266. doi:10.1007/s00467-009-1315-6.

Adequate use of allele frequencies in Hispanics—a problem elucidated in nephrotic syndrome

Gil Chernin,

Departments of Pediatrics and of Human Genetics, University of Michigan, Ann Arbor, MI, USA

Saskia F. Heeringa,

Departments of Pediatrics and of Human Genetics, University of Michigan, Ann Arbor, MI, USA

Virginia Vega-Warner,

Departments of Pediatrics and of Human Genetics, University of Michigan, Ann Arbor, MI, USA

Dominik S. Schoeb,

Departments of Pediatrics and of Human Genetics, University of Michigan, Ann Arbor, MI, USA

Peter Nürnberg, and

Center for Genomics (CCG) and Institute for Genetics, Universität zu Köln, Cologne, Germany

Friedhelm Hildebrandt

Departments of Pediatrics and of Human Genetics, University of Michigan, Ann Arbor, MI, USA.
Howard Hughes Medical Institute, University of Michigan, Ann Arbor, MI, USA. University of Michigan Health System, 8220C MSRB III, 1150 West Medical Center Drive, Ann Arbor, MI 48109-5646, USA

Friedhelm Hildebrandt: fhilde@umich.edu

Abstract

Previous studies in children with focal segmental glomerulosclerosis (FSGS) and nephrotic syndrome (NS) in the USA have revealed inter-ethnic differences in their clinical presentation and outcome. However, ethnicity was based on self-identification rather than on molecular genetic data. Here, we show that genetic heterogeneity exists in self-identified Hispanic (Spanish-American) patients with steroid-resistant nephrotic syndrome (SRNS), as patients may be either of Caucasian or Mesoamerican (Native-American) genetic background. Twenty-one self-identified Hispanic patients with SRNS from 18 families were initially evaluated for mutations in the *NPHS2* and *WT1* genes. All patients resided and were cared for in the USA. We performed a total genome search for linkage in all Hispanic patients using 250K single nucleotide polymorphism microarrays, comparing Caucasian with Mesoamerican allele frequencies to determine regions of homozygosity by descent and to establish the correct allele frequency for each family. We found that only ten families (56%) of the 18 self-identified Hispanic families are genetically of Mesoamerican descent, whereas the other eight families (44%) are of Caucasian descent. Due to the small number of families examined, we were unable to draw any conclusion on the prevalence of *NPHS2* and *WT1* in this ethnic group, but the data do suggest that self-identification of ethnicity in Hispanic-American patients is not an adequate basis for genetic studies, as this cohort may represent not only patients of Mesoamerican origin but also patients of Caucasian origin. Thus, one needs to critically review previous studies of FSGS/SRNS patients that involved Hispanic patients as a group. Future larger studies may employ

Correspondence to: Friedhelm Hildebrandt, fhilde@umich.edu.

Disclosure The authors declare that there is no conflict of interest.

a total genome search for linkage to test self-identified Hispanic ethnicity for true Mesoamerican versus Caucasian ethnicity in order to generate valid genetic data.

Keywords

Caucasian; FSGS; Hispanic; Mutation; SRNS

Introduction

Inter-ethnic differences in focal segmental glomerulosclerosis (FSGS) and steroid-resistant nephrotic syndrome (SRNS) have been found in pediatric patients in the USA [1]. In one study, African-American (AA) children were shown to suffer from FSGS or SRNS with a higher prevalence and with more severe outcome [resistant to steroid therapy and a more rapid deterioration to chronic kidney disease (CKD) stage 5] than Caucasian children [1–3]. The ethnicities in these studies were derived by patient self-identification. Another large minority group that has been considered in studies of FSGS and nephrotic syndrome (NS) in the USA is that of patients who self-identified as “Hispanics”. The prevalence and severity of FSGS and SRNS in this group of Hispanic children with SRNS/FSGS are not clear. However, an increasing incidence of FSGS in Hispanic children was found in Texas during the period 1990–1998 in comparison to the earlier period of 1978–1989, although Hispanic children with idiopathic NS had the highest incidence of minimal change nephrotic syndrome (MCNS) when compared with African-Americans (AA) or Caucasians [4].

