1. Introduction

Idiopathic membranous nephropathy (MN), common cause of nephrotic syndrome, accounts for about 40% of adult cases with clinical presentation of severe proteinuria, edema, hypoalbuminuria and hyperlipidemia [1]. Its characteristics include basement membrane thickening and subepithelial immune deposits without cellular proliferation or infiltration [2]. Prior study suggested MN as causing chronic kidney disease (CKD) and as final result of end-stage renal disease (ESRD) [3]. Therapy such as nonspecific antiproteinuric measures and immunosuppressive drugs yielded disappointing results, heightening interest in new therapeutic targets [4]. Taiwan has the highest prevalence of ESRD worldwide; MN may be one cause [5-7]. Genetic and environmental factors may contribute to progression and renal fibrosis in most renal diseases. Identifying genetic mechanisms related to high incidence of MN is crucial to current situation in Taiwan.

2. Genetic association studies on MN over three years in Taiwan

Table 1 displays characteristics of genetic polymorphisms in MN research across three years in Taiwan. Genes were discussed previously, all involved in pathogenesis: STAT4, TLR9, IL-6, TLR4, TRPC6, NPHS1, and MYH9 [8-14]. Our new information about polymorphisms on MYD88, ACTN4, and KIRREL2 relates to MN susceptibility. Figure 1 shows distributions of genotypic and allelic frequencies of 27 polymorphisms on 10 genes in normal population in Taiwan. We observed rs3024908 polymorphism on STAT4 gene without G/G genotype; rs1060186 and rs12986337 on ACTN4 without A/A and C/C genotype, respectively;
Table 1 - Characteristics of polymorphisms in study of idiopathic membranous nephropathy over these past three years in Taiwan.

| Gene name | SNP database ID | Location       | Variation Legend | References       |
|-----------|-----------------|----------------|------------------|------------------|
| STAT4     | rs3024908       | 2:191894141    | 3'UTR(G/T)       | Chen et al., 2011 [8] |
|           | rs3024912       | 2:191893087    | 3'UTR(A/G)       |                  |
|           | rs3024877       | 2:191904889    | intron15(A/G)    |                  |
| TLR9      | rs352140        | 3:52256697     | exon 2(C/T)      | Chen et al., 2013 [9] |
|           | rs352139        | 3:52258372     | intron 1(C/T)    |                  |
| MYD88*    | rs7744          | 3:38184021     | 3'UTR(A/G)       |                  |
| IL-6      | rs1800796       | 7:22766246     | C-572G           | Chen et al., 2010 [10] |
| TLR4      | rs10983755      | 9:120464670    | 5'UTR(A/G)       | Chen et al., 2010 [11] |
|           | rs1927914       | 9:120464725    | 5'UTR(A/G)       |                  |
|           | rs10759932      | 9:120465144    | 5'UTR(C/T)       |                  |
|           | rs11536889      | 9:120478131    | 3'UTR(C/G)       |                  |
| TRPC6     | rs3824935       | 11:101456002   | 3'UTR(C/T)       | Chen et al., 2010 [12] |
|           | rs17096918      | 11:101453995   | intron 1(C/T)    |                  |
|           | rs4326755       | 11:101449358   | intron 1(A/G)    |                  |
| NPHS1     | rs401824        | 19:36342909    | 5'UTR(A/G)       | Lo et al., 2010 [13] |
|           | rs437168        | 19:36334419    | exon 3(C/T)      |                  |
|           | rs3814995       | 19:36342212    | exon 17(A/G)     |                  |
| ACTN4*    | rs1060186       | 19:39221295    | 3'UTR(A/G)       |                  |
|           | rs3745859       | 19:39196745    | exon 5(C/T)      |                  |
|           | rs12986337      | 19:39215172    | exon 16(C/T)     |                  |
| KIRREL2*  | rs443186        | 19:36345951    | 5'UTR(A/C)       |                  |
|           | rs447707        | 19:36347400    | 5'UTR(A/G)       |                  |
|           | rs446014        | 19:36348078    | exon 1(A/C)      |                  |
| MYH9      | rs12107         | 22:36677982    | 3'UTR(A/G)       | Chen et al., 2013 [14] |
|           | rs11703176      | 22:36678476    | 3'UTR(A/G)       |                  |
|           | rs2269530       | 22:36684358    | 3'UTR(A/C)       |                  |
|           | rs7078          | 22:36677914    | exon 34(T/G)     |                  |

*: Unpublished new results by authors
and rs2269530 on MYH9 without G/G genotype in normal population. We assessed genotypic and allelic frequencies of these in MN cases and controls (Table 2) to find strong links between MN and rs3024908 on STAT4 gene, rs352139 on TLR9, rs1800796 on IL-6, rs10983755 and rs1927914 on TLR4, rs437168 on NPHS1, and rs443186 on KIRREL2. LD and haplotype block structure were estimated via 27 polymorphisms on 10 MN-linked genes (Fig. 2). According to chromosome type, structures appeared as (a) Chr2 (b) Chr3 (c) Chr9 (d) Chr11 (e) Chr19 (f) Chr22. Color scheme of linkage disequilibrium (LD) map is based on standard D'/LOD option in Haploview software, LD blocks calculated by CI method.

