Correlation of Oxford MEST-C Scores With Clinical Variables for IgA Nephropathy in South India

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IgA nephropathy (IgAN) has been reported as the most common glomerulopathy worldwide.[1] Its presentation is varied, with symptoms ranging from microscopic to macroscopic hematuria; varying degrees of proteinuria including nephrotic syndrome; hypertension; and renal failure as part of chronic kidney disease or even acute renal insufficiency.[2] The condition is also enigmatic in that in a proportion of patients, the course is benign, with intermittent episodes of hematuria, whereas in others it presents for the first time with advanced disease and renal failure. There are also those between these extremes,[1] and the disease has a variable outcome across populations.[3]

The prevalence of the disease in studies of renal biopsies across the world varies. Among 29 international centers surveyed by geographic region, the prevalence in biopsy series for IgAN varied from 6.1% in Latin America, to 11.8% in the US and Canada, 22.1% in Europe, and 39.5% in Asia.[3–6] Studies from Japan, Singapore, and China have also reported a high incidence. In the few studies that have been reported from India, this figure has varied from 7% to 16%.[7–9,S1,S2]

The Oxford classification and scoring system, proposed by the working group of the International IgA Nephropathy Network and the Renal Pathology Society, identified 4 independent histologic variables in predicting renal outcome: the mesangial hypercellularity score (M); segmental glomerulosclerosis (S); endocapillary hypercellularity (E); and tubular atrophy/interstitial fibrosis (T).[S3] Subsequently, the scoring of crescents (C) was also introduced as an Oxford score as a factor of predictive importance, creating the MEST-C score.[S4] The classification has been evaluated in multiple population cohorts.

The current study encompasses a large cohort of renal biopsies with a diagnosis of IgAN from a single geographic area of South India, from where there have been only a handful of reports. The Oxford classification has been used, according to strict criteria, and interobserver variation in the scoring has been analyzed.

RESULTS

In total, there were 3345 cases of IgAN from a total of 25,277 biopsies, comprising 13.23% of the native renal biopsies. The proportion of IgAN in the 4 centers, varying from 10.4% in Hyderabad to 17.1% in Kochi, is depicted in Figure 1. The mean age in the entire cohort was 35.83 years, with ages ranging from 2 to 85 years. The male:female ratio was 2.4:1. The age distribution is depicted in Figure 2. The prevalence of hypertension, proteinuria (semiquantitative, urine protein:creatinine ratio, 24-hour proteinuria), hematuria, and mean serum creatinine in the 4 groups and in the entire cohort is depicted in Table 1.

A total of 1445 cases (43.2%) had more than 8 viable glomeruli, allowing the MEST-C scoring to be done. In the others, there were a smaller number of viable glomeruli or a greater number of sclerosed glomeruli, and these were excluded from the scores. The MEST-C scores in the 4 groups and in the entire cohort are listed in Table 1. In the 872 cases of segmental sclerosis, type of sclerosis was recorded in 255 and was of the not otherwise specified type in the majority.

Instances of all MEST-C scores being 0 were seen in 199 of the biopsies with ≥8 viable glomeruli (13.8%). The mean age in this group was 33.76 years, with mean proteinuria of 3.6 gms/dl, and a mean serum creatinine level of

1.9 mg/dl. Chronic IgAN, defined as more than 50% sclerosed glomeruli and more than 50% tubular atrophy/interstitial fibrosis in biopsies with ≥8 glomeruli, was seen in 213 cases; the mean age in this group was 34.8 years; the male:female ratio was 3:1; the mean proteinuria was 4.2 gms/day, and the mean serum creatinine level was 5.3 mg/dl.

The MEST-C scores were correlated with the serum creatinine level and degree of proteinuria and hematuria (Table 2). The correlation was statistically significant ($P < 0.05$) for the E-score for creatinine and hematuria, the T-score for creatinine, proteinuria, and hematuria, and the C-score for creatinine and hematuria. The values were highly significant ($P < 0.0001$) for the T- and C-scores for creatinine.

