IgA nephropathy

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Abstract | Globally, IgA nephropathy (IgAN) is the most common primary glomerulonephritis that can progress to renal failure. The exact pathogenesis of IgAN is not well defined, but current biochemical and genetic data implicate overproduction of aberrantly glycosylated IgA1. These aberrant immunoglobulins are characterized by galactose deficiency of some hinge-region *O*-linked glycans. However, aberrant glycosylation alone is insufficient to induce renal injury: the participation of glycan-specific IgA and IgG autoantibodies that recognize the undergalactosylated IgA1 molecule is required. Glomerular deposits of immune complexes containing undergalactosylated IgA1 activate mesangial cells, leading to the local overproduction of cytokines, chemokines and complement. Emerging data indicate that mesangial-derived mediators that are released following mesangial deposition of IgA1 lead to podocyte and tubulointerstitial injury via humoral crosstalk. Patients can present with a range of signs and symptoms, from asymptomatic microscopic haematuria to macroscopic haematuria. The clinical progression varies, with 30–40% of patients reaching end-stage renal disease 20–30 years after the first clinical presentation. Currently, no IgAN-specific therapies are available and patients are managed with the aim of controlling blood pressure and maintaining renal function. However, new therapeutic approaches are being developed, building upon our ever-improving understanding of disease pathogenesis.

IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide (BOX 1). The primary defect of the disease is the systemic aberrant glycosylation of *O*-linked glycans (glycoproteins) in the hinge region of IgA1, which results in increased serum levels of galactose-deficient IgA1 (Gd-IgA1) that are recognized by glycan-specific IgA and IgG autoantibodies. IgA is an antibody that plays a crucial part in mucosal immunity. IgA exists as two isotypes, IgA1 and IgA2, and can exist in a dimeric form called secretory IgA. Secretory IgA is produced by plasma cells predominantly in the polymeric form that consists of two or more monomers linked by the J-chain (a 17-kDa polypeptide connecting two or more monomeric IgA). Polymeric IgA is actively released into mucosal secretions with a bound secretory component that protects the molecule from proteolytic enzymes. The molecular stability and effector immune functions make secretory IgA particularly well suited to provide mucosal protection against pathogens. Serum IgA is mostly of the IgA1 subclass (approximately 85% of total serum IgA) in its monomeric form; only about 10% is polymeric.

For reasons that are unclear, the kidney is the target of injury in IgAN; the disease takes a slow but relentless clinical course that eventually results in end-stage renal disease (ESRD) in 30–40% of patients within 20–30 years of diagnosis. Currently, IgAN can only be diagnosed upon renal biopsy and study of the kidney tissue using immunofluorescence microscopy. The pathology of IgAN is characterized by deposition (or possibly *in situ* formation) of pathogenetic polymeric IgA1 immune complexes (occasionally with IgG and IgM) in the glomerular mesangium, proliferation of mesangial cells, increased synthesis of extracellular matrix and variable infiltration of macrophages, monocytes and T cells. IgA and IgG that recognize the autoantigen IgA1 in IgAN are typically also reactive against antigens from extrinsic microorganisms involved in recurrent upper respiratory and gastrointestinal mucosal infections; the nephritogenic IgA1 molecules are produced by B cells following mucosal infections, particularly tonsillitis. Pathogenetic IgA is deposited only in the mesangial areas of the glomerulus (FIG. 1); no deposits are evident in podocytes and renal tubular epithelial cells, which do not express any known IgA receptors.

Patients can present with a range of symptoms, from haematuria or proteinuria to severe hypertension owing to renal damage. The severity of tubulointerstitial damage in IgAN correlates closely with the rate of renal function decline and long-term renal outcome. Given that the immunochemical abnormality is not corrected by renal transplantation, IgAN can, not surprisingly, frequently

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recur in patients after transplantation. In a Canadian epidemiological study comprising 2,026 sequential renal transplant recipients, IgAN recurred in 25.3% of patients after 15 years[1]. Indeed, the cumulative risk of allograft loss is high following the diagnosis of post-transplant glomerulonephritis (recurrent and *de novo* forms summed) with a hazard ratio of 7.45.

IgAN can occur in either sporadic (90–95%) or familial (5–10%) patterns. Patients with familial IgAN might have poorer prognoses than those with sporadic disease, with an increased risk of progression to renal failure, but this association remains controversial with few papers studying the familial disease. Patients with familial IgAN have increased serum levels of galactose-deficient polymeric IgA1 compared with patients with sporadic IgAN. Indeed, the levels of Gd-IgA1 in serum seem to be heritable in a dominant pattern, with reduced penetrance, but most relatives of patients with IgAN who have high serum levels of Gd-IgA1 do not exhibit clinical manifestations of renal injury. Polymeric IgA1 isolated from patients with familial IgAN demonstrate enhanced binding to mesangial cells *in vitro*[2]. These observations support the notion that genetic factors are involved in the pathogenesis of familial[3] as well as sporadic IgAN[4]. Indeed, risk factors of multiple candidate genes implicated in IgAN have been identified in different ethnic groups[5,6]. In this Primer, we describe these risk factors, as well as the epidemiology, clinical features, pathology and treatment of IgAN.

Epidemiology

Prevalence

Given that a biopsy specimen is required to diagnose IgAN, data on individuals undergoing biopsy for persistent microscopic haematuria and/or mild proteinuria can increase the prevalence of IgAN. Indeed, regional registries of kidney biopsy procedures and findings, and data from single-centre studies, show a marked difference in the prevalence of IgAN in patients; prevalence is modest in the United States (10–20% of primary glomerulonephritis), higher in some European countries (20–30%) and highest in developed countries in Asia (40–50%)[7]. The prevalence of IgAN is under-represented in some developing countries because conventional practice is not to biopsy patients with microscopic haematuria and low-grade proteinuria[8]. The disease is very uncommon in people of African ancestry[9], but the data are controversial because no urinary screenings are carried out in African populations — Wyatt *et al.*[10] demonstrated the same incidence of IgAN in Afro-Americans and Euro-Americans.

The frequency of IgAN varies widely from country to country (FIG. 2) and also within individual countries. This considerable geographical variability can be explained by two important bias factors: the variations in access to primary care (or insurance or health care payment assistance) and the differences in policies for performing renal biopsies. First, the lack of primary care medicine in developing countries can partially explain the low prevalence of IgAN in these regions[7]. By contrast, in developed countries, the high frequency of the disease can be attributed to better primary care and early diagnosis followed by effective follow-up management. Moreover, differences between countries can also be explained by early referral. For example, in some Asian countries (namely, Japan, Korea and Taiwan), urine screening tests are conducted in schools, and routine urinalyses are prescribed for military service and/or ahead of employment in some eastern and western countries — explaining the apparent high incidence of IgAN in these regions[11,12]. Second, indications for kidney biopsy strongly influence the detected prevalence of IgAN. Indeed, considerable variability in prevalence is evident when comparing single-centre studies with different kidney biopsy policies in a given region. In the United Kingdom, the first report by Sissons *et al.*[13] showed a low frequency of IgAN (4%), yet later, Power *et al.*[14] demonstrated that different indications for kidney biopsy increased the prevalence to 38% of primary glomerulonephritis. That is, when criteria for biopsy are widened, with more biopsies performed, the prevalence of IgAN increases[14]. Furthermore, improved techniques in performing renal biopsy have increased the safety and reduced the complications, leading to more biopsies being performed[15]. Thus, the increased frequency of IgAN over time is due, at least in part, to a greater willingness of nephrologists to biopsy individuals with normal serum creatinine concentrations or estimated glomerular filtration rate (eGFR) with persistent microscopic haematuria and/or proteinuria. Liu *et al.*[16] demonstrated that 43% of such individuals were affected by IgAN.

Increased IgAN frequency over time can also be related to diagnostic improvements. The use of immunofluorescence or immunohistochemistry is obligatory to detect deposits of IgA. When immunofluorescence was used routinely, a lower incidence of mesangial proliferative glomerulonephritis (that is, glomerulonephritis associated with mesangial proliferation from any cause) coincided with an increased frequency of IgAN in developing countries[17].

Others factors that might influence the difference in IgAN prevalence include socioeconomic status, ancestry and genetic background, age and sex.

Socioeconomic status

The socioeconomic status of the population reflects particular attention to health[18]. In developing countries, individuals with asymptomatic persistent urinary

abnormalities (the most frequent clinical presentation of IgAN) do not benefit from early referral to specialists because public assistance is modest and largely dedicated to more-severe clinical presentations, such as nephrotic or acute nephritic syndrome. Without urinalysis screening in developed countries, early IgAN can often escape detection.

Genetic background

Ethnic differences can contribute to the varying prevalence of IgAN. Genome-wide association studies (GWAS) have identified candidate genes, as well as risk-associated and protective alleles[5,19]. These studies further revealed that ethnic-based differences are evident in the number of risk alleles, with the highest number of risk alleles present in individuals of East Asian origin and the lowest number in those from Africa, correlating with the differences in the prevalence of IgAN[20].

Box 1 | **Glomerulonephritides**

Glomerulonephritis refers to kidney diseases (usually affecting both kidneys) that are characterized by inflammation either of the mesangial cells in the mesangial matrix or of endothelial and epithelial cells of the small blood vessels in the kidneys.

Primary glomerulonephritis

- Glomerulonephritis with no involvement of systemic illness

Proliferative glomerulonephritis

- Disease in which most of the glomeruli show proliferation of endothelial and/or mesangial cells that affects the entire glomerulus
- Characterized by diffuse hypercellularity of the glomeruli
- Immunofluorescence study frequently shows deposition of immunoglobulins or complements

Focal segmental glomerulosclerosis

- A specific pathological entity in which the sclerotic lesion affects segments of the glomerulus, with IgM and complement 3 deposition
- Frequently associated with heavy proteinuria and progressive kidney failure

Minimal change nephropathy

- A pathological entity in which the light microscopy and immunofluorescence findings are normal, but electron microscopy shows diffuse loss of visceral epithelial cell foot processes (podocyte effacement)
- Frequently associated with heavy proteinuria but preserved kidney function

Membranous nephropathy

- A pathological entity in which subepithelial immunoglobulin-containing immune complexes (frequently IgG) are deposited along the glomerular basement membrane
- Frequently associated with heavy proteinuria and progressive kidney failure
- Can occur as a primary glomerulonephritis or in association with other systemic illnesses

Crescentic glomerulonephritis

- A syndrome of glomerulonephritis that is characterized by a rapid loss of renal function (usually a 50% decline in the glomerular filtration rate within 3 months), with glomerular crescent formation seen in 50–75% of glomeruli
- Rapidly progresses into acute renal failure if untreated
- Crescents are formed when severe injury and glomerular basement membrane rupture occur, leading to leakage of plasma proteins (most importantly fibrin) through the glomerular basement membrane
- Epithelial cells lining the Bowman capsule respond to the leaked fibrin and proliferate
- Infiltrating monocytes and macrophages may also proliferate
- These proliferating cells surround and compress the glomerulus, forming a crescent-shaped scar

Age

IgAN incidence is higher in children and young adults (20–30 years of age) than in elderly (>65 years of age) individuals[21,22]. This frequency is also influenced by screening urinalysis, which is carried out more commonly in children and young adults.

Sex

Earlier reports in white patients indicate a male predominance in IgAN[23]. However, this male predominance is not evident in studies involving Asian patients or when measures, such as mass screening of urinary abnormalities, are performed[24]. In regional registries, the difference in frequency by sex is not present.

Mechanisms/pathophysiology

Multiple studies indicate that IgAN is an autoimmune disease. A 'multi-hit' hypothesis has been proposed to explain the pathogenesis of IgAN[25] (FIG. 3). Specifically, IgA1 — some of which is Gd-IgA1 — is produced (hit 1) and this is recognized as an autoantigen by circulating antiglycan autoantibodies (hit 2). Immune recognition results in the formation of nephritogenic immune complexes (hit 3) that deposit in the kidney and activate mesangial cells (hit 4). Alternatively, some have proposed a possibility of an initial *in situ* formation of immune deposits[26], but this is a minority view. The immune deposition leads to complement activation; mesangial cells are then activated to proliferate and overproduce components of extracellular matrix, cytokines and chemokines[27]. Some of these cytokines directly cause downstream podocyte injury and induce proteinuria[28]. These pathogenetic steps are probably modulated by various environmental and genetically determined factors, such as complement regulation[20,29].

Galactose deficiency

The Gd-IgA1 molecules that are characteristic of IgAN are produced by IgA1-secreting cells (normal functioning B cells) through abnormal biosynthesis of *O*-glycans[30]. The pathogenetic complexes themselves comprise Gd-IgA1 bound by circulating antiglycan IgA and IgG antibodies[31,32]. These findings confirm the initially suspected involvement of *O*-glycan abnormalities in IgAN[33,34], and refine and expand an earlier postulate that defective galactosylation of IgA1 molecules is a possible aetiopathogenetic factor in IgAN[35].

At the hinge-region segment of the IgA1 heavy chain, there are nine sites for potential attachment of *O*-glycans, of which three to six are usually glycosylated per hinge (that is, up to 12 glycans total per monomeric IgA molecule; FIG. 4a). *O*-linked glycans are commonly attached to the peptide chain at serine/threonine residues through the oxygen atoms. Several core structures (patterns of glycosylation) are known, and the most common begins with *N*-acetylgalactosamine (GalNAc) as the initial sugar. Indeed, human serum IgA1 has *O*-glycans with GalNAc linked to a galactose. Each saccharide, or both of them, can have a sialic acid attached: GalNAc with sialic acid and galactose with sialic acid. The composition of *O*-glycans on normal serum IgA1 is variable; prevailing

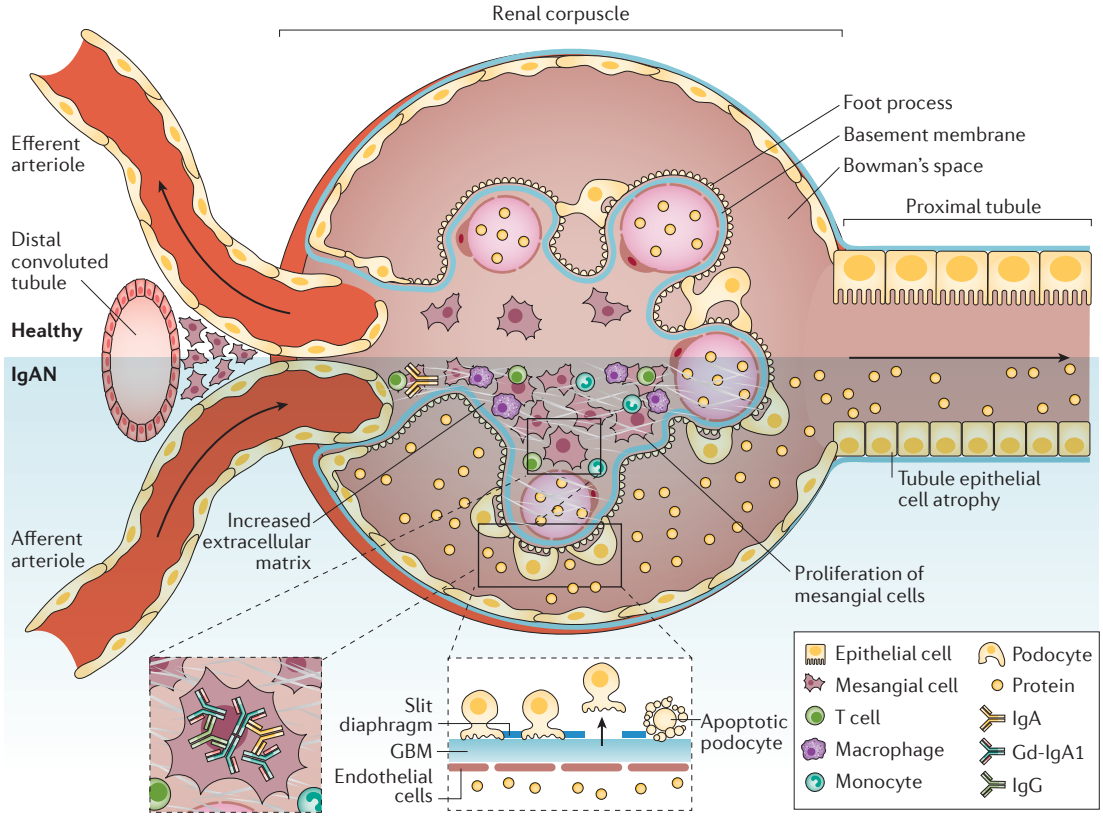

Figure 1 | **The glomerulus in IgA nephropathy.** In a normal glomerulus, normal filtration of plasma occurs and intact podocytes prevent the loss of proteins. In IgA nephropathy (IgAN), deposition (or possibly *in situ* formation) of pathogenetic polymeric IgA1 immune complexes in the glomerular mesangium induces proliferation of mesangial cells and increases the synthesis of extracellular matrix. Humoral mediators attract infiltrating macrophages, monocytes and T cells. Humoral mediators also downregulate the expression of podocyte proteins, leading to apoptosis and protein loss. GBM, glomerular basement membrane; Gd-IgA1, galactose-deficient IgA1.

forms include the GalNAc–galactose disaccharide and its mono-sialylated and di-sialylated forms.