To date, there have been no studies comparing the clinical course of FSGS or SRNS in a group of only Hispanic children versus patients of other ethnic groups although a number of studies have grouped self-identified Hispanic patients with AA patients and compared the outcome to that of Caucasian patients [5–7]. Hispanic and AA children with NS were found to have a higher prevalence of FSGS than Caucasians [5]. Ingulli et al. also detected a more severe course of FSGS in Hispanic and AA children treated in a single U.S. medical center in the state of New York these were compared to Caucasians patients [6]. The combined group of Hispanic and AA patients had a higher rate of SRNS and a more rapid deterioration from disease onset towards CKD the stage 5 [6]. A study of The North American Pediatric Renal Transplant Cooperative Study (NAPRTCS), which compared post-transplantation recurrence of FSGS in pediatric patients, found a similar rate of recurrence for Hispanic and Caucasian patients, which was significantly higher than the percentage found for AA patients [7]. In all of these studies, the “Hispanic” ethnicity was defined by self-identification.

Genetic studies conducted among the general population in recent years have clearly revealed that self-identification as “Hispanic” (Spanish-American) may either overestimate or underestimate the true genetic background of an individual [8–10]. The term “Hispanic” refers then to a nationally and geographically heterogeneous group that was generated by more than 400 years of biological and cultural mixture and which consists of individuals of mostly Caucasian (i.e. Europeans) and Mesoamerican (Native American) as well as West-African origin [8]. These findings in the general Hispanic population can have implications for how ethnicity and disease risk are assessed in a medical setting [8]. However, to the best of our knowledge, this heterogeneity has not yet been evaluated in pediatric patients with FSGS/SRNS.

Here we present a molecular genetic analysis of 18 self-described Hispanic families with SRNS. These families were initially evaluated for mutations of the *NPHS2* and *WT1* genes. Based on the results, we then subjected the families to a total genome search for linkage using the Affymetrix 250K single nucleotide polymorphism (SNP) microarray (Affymetrix, Santa

Clara, CA) to identify whether they truly are of “Native-American Hispanic”— i.e. Mesoamerican—genetic background. We found that 8/18 (44%) of the families were not truly of “Native-American Hispanic” genetic background but of Caucasian background. Thus, future trials in NS patients of Hispanic origin may need to utilize a molecular genetic approach by SNP analysis in order to generate valid data on the genetic origin of the patients.

Methods

Patients and data recruitment

A search of a worldwide cohort of 585 families with pediatric SRNS revealed 18 families with 21 non-syndromic SRNS patients of self-identified Hispanic descent. All patients were treated in U.S. medical centers. DNA samples and clinical data were obtained after the approval of the study was granted by the Institutional Review Board (IRB) of the University of Michigan, Ann Arbor. Patient recruitment following informed consent has been described previously [11]. The diagnosis of SRNS was established by pediatric nephrologists at different pediatric nephrology centers in accordance with published criteria using a standard questionnaire (www.renalgene.org) [11]. Hispanic ethnicity was defined by the patients and their parents and was reported on the clinical questionnaire. Exclusion criteria were: (1) known secondary cause for NS; (2) age >16 years; (3) presence of extra-renal manifestations. Characteristic features defining the clinical diagnosis were age of disease onset, response to steroid or other immunosuppressive therapy, histological features of kidney biopsy, interval time of progression towards CKD stage 5, and recurrence of disease after kidney transplantation. Standard steroid treatment and responses to steroid therapy were defined according to the Arbeitsgemeinschaft für Pädiatrische Nephrologie guidelines [12] as follows: (1) nephrotic range proteinuria as $>40 \text{ mg/m}^2/\text{h}$; (2) standard steroid therapy as $60 \text{ mg/m}^2/\text{day}$ prednisone administered orally in three divided doses for 6 weeks, followed by 4 weeks of $40 \text{ mg/m}^2/\text{day}$ on alternate days; (3) primary resistance to steroid treatment as the absence of remission to a trace or less of proteinuria on dipstick analysis for 3 consecutive days or $<4 \text{ mg/m}^2/\text{h}$ within the initial 6 weeks of standard steroid therapy.

Mutation analysis of *NPHS2* and *WT1* by direct sequencing

Genomic DNA was isolated from blood samples using the Puregene DNA purification kit (Gentra, Minneapolis, MN) following the manufacturer’s guidelines.