In the immunofluorescence study, in 2423 cases, a complete record of all 7 reagents including the intensity and pattern of deposits was available, and these were included. In the others, the records were incomplete. The results are depicted in Figure 3. C3c was seen accompanying IgA in up to 92% of the cases. The presence of lambda was of greater intensity by a factor of <2 in the majority of cases. The presence of lambda light chains to the exclusion of kappa light chains was seen in 12% of cases. For a measure of interobserver variability in MEST-scores, the alpha reliability estimates for the M-, E-, S-, T- and C-scores were 0.76, 0.851, 0.885, 0.844, and 0.891, respectively.

DISCUSSION

Health care in India is not uniform. Government-run hospitals cater to lower socioeconomic groups, large private hospitals serve wealthier clients, and a range of smaller hospitals and nursing homes serve those in between. This study focuses on data collected from 4 renal pathology laboratories, one from each of the 4 states of South India. As renal biopsy reporting including immunofluorescence study is specialized, renal biopsies done in teaching hospitals, and in small and large private centers, are sent to these referral labs. The data presented are therefore a fair representation of the disease in South India.

Although IgAN is purported to be the most common nephropathy worldwide, its prevalence in biopsy series across the world differs vastly, ranging from 2% to 50%.[7] Among 29 international centers surveyed by geographic region, involving over 41,000 biopsies, the prevalence of IgAN varied from 6.1% in Latin America, to 11.8% in the US/Canada, 22.8% in Europe, and 39.5% in Asia.[4] Even within the same geographic area, figures vary, as in Croatia at 19.3%[S7] compared with 34.5% in Czech Republic.[S8] Studies from the Far East have reported a biopsy prevalence as high as 47.2%, in Japan,[5] and 40%, in Singapore.[6] In a large study in East China by Zhou et al.,[S9] IgAN accounted for 50% of their biopsies.[S9] In the present study, IgAN, comprising a total of 3345 cases, accounted for 13.23% of the cases, with a range from 10.4% in Hyderabad to 17.1% in Kochi. In other studies from India, the range has been similar, from 7% to 16% (Table 3), but the numbers in these studies are smaller, varying from as few as 11 to a high of 478 cases, with 2 of these studies coming from the same geographic area.[7,S1]