Studies using immortalized IgA1-secreting cells derived from B cells in the blood of patients with IgAN and healthy and disease controls have revealed the basis for the galactose deficiency. Cells from patients with IgAN secrete IgA1 with greater degrees of galactose deficiency of the *O*-glycans owing to abnormalities in the expression and activities of key glycosyltransferases[31,36] (FIG. 4b). Specifically, decreased expression and activity of core 1 β1,3-galactosyltransferase 1 (also known as glycoprotein *N*-acetylgalactosamine 3-β-galactosyltransferase 1; encoded by *C1GALT1*) and increased expression and activity of α-*N*-acetylgalactosaminide α2,6-sialyltransferase 2 (encoded by *ST6GALNAC2*) are associated with increased galactose deficiency of the secreted IgA1 (REFS 31,36). Moreover, the expression of core 1 β1,3-galactosyltransferase-specific chaperone 1 (encoded by *COSMC*; also known as *C1GALT1C1*), necessary for stability of the nascent enzyme[37,38], is decreased[39]. Notably, the expression of these enzymes is altered by some cytokines, including IL-6, to enhance the enzyme imbalance to favour the production of Gd-IgA1 (REF. 36). Specific microRNAs (miRNAs), which regulate gene expression, represent another type of regulation affecting the expression of specific glycosyltransferases[40].

Immune complex formation

IgG and/or IgA1 autoantibodies recognize Gd-IgA1 in a glycan-specific manner to form immune complexes[33,41]. Our understanding of the nature of these autoantibodies emerged from studies of cloned cell lines derived from patients with IgAN that produced IgG specific for Gd-IgA1. Cloning and sequence analysis of the heavy-chain and light-chain antigen-binding domains of these IgG autoantibodies revealed unique features in the complementarity-determining region 3 (CDR3) of the heavy chains[30]. Specifically, the amino acid in the third position in CDR3 was serine in patients with IgAN rather than alanine in the healthy individuals[30]. Additional experiments with recombinant glycan-specific IgG revealed that this serine residue is necessary for efficient binding to Gd-IgA1 (REF. 30). Furthermore, IgG recognition relied on GalNAc in the terminal position. However, it remains to be determined precisely which glycoforms of Gd-IgA1 are recognized by which types of autoantibodies and what the precise nature of the epitope (or epitopes) is. Which of these characteristics are crucial for disease expression and/or progression are

also undetermined. Notably, the serum level of these IgG autoantibodies is associated with disease activity[41] as well as disease progression[42], further supporting the key role of the autoantibodies in the pathogenesis of IgAN. IgA1 autoantibodies also bind to Gd-IgA1, but their precise role and significance are not fully understood.

Recognition of Gd-IgA1 by the autoantibodies results in the formation of nephritogenic immune complexes that include other (unknown) serum proteins and can activate complement via the alternative or the mannose-binding lectin pathway[43]. The biological activities of these complexes are affected by various factors, such as the size and composition of the complex[2,33]. The receptors on mesangial cells that are engaged by these nephritogenic immune complexes are not well understood[44] (BOX 2). Several studies have identified the transferrin receptor (CD71) as a key receptor for binding polymeric Gd-IgA1 and Gd-IgA1-containing immune complexes[45,46]. However, an alternative mechanism for the formation of IgA1-containing complexes has been proposed: a soluble form of the Fcα receptor (sCD89) generates circulatory complexes with Gd-IgA1 (REF. 47). Studies using an animal model suggested that activation of mesangial cells by complexes containing Gd-IgA1 requires sCD89 and transglutaminase 2 for disease development[48]. However, patients with IgAN and a stable clinical course have been shown to have high levels of sCD89, which contrasts with the low levels evident in patients with progressive disease[49]. This finding suggests that the binding of sCD89 to polymeric Gd-IgA1 could be protective. A recent study revealed that disease recurrence after kidney transplantation is associated with increased serum levels of Gd-IgA1, Gd-IgA1–IgG complexes and Gd-IgA1–sCD89 complexes[50]. Further studies are needed to clarify all of the processes induced by immune complexes containing Gd-IgA1 in the pathogenesis of IgAN and to identify those that are driving disease development and progression.

Glomerular injury

Although some patients have relatively minor renal injury characterized by minimal increases in mesangial cell numbers and mesangial matrix without substantial interstitial scarring, others develop more serious damage, characterized by glomerulosclerosis and/or tubulointerstitial fibrosis, and progress to ESRD. Binding of Gd-IgA1-containing immune complexes to mesangial cells induces the local release of cytokines, complement components and angiotensin II, leading to glomerular injury[51]. In particular, glomerulosclerosis in patients with IgAN is associated with podocytopenia[52,53] as well as alterations of podocyte components, such as podocalyxin (which functions to keep adjacent foot processes separated and control urinary filtration) and dendrin (a component of the glomerular slit diaphragm).

Podocyte injury, typically leading to proteinuria, can involve apoptosis, necrosis, detachment from the glomerular basement membrane and defective autophagy. Deposition of IgA, IgG and complement 3 in the glomerular capillary walls and/or the presence of cytokines or reactive oxygen species produced by resident glomerular cells can also induce podocyte injury. It seems that patterns of podocyte abnormalities differ depending on disease activity in IgAN, with increased levels of urinary podocalyxin evident in the acute phase and loss of podocytes in the chronic phase[54]. In an experimental model of glomerulonephritis, abundant dendrin was detected in the nuclei of injured podocytes[54]. In another report, Kodama *et al.*[55] noted that increased numbers of dendrin-positive nuclei per glomerulus correlated with acute extracapillary changes and disease progression in IgAN. The number of dendrin-positive nuclei in renal biopsy specimens could, therefore, be useful for evaluating disease activity of IgAN. Podocytes that express the apoptosis marker annexin V are also detected in urine. Translocation of dendrin to podocyte nuclei

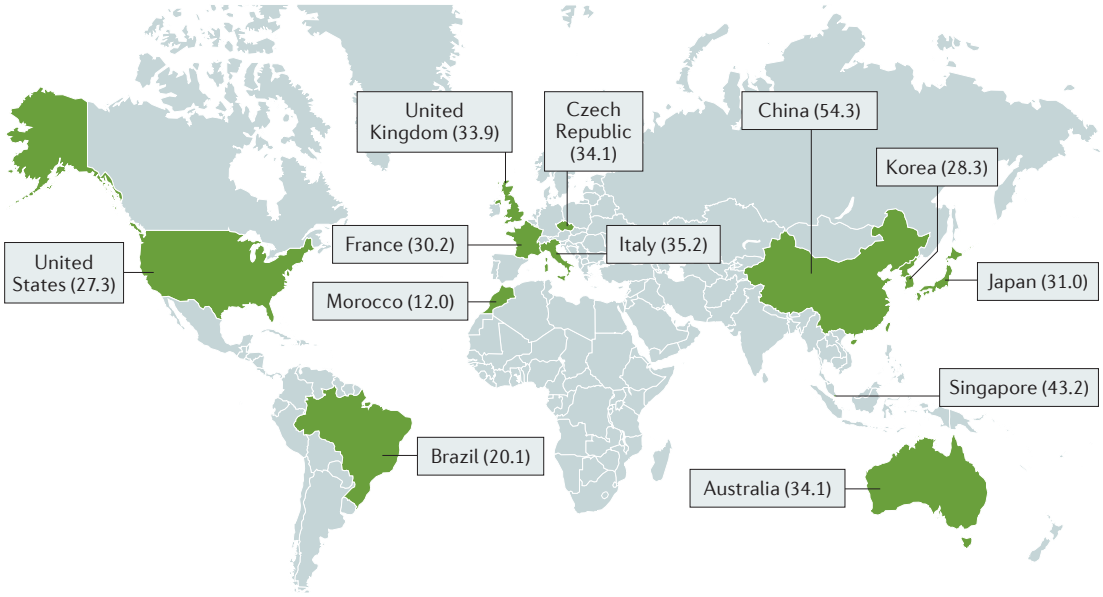

Figure 2 | **Global distribution of patients with IgA nephropathy in some key regions of the world.** Prevalence is shown as percentage of biopsy-proven primary glomerulonephritis.

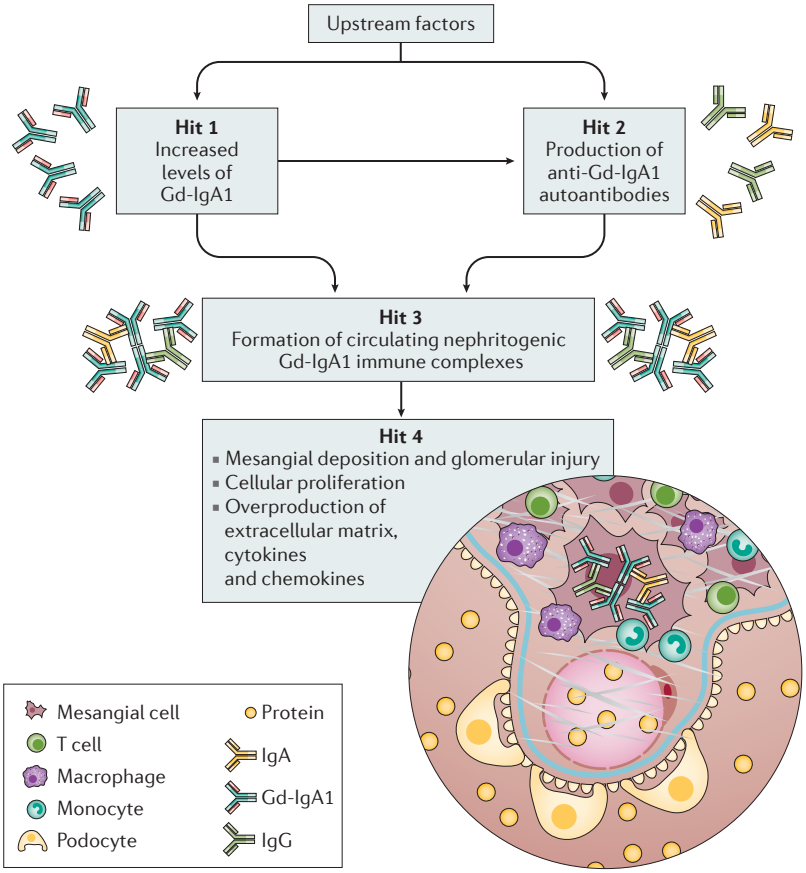

Figure 3 | **Pathogenetic model of IgA nephropathy.** Upstream factors (such as defective mucosal immune responses and antigen processing) directly influence one or more of the pathogenetic pathways. Specifically, the level of IgA1 bearing galactose-deficient *O*-glycans (Gd-IgA1) is increased in the circulation of patients with IgA nephropathy (hit 1). These IgA1 glycoforms are recognized as autoantigens by antiglycan autoantibodies (anti-Gd-IgA1 autoantibodies; hit 2), resulting in the formation of nephritogenic immune complexes (hit 3), some of which deposit in the kidney and activate mesangial cells (hit 4). Mesangial cells start to proliferate and overproduce components of extracellular matrix, cytokines and chemokines. Some of these cytokines can then cause podocyte injury and induce proteinuria. These pathogenetic steps are probably affected by various environmental and genetic factors.

could enhance podocyte apoptosis in acute glomerular injury and lead to podocytopenia in IgAN[55].

Mesangial–podocytic–tubular crosstalk

In vitro experiments have revealed that mesangial cell-derived humoral factors (predominantly tumour necrosis factor (TNF), transforming growth factor-β (TGFβ) and angiotensin II) alter the glomerular permeability in the event of proteinuria and tubulointerstitial injury in IgAN. Before reaching the tubulointerstitium, these humoral factors activate podocytes either by glomerular filtration or by transportation via the post-glomerular capillaries[56].

TNF released from mesangial cells further enhances podocytic synthesis of TNF in an autocrine manner[56]. Alongside this, the expression of TNF receptor 1 (TNFR1; also known as TNFRSF1A) and TNFR2 (also known as TNFRSF1B) in podocytes is upregulated in patients with IgAN. One *in vitro* study suggested two functional roles for TNFR1 in podocytes following stimulation by mesangial-derived TNF: increasing IL-6 synthesis and inducing apoptosis[28]. IL-6 regulates the expression of tubular angiotensin II receptor type 1 (AGTR1) and upregulates the production of tubular angiotensin II[57]. Interaction of angiotensin II and AGTR1 activates the protein kinase C and mitogen-activated protein kinase pathways, leading to inflammatory responses in the tubulointerstitium.

Furthermore, the upregulation of TNFR2 observed in an *in vitro* study suggests that podocytes are in a chronic pro-inflammatory state in IgAN[28]. Indeed, reduction in podocyte proteins (including nephrin, ezrin and podocin) has been demonstrated in renal tissues from patients with IgAN[56]. Downregulation of these podocyte markers is mediated through mesangial cell-derived TNF and TGFβ. The clinical importance is suggested by the finding that the gene expression of nephrin, erzin and podocin correlates with the degree of proteinuria, the increase in the levels of serum creatinine and the reduction in creatinine clearance[56].

Similarly, mesangial cell-derived inflammatory cytokines, including angiotensin II, activate tubular epithelial cells after reaching the tubulointerstitium. These mediators amplify the inflammatory cascade, attracting even more inflammatory competent cells following local production of chemotactic mediators[57]. The tubular epithelial cells proliferate and enhance the local expression of inflammatory mediators — including IL-6, TNF, TGFβ, soluble intercellular adhesion molecule 1 and angiotensin II — that generate a positive feedback loop of activation, leading to the overproduction of extracellular matrix components that result in fibrosis and renal failure.

Angiotensin II has a pivotal role as a mediator of glomerular haemodynamic adaptation and also in immunological injury. A reduction of mesangial AGTR1 expression has been shown *in vitro* after acute exposure to Gd-IgA1-containing immune complexes derived from patients with IgAN, supporting the notion that local downregulation of AGTR1 results from a negative feedback owing to enhanced intraglomerular renin–angiotensin system (RAS) components and, hence, angiotensin II activity[58]. Interestingly, such adaptive changes are lost gradually with prolonged exposure of mesangial cells to Gd-IgA1-containing immune complexes in IgAN. Accordingly, proliferative and inflammatory processes in mesangial cells develop continuously following the failure to suppress the AGTR1 expression in the presence of defective AGTR2 activation. These events perpetuate mesangial–podocytic–tubular crosstalk that finally leads to the progression of renal deterioration in IgAN (FIG. 5).

Genetic data

Genetic factors influencing the pathogenesis and natural history of IgAN were initially recognized through the discovery of familial forms of the disease[59]. Specific loci and genes were later identified through linkage studies and GWAS[20]. Currently, 18 susceptibility loci have been identified by GWAS in cohorts from Europe, North America and East Asia[19,60]. Contrary to the genetic approaches using linkage studies and GWAS that require

large patient cohorts of sporadic IgAN, Liu *et al.*[61] studied ten families with IgAN of Han Chinese descent using exome-sequencing techniques. The technique of exome sequencing enables the interrogation of the whole exome to identify genes and gene variants that underlie both monogenic and complex diseases. In these families, six deleterious variants in four genes (defensin alpha 4 (*DEFA4*), MYC target 1 (*MYCT1*), caspase recruitment domain family member 8 (*CARD8*) and zinc-finger protein 543 (*ZNF543*)) associated with familial IgAN were identified. Of interest is the association of the *DEFA* gene cluster (encoding α-defensins) and disease susceptibility in both sporadic[62] and familial IgAN[61].

Disease susceptibility has also been shown to be affected by common variations in genes involved in antigen processing and presentation (major histocompatibility complex locus) as well as in the mucosal defence system (the *DEFA* gene cluster) and the alternative complement pathway (a common deletion of the complement factor H-related 3 (*CFHR3*) and *CFHR1* genes)[19], further supporting an autoimmune nature of IgAN[25]. Common genetic variants influence the risk of IgAN across world populations and suggest a multi-locus adaptation process, possibly related to the variation in local pathogens[19]. Notably, serum levels of Gd-IgA1 are genetically co-determined[63]. Future genomic studies in large and diverse populations are needed to refine our understanding of genetic pathways in the pathogenesis of IgAN.