Mutation analysis was performed by exon-flanking PCR with consecutive direct sequencing of all eight exons of *NPHS2* and exons 8 and 9 of *WT1*, as described previously [11,13]. The *WT1* analysis was limited to exons 8 and 9 as mutations of this gene accounting for isolated SRNS have only been reported in these two exons [13]. Exon primer sequences are available from the authors upon request. The software SEQUENCHER (Gene Code Corp, Ann Arbor, MI) was used for sequence analysis. The sequencing of both strands was performed for the detected mutations and other sequence variants. Absence of the novel *NPHS2* mutation was demonstrated in 90 healthy individuals by direct sequencing.

Total genome search

We performed a genome-wide scan for linkage in all self-ascribed Hispanic patients using the 250K StyI Affymetrix SNP DNA microarray. The results were evaluated using the programs GENEHUNTER and ALLEGRO [14]. We then evaluated the data in a “MAKESCAN” format, which plots regions of homozygosity by descent across the entire genome, using GENEHUNTER NPL and ZLR scores. The parameters were set for a disease allele frequency of 0.001. We compared data based on marker allele frequencies that had been generated by Affymetrix for Caucasian individuals (www.affymetrix.com) to previously published Mesoamerican (i.e. of Native-American origin) marker allele frequency [15]. In brief, the

Mesoamerican allele frequency data were obtained from a sub-group of individuals from a low non-Native American ancestry of the Maya and Nahua from Mexico. Caucasian and Mesoamerican marker allele frequencies were used under three conditions of minor allele frequencies of >0.2, >0.3 and >0.4 [14,15].

Results

A summary of the clinical data of the 21 patients with SRNS and self-described Hispanic descent is given in Table 1. A renal biopsy was performed in all cases. In the 21 Hispanic children with SRNS, biopsy revealed FSGS in 17 patients (81%). Four patients (19%) had the histological pattern of MCNS (Table 1).

Mutation analysis of *NPHS2* and *WT1*

We performed mutation analysis of all eight exons of *NPHS2* and exons 8 and 9 of *WT1* and a total genome search in 21 self-identified Hispanic children from 18 families with SRNS. A summary of the results from the mutation analysis of *NPHS2* in the self-identified Hispanic children is given in Table 2. One patient (A1934) was found to have a novel nonsense homozygous *NPHS2* mutation, c.486 C>A; p.Y162X (Table 2). Another patient (A2200) was found to have a compound heterozygous *NPHS2* mutation, c.851C>T; p.A284V with the mutation c.686G>A; p.R229Q (Table 2).

A summary of the *WT1* mutation analysis in 21 Hispanic children is also given in Table 2. The heterozygous mutation c.1119 C>A; H373Q was detected in one patient (A644).

Total genome search for linkage

In order to define ethnic origin on a molecular genetic basis, we performed a total genome search for linkage in the 21 self-identified Hispanic individuals of the study cohort. We evaluated total genome haplotype data for regions of homozygosity by descent in the “MAKESCAN” format as done before [14]. In ten families (56%) we found that Mesoamerican allele frequencies more adequately represented the data than Caucasian allele frequencies by reducing inconsistent peaks of homozygosity in the MAKESCAN evaluation (Fig. 1). In contrast, the data of the remaining eight families (44%) were found to be most adequately represented by Caucasian rather than Mesoamerican allele frequencies. The adequate set of allele frequencies (Meso-american vs. Caucasian) for each family is given in Table 2.

Patient A1934 with the novel homozygous p.Y162X mutation in *NPHS2* was found to be most adequately evaluated by Mesoamerican allele frequencies. This MAKESCAN analysis revealed a peak of homozygosity with a ZLR score (>3) on chromosome 1q, in the region where *NPHS2* is located (Fig. 1). The peak represented a 9.6-Mb region of homozygosity.