3. Transducer and Activator of Transcription 4 (STAT4)

The signal transducer and activator of transcription 4 (STAT4) gene, located on chromosome 2q32.2-32.3, encodes a transcription factor essential to inflammation in various immune-mediated diseases [15]. STAT4 plays a key role in regulating immune response by transmitting signals activated in response to cytokines like Type 1 IFN, IL-12, and IL-23 [16]. STAT4 is vital for IL-12 inducing naïve CD4+ T differentiation of into Th1 cells that drive chronic inflammation by secreting high levels of cytokines like IFN-γ and TNF-α [17]. STAT4 haplotype characterized by rs7574865 exhibited strong linkage with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and autoimmune disease: e.g., systemic sclerosis, Sjögren’s syndrome, Type 1 diabetes [18-22]. SY Chen et al. (2011) reported significant difference in genotype frequency at rs3024908 SNP in MN patients versus controls (p = 0.014); those with GG genotype at rs352139 SNP face higher risk of kidney failure in MN cases (adjusted odds ratio [OR]=3.255; 95% confidence interval [CI]=1.155-9.176, p = 0.026) [8].

5. Interleukin-6 (IL-6)

Mounting evidence hints pro-inflammatory cytokines like tumor necrosis factor and interleukin-1 (IL-1), playing a crucial role in lupus nephritis and proliferative IC glomerulonephritis [29-31]. Interleukin-6 (IL-6) is also implicated in manifestations of nephropathy [32-33]. Urinary IL-6 stimulated proliferation of rat mesangial cells yielding IL-6 in vitro [32]. Urinary IL-6 has been identified as a marker of renal IL-6 production [34]: high levels of it arise in 30-50% of IgA nephropathy cases [32-33]. IL-6 may thus act as an autocrine growth factor in the mesangium and dysregulated IL-6 production in mesangial proliferation linked with glomerulonephritis. Among Taiwan’s Han Chinese, data show starkly different genotype and allele frequency at IL-6 C-572G SNP in MN cases versus controls (p=1.6E-04 and 1.7E-04, respectively). People with C allele or with CC genotype at IL-6 C-572G SNP show higher risk of MN (OR=2.42 and 2.71; 95% CI=1.51-3.87 and 1.60-4.60, respectively) [10].

6. Toll-like receptors 4 (TLR-4)

Toll-like receptors (TLRs), a key element of human innate immune response, up-regulate proinflammatory cytokines and co-stimulatory molecules as a first line host defence [35]. TLRs are cited as key components of pathogen-recognition process mediating inflammatory response [36]. TLR4 interacts with ligands such as heat-shock proteins [37]; TLR4 polymorphisms reportedly link with inflammatory disease and/or cancer: e.g., Crohn’s disease, ulcerative colitis, cervical cancer [38-40]. Recent report indicated significant difference of TLR4 gene rs10983755 A/G (p < 0.001) and rs1927914 A/G (p < 0.05) polymorphisms between controls and MN patients. Distributions of rs10759932 C/T and rs11536889 C/T polymorphisms differed significantly. Higher triglyceride level arose in non-GG versus GG group. Genotype of non-AA had a far higher proteinuria ratio than AA group [11].

7. Nephrin (NPHS1)
**Fig. 1** - Distributions of genotypic and allelic frequencies of polymorphisms in normal population in Taiwan.