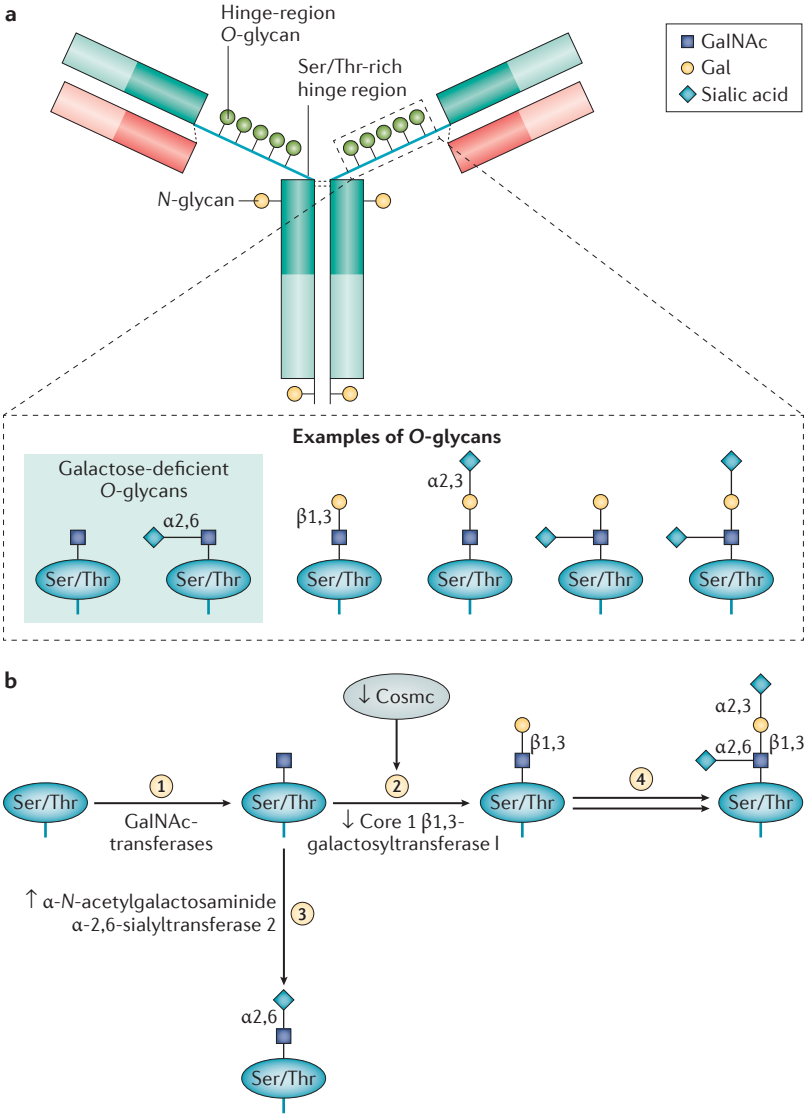

Figure 4 | **Structure and synthesis of human IgA1 *O*-glycans. a** | IgA1 usually has three to six clustered *O*-glycans in the hinge region (IgA1 with five *O*-glycans per hinge region is shown; dashed box). The most common *O*-glycan attached to circulatory IgA1 comprises a disaccharide of *N*-acetylgalactosamine (GalNAc) and galactose (Gal), with or without sialic acid. Serum levels of IgA1 with some *O*-glycans deficient in galactose are increased in patients with IgA nephropathy (IgAN). **b** | Glycosylation of IgA is initiated by the attachment of GalNAc residues to the protein, catalysed by GalNAc transferases (step 1). Next, core 1 β1,3-galactosyltransferase (also known as glycoprotein *N*-acetylgalactosamine 3-β-galactosyltransferase 1) adds galactose (step 2), or alternatively, α-*N*-acetylgalactosaminide α2,6-sialyltransferase 2 adds α2,6-linked sialic acid to GalNAc (step 3). Notably, sialylated GalNAc cannot be subsequently galactosylated, whereas the GalNAc–galactose disaccharide can be further modified at each glycan by sialic acid, with galactose having an α2,3-linked sialic acid (step 4). IgA1-producing cells from patients with IgAN secrete IgA1 with higher degrees of galactose-deficient *O*-glycans, owing to abnormalities in the expression and activities of key glycosyltransferases, decreased expression and activity of core 1 β1,3-galactosyltransferase (and its chaperone Cosmc) and increased expression and activity of α-*N*-acetylgalactosaminide α2,6-sialyltransferase 2.

Diagnosis, screening and prevention

Routine screening for IgAN is not feasible given that no specific diagnostic laboratory tests are available. Diagnosis relies on clinical and histological assessment.

Clinical features

The clinical presentation of patients with IgAN is highly variable, ranging from asymptomatic microscopic haematuria to a rapidly progressive form of glomerulonephritis, which is often associated with severe hypertension. Uncommonly, nephrotic syndrome (characterized by oedema and proteinuria) or a thrombotic microangiopathy (characterized by thrombocytopenia, microangiopathic haemolytic anaemia and microvascular occlusion) can be present initially. Spontaneous full recovery is rare. Between these extremes, most patients with IgAN pursue a chronic indolent course.

Not infrequently, patients first present with non-specific mucosal infection (synpharyngitic macrohaematuria) complicated by macroscopic haematuria that is often associated with a reversible form of acute kidney injury. Urine microscopy reveals dysmorphic red blood cells or even red cell casts. Microscopic haematuria can be associated with proteinuria that tends to fluctuate within a narrow range in most patients; proteinuria is usually not marked and <30% of patients excrete >1 g per day. A transient increase in proteinuria can be observed with gross haematuria during a mucosal infection; a considerable proportion of these patients progress with time[64]. However, some patients present with more-severe proteinuria, hypertension and renal progression over time, typically reaching ESRD over a span of ≥20 years. Fifteen per cent of patients have chronic kidney disease (CKD) stage 3B or higher at first presentation. Occasionally, IgAN initially manifests as ESRD, which is more common in populations with

limited access to health care facilities. Finally, in a small group of patients, most frequently in children, nephrotic syndrome is the main presentation and light-microscopic histological features are indistinguishable from those of minimal change nephropathy (BOX 1). This occurrence has been referred to as an overlapping syndrome of IgAN and minimal change nephropathy[65].

Laboratory findings

There is no single or combined laboratory test that can diagnose IgAN. The final diagnosis is determined by a histological examination. Preliminary tests are conducted to determine the need for kidney biopsy.

Urinalysis and quantifying proteinuria. The first clue in making a diagnosis of IgAN comes after careful examination of a first morning, freshly voided urine sample using unstained bright-field microscopy or phase-contrast microscopy. The presence of red blood cell casts and dysmorphic red blood cells indicates glomerular bleeding. This finding should spare the patient from unnecessary urological procedures such as cystoscopy or retrograde pyelography. However, the presence of glomerular bleeding is not uniquely characteristic of IgAN. The main differential diagnoses include hereditary nephritis (X-linked Alport syndrome) and thin basement membrane lesion (the so-called benign familial haematuria, which is often attributable to the carrier state of autosomal recessive mutations in collagen type 4 alpha 3 (*COL4A3*) or *COL4A4,* the genes associated with Alport syndrome). Varying degrees of proteinuria are present in patients with IgAN. Proteinuria can be quantified with a timed urine collection or a spot urine protein to creatinine ratio measurement. Serum complement values are typically normal, but occasionally are reduced.

Renal function. In most patients with IgAN, assessment of renal function by endogenous creatinine clearance and/or eGFR at baseline — and serially thereafter every 6 months for eGFR — is important because profound CKD at baseline has prognostic implications. For example, patients with an eGFR of just below 60 ml/min/1.73m^2 at the time of renal biopsy have worse outcomes than those with normal eGFR (90–120 ml/min/1.73m^2). However, the overall rate of decline of eGFR is often difficult to predict as some patients with mild-to-moderate renal impairment remain stable for years, particularly when treated with a RAS blocker. Apart from baseline renal function, the degree of histological injury is also of prognostic value. In the Oxford classification of IgAN study cohort[66,67], the rate of GFR decline correlated with glomerulosclerosis and tubular atrophy or interstitial fibrosis, whereas mesangial hypercellularity and tubular atrophy or interstitial fibrosis were predictive of the composite end points of 50% reduction in eGFR or ESRD.

Serum IgA. Serum total IgA level is increased in 33–50% of patients, signifying either enhanced endogenous IgA production or reduced catabolism; neither process serves as a sensitive or specific biomarker for IgAN. In the absence of a histological diagnosis, increased serum IgA levels at best only suggest IgAN in the correct clinical setting of microscopic haematuria or macroscopic haematuria with proteinuria, with or without hypertension. Unlike renal function or histological changes, the serum IgA level bears no prognostic value and the evolution of the level during the course of the disease remains undefined.

Serum levels of Gd-IgA1 have been reported to have 90% specificity and 76% sensitivity for diagnosing sporadic IgAN in a large cohort of white patients in the United States[68]. However, although increased serum Gd-IgA1 is common, it is insufficient to produce IgAN alone — additional co-factors must be present to trigger the formation of immune complexes.

Other ancillary markers. High levels of circulating IgA immune complexes are thought to be very common in IgAN, but the finding currently has no diagnostic use. Similarly, sophisticated urinalysis for growth factors and cytokines shows promise as a predictor of disease or disease activity, but is mainly a research tool at present. Urinary cytokines and chemokines, such as monocyte chemoattractant protein 1 (MCP1; also known as CCL2), IL-6, IL-8 and epidermal growth factor, have the potential to predict renal outcome[69]. Urinary angiotensinogen is a powerful tool for determining intra-renal RAS activity and is associated with renal dysfunction[70]. Urinary complement factor H has been shown to correlate closely with disease activity[71]. In crescentic IgAN (BOX 1), urinary fractional excretion of IgG in relation to the degree of nephron loss predicts disease progression[72]. Urinary IgA levels have been associated with high-grade histological changes and proteinuria, and might be used as a non-invasive biomarker to evaluate kidney injury. Urinary podocytes or their fragments can be identified by immunohistochemical approaches or by mRNA and protein analysis. Podocyte loss may be a marker for progressive renal disease. Finally, recent evidence suggests that several miRNAs or proteins in the urine are altered in IgAN and, therefore, have the potential role of being biomarkers in the future[40].

Pathology

IgAN has variable appearances in the kidney biopsy, ranging (by light microscopy) from normal to variable degrees of mesangial cell proliferation (FIG. 6a,b) to florid

Box 2 | **The IgA receptor on the mesangial cell in IgA nephropathy**

No known IgA receptors have been identified in human mesangial cells except for the transferrin receptor (CD71), which is ubiquitous in renal cells[45]. Moura *et al.*[141] proposed that, instead of mesangial localization of Fcα receptor I (FcαRI; a receptor for IgA on myeloid cells), activation of the classic Fcα receptor γ-chain (FcRγ)-associated transmembrane FcαRI expressed on circulating myeloid leukocytes takes place as a secondary event. FcαRI–FcRγ transmembane crosslinking in human FcαRI-transgenic animals promotes disease progression by enhancing leukocyte chemotaxis and cytokine production. However, other investigators have failed to demonstrate the expression of FcαRI by human mesangial cells[45,142], despite the fact that mesangial cells showed Fc-dependent IgA binding that was saturable and dose-dependent. The nature of the IgA receptor in IgA nephropathy remains uncertain.

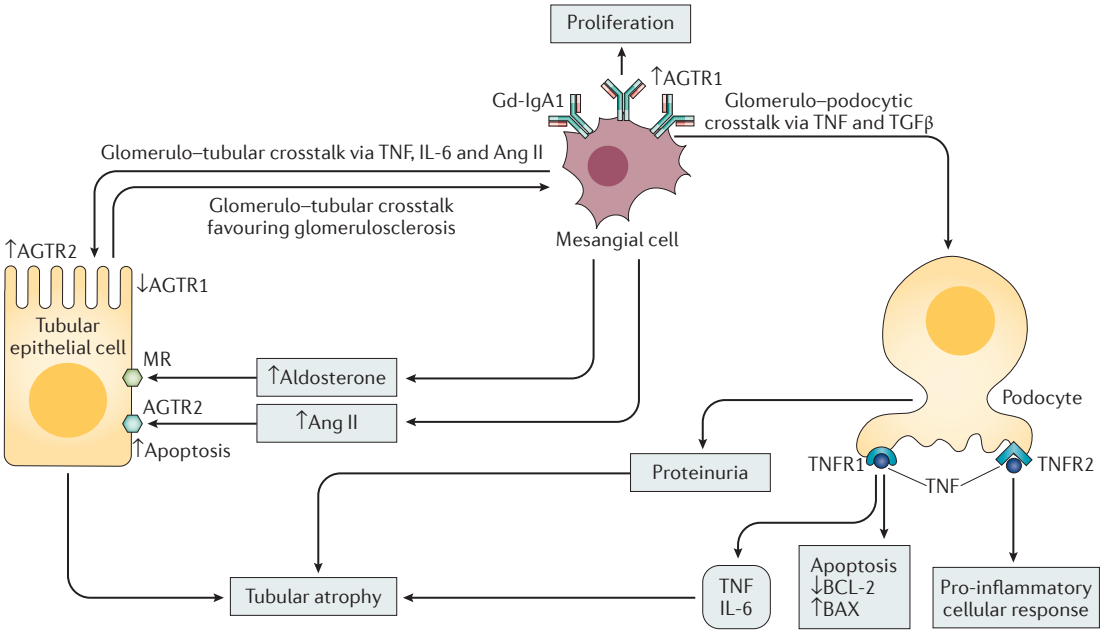

Figure 5 | **Pathways leading to glomerular damage, podocyte dysfunction and tubulointerstitial injury in IgA nephropathy.** Mesangial deposition of IgA immune complexes leads to the activation of mesangial cells, triggering cell proliferation and the release of pro-inflammatory and profibrotic mediators, including tumour necrosis factor (TNF), transforming growth factor-β (TGFβ), IL-6 and angiotensin II (Ang II). The immune complexes do not particularly bind to podocytes or tubular epithelial cells. TNF released from the mesangium after IgA deposition induces TNF synthesis by podocytes. Podocyte-derived TNF further upregulates the production of TNF in an autocrine manner. TNF upregulates the expression of TNF receptors in podocytes: TNF receptor 1 (TNFR1; also known as TNFRSF1A) and TNFR2 (also known as TNFRSF1B). The binding of TNF to TNFR1 leads to IL-6 synthesis and apoptosis, whereas binding to TNFR2 maintains pro-inflammatory cellular responses. Podocytes enhance interstitial damage in IgA nephropathy by amplifying the activation of tubular epithelial cells with enhanced TNF synthesis. In the renal tubulointerstitium, the interaction of Ang II and angiotensin receptor type 1 (AGTR1) leads to inflammatory responses through the upregulation of protein kinase C and mitogen-activated protein kinase (MAPK) pathways (not shown). The activation of AGTR2 leads to apoptosis through downregulation of the MAPK pathway. Aldosterone released from mesangial cells following IgA immune complex deposition acts synergistically with Ang II to induce apoptosis in renal tubular epithelial cells. Mesangial-derived Ang II maintains the tubulointerstitial injury. The enhanced apoptosis (reduced BCL-2 and enhanced BAX levels) in podocytes and tubular epithelial cells favours proteinuria. Gd-IgA1, galactose-deficient IgA1; MR, mineralocorticoid receptor. Figure from REF. 181, Nature Publishing Group.

crescentic necrotizing glomerular lesion or advanced sclerosing appearances (FIG. 7). All phases of IgAN share dominant mesangial IgA deposits (FIG. 6c), with λ-light chains being slightly more prevalent than κ-light chains. Very rarely are the deposits monoclonal, signifying an underlying B cell neoplasia. Deposits are specifically located by electron microscopy, and are present in the mesangium, adjacent to activated mesangial cells with occasional subendothelial location associated with proliferative lesions (FIG. 6d). Subepithelial deposits are rare. Sclerosis develops either secondary to aggressive proliferative lesions, or as a result of chronic injury.

Immune deposits can present in other glomerular diseases and are often observed in lupus nephritis. Lupus nephritis can be easily differentiated from IgAN using staining for all three immunoglobulins (IgA, IgG and IgM) and staining for classic complement pathway proteins (C1q and C3) that are present in deposits, tubule reticular aggregates (interferon fingerprints) and clinical history. Henoch–Schönlein purpura (now known as IgA vasculitis) has distinct extra-renal clinical manifestations, but the renal pathology is not distinguishable from that of primary IgAN except for a greater propensity to produce necrotizing crescentic glomerulonephritis. IgA-dominant deposits can also occur in infection-related glomerulonephritis, particularly those associated with staphylococcal infection. This entity is distinguished from IgAN by an exudative appearance with numerous polymorphs in glomerular tufts, dominant C3 staining, greater κ-light-chain staining than λ-light-chain staining, and the presence of subepithelial 'hump-type' deposits in addition to mesangial deposits.