The mean age in this study was 35.83 years, with the youngest aged 2 years and the oldest 85 years. This range is similar to that in other studies from across the world, in which the mean age has varied
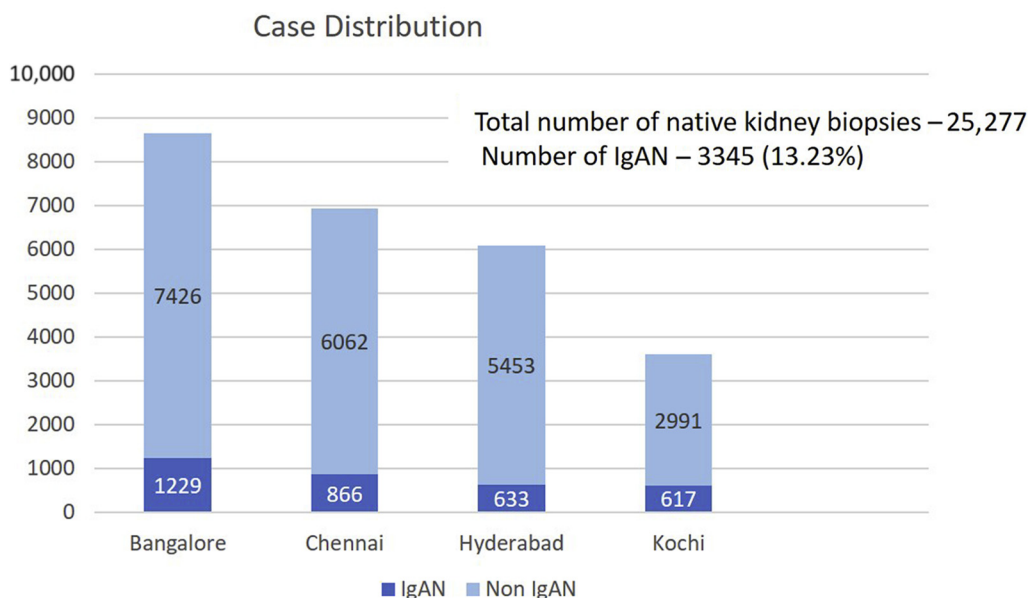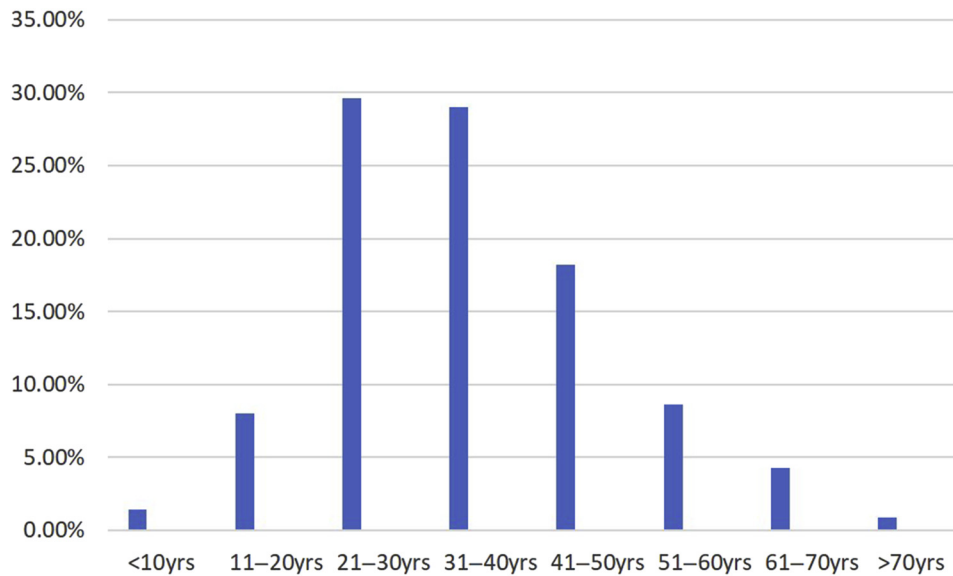

Figure 1. Distribution of cases.

Age distribution of the entire cohort (N=3345)

Figure 2. Age distribution of cases.

from 28 to 38 years (Table 4). It is possible that, in India, the disease is detected at a more advanced stage and hence the mean age is a little higher than that in other parts of the world. The male:female ratio in this study was 2.4:1, similar to the western data, whereas in Japan and China, the ratio is more on the order of 1:1.

There is no unifying factor in IgAN other than the mesangial deposits of IgA, and many believe that IgAN is not a single disease or even the same disease in

different parts of the world.[S9] Table 4 summarizes the clinical and laboratory data from studies with more than 200 cases of IgAN, and Table 3 summarizes the data from India where these results are available.

Hypertension is variable across the studies, ranging from as low as 6% to as high as 65% in the VALIGA (Validation Study of the Oxford Classification of IgAN) cohort.[S11] In the Indian studies, in all but one, hypertension is present in upwards of 35% of cases, approaching 60% in our group. In most of

Table 1. Demographic, laboratory, and histologic data in the 4 centers and in the entire cohort

Center	Bangalore	Chennai	Hyderabad	Kochi	Total
No. of IgAN cases	1229	866	633	617	3345
IgAN as a % of native biopsies	14.2	12.5	10.4	17.1	13.23
Mean age (yr)	36.78	33.84	34.92	37.65	35.83
Male:female ratio	2.5:1	1.6:1	2.5:1	4.0:1	2.4:1
Hypertension[a]	647/1103	445/828	373/532	397/617	1862/3080
Proteinuria[a]					
Semiquantitative (≥3+)	625/1218	400/861	343/627	368/614	1736/3320
Urine Pr:Cr ratio (≥1)	393/420	253/318	64/78	134/150	844/966
Urine Pr:Cr ratio (≥3)	202/420	144/318	30/78	64/150	440/966
24 h proteinuria (≥3 gm/d)	123/308	0	102/269	95/278	320/855
Hematuria (≥2/hpf)[a]	720/961	568/661	422/528	385/469	2095/2619
Mean serum creatinine	3.9	2.8	3.3	3.1	3.27
Histology-adequate biopsies	426	416	242	361	1445
M1	149	263	179	266	857
E1	190	140	95	136	561
S1	216	254	150	252	872
T1	76	63	55	104	298
T2	17	13	8	23	61
C1	73	35	87	104	299
C2	62	4	40	28	134