| Gene (Chr) | SNP | Type 1 (%) | Hetero Type (%) | Type 2 (%) | Allele 1 (%) | Allele 2 (%) |
|------------|-----|------------|-----------------|------------|--------------|--------------|
| STAT4 (Chr 2) | rs3024908 (G/A) | 29.1 | 48.1 | 22.8 | 14.35 | 14.5 |
| | rs3024912 (T/G) | 22 | 44.1 | 33.9 | 18.2 | 18.1 |
| | rs3024877 (G/A) | 33.1 | 51.1 | 15.8 | 18.2 | 18.1 |
| TLR9 (Chr 3) | rs352139 (G/A) | 34.1 | 39.2 | 20.2 | 35.2 | 44.3 |
| | rs352140 (G/A) | 41.1 | 40.3 | 18.4 | 31.2 | 34.8 |
| MYD88 (Chr 3) | rs7744 (A/G) | 38.6 | 32.5 | 17.9 | 31.9 | 36.1 |
| IL-6 (Chr 7) | rs1800796 (C/G) | 58.5 | 38.5 | 2.9 | 78.4 | 21.6 |
| TLR4 (Chr 9) | rs10983755 (A/G) | 34.6 | 38.3 | 12.1 | 29 | 73 |
| | rs1927914 (A/G) | 45.7 | 30.2 | 13.1 | 35.3 | 34.7 |
| | rs10759932 (C/T) | 30.9 | 56.5 | 12.6 | 29 | 73 |
| | rs11556889 (C/T) | 24.7 | 67.1 | 8.2 | 24.7 | 67.1 |
| TRPC6 (Chr 11) | rs3824935 (T/C) | 38.3 | 37.2 | 24.5 | 38.5 | 37 |
| | rs17096918 (C/T) | 26.2 | 33.6 | 35.2 | 38.5 | 37 |
| | rs4324755 (G/A) | 34.7 | 32.6 | 32.7 | 49 | 60 |
| NPHS1 (Chr 19) | rs401824 (A/G) | 38.5 | 33.3 | 23.8 | 35.8 | 14.2 |
| | rs471668 (A/G) | 30.5 | 46.1 | 23.4 | 35.8 | 14.2 |
| | rs5814995 (C/T) | 16.3 | 41.3 | 42.4 | 37 | 63 |
| ACTN4 (Chr 19) | rs1060186 (G/A) | 39.6 | 40.4 | 6.6 | 49.9 | 30.1 |
| | rs5748659 (T/C) | 16.7 | 47.3 | 36 | 48 | 52 |
| | rs12086337 (T/C) | 51.7 | 38.3 | 0.1 | 95.5 | 4.5 |
| KIRREL2 (Chr 19) | rs4431386 (C/A) | 28.5 | 49.6 | 21.9 | 83.8 | 16.2 |
| | rs447707 (A/G) | 52.1 | 34.7 | 14.3 | 76.6 | 20.4 |
| | rs4466014 (C/A) | 18.8 | 20.2 | 0.1 | 34 | 66 |
| MYH9 (Chr 22) | rs12107 (G/A) | 8.3 | 49.3 | 41.9 | 20.2 | 66.8 |
| | rs11701376 (C/A) | 8.3 | 40.7 | 51.1 | 8.3 | 91.7 |
| | rs2209530 (T/G) | 37.7 | 42.3 | 12.3 | 48.7 | 31.3 |
| | rs7078 (C/T) | 84.4 | 15.6 | 0.1 | 57.4 | 42.6 |
Table 2 - Genotypic and allelic frequencies of polymorphisms in MGN patients versus controls.

| Gene   | bSNP ID      | Patient with MGN (%) | Control (%) | p value     | Allele frequency | Patient with MGN (%) | Control (%) | p value     |
|--------|--------------|-----------------------|-------------|-------------|------------------|-----------------------|-------------|-------------|
|        |              | 1         | 2         | 1         | 2         | 1         | 2         | 1         | 2         |
| STAT4  | rs2994059 (106) | 49.59 | 32.82 | 9.73 | 7.18 | 0.01  | 0.965  | 1.15 | 2136 | 775.2 | 1830 | 453.5 | 1.055 |
|        | rs2994059 (106) | 51.29 | 36.31 | 6.63 | 7.01 | 0.02  | 0.725  | 1.39 | 3805 | 468.2 | 2914 | 546.1 | 1.375 |
|        | rs2994059 (106) | 51.29 | 36.31 | 6.63 | 7.01 | 0.02  | 0.725  | 1.39 | 3805 | 468.2 | 2914 | 546.1 | 1.375 |
| TLRAg  | rs2994059 (106) | 51.29 | 36.31 | 6.63 | 7.01 | 0.02  | 0.725  | 1.39 | 3805 | 468.2 | 2914 | 546.1 | 1.375 |
|        | rs2994059 (106) | 51.29 | 36.31 | 6.63 | 7.01 | 0.02  | 0.725  | 1.39 | 3805 | 468.2 | 2914 | 546.1 | 1.375 |
|        | rs2994059 (106) | 51.29 | 36.31 | 6.63 | 7.01 | 0.02  | 0.725  | 1.39 | 3805 | 468.2 | 2914 | 546.1 | 1.375 |
| MYD88  | rs2994059 (106) | 51.29 | 36.31 | 6.63 | 7.01 | 0.02  | 0.725  | 1.39 | 3805 | 468.2 | 2914 | 546.1 | 1.375 |
|        | rs2994059 (106) | 51.29 | 36.31 | 6.63 | 7.01 | 0.02  | 0.725  | 1.39 | 3805 | 468.2 | 2914 | 546.1 | 1.375 |
|        | rs2994059 (106) | 51.29 | 36.31 | 6.63 | 7.01 | 0.02  | 0.725  | 1.39 | 3805 | 468.2 | 2914 | 546.1 | 1.375 |
| IL16 (106) | rs2994059 (106) | 51.29 | 36.31 | 6.63 | 7.01 | 0.02  | 0.725  | 1.39 | 3805 | 468.2 | 2914 | 546.1 | 1.375 |