Prognosis

Pathology. To determine whether the renal biopsy appearance could add any prognostic information to clinical parameters, an international study group composed of the International IgAN Network and the Renal Pathology Society studied archival biopsies of IgAN[73]. Patients were excluded from this initial cohort if they had minimal or no proteinuria or reached ESRD within 1 year of their diagnosis. All renal biopsy lesions were then defined and definitions for scoring developed, with iterative working groups refining this process.

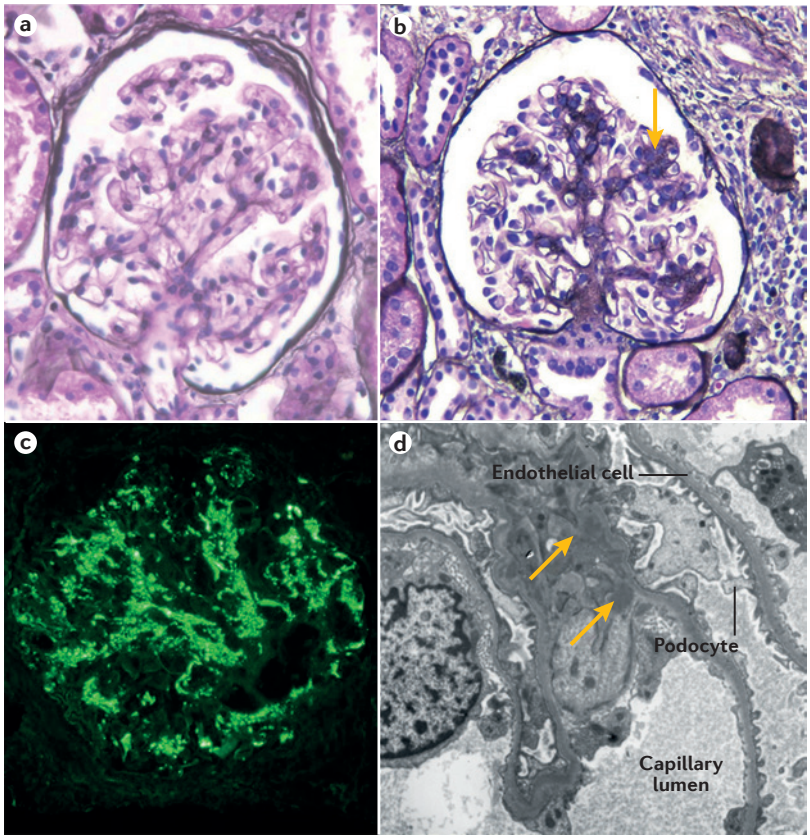

Figure 6 | **Renal biopsy findings in a patient with IgA nephropathy. a** | Light microscopy image of a normal glomerulus (Jones' silver stain; 200× magnification). **b** | Light microscopy image of a glomerulus showing mild increase in the mesangial matrix and cellularity (arrow; Jones' silver stain; 200× magnification). **c** | Immunofluorescence image of a glomerulus showing heavy granular staining of IgA in the mesangium (200× magnification). **d** | Transmission electron micrograph of the mesangium demonstrating electron-dense mesangial deposits (arrows; 5,000× magnification).

Lesions that could be reliably scored were then further assessed. These initial lesions included vascular sclerosis, crescents, mesangial hypercellularity, endocapillary hypercellularity, segmental glomerulosclerosis and tubulointerstitial fibrosis (FIGS 6,7). Four of these variables were associated with a higher rate of decline of GFR, independent of clinical variables; namely, mesangial hypercellularity in most of the glomeruli (M), any endocapillary hypercellularity (E), any segmental sclerosis or adhesion (S) and significant (≥25%) tubulointerstitial fibrosis (T). Subsequent studies have validated and refined these criteria, the so-called Oxford-MEST classification approach of IgAN. Of note, the data did not support hierarchical classification of mutually exclusive classes of lesions of the biopsies, but rather a cumulative scoring of lesions with worse prognosis.

The VALIGA study[67] further expanded on these findings, demonstrating the validity of including biopsy findings in a prognostic, 'staging' assessment of patients. Additional studies in patients not receiving immunosuppressive treatment support the opinion that crescents (BOX 1) indicate adverse prognosis if not treated[74,75]. Of note, crescentic disease was under-represented in the initial Oxford cohort owing to study inclusion criteria. Furthermore, in those archival cases, patients were treated differently based on biopsy findings. Thus, patients with active lesions, including crescents, more often received immunosuppressive therapy, which confounded analysis of the influence of treatment on prognosis[76].

Clinical. Owing to the indolent clinical course in most instances, using the definitive end point of ESRD is unrealistic for most patients. Certain clinicopathological features are generally accepted as indicative of a less-favourable prognosis in patients who have relatively preserved renal function at diagnosis (BOX 3). Those patients with poor prognostic markers at presentation should be seen by a nephrologist regularly at 3-month intervals. The 10-year renal survival stands at 80–90% according to published life-table analysis from Asia, Australia, Europe and North America[77].

Traditionally, the severity of proteinuria upon presentation has carried prognostic implications. More importantly, rather than a single measurement upon presentation, the change in proteinuria over time is being regarded as a better prognostic indicator[78]. In the Toronto Glomerulonephritis Registry, which included >500 patients, those who had heavy proteinuria and achieved a partial remission of <1 g per day had a similar course to those who had <1 g per day throughout, and fared far better than patients who never achieved remission[78]. Another study in Hong Kong[79] demonstrated change in the urine albumin to creatinine ratio at 1 year to be an independent predictor of progression to ESRD during a 6-year follow-up period. In a Spanish study, the long-term prognoses of patients who presented with minimal or no proteinuria and normal renal function was excellent after a 20-year follow-up period[80]. Using multivariate Cox analysis, age and mean proteinuria at follow-up were shown to be powerful independent prognostic predictors in a cohort of Italian patients[81]. These observations support the notion that every effort should be made to reduce proteinuria in IgAN.

Management

Patients with minor urine abnormalities, normal blood pressure and normal GFR usually do well and require only periodic monitoring, such as biennial clinic visits. For other patients, the therapeutic options are limited and include nonspecific treatment to reduce blood pressure and proteinuria by RAS blockade, as well as other general measures, such as lipid lowering, dietary restriction of sodium, smoking cessation and avoidance of NSAIDs and other nephrotoxins. Systematic reviews on the benefits of fish oils, anticoagulants, tonsillectomy (given the evidence that tonsillitis might be a precipitating event for nephritogenic IgA1 production) and antihypertensive medications have provided valuable insight into the role of non-immunosuppressive therapy for IgAN[82]. However, no disease-specific therapies are currently available, and an unmet need persists for novel interventions, particularly in patients who are at risk of progressive disease (FIG. 8).

Conventional therapy

RAS blockade. RAS blockers are often prescribed for patients with IgAN who have proteinuria. In a meta-analysis of 585 patients from 11 randomized clinical trials (RCTs)[82], treatment with an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) had significant effects on renoprotection and reduction of proteinuria versus control. The beneficial effects of these drugs are enhanced by concomitant dietary sodium and phosphate restriction. Although studies have looked at other interventions, evidence accumulated from 56 studies and 2,838 participants have shown that only antihypertensive drugs (mostly ACEIs and ARBs) provide useful relief to patients, mainly by reducing proteinuria[83].

The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines for glomerulonephritis[84] aimed to provide comprehensive evidence-based recommendations for treatment and help to define areas for which evidence is lacking. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to rate the strength of evidence (A: high; B: moderate; C: low; and D: very low) and the strength of recommendations (level 1: 'we recommend'; level 2: 'we suggest'; or not graded). The guideline on IgAN suggested blood pressure treatment goals of <130/80 mm Hg in patients with proteinuria of <1 g per day, and <125/75 mm Hg for those with initial proteinuria of ≥1 g per day (level of evidence: not graded). Other non-immunosuppressive modalities (such as fish oils, anticoagulants, other antihypertensive agents and tonsillectomy) had a lack of evidence from RCTs to demonstrate treatment efficacy in IgAN.

Aliskiren is an oral direct renin inhibitor that is thought to fully suppress the RAS because ACEI or ARB treatment leads to a reactive increase in plasma renin activity. Thus far, only two trials from Hong Kong have tested its use in patients with IgAN and have shown an anti-proteinuric effect when given with ACEI or ARB therapy[85,86]. Patients with more-advanced CKD (stage 3b or higher) are prone to developing hyperkalaemia when taking aliskiren. Long-term outcomes have not been reported.

Fish oil. Fish oil contains omega-3 polyunsaturated fatty acids and reduces intra-renal inflammation by mitigating inflammatory cytokines and eicosanoids in patients with IgAN[87]. Despite the favourable report first published in 1994 (REF. 88), conflicting results have been subsequently reported showing no significant benefits[89,90].

Although fewer patients assigned to fish oil treatment in a cohort of 106 subjects reached the end point of a ≥50% increase in serum creatinine levels in the original Mayo Clinic multicentre study[88], therapy with fish oil in this and a subsequent trial[91] did not significantly reduce proteinuria. This is an important caveat given that proteinuria is a key therapeutic target because it may itself cause renal injury and because its reduction correlates with the preservation of renal function. A more-recent trial of 30 patients suggested that combining polyunsaturated fatty acids with a RAS blocker reduced proteinuria more than RAS blocker alone[92]. The KDIGO 2012 clinical practice guidelines[84] suggest optional use of fish oil in the treatment of patients with persistent proteinuria of >1 g per day, despite 3–6 months of optimized supportive care, including ACEIs or ARBs and blood pressure control (the level of recommendation and quality of evidence: 2D), but long-term benefits on preventing ESRD are uncertain.

Immunosuppressive therapy

Immune modulation that targets the putative pathogenetic pathways in IgAN might alter the natural history of disease progression. However, to date, no medications have been approved by the US FDA specifically for IgAN. The availability of new agents with novel mechanisms and activities against the humoral immune response might enable targeted treatment, such as developing antibody targeting cells producing the autoantibody that is specific for Gd-IgA1.

Corticosteroids. The use of corticosteroids (as anti-inflammatory agents) for IgAN began in the 1980s and remains a choice for patients with moderate-to-severe persisting proteinuria (variously defined as >0.5–1.0 g per day lasting for ≥3 months). A meta-analysis of nine RCTs

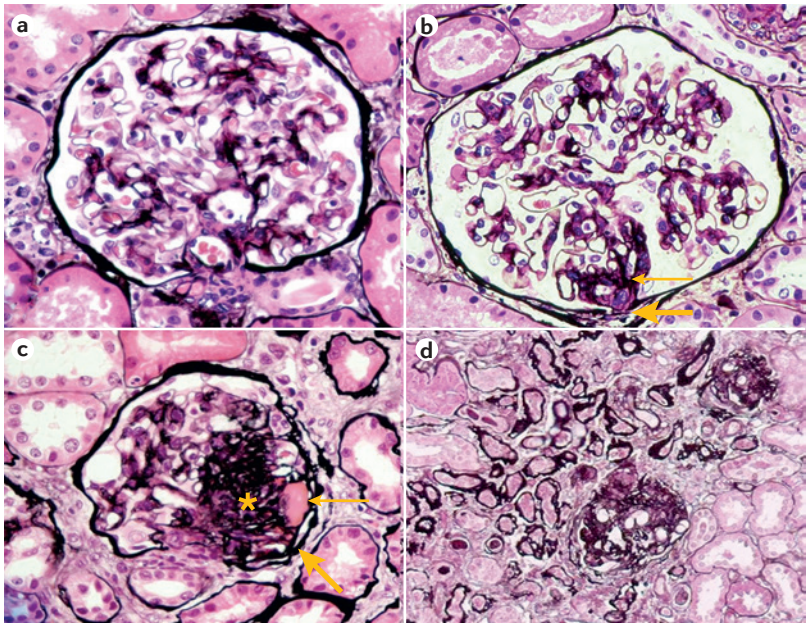

Figure 7 | **Different stages of pathology in IgA nephropathy. a** | IgA nephropathy (IgAN) at an early stage, with minimal mesangial expansion and preserved glomerular capillary tufts (that is, a network of capillaries) architecture. Periodic acid-silver methanamine, haematoxylin and eosin counterstain, 360× magnification. **b** | Small segmental sclerosis (25%) with capillary collapse (thin arrow) and capsular adhesion (thick arrow). Periodic acid-silver methanamine, haematoxylin and eosin counterstain, 360× magnification. **c** | Significant segmental sclerosis (50% of the glomerular area) with capillary collapse and consolidation (*), hyalinosis (thin arrow) and capsular adhesion (thick arrow). Periodic acid-silver methanamine, haematoxylin and eosin counterstain, 360× magnification. **d** | Advanced glomerulosclerosis or glomerular obsolescence (>75%), with associated tubular atrophy and interstitial fibrosis. Periodic acid-silver methanamine, haematoxylin and eosin counterstain, 180× magnification. Figure adapted from *Recent Advances in IgA Nephropathy*, Lai, K. N. (ed.) Copyright © 2009 World Scientific Publisher.

(including 536 patients with urinary protein excretion of >1 g per day and normal renal function) suggested that high-dose, short-term corticosteroid therapy produced significant renal protection, whereas low-dose, long-term corticosteroid use did not[93]. The 2012 KDIGO guidelines[84] recommend that patients with persistent proteinuria of >1 g per day despite adequate ACEI or ARB use, blood pressure control and a GFR of >50 ml/min/1.73m^2 can receive a 6-month course of steroid therapy (level of recommendation and quality of evidence: 2C).

However, the KDIGO recommendation highlighted an important knowledge gap; patients with an eGFR of 30–50 ml/min/1.73m^2 have been excluded from virtually all major clinical trials. A retrospective analysis of the European VALIGA cohort of 1,147 (mostly white) patients attempted to address this gap[94]. In the propensity score analysis, 184 patients who received corticosteroids and RAS blockers had reduced proteinuria, a slower rate of renal function decline and increased renal survival compared with 184 patients with a similar risk profile of progression but who only received RAS blocker treatment. These benefits also extended to 115 patients with an eGFR of <50 ml/min/1.73m^2, and the benefits increased proportionally with the level of proteinuria. However, the study was limited by its retrospective nature, unknown corticosteroid-dosing regimens, frequent combination of corticosteroids with other immunosuppressive therapies, the potential for unmeasured and selection bias and the potential for selection of patients by the participating centre[94]. One interesting observation from this study is the legacy effect, in which even a short course of corticosteroids (≤6 months) exerted long-term effects that extended well beyond the treatment duration with a median follow-up of 4.7 years.

Box 3 | **Markers of poor prognosis in IgA nephropathy**

Demographic
Male sex[143,144]
Older age at diagnosis (>60 years)[145,146]
Obesity[147]

Clinical
No history of macroscopic haematuria[148]
Persistent microscopic haematuria[149,150]
Persistent hypertension[151,152]
Increased serum creatinine levels at presentation[149,153]

Laboratory
Persistent proteinuria (>1,000 mg per day)[81,154]
Hyperuricaemia[155,156]
Hypertriglyceridaemia[157]
Angiotensin-converting enzyme DD genotype[145]

Histological — light microscopy
Glomerular sclerosis[150,154]
Endocapillary cellular proliferation[158]
Capillaritis[159]
Interstitial fibrosis[152,160,161]
Thrombotic microangiopathy[162]
Loss of podocytes[163]
Collectively increased Oxford-MEST scores[164]

Histological — immunofluorescence microscopy
Mesangial IgG co-staining[165,166]

STOP-IgAN[95], a German trial, randomly assigned adults with an eGFR of >30 ml/min/1.73m^2 and persistent proteinuria of >0.75 g per day despite 6 months of supportive care (in particular, blockade of the RAS to a target blood pressure of <125/75 mm Hg) to receive supportive care alone or supportive care plus immunosuppression (corticosteroids alone if the eGFR was 60–89 ml/min/1.73m^2, or in combination with cyclophosphamide for the initial 3 months followed by azathioprine if the eGFR was 30–59 ml/min/1.73m^2). During the run-in phase completed by 309 of the 337 patients, proteinuria decreased to <0.75 g per day in 30% of the participants who then became ineligible for random assignment. Of the 154 patients who underwent randomization and completed 3 years of treatment, more patients in the immunosuppression group achieved full clinical remission (urine protein to creatinine ratio of <0.2 and a reduction in eGFR of <5 ml/min/1.73m^2). However, no significant difference was evident in the annual decline in eGFR between the two groups. Patients in the immunosuppression group had a significantly lower mean proteinuria level than the supportive care group at 12 months after randomization, but this difference disappeared at 36 months. The main conclusion from this study was that the addition of immunosuppressive therapy to intensive supportive care did not significantly improve the outcome and might increase adverse effects. First, the lack of histology-based stratification is a confounding factor. Validation of Oxford-MEST histological scores have indicated the predictive value of histology on treatment response to steroid and immunosuppression. Second, it remains unclear why heavy immunosuppression (pulse steroid plus cyclophosphamide) might benefit patients with more-advanced CKD (eGFR 30–59 as opposed to 60–89 ml/min/1.73m^2), and hence, organ fibrosis, with eGFR down to 30 ml/min/1.73m^2 without inducing adverse events. Third, the authors did not consider reduction of proteinuria, albeit transient, to be a benefit. Experience from the VALIGA study[94] and other studies of IgAN[70], as well as diabetic[96] and CKD[97] populations, have clearly shown a legacy effect of proteinuria reduction over time. Fourth, an unusually high percentage (>30%) of participants were on dual ACEI with ARB, contradicting contemporary recommendations, and how this could have affected outcome cannot be ascertained. Finally, with two rather different studies powered as one study, the steroid-monotherapy group could be underpowered to examine the chosen end points.

