Declaration

I do hereby declare that this research work has been originally carried out by me under the supervision and guidance of Dr. Prabha Senguttuvan, Professor and Head (Retd.,) Department of Pediatric Nephrology, Institute of Child Health and Hospital for Children (Madras Medical College), Halls road, Egmore, Chennai – 600 008, India and this work has not been submitted elsewhere for any other degree, diploma or other similar titles.

Place : Chennai

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## Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outline of the Thesis</td>
<td>1</td>
</tr>
<tr>
<td>Introduction</td>
<td>2</td>
</tr>
<tr>
<td>Aims and Objectives</td>
<td>9</td>
</tr>
<tr>
<td>Materials and Methods</td>
<td>10</td>
</tr>
<tr>
<td><strong>Chapter 1</strong></td>
<td></td>
</tr>
<tr>
<td>WT1 Mutation Analysis of Steroid Resistant Nephrotic Syndrome in South Indian Children</td>
<td>20</td>
</tr>
<tr>
<td>1.1 Introduction</td>
<td></td>
</tr>
<tr>
<td>1.2 Review of Literature</td>
<td></td>
</tr>
<tr>
<td>1.3 Materials and Methods</td>
<td></td>
</tr>
<tr>
<td>1.4 Results</td>
<td></td>
</tr>
<tr>
<td>1.5 Discussion</td>
<td></td>
</tr>
<tr>
<td><strong>Chapter 2</strong></td>
<td></td>
</tr>
<tr>
<td>NPHS2 Mutation Analysis of Steroid Resistant Nephrotic Syndrome in South Indian Children</td>
<td>30</td>
</tr>
<tr>
<td>2.1 Introduction</td>
<td></td>
</tr>
<tr>
<td>2.2 Review of Literature</td>
<td></td>
</tr>
<tr>
<td>2.3 Materials and Methods</td>
<td></td>
</tr>
<tr>
<td>2.4 Results</td>
<td></td>
</tr>
<tr>
<td>2.5 Discussion</td>
<td></td>
</tr>
<tr>
<td><strong>Chapter 3</strong></td>
<td></td>
</tr>
<tr>
<td>HLA-Class II DR and DQ polymorphism Analysis of Nephrotic Syndrome in South Indian Children</td>
<td>41</td>
</tr>
<tr>
<td>3.1 Introduction</td>
<td></td>
</tr>
<tr>
<td>3.2 Review of Literature</td>
<td></td>
</tr>
<tr>
<td>3.3 Materials and Methods</td>
<td></td>
</tr>
<tr>
<td>3.4 Results</td>
<td></td>
</tr>
<tr>
<td>3.5 Discussion</td>
<td></td>
</tr>
<tr>
<td><strong>Chapter 4</strong></td>
<td></td>
</tr>
<tr>
<td>ACE (I/D) gene polymorphism Analysis of Nephrotic Syndrome in South Indian Children</td>
<td>60</td>
</tr>
<tr>
<td>4.1 Introduction</td>
<td></td>
</tr>
<tr>
<td>4.2 Review of Literature</td>
<td></td>
</tr>
<tr>
<td>4.3 Materials and Methods</td>
<td></td>
</tr>
<tr>
<td>4.4 Results</td>
<td></td>
</tr>
<tr>
<td>4.5 Discussion</td>
<td></td>
</tr>
<tr>
<td>Summary and Conclusion</td>
<td>70</td>
</tr>
<tr>
<td>Recommendations of the Study</td>
<td>74</td>
</tr>
<tr>
<td>Bibliography</td>
<td></td>
</tr>
<tr>
<td>Appendix</td>
<td></td>
</tr>
<tr>
<td>Publication</td>
<td></td>
</tr>
</tbody>
</table>
Outline of the Thesis

This research work attempts to tell the story of the last seven years’ study of genetic work on Nephrotic Syndrome (NS) in south Indian children.

It does not pretend to be a formal history of the subject nor does it try to undertake detail genetic analysis of NS patients. In India, NS and their genetic stories were mostly untold which made it important and imperative to record them in some permanent and accessible form before it was too late. To our knowledge, this is the first ethnic/geographical based NS study in India.