Fig. 2 - LD and haplotype structure of genes associated with MN by different chromosomes: (a) Chr2 (b) Chr3 (c) Chr9 (d) Chr11 (e) Chr19 (f) Chr22. Color scheme of linkage disequilibrium LD map is based on standard D’/LOD option in Hapview software, LD blocks calculated based on CI method.
This signaling adhesion protein is believed to play a vital role in modulating renal function [41]. Research on nephrin function initially focused on interaction of slit diaphragm structural components (SD) [42]. Recent research demonstrates nephrin as involved in signal processes critical to podocyte function, survival and differentiation [43]. Polymorphisms in NPHS1 demonstrably play a pivotal role in progression of renal failure [44]. Mutations of NPHS1 or NPHS2 reportedly associate with severe nephrotic syndrome that progresses to end-stage renal failure in children [45]. R229Q, a NPHS1 variant, meant 20-40% higher risk of focal segmental glomerulosclerosis in European populations [46]. Lo et al., 2010 reported significant difference in genotype frequency distribution of rs437168 polymorphism between MN patients and controls. Their results also showed frequency of G allele significantly higher in the MN group; stratified analysis linked high disease progression in AA genotype of rs401824 and GG genotype of rs437168 patients with low rate of remission [13].

8. Myosin Heavy Chain 9 (MYH9)

This gene, expressed in glomerular podocytes and mesangial cells, encodes nonmuscle myosin IIA [47, 48]. Currently, 44 of it mutations have been reported [49], possibly involving either N-terminal motor or C-terminal tail domain of MYH9 gene encoding for the heavy chain of nonmuscle myosin-IIA. The MYH9 haplotypes show replicated association with risk and protection [50, 51]. They are proven as associated with kidney disease in African Americans and European Americans [52, 53]; MYH9 also affects kidney function in Europeans [54]. Results portend statistically significant difference in allele frequency distribution at rs12107 between MN cases and controls (p = 0.04). Persons with AA genotype at rs12107 SNP who contract MN face higher risk of kidney failure than other MN cases (adjusted odds ratio: 1.63; 95% confidence interval: 1.08-2.48, p = 0.02). C-A haplotype is susceptible to MN [14].

9. Kin of IRRE Like 2 (Drosophila) (KIRREL2)

This protein exhibits sequence resembling that of several cell adhesion proteins: e.g., Drosophila RST (irregular chiasm C-roughest), mammalian KIRREL (akin to irregular chiasm C-roughest; NEPH1), NPHS1 (nephrin). The former, a complex gene with mutations originally assigned to separate loci, has alleles originally assigned to irregular chiasm locus, affecting axonal migration in the optic lobes. Other alleles, originally assigned to the roughest locus, link with reduced apoptosis in the retina, inducing roughened appearance of the compound eye [55] and [56]. The mammalian KIRREL/NEPH1 and NPHS1 genes both encode components of the glomerular slit diaphragm in kidneys [57], [58] and [59]. We noted significant difference in genotype frequency distribution of rs443186 polymorphism between MN patients and controls. Data showed frequency of C allele at rs443186 and A allele at rs447707 definitely higher in the MN group. Data indicate individuals with AA genotype at rs443186 SNP face higher risk of MN (Table 2).

10. Conclusion

Genetic susceptibility plays a major role in pathogenesis [60]. Research efforts, including GWASs, have been invested worldwide to identify susceptibility genes for several diseases. GWASs are considered as a powerful and promising approach [61]. Candidate gene approach along with an appropriate analysis remains the method of choice to evaluate genes of interest conferring susceptibility to specific disease. Most genes contributing to MN susceptibility remain unidentified; well-organized approach like GWASs may obtain definite conclusions regarding such genes in the near future.

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