A large international multicentre double-blinded RCT (TESTING)[98] of corticosteroid therapy in IgAN is currently in progress. TESTING started recruitment in 2012 to investigate the efficacy of oral methylprednisolone versus placebo in IgAN, and randomization is expected to be completed in 2017. The study includes patients with an eGFR in the range of 20–90 ml/min/1.73m^2 and, as with STOP-IgAN, patients enter a pre-random assignment phase wherein RAS blockade and blood pressure are optimized.

Combined corticosteroids and cyclophosphamide. In non-Chinese populations, cyclophosphamide plus corticosteroid therapy has shown benefit in patients at

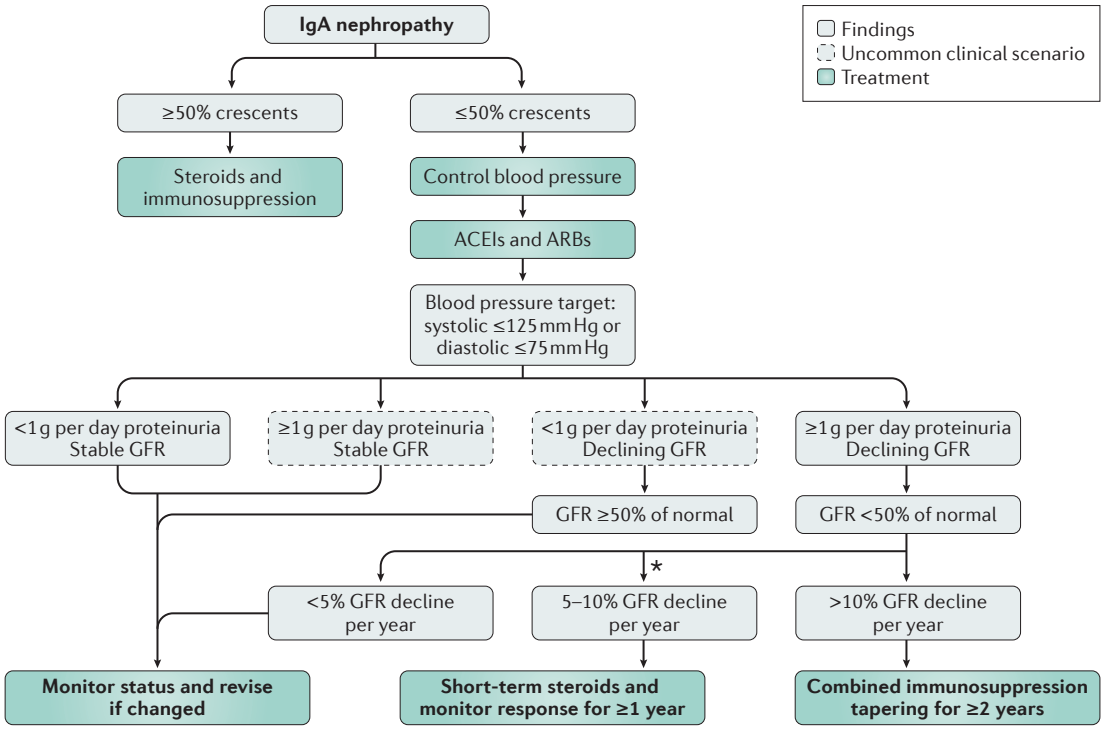

Figure 8 | **An algorithm of proposed treatment options for IgA nephropathy.** Patients are treated for IgA nephropathy (IgAN) depending on the severity of disease. Patients with substantial crescentic disease (BOX 1) receive immunosuppression and steroids to control renal inflammation; those with less-severe crescentic disease must achieve blood pressure control. If proteinuria develops upon blood pressure control, the level of proteinuria and the decline in glomerular filtration rate (GFR) determine the course of action. For white patients with >10% GFR decline per year, cyclophosphamide-based immunosuppression is given; Chinese patients benefit from mycophenolate mofetil-based immunosuppression. *Monitoring of acid–base balance and blood pressure, and restriction of nephrotoxic drug use. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

high risk of developing ESRD, namely, those with crescentic glomerular lesions and rapidly progressive clinical course[99,100]. In Chinese patients, crescentic IgAN carries a poor prognosis. Among 113 such patients from 8 centres across China, renal survival or progression to ESRD was not different between those who received cyclophosphamide and pulse corticosteroid, and patients who did not receive immunosuppression, although there was a trend that immunosuppressive therapy reduced the risk of ESRD in patients with dominant active crescents (cellular or fibrocellular crescents of >50%)[75].

The 2012 KDIGO guidelines[84] suggest the use of corticosteroids and cyclophosphamide in patients with IgAN and rapidly progressive crescentic disease, analogous to the treatment of anti-neutrophil cytoplasmic antibody (ANCA) vasculitis (level of recommendation and quality of evidence: 2D).

Corticosteroids with tonsillectomy. The practice of tonsillectomy in IgAN is based on observation of disease activation manifested as macroscopic haematuria and renal dysfunction following upper respiratory tract infection. Tonsillectomy was thought to be useful for IgAN under the premise that it can remove a relevant source of pathogens, which can multiply in tonsil crypts, and remove a source of macrophages and B cells within lymphoid tonsil follicles. Recently, the gene expression of glycosyltransferases involved in the glycosylation of IgA1 has been demonstrated to be downregulated in tonsillar B lymphocytes from patients with IgAN leading to underglycosylation of IgA1 (REF. 101).

Tonsillectomy as a management strategy for IgAN has mainly been documented in Japan. A meta-analysis of seven non-randomized studies (mostly from Japan) comprising 858 patients (of whom 534 underwent tonsillectomy and 324 did not) showed that tonsillectomy combined with either standard or pulse corticosteroid treatment, but not either tonsillectomy or corticosteroid treatment alone, resulted in higher remission rates with favourable long-term outcomes[102]. A recent multicentre RCT from Japan showed that tonsillectomy combined with steroid pulse therapy had no beneficial effect over steroid pulse therapy alone to attenuate haematuria or to increase the rate of clinical remission[103]. Although the anti-proteinuric effect was greater in the combined therapy arm of this study, the difference was marginal. The 2012 KDIGO guidelines[84] suggest that tonsillectomy should not be performed for IgAN (level of recommendation and quality of evidence: 2C).

Azathioprine. A moderately large-scale study randomly assigned 207 patients with IgAN to either corticosteroids alone ($n = 106$) or in combination with the immunosuppressive drug azathioprine ($n = 101$) for 6 months[104].

Box 4 | **Domains of quality of life affected by IgA nephropathy**

The following domains of quality of life affected by IgA nephropathy have been taken from the 36-Item Short-Form Health Survey:

Vitality
Limited effects, except when renal function is impaired (in those with an estimated glomerular filtration rate of <30 ml/min/1.73m^2)

Physical functioning
Limited effects, except when exercise-induced haematuria is prominent or when renal function is markedly impaired

Bodily pain
Mild flank pain is common; renal biopsy can be painful

General health perceptions
Living with a chronic disease, with no certainty of a cure
Concern about transmission to offspring (in familial cases only)

Physical role functioning
Limitations on vigorous exercise only if exercise induces episodes of macroscopic haematuria

Emotional role functioning
Limited effects, unless complicated by adverse events stemming from treatment

Social role functioning
No or very limited effects

Mental health
Depression, anxiety, fear of an uncertain future and complications of treatment can impair overall mental health

Azathioprine conferred no additional benefit but resulted in more adverse events, namely, hepatotoxicity, anaemia and gastrointestinal symptoms. The 2012 KDIGO guidelines[84] do not recommend the use of azathioprine in IgAN (level of recommendation and quality of evidence: 2D).

Mycophenolate mofetil. Three studies in Chinese patients have shown a benefit of the immunosuppressive drug mycophenolate mofetil. The first trial included 62 patients with severe IgAN and proteinuria of >2 g per day. Patients who received mycophenolate mofetil showed significant improvement in proteinuria and serum lipid levels compared with those who received prednisone, a corticosteroid[82]. The second study included 40 patients with mild tubulointerstitial lesions and persistent proteinuria of >1 g per day despite RAS blockade. Mycophenolate mofetil treatment for 6 months resulted in significant reduction in proteinuria[105], and improved renal survival at 6-year follow-up compared with using RAS blocker alone[106]. The third study compared mycophenolate mofetil and prednisone to cyclophosphamide and prednisone in patients with severe IgAN[107]. The mycophenolate mofetil-based regimen achieved a higher remission rate with better reduction of proteinuria and improvement of renal function, and fewer adverse effects.

Another three studies in white patients have shown mixed results. The first included 34 patients in Belgium with impaired renal function, histologically unfavourable criteria and arterial hypertension. All patients received salt restriction and ACEI therapy, and 21 patients who were randomized to receive high-dose mycophenolate mofetil failed to demonstrate a better beneficial effect after 3 years of evaluation[108]. The second study, conducted in the United States, recruited patients with even more advanced renal insufficiency than the Belgian study. All were receiving ACEIs or ARBs; 35% and 16% had previous fish oil or steroid use, respectively. Here, worse outcomes occurred with mycophenolate mofetil when used as a 'salvage' therapy[109]. In the third, non-controlled study, Italian patients with IgAN with florid glomerular changes treated with mycophenolate mofetil and corticosteroids for 6 months showed remission of proteinuria and reversal of progressive renal failure[110].

More recently, one trial conducted in 52 children, adolescents and adults with IgAN in the United Stated and Canada was terminated early as mycophenolate mofetil did not reduce proteinuria[111]. Patients were treated with an ACEI (lisinopril) or an ARB (losartan) plus a highly purified omega-3 fatty acid (Omaco, Pronova Biocare, Bærum, Norway) for 3 months before random assignment. Only those with a persistent urinary albumin to creatinine ratio of >0.6 (for male patients) and >0.8 (for female patients) were randomized.

Given these mixed results across different ethnic groups and given that none of these studies were adequately powered to provide a definitive answer, the 2012 KDIGO guidelines[84] suggest that mycophenolate mofetil should not be used in IgAN (level of recommendation and quality of evidence: 2C).

Quality of life

For many patients with biopsy-proven IgAN, the overall quality of life (QOL) is affected in a minimal way. QOL can be assessed by several instruments, but the 36-Item Short-Form Health Survey (SF-36; BOX 4)[112] questionnaire is the simplest and most widely used.

The anxiety provoked by a new diagnosis of a CKD can be very unsettling and can have untoward consequences in terms of employment, relocation to foreign countries (extended stay visas) and obtaining life or health insurance. Worry about transmission of the disease to offspring frequently arises, even though a minority of cases show clear-cut Mendelian inheritance. Frequent episodes of gross haematuria, often in association with nonspecific upper respiratory infections, can lead to repetitive encounters with physicians. Some physicians will mistake the symptoms as signs of non-glomerular or infectious causes, such as bladder, kidney or prostate cancer or a urinary tract infection, and will perform unnecessary invasive (cystoscopy) or imaging investigations. Mild fever, vague flank pain and malaise, which can be observed commonly in patients with IgAN, only heighten these concerns, but a careful examination of the urine sediment (for dysmorphic red blood cells and/or red blood cell casts) and a test for proteinuria can most often provide clues leading to avoidance of such unnecessary and uncomfortable procedures. For patients with a biopsy-proven diagnosis of IgAN who have no or minimal proteinuria, normal renal function (for their age), normal blood pressure and a biopsy finding of mild disease (such as pathological scores of M0, E0, S0 and T0–1 according to the Oxford-MEST classification or an absolute renal

risk score of zero), simple reassurance combined with a mutually understood schedule of regular follow-up can alleviate much of the QOL-interfering anxiety. Such patients have a very favourable prognosis in the long term, but uncommon exceptions to this general rule have been observed[113–115].

However, when features suggestive of a progressive course are present (BOX 3), interventions (as discussed above) might well be indicated. Each of the interventions has its own unique adverse-effect profile that can contribute to a deterioration of QOL, especially in patients with few symptoms in the absence of active treatment. Explaining the possible consequences of treatment on QOL in advance can help, but might also aggravate anxiety. Every means should be taken to minimize undesirable adverse effects of treatment without compromising the efficacy of the chosen regimen. Nephrotic syndrome, although relatively uncommon as a presenting feature in IgAN, carries special features, such as oedema, ascites, pleural effusions, thrombophilia and accelerated atherogenesis, that can add considerably to an impaired QOL and requires a different approach to management compared with patients with asymptomatic haematuria and non-nephrotic proteinuria.

The most serious impact on QOL occurs in those patients with IgAN who progress to advanced stages of kidney impairment (CKD stage 4 and stage 5) and eventually require renal replacement therapy. Fortunately, this occurs in only about 30–50% of patients after 15–30 years of follow-up, and only in those who exhibit persistent poor blood pressure control and proteinuria (>0.5–1.0 g per day) despite adequate treatment (and compliance) with RAS inhibitors or in those few patients who present with a syndrome of rapidly progressive glomerulonephritis with extensive (≥50%) crescent formation[116].

The consequences of advanced-stage CKD (uraemia) and its treatment by renal dialysis on QOL are all too familiar (BOX 5), and include depression, sexual dysfunction, fatigue, weakness, insomnia, anorexia, dysgeusia (foul, salty, rancid or metallic taste sensation), nausea, muscle cramps, pruritus, bone pain and fractures, cognitive dysfunction, visual disturbances and neuropathy[117,118]. Although dialysis treatment can correct many of these disturbances and improve but not fully normalize QOL, renal transplantation affords a much higher likelihood of achieving a satisfactory level of QOL and is the preferred treatment whenever possible.

Box 5 | **Effects of dialysis on patients' quality of life**

The use of dialysis to treat patients with IgA nephropathy and end-stage renal disease can have both positive and negative effects on the patients' quality of life.

Benefits

- Alleviation of the symptoms of uraemia (partial)
- Correction of the fluid balance and electrolyte disorders of end-stage renal disease (volume overload, acidosis, hyperkalaemia, hyperphosphataemia and hypocalcaemia) (partial)
- Improvement of appetite and nutrition
- Improvement of strength and vitality (limited to non-frail individuals); better control of anaemia (with erythropoesis-stimulating agents)
- Improvement in cognitive function (partial)
- Improved life expectancy, in the absence of other life-curtailing disorders (for example, metastatic cancer, advanced dementia, frailty or advanced age)

Consequences

- Requirement for a permanent access to the circulation (haemodialysis) or peritoneal cavity (peritoneal dialysis)
- Increased risk of infection
- Increased risk of life-altering symptoms or accidents related to treatment (hypotension, haemolysis, air embolism, sepsis, fluid or electrolyte disturbances and ischaemic cardiac injury)
- Depression, anxiety and augmented feeling of dependency
- Pain (use of arteriovenous–venous access and peritonitis)
- Requirement for travel to and from treatment centres (only for centre-based treatment)
- Cost of treatment (if not covered by private or public insurance)
- Limitations on certain kinds of activities (for example, swimming and sauna use)

Outlook

Despite the progress in the understanding of IgAN pathogenesis over the past four decades, important issues remain major clinical and research challenges. For example, the mechanism by which IgA binds to the mesangial areas is still unclear (BOX 2). Furthermore, whether IgAN is a single disease or a different disease entity in different ethnic groups is also unclear (BOX 6).

At present, the diagnosis of IgAN is established only following a renal biopsy. It is evident that the urinary screening and biopsy policies greatly affect the discovery rate of IgAN. More widespread urinary screening might partly explain the high prevalence in East Asian countries and the restricted biopsy policy might be pivotal in the lower prevalence among white patients in the United States, Europe and Australasia. Although immunochemical anomalies of IgA1 are well known, the underlying molecular mechanisms that lead to these anomalies remain to be fully clarified. Similarly, the pathophysiological events following the mesangial binding of IgA1-containing immune complexes that lead to progressive renal failure are little understood. These are individual areas in which we envision research progress in the future.