Discussion

Here we present a genetic analysis of a cohort of 21 SRNS patients from 18 families. All patients were self-identified as “Hispanics”, resided in the USA and manifested the disease in childhood. We initially analyzed these families for mutations in *NPHS2* and *WT1* and found that mutations in these two genes were responsible for SRNS in three of the 18 families. We then performed a total genome search for linkage using the StyI 250K SNP array in all families of this cohort. Although self-identified “Hispanics” have been considered in clinical studies to be a distinct ethnic group, based on our results this group is genetically heterogeneous: almost half of the patients in our cohort can in fact be considered genetically to be predominantly of Caucasian origin. This result reflects the genetic diversity previously described in the general population from Hispanic origin [8–10]. Discrepancies between self-identified ethnicity and

the actual genetic admixture have been previously reported in the general Hispanic population and also in specific regions in the USA that are highly populated with Hispanic individuals [8–10]. To the best of our knowledge, this is the first report of such a discrepancy in self-identified Hispanic patients with SRNS.

The rather small number of families that were examined by mutation analysis of *NPHS2* and *WT1* in our study does not allow us to draw any conclusion on the mutation prevalence of *NPHS2* and *WT1* in this ethnic group of SRNS patients, as has been done for other ethnic groups in earlier studies [16]. In addition, the small number of patients also excludes us from drawing any conclusion on the prevalence of self-identified Hispanic SRNS patients with Mesoamerican genetic background *versus* Hispanic SRNS patients with Caucasian genetic background. Nevertheless, this study emphasizes the need for testing for the “true” ethnic genetic background in clinical studies from the USA that involve a group of patients classified as “Hispanics”. It also supports our critical view of previous studies that described the prevalence or the clinical outcome of FSGS/SRNS in a group of Hispanic patients from the USA [1,3–6]. Any previous conclusion on the prevalence, severity and histology findings in Hispanic children with FSGS or NS should now be re-examined with care. In this context, it has been shown in the general population that Hispanics in the West of the USA are—genetically—mostly of Mexican origin and that those in the East of the USA are predominantly of Cuban and Puerto Rican origin [9]. This may have influenced the different histological pattern reported in Hispanic children with NS from the state of Texas [4] in comparison to that reported in NS patients from the state of New York [6].

A more general aspect of our study is that many conclusions reported to date regarding differences between Hispanics and other ethnic groups in the USA may be invalid. For example, the recent suggestion to consider the Hispanic race in the interpretation of urinary markers in children [17] or the different outcome reported by the ESRD Clinical Performance Measures Project for Hispanic children treated with peritoneal dialysis may be reevaluated following a molecular genetic definition of ethnicity [18].

Based on the results of this study, it will be important to use total genome haplotype data with adequate allele frequencies [14] in future studies that address clinical differences in cohorts of NS patients that are self-identified as of “Hispanic” descent, because genetic studies will be only valid if the group studied is not defined by “self-identify” ethnicity alone. Sub-classification according to the correct genetic ethnicity may add considerably to the interpretation of clinical as well as epidemiological results [19].

Acknowledgments

We would like to thank the patients and their parents for their participation in this study. We would also like to thank MD Shriver (Penn State University, University Park, Pennsylvania, USA) for sharing the Mesoamerican allele frequency data. F.H. is the Frederick G.L. Huetwell professor and Doris Duke Distinguished Clinical Scientist and is supported by grants from the NIH (P50-DK039255, R01-DK076683), the KMD Foundation and the Thrasher Research Fund.

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Fig. 1.

Total genome search for linkage using the 250K Affymetrix SNP DNA microarray presented in MAKESCAN format for patient A1934, who is of Mesoamerican descent and carries a homozygous Y162X mutation in *NPHS2*. **a** Calculation using Caucasian allele frequencies, **b** calculation using Mesoamerican (Native-American) allele frequencies [14,15]. The *X-axis* represents genetic distance in centiMorgans, with the corresponding chromosome number written *above* the panel. Chromosomes are concatenated from p-ter to q-ter from *left to right along the X-axis*. The *Y-axis* represents the non-parametric (ZLR) LOD score. The *NPHS2* gene is located at the position of the *arrow* on Chr1q peak of homozygosity, detected using both allele frequencies. Multiple background peaks seen in **a** were not persistent when calculations were carried out under the three conditions of minor allele frequency (>0.2 , >0.3 , >0.4). Their absence from **b** indicates that the adequate allele frequencies for the calculation in this patient is the Mesoamerican and that the patient is predominantly of Mesoamerican descent

Table 1

Clinical data of 21 self-identified Hispanic children with steroid-resistant nephrotic syndrome