For this study, the need for collaboration between the two very different worlds of experts like basic scientists (medical genetics) and clinicians suddenly become essential. An important factor in this early phase was the involvement of key linking individuals who had both clinical and genetic expertise and who were thus able to play a particularly active role in initiating and focusing the collaboration. Our result output regarding genetic (molecular/cytogenetic/immunogenetic) is due to the joint efforts of basic scientists and clinicians. These collaborations seem to have been fruitful and useful for both, each recognizing and respecting the others’ skills and role.

The molecular mechanisms of proteinuria in kidney diseases that lead to renal failure are poorly understood. This research work has four chapters. Chapters I and II focus on mutation analysis in WT1 and NPHS2 genes, and then III and IV Chapters deal with polymorphism analysis of HLA-class II and ACE of NS and control subjects.

Chapter I describes and identifies WT1 gene mutation in steroid resistant nephrotic syndrome (SRNS) patients. This molecular diagnostic analysis helps us to identify the syndrome and decide on further treatment and genetic counseling. In Chapter II, we describe patients with SRNS due to mutation in NPHS2 gene, furnishing details to inform physicians for further treatment. The results of the polymorphism study of HLA class II alleles (DR&DQ) and haplotypes present in NS cases (SSNS/SRNS) and controls are presented. These results are summarized, discussed and put into perspective in Chapter III. In chapter IV, analysis of ACE (I/D) polymorphism in NS cases and controls is explained and its outcome is described in ‘Results’. These chapters explain how these genetic mutation/variations can lead to NS/SRNS.
Abbreviation

AIDS : Acquired immune deficiency syndrome
α : Alpha
ACE : Angiotensin Converting Enzyme
AGT : Angiotensinogen
bp : Base pair
CD2AP : CD2 Associated protein
χ² : Chi-square test
CKD : Chronic Kidney Disease
CNS : Congenital Nephrotic Syndrome
DDS : Denys-Drash syndrome
dNTP's : Deoxy Nucleotide Tri-Phosphates
DMS : Diffuse Mesangial Sclerosis
ESRD : End Stage Renal Disease
EtBr : Ethidium Bromide
EDTA : Ethylenediaminetetraacetic acid
FSGS : Focal Segmental Glomerulosclerosis
GBM : Glomerular Basement Membrane
g/dl : Gram/Deciliter
HBV : Hepatitis B Virus
HCV : Hepatitis C Virus
HIV : Human immunodeficiency virus
HLA : Human Leukocyte Antigen
HLA-DQ : Human Leukocyte Antigen- DQ locus
HLA-DR : Human Leukocyte Antigen- DR locus
IGF's : Insulin-like Growth Factors
IHWC : International Histocompatibility Working Group
ISKDC : International Study of Kidney Disease in Children
kb : Kilo Base
KDa : Kilo Dalton
LD : Linkage Disequilibrium
MgCl₂ : Magnesium Chloride
mRNA : Messenger ribonucleic acid
μg : microgram
μl : microliter
μm : micrometer
mg : Milligram
ml : milliliter
mM : millimolar
MCNS : Minimal Change Nephrotic Syndrome
min : minutes
M : Molar
NS : Nephrotic Syndrome
OR : Odds Ratio
OD : Optical Density
pMol : pico mole
PCR : Polymerase Chain Reaction
PCR-SSP : Polymerase Chain Reaction-Sequence-specific amplification
KCl : Potassium Chloride
RBC : Red Blood Cells
RAS : Renin Angiotensin System
RASS : Renin-Angiotensin-Aldosterone System
rpm : Revolutions per minute
SNP : Single Nucleotide Polymorphism
SSCP : Single Strand Conformation Polymorphism
NaCl : Sodium Chloride
SDS : Sodium Dodecyl Sulfate
SSNS : Steroid Sensitive Nephrotic Syndrome
SDNS : Steroid Dependent Nephrotic Syndrome
SRNS : Steroid Resistance Nephrotic Syndrome
TGF-β1 : Transforming Growth Factor beta 1
TBE : Tris-Boric Acid EDTA Buffer
UV : Ultraviolet
VUR : Vesicoureteral reflux
WCLB : White Cell Lysis Buffer
WAGR : Wilms tumour Aniridia Genitourinary anomalies and Retardation