Non-invasive diagnostic and prognostic approaches

Renal biopsy, an invasive procedure, remains the definitive diagnostic method for IgAN. Patients with isolated microscopic and dysmorphic haematuria often refuse renal biopsy because they are asymptomatic. Non-invasive approaches might provide additional diagnostic criteria for patients for whom there is a high suspicion of an underlying glomerulonephritis such as IgAN; these might include serum and urinary biomarkers. Combining biomarkers might increase the diagnostic sensitivity and specificity, providing an alternative to renal biopsy.

Serum biomarkers. Gd-IgA1 and the corresponding autoantibodies that recognize it are the most promising serum biomarkers[25,119]. In a small cohort of familial patients with IgAN ($n = 5$), Gharavi *et al.*[63] observed high levels of Gd-IgA1 in all individuals, in 47% of their

Box 6 | **Is IgA nephropathy different between East Asian and white people?**

Available genome-wide association studies have revealed that there are ethnic-based differences in the number of risk alleles for IgA nephropathy (IgAN), with the highest number of risk alleles in individuals in eastern Asia and the lowest numbers in Africa, correlating with the differences in the prevalence of IgAN[18]. In areas where urine examination is mandatory for school children or for the general population undergoing routine health examination, the prevalence of IgAN is higher with earlier detection and better continuous care[12,167]. As previously discussed, when policy changed to include more biopsies, the prevalence of IgAN increased[7]. Thus, the increased frequency of IgAN over time might also be due, at least in part, to a greater willingness of nephrologists to biopsy individuals with microscopic haematuria of glomerular origin and normal serum creatinine concentrations. Small cohort clinical studies indicate a difference in clinical response to immunomodulatory therapy between white and East Asian patients with IgAN. Surprisingly, the Toronto Glomerulonephritis Registry demonstrated a higher risk of progression to end-stage renal disease after analysing a cohort of 202 patients with IgAN of Pacific Asian origin and 467 patients with IgAN of other origin despite the two groups receiving the same standard of health care[168]. Despite these differences in prevalence and clinical prognosis, the pathological findings in patients with IgAN worldwide are indistinguishable. Moreover, the same pathogenetic mechanism (or mechanisms) of aberrant glycosylation resulting in the formation of galactose-deficient IgA1 operates in all patients[2,30,33], supporting the notion that IgAN remains a single entity of glomerulopathy.

at-risk relatives (assuming autosomal dominant inheritance ($n = 45$)) and in 5% of unrelated individuals who married into the family ($n = 19$). Similarly, Gd-IgA1 levels were high in 78% of patients with sporadic IgAN and in 25% of their blood relatives[63].

A major dominant gene on a polygenic background is suggested by segregation analysis. Similar findings were found in Chinese patients with IgAN[2]. Compared with patients with sporadic IgAN, patients with familial disease had higher serum Gd-IgA1 levels with more-advanced renal histopathology. The polymeric IgA1 isolated from familial clusters showed enhanced binding to mesangial cells, with increased release of IL-6, TNF and MCP1. The serum Gd-IgA1 levels from patients with sporadic or familial IgAN and relatives of those with familial IgAN were higher than those of healthy controls. Furthermore, significant age-adjusted, sex-adjusted and household-adjusted heritability has been demonstrated for serum Gd-IgA1 — estimated at 76% in paediatric patients[120]. Antiglycan antibody recognizes the Gd-IgA1 to form pathogenetic immune complexes[30–32], and measurement of antiglycan antibody may be an attractive serum marker for diagnosing IgAN.

The other potential serum biomarkers are miRNAs that regulate gene expression. Serino *et al.*[121] showed that the expression of miR-148b, which potentially targets *C1GALT1*, correlated directly with serum levels of Gd-IgA1. Patients with IgAN exhibited lower *C1GALT1* expression than healthy controls and this expression negatively correlated with miR-148b expression. Endogenous *C1GALT1* mRNA levels were reduced threefold following transfection of peripheral blood mononuclear cells from healthy individuals with a miR-148b mimic[121]. Conversely, reduction of miR-148b function in peripheral blood mononuclear cells of patients with IgAN restored *C1GALT1* mRNA and protein levels to those observed in healthy individuals[121].

The same investigators also showed that deregulated expression of miRNA let-7b was associated with altered expression of GalNAc transferase 2, which catalyses the attachment of GalNAc to the serine/threonine of the hinge region of IgA1 (REF. 122). A recent study involving 176 biopsy-proven patients with IgAN from Hong Kong, Japan, Greece and Italy provided encouraging support for combined miRNA biomarkers, using let-7b and miR-148b serum levels. This work showed that, combined as a biomarker, let-7b and miR-148b serum levels could predict the diagnosis of IgAN with a high accuracy as assessed by the area under the receiver operating characteristic curve (0.85: $P < 0.0001$)[123].

Urinary biomarkers. Currently, the prognostic value of the history of macroscopic haematuria versus the lack of macroscopic haematuria (that is, only microscopic haematuria) is unclear (BOX 7). Furthermore, increased urinary levels of selected cytokines and growth factors are observed in patients with IgAN. Indeed, increased levels of urinary cytokines and/or growth factors might be associated with advanced renal histopathology but provide little value as a diagnostic tool. However, urinary peptides could be of future interest for developing diagnostic and prognostic biomarkers that are relevant to IgAN. Such markers may be developed, for example, using urinary peptidomics[124,125].

Cellular crosstalk and disease modification

An *in vivo* study of IgAN is difficult owing to the lack of good animal models. With an improved ddY mouse model[126], mice developed proteinuria and glomerular IgA deposits within 8 weeks of birth. One could anticipate therapeutic advances through pharmacological blockade and manipulation of the signals involved in mesangial–podocytic–tubular cell crosstalk, such as angiotensin II and TNF.

Pathogenesis and future therapeutic options

Building on the biomarker work of Serino and coworkers[121,122], which showed that upregulation of miR-148b and let-7b reduces the expression of *CIGALT1* and GalNAc transferase 2, respectively, the development of antisense miRNA has been proposed to correct the deregulated expression of miRNAs in IgAN. This approach might provide a means to correct the aberrant glycosylation in IgAN[127]. Other therapeutic options have also been proposed.

Blocking the attachment of Gd-IgA1-containing complexes to mesangial cells. The charge and size of the component protein exert profound effects on the deposition of immune complexes in the kidney[128]. Indeed, the binding of plasma polymeric IgA1 to human mesangial cells is dependent on charge. Polymeric IgA from patients with IgAN with the highest net anionic charge binds strongly to human mesangial cells. An *in vitro* study showed that pre-incubation with polyanions decreases the binding of polymeric IgA1 to mesangial cells, indicating that the anionic charge of IgA1 plays an important part in mesangial deposition[129]. The negative charge of IgA1 molecules increases with higher sialic acid content, which

also enhances steric hindrance for binding to mesangial cells[130]. Other work has shown that the formation of IgA1-containing immune complexes in IgAN can be altered when B cells are programmed to sialylate IgA1 early in post-translational glycosylation (which, therefore, precludes the addition of galactose)[131]. Thus, augmenting sialylation could be a possible means to alter the mesangial binding of Gd-IgA1.

Targeting the activation of the immune complex. The alternative and mannose-binding lectin complement pathways are involved in IgAN; IgA1 can activate both pathways *in vitro*. Properdin and complement factor H in the alternative pathway and mannose-binding lectin-associated serine proteases 1 and 2, and C4d, in the mannose-binding lectin pathway are present in the mesangial deposits. Complement activation can take place directly on the circulating IgA1-containing immune complexes and/or after their renal deposition. Complement factors and their fragments in the serum, urine or renal tissue might serve as biomarkers of IgAN. Indeed, better understanding of complement could provide potential targets and rationale for the development of complement-targeting therapy in IgAN[43].

Novel therapies in early clinical trials

Increased knowledge on the pathogenetic mechanisms of IgAN, particularly on the role of mucosal immunity and B cell activation, has provided the impetus for several new Phase II/III clinical trials. None of these have reached any conclusions yet.

Enteric budesonide. Multiple observations have revealed the mucosal immune system to be an important source of IgA1. Nefecon® (Pharmalink AB, Stockholm, Sweden) is a modified-release formulation of budesonide. The drug is delivered specifically to the ileocecal Peyer's patches (lymphoid nodules), and therefore has negligible systemic adverse effects. Nefecon® has been shown to reduce proteinuria by 23% and modestly augment eGFR by 8% in 16 patients (with proteinuria of >0.5 g per day and serum creatinine levels of <200 µmol per l) who were treated for 6 months followed by 3 months of further observation[132]. On the basis of these encouraging results, NEFIGAN, a Phase IIb trial, was conceived in 2012 to evaluate the efficacy and safety of two different doses of Nefecon® in patients with primary IgAN in 10 European countries. The primary end point is change in proteinuria at 9 months. Recruitment of patients was completed in January 2014 and results are pending.

B cell depletion and/or inhibition. As IgA is derived from a specific subset of B cells, there is considerable interest in targeting B cells specifically as a therapeutic approach. In a small case series, a single dose of the CD20-specific antibody rituximab given to five patients with IgAN failed to reduce proteinuria compared with conventional treatment[133]. Nevertheless, a Phase IV open-label trial[134] for the treatment of progressive IgAN with rituximab has begun in the United States, with a recruitment target of 54 patients. The primary end point is change in proteinuria at 12 months. A repeat renal biopsy is planned to assess treatment impact on histopathology.

Blisibimod is a selective antagonist of B cell-activating factor (BAFF) that can be administered subcutaneously. Given the initial success of treatment with BAFF inhibitors for systemic lupus erythematosus[135], the BRIGHT-SC study[136] started recruiting patients from Asia and Europe in 2013. The primary end point is change in proteinuria at 24 weeks.

Spleen tyrosine kinase inhibition. Both BAFF and signalling through the B cell receptor are essential for B cell maturation and survival. An important intracellular signalling pathway that is activated upon ligation of the B cell receptor is spleen tyrosine kinase (SYK), which mediates maturation and survival of the B cell lineage. Increased expression of total and phosphorylated SYK has been observed in renal biopsies of patients with IgAN[137]. Pharmacological inhibition of SYK or its knockdown using short interfering RNAs significantly reduced cellular proliferation and the synthesis of pro-inflammatory mediators in human mesangial cells that were exposed to IgA1 from patients with IgAN[137]. Accordingly, the SIGN international multicentre study started recruitment in 2014 to evaluate the efficacy of fostamatinib (a selective oral SYK inhibitor) in patients with IgAN[138]. The primary end point is change in proteinuria at 24 weeks. Patients will undergo a repeat renal biopsy after treatment to evaluate histopathological changes.

Proteasome inhibition. Preliminary evidence suggests a role of increased immunoproteasome activity in IgAN[139]. A single-centre open-label exploratory study examining the effects of the proteasome inhibitor bortezomib in IgAN began in 2010 in the United States[140]. The primary end point is change in proteinuria at 1 year.

Box 7 | **The role of macroscopic haematuria in IgA nephropathy**

Notably, acute kidney injury can complicate an episode of massive macroscopic haematuria in IgA nephropathy (IgAN), but is frequently reversible with no damaging effect on long-term renal function or prognosis[169]. However, a history of recurrent macroscopic haematuria — or the finding of asymptomatic microscopic haematuria associated with a better prognosis — remains a subject of debate. For example, contradicting opinions have arisen from centres in the same city caring for patients with similar ethnic backgrounds and health care access, as exemplified in Melbourne, Victoria, Australia. There, the Royal Melbourne Hospital[170] reported that recurrent macroscopic haematuria was a good prognostic indicator, whereas the Monash Medical Center[171] took the opposite view: patients with asymptomatic microscopic haematuria had better outcomes. These conflicting views prevail in both paediatric and adult patient populations among different ethnic groups. Poor renal survival associated with asymptomatic microscopic haematuria was reported in Chinese and Swedish children[172,173], but recurrent macroscopic haematuria bore bad outcomes in Japanese and Turkish children[174,175]. Conflicting findings were similarly reported in adult patients with IgAN in studies from Australia[149], Italy[143], Korea[176] and Poland[150], which reported poor renal survival with asymptomatic microscopic haematuria, and in China[177,178] and France[179], which reported that macroscopic haematuria was associated with poor prognosis. Most intriguingly, a Finnish study reported poor prognosis with both asymptomatic microscopic haematuria and macroscopic haematuria[180]. There is a lack of consensus opinion on the prognostic value of macroscopic haematuria as these reports are retrospective and history of macroscopic haematuria may only be based on the clinical history instead of urinalysis.

