



A Modified Disease Concept of Alport Syndrome (AS) and Related Disorders may soon be Developed– Can a Case Report Contribute toward the Development?

Hiroyuki Morita^{1*}, Junko Takagi¹ and Koji Kimata²

¹Division of Endocrinology and Metabolism, Department of Internal Medicine, Aichi Medical University School of Medicine, Japan

²Research Creation Support Center, Aichi Medical University School of Medicine, Japan

Editorial

Major molecular constituents of the Glomerular Basement Membrane (GBM) of the kidney are type IV collagen, laminin, and heparin sulfate proteoglycan (s) [1,2]. Interweaving of type IV collagen to form a basic network is particularly important in that it gives mechanical support to the GBM and probably provides a scaffold for specific interactions with other molecular constituents [3]. Six α -chains of type IV collagens, α 1(IV), α 2(IV), α 3(IV), α 4(IV), α 5(IV), and α 6(IV), are encoded by *COL4A1*, *COL4A2*, *COL4A3*, *COL4A4*, *COL4A5* and *COL4A6* genes, respectively, [4]. Type IV collagen exists in the body as a homotrimer or heterotrimer of the α -chain, and the most common combination in the normal adult GBM is [α 3, α 4, α 5] heterotrimer [5,6]. Hemizygous mutations in the *COL4A5* gene, and homozygous or compound heterozygous mutations in the *COL4A3* or *COL4A4* gene lead to X-Linked Alport Syndrome (XLAS), and Autosomal Recessive AS (ARAS), respectively. Heterozygous mutations in the *COL4A3* or *COL4A4* gene may lead to Autosomal Dominant AS (ADAS), or Thin Basement Membrane Nephropathy (TBMN) [3,5,7].

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*Correspondence:

Hiroyuki Morita, Division of Endocrinology and Metabolism, Department of Internal Medicine, Aichi Medical University School of Medicine, 1-1 Nagakute, Aichi 480-1195, Japan, Tel: +81 561 62 3311; Fax: +81 561 63 1098;

E-mail: moritahi@aichi-med-u.ac.jp

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Three forms of AS and TBMN are conjointly referred to as “collagen IV nephropathy [8]”. AS, in principle, leads to End-Stage Renal Disease (ESRD), but ESRD in TBMN is not necessary common [8,9]. Although it was believed ultra structure of the GBM in AS is different from that in TBMN, this issue might need re-evaluation [7,10,11]. Recent progress in gene sequencing technique, including easier accessibility to next generation sequencing, makes it relatively easy to examine whether there are target gene mutations in a patient with “collagen IV nephropathy”. Phenotype variation, or clinical heterogeneity, is observed among family members [8,12]. Thus, to identify another gene modulating disease progression is a challenge. The gene has the potential for designing a new drug not only for collagen IV nephropathy but also for other chronic kidney diseases. If we find an interesting patient or family, we can now make approaches to the whole genome sequencing. Correct and detailed descriptions of a patient and/or family are of inestimable value, because it could play a pivotal role in the first step of identifying the gene.

It is far from easy to predict clinic-pathologic features of a patient from a given mutation in the *COL4A3*, *COL4A4*, and *COL4A5* genes. To learn it, we must be able to predict how a missense mutation alters 3 dimensional structure of [α 3, α 4, α 5] heterotrimer, intramolecular/intermolecular associations among molecular constituent of the GBM, and ultrastructure of the GBM. We must await another innovation in bioinformatics. What we should do now is to accumulate descriptions of detailed clinical pictures resulting from a given mutation [9]. It is currently believed that XLAS, ARAS, and ADAS comprise about 80-85%, 10-15%, and 1-5% of all AS, respectively [5,8,12], but in theory, mother and sister(s) of a male XLAS patient may have collagen IV nephropathy, and parents of ARAS patients may have ADAS or TBMN. Individuals in these cohorts are not well examined, although there are pioneer reports [13-15]. Again, correct and detailed descriptions of a patient and/or family are of inestimable value.

Furthermore, little is known as to how DNA methylation, translational regulation by microRNA (miRNA) as well as long non-coding RNA (lncRNA), and posttranslational modification of histone proteins alter type IV collagen expression in the GBM, although recent reports have indicated these epigenetic factors play an important role in fibrosis [16]. Collagen IV nephropathy is a genetic disorder, but its prognosis may well be improved by steadily controlling body weight and blood pressure, by properly inhibiting renin-angiotensin-aldosterone system [17], and by applying a new

therapeutic strategy including collagen receptor blockade and anti-miRNA therapy [6].

Pathogenesis of collagen IV nephropathy has been elucidated little by little at the molecular level. Human gene analysis has to be accompanied by accurate and detailed descriptions of clinical pictures, otherwise it could be misleading. In conclusion, we can now find out a number of issues to be discussed and/or settled in collagen IV nephropathy. Medical practitioners would be interested in reading case reports clearly illustrating any one of the issues, which should, in the end, benefit patients.

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