Clinical parameters	Value
Age of onset in years (median (range))	9.1 (0.2–14.6)
Gender (male; female)	13; 8
Renal biopsy, <i>n</i> (%)	21/21 (100%)
FSGS, <i>n</i> (%)	17/21 (81%)
MCNS, <i>n</i> (%)	4/21 (19%)
CKD stage 5, <i>n</i> (%)	8/21 (38%)
Renal transplantation, <i>n</i> (%) of CKD stage 5)	3/8 (38%)
Recurrence after renal transplantation, <i>n</i> (%)	1/3 (33%)
<i>NPHS2</i> and <i>WT1</i> disease causing mutations (of families), <i>n</i>	3/18

FSGS, focal segmental glomerulosclerosis; MCNS, minimal change nephrotic syndrome; CKD, chronic kidney disease

Table 2

Mutation analysis of *NPHS2* and *WT1* genes in 21 self-identified Hispanic children with SRNS

Family	Gender ^a	Mutations in <i>NPHS2</i> ^b	Mutation in <i>WT1</i> ^b	Age of onset (years)	State of origin ^c	Response to second line immunosuppression ^d	CKD stage 5 (age in years)	Renal biopsy	Transplantation ^e
A573 ^f	m	No	No	11.4	MI	CP-nr	13.2	FSGS	No
A644 ^f	f	No	p. H373Q (h)	5.8	CA	CSA-dependent for 3 years then nr	11.7	First-MCNS Second-FSGS	Yes-NR
A769 ^g	m	No	No	5.5	MI	CSA-nr	6.8	FSGS	Yes-NR
A892 II-1 ^f	m	No	No	14.6	NY	CSA-pr	18.6	FSGS	Yes-NR
A892 II-2 ^f	m	No	No	12.5	NY	CP-nr	–	MCNS	No
A892 II-3 ^f	m	No	No	10.1	NY	CP-nr; CSA-pr	–	FSGS	No
A994 ^f	f	No	No	5.9	CA	Tac-nr; MMF-nr	–	FSGS	No
A1644 ^f	m	No	No	11.0	DC	CSA-pr for 1 year	–	FSGS	No
A1684 ^f	f	No	No	2.5	NJ	MMF-nr	–	FSGS	No
A1717 ^g	f	No	No	4.5	IN	MMF-nd	–	FSGS	No
A1755 ^f	m	No	No	10.1	NJ	MMF-nr	–	FSGS	No
A1757 II-1 ^g	m	No	No	13.1	CA	MMF-nr	–	FSGS	No
A1757 II-2 ^g	f	No	No	13.4	CA	–	–	FSGS	No
A1893 ^g	f	No	No	0.4	AZ	–	–	MCNS	No
A1934 ^f	m	p.Y162X	No	0.2	CA	–	4.4	First-MCNS Second-FSGS	No
A1963 ^{g,h}	m	No	No	14.2	CA	CSA-nr	24.6	FSGS	No
A1978 ^f	m	No	No	2.5	NJ	CP-nr	5.6	MCNS	Rec
A2199 ^g	f	No	No	2.9	NY	–	–	FSGS	No
A2200 ^g	f	p.A284V (h); p. R229Q (h)	No	9.1	NJ	Tac-nr	13.12	FSGS	No
A2238 ^f	m	No	No	8.5	IN	CSA-nr	–	FSGS	No

Family	Gender ^a	Mutations in <i>NPHS2</i> ^b	Mutation in <i>WT1</i> ^b	Age of onset (years)	State of origin ^c	Response to second line immunosuppression ^d	CKD stage 5 (age in years)	Renal biopsy	Transplantation ^e
A2348 ^g	m	No	No	9.9	IL	–	–	MCNS	No

^af, Female; m, male

^b(h), Heterozygous; (H), homozygous

^cAZ, Arizona; CA, California; DC, District of Columbia; IL, Illinois; IN, Indiana; MI, Michigan; NJ, New-Jersey; NY, New York

^dCP, cyclophosphamide; cr, complete remission; CSA, cyclosporine A; MMF, mycophenolate mofetil; Tac, tacrolimus; nd, no data; ; nr, no response; pr, partial response

^eNR, No recurrence; Rec, recurrence

^fAdequately calculated by Mesoamerican allele frequencies

^gAdequately calculated by Caucasian allele frequencies

^hConsanguineous