1. Chailimpamontree, W. *et al.* Probability, predictors, and prognosis of posttransplantation glomerulonephritis. *J. Am. Soc. Nephrol.* **20**, 843–851 (2009).
2. Tam, K. Y. *et al.* Macromolecular IgA1 taken from patients with familial IgA nephropathy or their asymptomatic relatives have higher reactivity to mesangial cells *in vitro*. *Kidney Int.* **75**, 1330–1339 (2009).
3. Bisceglia, L. *et al.* Genetic heterogeneity in Italian families with IgA nephropathy: suggestive linkage for two novel IgA nephropathy loci. *Am. J. Hum. Genet.* **79**, 1130–1134 (2006).
4. Gharavi, A. *et al.* Genome-wide association study identifies susceptibility loci for IgA nephropathy. *Nat. Genet.* **43**, 321–327 (2011).
5. Kiryluk, K. *et al.* Geographic differences in genetic susceptibility to IgA nephropathy: GWAS replication study and geospatial risk analysis. *PLoS Genet.* **8**, e1002765 (2012).
6. Yu, X. Q. *et al.* A genome-wide association study in Han Chinese identifies multiple susceptibility loci for IgA nephropathy. *Nat. Genet.* **44**, 178–182 (2011).
7. Woo, K. *et al.* The changing pattern of primary glomerulonephritis in Singapore and other countries over the past 3 decades. *Clin. Nephrol.* **74**, 372–383 (2010).
8. Barsoum, R. S. Glomerulonephritis in disadvantaged populations. *Clin. Nephrol.* **74**, S44–S50 (2010).
9. Khalifa, E. H., Kaballo, B. G., Suleiman, S. M., Khalil, E. A. & El-Hassan, A. M. Pattern of glomerulonephritis in Sudan: histopathological and immunofluorescence study. *Saudi J. Kidney Dis. Transpl.* **15**, 176–179 (2004).
10. Wyatt, R. J. *et al.* Epidemiology of IgA nephropathy in central and eastern Kentucky for the period 1975 through 1994. Central Kentucky Region Southeastern United States IgA Nephropathy DATABANK Project. *J. Am. Soc. Nephrol.* **9**, 853–858 (1998).
11. Imai, E. *et al.* Kidney disease screening program in Japan: history, outcome, and perspectives. *Clin. J. Am. Soc. Nephrol.* **2**, 1360–1366 (2007).
12. Cho, B. S. *et al.* A nationwide study of mass urine screening tests on Korean school children and implications for chronic kidney disease management. *Clin. Exp. Nephrol.* **17**, 205–210 (2013).
13. Sissons, J. G. *et al.* Isolated glomerulonephritis with mesangial IgA deposits. *Br. Med. J.* **3**, 611–614 (1975).
14. Power, D. A. *et al.* IgA nephropathy is not a rare disease in the United Kingdom. *Nephron* **40**, 180–184 (1985).
15. Manno, C. *et al.* Desmopressin acetate in percutaneous ultrasound-guided kidney biopsy: a randomized controlled trial. *Am. J. Kidney Dis.* **57**, 850–855 (2011).
16. Liu, H. *et al.* Renal biopsy findings of patients presenting with isolated hematuria: disease associations. *Am. J. Nephrol.* **36**, 377–385 (2012).
17. Das, U., Dakshinamurty, K. V. & Prayaga, A. Pattern of biopsy-proven renal disease in a single center of south India: 19 years experience. *Indian J. Nephrol.* **21**, 250–257 (2011).
18. McQuarrie, E. P., Mackinnon, B., McNeice, V., Fox, J. G. & Geddes, C. C. The incidence of biopsy-proven IgA nephropathy is associated with multiple socioeconomic deprivation. *Kidney Int.* **85**, 198–203 (2014).
This paper highlights the failure to detect IgAN early in regions deprived of good primary health care.
19. Kiryluk, K. *et al.* Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens. *Nat. Genet.* **46**, 1187–1196 (2014).
20. Kiryluk, K., Novak, J. & Gharavi, A. G. Pathogenesis of immunoglobulin A nephropathy: recent insight from genetic studies. *Annu. Rev. Med.* **64**, 339–356 (2013).
21. Yokoyama, H. *et al.* Renal disease in the elderly and the very elderly Japanese: analysis of the Japan Renal Biopsy Registry (J-RBR). *Clin. Exp. Nephrol.* **16**, 903–920 (2012).
22. Pontier, P. J. & Patel, T. G. Racial differences in the prevalence and presentation of glomerular disease in adults. *Clin. Nephrol.* **42**, 79–84 (1994).
23. Schena, F. P. A retrospective analysis of the natural history of primary IgA nephropathy worldwide. *Am. J. Med.* **89**, 209–215 (1990).
24. Shen, P. *et al.* Clinicopathological characteristics and outcome of adult patients with hematuria and/or proteinuria found during routine examination. *Nephron Clin. Pract.* **103**, c149–c156 (2006).
25. Suzuki, H. *et al.* The pathophysiology of IgA nephropathy. *J. Am. Soc. Nephrol.* **22**, 1795–1803 (2011).
26. Glassock, R. J. The pathogenesis of IgA nephropathy. *Curr. Opin. Nephrol. Hypertens.* **20**, 153–160 (2011).
27. Mestecky, J. *et al.* IgA nephropathy: molecular mechanisms of the disease. *Annu. Rev. Pathol.* **8**, 217–240 (2013).
28. Lai, K. N. *et al.* Activation of podocytes by mesangial-derived TNF-α: glomerulo–podocytic communication in IgA nephropathy. *Am. J. Physiol. Renal Physiol.* **294**, F945– F955 (2008).
This study explores podocytes in IgAN.
29. Kiryluk, K. & Novak, J. The genetics and immunobiology of IgA nephropathy. *J. Clin. Invest.* **124**, 2325–2332 (2014).
An in-depth review of the genetics and immunobiology of IgAN.
30. Suzuki, H. *et al.* IgA1-secreting cell lines from patients with IgA nephropathy produce aberrantly glycosylated IgA1. *J. Clin. Invest.* **118**, 629–639 (2008).
31. Suzuki, H. *et al.* Aberrantly glycosylated IgA1 in IgA nephropathy patients is recognized by IgG antibodies with restricted heterogeneity. *J. Clin. Invest.* **119**, 1668–1677 (2009).
This study revealed the importance of antiglycan IgA immune complexes in the pathogenesis of IgAN.
32. Novak, J. *et al.* IgA1-containing immune complexes in IgA nephropathy differentially affect proliferation of mesangial cells. *Kidney Int.* **67**, 504–513 (2005).
33. Tomana, M. *et al.* Galactose-deficient IgA1 in sera of IgA nephropathy patients is present in complexes with IgG. *Kidney Int.* **52**, 509–516 (1997).
34. Allen, A. C., Harper, S. J. & Feehally, J. Galactosylation of *N*- and *O*-linked carbohydrate moieties of IgA1 and IgG in IgA nephropathy. *Clin. Exp. Immunol.* **100**, 470–474 (1995).
35. Mestecky, J. *et al.* Defective galactosylation and clearance of IgA1 molecules as a possible etiopathogenic factor in IgA nephropathy. *Contrib. Nephrol.* **104**, 172–182 (1993).
36. Suzuki, H. *et al.* Cytokines alter IgA1 *O*-glycosylation by dysregulating C1GalT1 and ST6GalNAc-II enzymes. *J. Biol. Chem.* **289**, 5330–5339 (2014).
37. Ju, T. & Cummings, R. D. A unique molecular chaperone Cosmc required for activity of the mammalian core 1 β3-galactosyltransferase. *Proc. Natl Acad. Sci. USA* **99**, 16613–16618 (2002).
38. Aryal, R. P., Ju, T. & Cummings, R. D. The endoplasmic reticulum chaperone Cosmc directly promotes *in vitro* folding of T-synthase. *J. Biol. Chem.* **285**, 2456–2462 (2010).
39. Qin, W. *et al.* External suppression causes the low expression of the *Cosmc* gene in IgA nephropathy. *Nephrol. Dial. Transplant.* **23**, 1608–1614 (2008).
40. Szeto, C. C. & Li, P. K. MicroRNAs in IgA nephropathy. *Nat. Rev. Nephrol.* **10**, 249–256 (2014).
41. Tomana, M. *et al.* Circulating immune complexes in IgA nephropathy consist of IgA1 with galactose-deficient hinge region and antiglycan antibodies. *J. Clin. Invest.* **104**, 73–81 (1999).
42. Berthoux, F. *et al.* Autoantibodies targeting galactose-deficient IgA1 associate with progression of IgA nephropathy. *J. Am. Soc. Nephrol.* **23**, 1579–1587 (2012).
43. Maillard, N. *et al.* Current understanding of the role of complement in IgA nephropathy. *J. Am. Soc. Nephrol.* **26**, 1503–1512 (2015).
This is an excellent review of complement biology in IgAN.
44. Leung, J. C., Tsang, A. W., Chan, D. T. & Lai, K. N. Absence of CD89, polymeric immunoglobulin receptor, and asialoglycoprotein receptor on human mesangial cells. *J. Am. Soc. Nephrol.* **11**, 241–249 (2000).
This is the first study to conclusively exclude the known IgA receptor as being involved in mesangial binding of IgA in IgAN.
45. Moura, I. C. *et al.* Glycosylation and size of IgA1 are essential for interaction with mesangial transferrin receptor in IgA nephropathy. *J. Am. Soc. Nephrol.* **15**, 622–634 (2004).
46. Moura, I. C. *et al.* Identification of the transferrin receptor as a novel immunoglobulin (Ig)A1 receptor and its enhanced expression on mesangial cells in IgA nephropathy. *J. Exp. Med.* **194**, 417–425 (2001).
47. Launay, P. *et al.* Fcα receptor (CD89) mediates the development of immunoglobulin A (IgA) nephropathy (Berger's disease). Evidence for pathogenic soluble receptor-Iga complexes in patients and CD89 transgenic mice. *J. Exp. Med.* **191**, 1999–2009 (2000).
48. Berthelot, L. *et al.* Transglutaminase is essential for IgA nephropathy development acting through IgA receptors. *J. Exp. Med.* **209**, 793–806 (2012).
49. Vuong, M. T. *et al.* Association of soluble CD89 levels with disease progression but not susceptibility in IgA nephropathy. *Kidney Int.* **78**, 12871–12877 (2010).
50. Berthelot, L. *et al.* Recurrent IgA nephropathy is predicted by altered glycosylated IgA, autoantibodies and soluble CD89 complexes. *Kidney Int.* **88**, 815–822 (2015).
51. Lai, K. N. *et al.* Polymeric IgA1 from patients with IgA nephropathy upregulates transforming growth factor-β synthesis and signal transduction in human mesangial cells via the renin-angiotensin system. *J. Am. Soc. Nephrol.* **14**, 3127–3137 (2003).
This is the first study examining the glomerulo–tubular crosstalk in IgAN.
52. Hishiki, T. *et al.* Podocyte injury predicts prognosis in patients with IgA nephropathy using a small amount of renal biopsy tissue. *Kidney Blood Press. Res.* **24**, 99–104 (2001).
53. Lemley, K. V. *et al.* Podocytopenia and disease severity in IgA nephropathy. *Kidney Int.* **61**, 1475–1485 (2002).
54. Asao, R. *et al.* Relationships between levels of urinary podocalyxin, number of urinary podocytes, and histologic injury in adult patients with IgA nephropathy. *Clin. J. Am. Soc. Nephrol.* **7**, 1385–1393 (2012).
55. Kodama, F. *et al.* Translocation of dendrin to the podocyte nucleus in acute glomerular injury in patients with IgA nephropathy. *Nephrol. Dial. Transplant.* **28**, 1762–1772 (2013).
56. Lai, K. N. *et al.* Podocyte injury induced by mesangial-derived cytokines in IgA nephropathy. *Nephrol. Dial. Transplant.* **24**, 62–72 (2009).
57. Chan, L. Y., Leung, J. C., Tang, S. C., Choy, C. B. & Lai, K. N. Tubular expression of angiotensin II receptors and their regulation in IgA nephropathy. *J. Am. Soc. Nephrol.* **16**, 2306–2317 (2005).
58. Wagner, J., Gehlen, F., Ciechanowicz, A. & Ritz, E. Angiotensin II receptor type 1 gene expression in human glomerulonephritis and diabetes mellitus. *J. Am. Soc. Nephrol.* **10**, 545–551 (1999).
59. Julian, B. A. *et al.* Familial IgA nephropathy. Evidence of an inherited mechanism of disease. *N. Engl. J. Med.* **312**, 202–208 (1985).
60. Li, M. *et al.* Identification of new susceptibility loci for IgA nephropathy in Han Chinese. *Nat. Commun.* **6**, 7270 (2015).
This is a comprehensive genome-wide association study reporting risk alleles for IgAN in Chinese people.
61. Liu, R. *et al.* Novel genes and variants associated with IgA nephropathy by co-segregating with the disease phenotypes in 10 IgAN families. *Gene* **571**, 43–51 (2015).
62. Xu, R. *et al.* Polymorphism of *DEFA* in Chinese Han population with IgA nephropathy. *Hum. Genet.* **133**, 1299–1309 (2014).
63. Gharavi, A. G. *et al.* Aberrant IgA1 glycosylation is inherited in familial and sporadic IgA nephropathy. *J. Am. Soc. Nephrol.* **19**, 1008–1014 (2008).
This study reports the inherited glycosylation defect in familial and sporadic IgAN.
64. Szeto, C. C. *et al.* The natural history of immunoglobulin a nephropathy among patients with hematuria and minimal proteinuria. *Am. J. Med.* **110**, 434–437 (2001).
65. Lai, K. N. *et al.* An overlapping syndrome of IgA nephropathy and lipoid nephrosis. *Am. J. Clin. Pathol.* **86**, 716–723 (1986).
66. Working Group of the International IgA Nephropathy Network and the Renal Pathology Society *et al.* The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. *Kidney Int.* **76**, 534–545 (2009).
67. Coppo, R. *et al.* Validation of the Oxford classification of IgA nephropathy in cohorts with different presentations and treatments. *Kidney Int.* **86**, 828–836 (2014).
68. Moldoveanu, Z. *et al.* Patients with IgA nephropathy have increased serum galactose-deficient IgA1 levels. *Kidney Int.* **71**, 1148–1154 (2007).
69. Stangou, M. *et al.* Urinary levels of epidermal growth factor, interleukin-6 and monocyte chemoattractant protein-1 may act as predictor markers of renal function outcome in immunoglobulin A nephropathy. *Nephrology* **14**, 613–620 (2009).

70. Nishiyama, A. *et al.* Urinary angiotensinogen reflects the activity of intrarenal renin–angiotensin system in patients with IgA nephropathy. *Nephrol. Dial. Transplant.* **26**, 170–177 (2011).
71. Zhang, J. J. *et al.* Levels of urinary complement factor H in patients with IgA nephropathy are closely associated with disease activity. *Scand. J. Immunol.* **69**, 457–464 (2009).
72. Bazzi, C. *et al.* In crescentic IgA nephropathy, fractional excretion of IgG in combination with nephron loss is the best predictor of progression and responsiveness to immunosuppression. *Clin. J. Am. Soc. Nephrol.* **4**, 929–935 (2009).
73. Working Group of the International IgA Nephropathy Network and the Renal Pathology Society *et al.* The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. *Kidney Int.* **76**, 546–556 (2009).
This paper reports the new Oxford classification on the pathology of IgAN.
74. Tumlin, J. A. & Hennigar, R. A. Clinical presentation, natural history, and treatment of crescentic proliferative IgA nephropathy. *Semin. Nephrol.* **24**, 256–268 (2004).
75. Lv, J. *et al.* Prediction of outcomes in crescentic IgA nephropathy in a multicenter cohort study. *J. Am. Soc. Nephrol.* **24**, 2118–2125 (2013).
76. Roberts, I. S. Pathology of IgA nephropathy. *Nat. Rev. Nephrol.* **10**, 445–454 (2014).
77. D'Amico, G., Ragni, A., Gandini, E. & Fellin, G. Typical and atypical natural history of IgA nephropathy in adult patients. *Contrib. Nephrol.* **104**, 6–13 (1993).
78. Reich, H. N., Troyanov, S., Scholey, J. W., Cattran, D. C. & Toronto Glomerulonephritis Registry. Remission of proteinuria improves prognosis in IgA nephropathy. *J. Am. Soc. Nephrol.* **18**, 3177–3183 (2007).
79. Tang, S. C. *et al.* Long-term study of mycophenolate mofetil treatment in IgA nephropathy. *Kidney Int.* **77**, 543–549 (2010).
80. Gutierrez, E. *et al.* Long-term outcomes of IgA nephropathy presenting with minimal or no proteinuria. *J. Am. Soc. Nephrol.* **23**, 1753–1760 (2012).
81. Coppo, R. & D'Amico, G. Factors predicting progression of IgA nephropathies. *J. Nephrol.* **18**, 503–512 (2005).
82. Cheng, J. *et al.* ACEI/ARB therapy for IgA nephropathy: a meta analysis of randomised controlled trials. *Int. J. Clin. Pract.* **63**, 880–888 (2009).
This meta-analysis examines the therapeutic benefit of RAS blockade in IgAN.
83. Reid, S. *et al.* Non-immunosuppressive treatment for IgA nephropathy. *Cochrane Database Syst. Rev.* **3**, CD003962 (2011).
84. Radhakrishnan, J. & Cattran, D. C. The KDIGO practice guideline on glomerulonephritis: reading between the (guide)lines — application to the individual patient. *Kidney Int.* **82**, 840–856 (2012).
This is the KDIGO practice guideline recommended for IgAN.
85. Tang, S. C. *et al.* Aliskiren combined with losartan in immunoglobulin A nephropathy: an open-labeled pilot study. *Nephrol. Dial. Transplant.* **27**, 613–618 (2012).
86. Szeto, C. C., Kwan, B. C., Chow, K. M., Leung, C. B. & Li, P. K. The safety and short-term efficacy of aliskiren in the treatment of immunoglobulin a nephropathy — a randomized cross-over study. *PLoS ONE* **8**, e62736 (2013).
87. De Caterina, R., Endres, S., Kristensen, S. D. & Schmidt, E. B. n-3 fatty acids and renal diseases. *Am. J. Kidney Dis.* **24**, 397–415 (1994).
88. Donadio, J. V. *et al.* A controlled trial of fish oil in IgA nephropathy. *N. Engl. J. Med.* **331**, 1194–1199 (1994).
89. Dillon, J. J. Fish oil therapy for IgA nephropathy: efficacy and interstudy variability. *J. Am. Soc. Nephrol.* **8**, 1739–1744 (1997).
90. Hogg, R. J. *et al.* Clinical trial to evaluate omega-3 fatty acids and alternate day predisone in patients with IgA nephropathy; report from the Southwest Pediatric Nephrology Study Group. *Clin. J. Am. Soc. Nephrol.* **1**, 467–474 (2006).
91. Donadio, J. V., Larson, T. S., Bergstralh, E. J. & Grande, J. P. A randomized trial of high-dose compared with low-dose omega-3 fatty acids in severe IgA nephropathy. *Am. J. Soc. Nephrol.* **12**, 791–799 (2001).
92. Ferraro, P. M., Ferraccioli, G. F., Gambaro, G., Fulignati, P. & Costanzi, S. Combined treatment with renin–angiotensin system blockers and polyunsaturated fatty acids in proteinuric IgA nephropathy: a randomized controlled trial. *Nephrol. Dial. Transplant.* **24**, 156–160 (2009).
93. Lv, J. *et al.* Corticosteroid therapy in IgA nephropathy. *J. Am. Soc. Nephrol.* **23**, 1108–1116 (2012).
94. Tesar, V. *et al.* Corticosteroids in IgA nephropathy: a retrospective analysis from the VALIGA study. *J. Am. Soc. Nephrol.* **26**, 2248–2258 (2015).
95. Rauen, T. *et al.* Intensive supportive care plus immunosuppression in IgA nephropathy. *N. Engl. J. Med.* **373**, 2225–2236 (2015).
This is the latest clinical trial examining the value of corticosteroid therapy in IgAN.
96. de Zeeuw, D. *et al.* Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL. *Kidney Int.* **65**, 2309–2320 (2004).
97. Ruggenenti, P. *et al.* Chronic proteinuric nephropathies: outcomes and response to treatment in a prospective cohort of 352 patients with different patterns of renal injury. *Am. J. Kidney Dis.* **35**, 1155–1165 (2000).
98. US National Library of Science. Therapeutic Evaluation of Steroids in IgA Nephropathy Global study (TESTING study). *ClinicalTrials.gov* [online], https://clinicaltrials.gov/ct2/show/NCT01560052 (2012).
99. Ballardie, F. W. & Roberts, I. S. Controlled prospective trial of prednisolone and cytotoxics in progressive IgA nephropathy. *J. Am. Soc. Nephrol.* **13**, 142–148 (2002).
100. Mitsuiki, K., Harada, A., Okura, T. & Higaki, J. Histologically advanced IgA nephropathy treated successfully with prednisolone and cyclophosphamide. *Clin. Exp. Nephrol.* **11**, 297–303 (2007).
101. Inoue, T. *et al.* Abnormalities of glycogenes in tonsillar lymphocytes in IgA nephropathy. *Adv. Otorhinolaryngol.* **72**, 71–74 (2011).
102. Wang, Y. *et al.* A meta-analysis of the clinical remission rate and long-term efficacy of tonsillectomy in patients with IgA nephropathy. *Nephrol. Dial. Transplant.* **26**, 1923–1931 (2011).
103. Kawamura, T. *et al.* A multicenter randomized controlled trial of tonsillectomy combined with steroid pulse therapy in patients with immunoglobulin A nephropathy. *Nephrol. Dial. Transplant.* **29**, 1546–1553 (2014).
104. Pozzi, C. *et al.* Addition of azathioprine to corticosteroids does not benefit patients with IgA nephropathy. *J. Am. Soc. Nephrol.* **21**, 1783–1790 (2010).
105. Chen, X. *et al.* A randomized control trial of mycophenolate mofeil treatment in severe IgA nephropathy. *Zhonghua Yi Xue Za Zhi* **82**, 796–801 (2002).
106. Tang, S. *et al.* Mycophenolate mofetil alleviates persistent proteinuria in IgA nephropathy. *Kidney Int.* **68**, 802–812 (2005).
107. Liu, X. *et al.* Treatment of severe IgA nephropathy: mycophenolate mofetil/prednisone compared to cyclophosphamide/prednisone. *Int. J. Clin. Pharmacol. Ther.* **52**, 95–102 (2014).
108. Maes, B. D. *et al.* Mycophenolate mofetil in IgA nephropathy: results of a 3-year prospective placebo-controlled randomized study. *Kidney Int.* **65**, 1842–1849 (2004).
109. Frisch, G. *et al.* Mycophenolate mofetil (MMF) versus placebo in patients with moderately advanced IgA nephropathy: a double-blind randomized controlled trial. *Nephrol. Dial. Transplant.* **20**, 2139–2145 (2005).
110. Roccatello, D. *et al.* Long-term effects of methylprednisolone pulses and mycophenolate mofetil in IgA nephropathy patients at risk of progression. *J. Nephrol.* **25**, 198–203 (2012).
111. Hogg, R. J. *et al.* Randomized controlled trial of mycophenolate mofetil in children, adolescents, and adults with IgA nephropathy. *Am. J. Kidney Dis.* **66**, 783–791 (2015).
112. RAND Health. Medical Outcomes Study: 36-Item Short Form Survey instrument. *RAND* [online], http://www.rand.org/health/surveys_tools/mos/mos_core_36item_survey.html (2009).
113. Berthoux, F. C. *et al.* Predicting the risk for dialysis or death in IgA nephropathy. *J. Am. Soc. Nephrol.* **22**, 752–761 (2011).
114. Moriyama, T. *et al.* Prognosis in IgA Nephropathy: a 30 year analysis of 1,012 patients at a single center. *PLoS ONE* **9**, e91756 (2014).
115. Lee, H. *et al.* Long-term prognosis of clinically early IgA nephropathy is not always favorable. *BMC Nephrol.* **15**, 94–103 (2014).
116. Lee, M. J. *et al.* Clinical implication of crescentic lesions in immunoglobulin A nephropathy. *Nephrol. Dial. Transplant.* **29**, 356–364 (2014).
117. Schreiner, G. E. & Maher, J. F. *Uremia: Biochemistry, Pathogenesis & Treatment* (Thomas, 1961).
118. Hampers, C. L., Schupak, E., Lowrie, E. G. & Lazarus, J. M. (eds) *Long-term Hemodialysis* 2nd edn (Grune and Stratton, 1973).
119. Hastings, M. C. *et al.* Biomarkers in IgA nephropathy: relationship to pathogenetic hits. *Expert Opin. Med. Diagn.* **7**, 615–627 (2013).
120. Kiryluk, K. *et al.* Aberrant glycosylation of IgA1 is inherited in both pediatric IgA nephropathy and Henoch–Schonlein purpura nephritis. *Kidney Int.* **80**, 79–87 (2011).
121. Serino, G., Sallustio, F., Cox, S. N., Pesce, F. & Schena, F. P. Abnormal miR-148b expression promotes aberrant glycosylation of IgA1 in IgA nephropathy. *J. Am. Soc. Nephrol.* **23**, 814–824 (2012).
122. Serino, G. *et al.* Role of let-7b in the regulation of *N*-acetylgalactosaminyltransferase 2 in IgA nephropathy. *Nephrol. Dial. Transplant.* **30**, 1132–1139 (2015).
123. Serino, G. *et al.* In a retrospective international study, circulating miR-148b and let-7b were found to be serum markers for detecting primary IgA nephropathy. *Kidney Int.* http://dx.doi.org/10.1038/ki.2015.333 (2015).
This paper reports an international study validating the use of selective miRNAs as biomarkers in diagnosing IgAN.
124. Julian, B. A. *et al.* Application of proteomic analysis to renal disease in the clinic. *Proteomics Clin. Appl.* **3**, 1023–1028 (2009).
125. Mischak, H. *et al.* Implementation of proteomic biomarkers: making it work. *Eur. J. Clin. Invest.* **42**, 1027–1036 (2012).
126. Suzuki, H., Suzuki, Y., Novak, J. & Tomino, Y. Development of animal models of human IgA nephropathy. *Drug Discov. Today Dis. Models* **11**, 5–11 (2014).
127. Haghpanah, V. *et al.* Antisense-*miR-21* enhances differentiation/apoptosis and reduces cancer stemness state on anaplastic thyroid cancer. *Tumour Biol.* http://dx.doi.org/10.1007/s13277-015-3923-z (2015).
128. Isaacs, K. L. & Miller, F. Antigen size and charge in immune complex glomerulonephritis. II. Passive induction of immune deposits with dextran–anti-dextran immune complexes. *Am. J. Pathol.* **111**, 298–306 (1983).
129. Leung, J. C., Tang, S. C., Lam, M. F., Chan, T. M. & Lai, K. N. Charge-dependent binding of polymeric IgA1 to human mesangial cells in IgA nephropathy. *Kidney Int.* **59**, 277–285 (2001).
130. Leung, J. C., Poon, P. Y. & Lai, K. N. Increased sialylation of polymeric immunoglobulin A1: mechanism of selective glomerular deposition in immunoglobulin A nephropathy? *J. Lab. Clin. Med.* **133**, 152–160 (1999).
131. Smith, A., Molyneux, K., Feehally, J. & Barratt, J. Is sialylation of IgA the agent provocateur of IgA nephropathy? *Nephrol. Dial. Transplant.* **23**, 2176–2178 (2008).
132. Smerud, H. K. *et al.* New treatment for IgA nephropathy: enteric budesonide targeted to the ileocecal region ameliorates proteinuria. *Nephrol. Dial. Transplant.* **26**, 3237–3242 (2011).
133. Sugiura, H. *et al.* Effect of single-dose rituximab on primary glomerular diseases. *Nephron Clin. Pract.* **117**, c98–c105 (2011).
134. US National Library of Science. Rituximab in progressive IgA nephropathy. *ClinicalTrials.gov* [online], https://clinicaltrials.gov/ct2/show/NCT00498368?term = NCT00498368&rank = 1 (2007).
135. Navarra, S. V. *et al.* Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, Phase 3 trial. *Lancet* **377**, 721–731 (2011).
136. US National Library of Science. BRIGHT-SC: blisibimod response in IgA nephropathy following at-home treatment by subcutaneous administration. *ClinicalTrials.gov* [online], https://clinicaltrials.gov/ct2/show/NCT02062684?term = NCT02062684&rank = 1 (2014).
137. Kim, M. J. *et al.* Spleen tyrosine kinase is important in the production of proinflammatory cytokines and cell proliferation in human mesangial cells following stimulation with IgA1 isolated from IgA nephropathy patients. *J. Immunol.* **189**, 3751–3758 (2012).

138. US National Library of Science. Safety and efficacy study of fostamatinib to treat immunoglobin A (IgA) nephropathy. *ClinicalTrials.gov* [online], https://clinicaltrials.gov/ct2/show/NCT02112838?term=%22Fostamatinib%22+%22IgA+Nephropathy%22&rank=2 (2014).
139. Tang, S. C. & Lai, K. N. The ubiquitin-proteasome pathway and IgA nephropathy: a novel link? *Kidney Int.* **75**, 457–459 (2009).
140. US National Library of Science. Pilot study of Velcade® in IgA nephropathy. *ClinicalTrials.gov* [online], https://clinicaltrials.gov/ct2/show/NCT01103778?term=NCT01103778&rank=1 (2010).
141. Moura, I. C. *et al.* The glomerular response to IgA deposition in IgA nephropathy. *Semin. Nephrol.* **28**, 88–95 (2008).
142. Diven, S. C. *et al.* IgA induced activation of human mesangial cells: independent of FcαR1 (CD 89). *Kidney Int.* **54**, 837–847 (1998).
143. D'Amico, G. *et al.* Idiopathic IgA mesangial nephropathy. Clinical and histological study of 374 patients. *Medicine (Baltimore)* **64**, 49–60 (1985). **A good review of the clinicopathological features of 374 Italian patients with IgAN.**
144. Cattran, D. C. *et al.* The impact of sex in primary glomerulonephritis. *Nephrol. Dial. Transplant.* **23**, 2247–2253 (2008).
145. Stratta, P. *et al.* Angiotensin I-converting enzyme genotype significantly affects progression of IgA glomerulonephritis in an Italian population. *Am. J. Kidney Dis.* **33**, 1071–1079 (1999).
146. Knoop, T. *et al.* Addition of eGFR and age improves the prognostic absolute renal risk-model in 1,134 Norwegian patients with IgA nephropathy. *Am. J. Nephrol.* **41**, 210–219 (2015).
147. Kataoka, H. *et al.* Overweight and obesity accelerate the progression of IgA nephropathy: prognostic utility of a combination of BMI and histopathological parameters. *Clin. Exp. Nephrol.* **16**, 706–712 (2012).
148. D'Amico, G. Clinical features and natural history in adults with IgA nephropathy. *Am. J. Kidney Dis.* **12**, 353–357 (1988).
149. Ibels, L. S. & György, A. Z. IgA nephropathy: analysis of the natural history, important factors in the progression of renal disease, and a review of the literature. *Medicine (Baltimore)* **73**, 79–102 (1994).
150. Rafalska, A. *et al.* Stratifying risk for progression in IgA nephropathy: how to predict the future? *Pol. Arch. Med. Wewn.* **124**, 365–372 (2014).
151. Lv, J. *et al.* Natural history of immunoglobulin A nephropathy and predictive factors of prognosis: a long-term follow up of 204 cases in China. *Nephrology (Carlton)* **13**, 242–246 (2008).
152. Fofi, C. *et al.* IgA nephropathy: multivariate statistical analysis aimed at predicting outcome. *J. Nephrol.* **14**, 280–285 (2001).
153. Rekola, S., Bergstrand, A. & Bucht, H. IgA nephropathy: a retrospective evaluation of prognostic indices in 176 patients. *Scand. J. Urol. Nephrol.* **23**, 37–50 (1989).
154. To, K. F. *et al.* Outcome of IgA nephropathy in adults graded by chronic histological lesions. *Am. J. Kidney Dis.* **35**, 392–400 (2000).
155. Shi, Y. *et al.* Clinical outcome of hyperuricemia in IgA nephropathy: a retrospective cohort study and randomized controlled trial. *Kidney Blood Press. Res.* **35**, 153–160 (2012).
156. Cheng, G. Y. *et al.* Clinical and prognostic implications of serum uric acid levels on IgA nephropathy: a cohort study of 348 cases with a mean 5-year follow-up. *Clin. Nephrol.* **80**, 40–46 (2013).
157. Myllymäki, J. M. *et al.* Severity of tubulointerstitial inflammation and prognosis in immunoglobulin A nephropathy. *Kidney Int.* **71**, 343–348 (2007).
158. Katafuchi, R. *et al.* Validation study of Oxford classification of IgA nephropathy: the significance of extracapillary proliferation. *Clin. J. Am. Soc. Nephrol.* **6**, 2806–2813 (2011).
159. Ferrario, F., Napodano, P., Rastaldi, M. P. & D'Amico, G. Capillaritis in IgA nephropathy. *Contrib. Nephrol.* **111**, 8–12 (1995).
160. Mera, J., Uchida, S. & Nagase, M. Clinicopathologic study on prognostic markers in IgA nephropathy. *Nephron* **84**, 148–157 (2000).
161. Shen, P., He, L. & Huang, D. Clinical course and prognostic factors of clinical early IgA nephropathy. *Neth. J. Med.* **66**, 242–247 (2008).
162. Sevillano, Á. M. *et al.* Malignant hypertension: a type of IgA nephropathy manifestation with poor prognosis. *Nefrologia* **35**, 42–49 (2015).
163. Xu, L. *et al.* Podocyte number predicts progression of proteinuria in IgA nephropathy. *Mod. Pathol.* **23**, 1241–1250 (2010).
164. Edström Halling, S., Söderberg, M. P. & Berg, U. B. Predictors of outcome in paediatric IgA nephropathy with regard to clinical and histopathological variables (Oxford classification). *Nephrol. Dial. Transplant.* **27**, 715–722 (2012).
165. Nieuwhof, C., Kruytzer, M., Frederiks, P. & van Breda Vriesman, P. J. Chronicity index and mesangial IgG deposition are risk factors for hypertension and renal failure in early IgA nephropathy. *Am. J. Kidney Dis.* **31**, 962–970 (1998).
166. Arroyo, A. H. *et al.* Predictors of outcome for severe IgA nephropathy in a multi-ethnic U. S. cohort. *Clin. Nephrol.* **84**, 145–155 (2015).
167. Yamagat, K. *et al.* Chronic kidney perspectives in Japan and the importance of urinalysis screening. *Clin. Exp. Nephrol.* **12**, 1–8 (2008).
168. Barbour, S. J. *et al.* Individuals of Pacific Asian origin with IgA nephropathy have an increased risk of progression to end-stage renal disease. *Kidney Int.* **84**, 2017–2024 (2013).
169. Delclaux, C., Jacquot, C., Callard, P. & Kleinknecht, D. Acute reversible renal failure with macroscopic haematuria in IgA nephropathy. *Nephrol. Dial. Transplant.* **8**, 195–199 (1993).
170. Bennett, W. M. & Kincaid-Smith, P. Macroscopic hematuria in mesangial IgA nephropathy: correlation with glomerular crescents and renal dysfunction. *Kidney Int.* **23**, 393–400 (1983).
171. Boyce, N. W., Holdsworth, S. R., Thomson, N. M. & Atkins, R. C. Clinicopathological associations in mesangial IgA nephropathy. *Am. J. Nephrol.* **6**, 246–252 (1986).
172. Feng, C. Y. *et al.* Persistent asymptomatic isolated hematuria in children: clinical and histopathological features and prognosis. *World J. Pediatr.* **9**, 163–168 (2013).
173. Berg, U. B. Long-term follow up of renal function in IgA nephropathy. *Arch. Dis. Child* **66**, 588–592 (1991).
174. Yoshikawa, N. *et al.* Macroscopic hematuria in childhood IgA nephropathy. *Clin. Nephrol.* **28**, 217–221 (1987).
175. Bulut, I. K. *et al.* Outcome results in children with IgA nephropathy: a single center experience. *Int. J. Nephrol. Renovasc. Dis.* **5**, 23–28 (2012).
176. Kim, B. S. *et al.* Natural history and renal pathology in patients with isolated microscopic hematuria. *Korean J. Intern. Med.* **24**, 356–361 (2009).
177. Ng, W. L. *et al.* Clinical and histopathological predictors of progressive disease in IgA nephropathy. *Pathology* **18**, 29–34 (1986).
178. Le, W. *et al.* Long-term outcome of IgA nephropathy patients with recurrent macroscopic hematuria. *Am. J. Nephrol.* **40**, 43–50 (2014).
179. Frimat, L. *et al.* IgA nephropathy: prognostic classification of end-stage renal failure. L'Association des Néphrologues de l'Est. *Nephrol. Dial. Transplant.* **12**, 2569–2575 (1997).
180. Mustonen, J., Pasternack, A., Helin, H., & Nikkilä, M. Clinicopathologic correlations in a series of 143 patients with IgA glomerulonephritis. *Am. J. Nephrol.* **5**, 150–157 (1985).
181. Lai, K. N. Pathogenesis of IgA nephropathy. *Nat. Rev. Nephrol.* **8**, 275–283 (2012).

Author contributions

Introduction (K.N.L.); Epidemiology (F.P.S.); Mechanisms/pathophysiology (J.N., Y.T. and K.N.L.); Diagnosis, screening and prevention (A.B.F., K.N.L. and S.C.W.T.); Management (K.N.L. and S.C.W.T.); Quality of life (R.J.G.); Outlook (K.N.L. and S.C.W.T.); Overview of the Primer (K.N.L.).

Competing interests

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