C, crescents; Cr, creatinine; E, endocapillary hypercellularity; IgAN, IgA nephropathy; M, mesangial hypercellularity; Pr, protein; S, segmental glomerulosclerosis; T, tubular atrophy/interstitial fibrosis.
[a]The denominator indicates the total number in which the value of this variable was recorded.

Table 2. MEST-C correlation with clinical variables

Oxford scores	Serum creatinine (mg/dl); 1445 cases		Proteinuria (gm/d); 365 cases		Hematuria (number/hpf); 903 cases	
	Mean ± SD	*P* value	Mean ± SD	*P* value	Mean ± SD	*P* value
M score 0	2.39 ± 5.03	0.776	3.57 ± 3.55	0.481	20.04 ± 22.5	0.8
1	2.45 ± 2.31		6.32 ± 9.69		21.08 ± 24.6	
E score 0	2.25 ± 3.94	**0.018**	6.40 ± 3.63	0.447	17.83 ± 19.87	**0.012**
1	2.71 ± 2.58		3.43 ± 2.85		25.82 ± 28.95	
S score 0	2.32 ± 2.42	0.366	3.49 ± 3.61	0.446	22.01 ± 22.18	0.510
1	2.50 ± 4.01		6.43 ± 4.35		20.4 ± 25.0	
T score 0	2.05 ± 3.66	**0.00001**	3.29 ± 3.19	**0.045**	23.06 ± 26.25	**0.018**
1	3.07 ± 2.17		15.44 ± 10.31		23.06 ± 26.25	
2	5.75 ± 3.39		4.59 ± 3.01		15.80 ± 18.27	
C score 0	2.14 ± 3.66	**0.00001**	3.53 ± 3.64	0.215	17.98 ± 20.17	**0.002**
1	2.41 ± 2.33		11.50 ± 9.13		22.66 ± 22.60	
2	4.69 ± 3.52		3.99 ± 3.09		30.22 ± 39.50	

C, crescents; E, endocapillary hypercellularity; M, mesangial hypercellularity; S, segmental glomerulosclerosis; T, tubular atrophy/interstitial fibrosis.
The figures in bold indicate the correlations that were significant (*P* < 0.05).

these studies, the details of when the hypertension was detected are not available. We presume that the IgAN would have been detected earlier, probably with less chronicity, had a complete evaluation for hypertension been done at the time of detection and the patient subjected to biopsies if urinary and/or renal functional abnormalities were detected at that time.

The one finding that seems to be distinctive in IgAN in India, as compared with the rest of the world, is the degree of proteinuria. Nephrotic-range proteinuria is uncommon in IgAN in the western population and even in Japan.[S12–S15] Table 4 shows a maximum of 16% in the Japanese group having significant proteinuria, whereas the prevalence of nephrotic-range proteinuria in all studies from India is high, with a minimum of

23% and a maximum of 63.1%.[S16] In this study, a semiquantitative dipstick reading of proteinuria was what was available in all records, and a grade of ≥3 was present in 51%. Urine protein-to-creatinine ratios were available in 966 records (28.9% of cases); a value of ≥1 was seen in 87.4%, and ≥3 in 44.6%. A quantitative 24-hour proteinuria reading was available in 855 records (25.6% of cases); 86.3% of them had a proteinuria level of ≥1 gm/24 h, and 37.4% had a value of ≥3 gms/24 h.

Macroscopic hematuria is not an uncommon finding in studies outside India (Table 4). The quantitative data on hematuria, whether microscopic or macroscopic, are not available in the Indian studies. The figure varies from 5.1% to 91% and could be ascribed to the rigor with which this test was done. In our study,
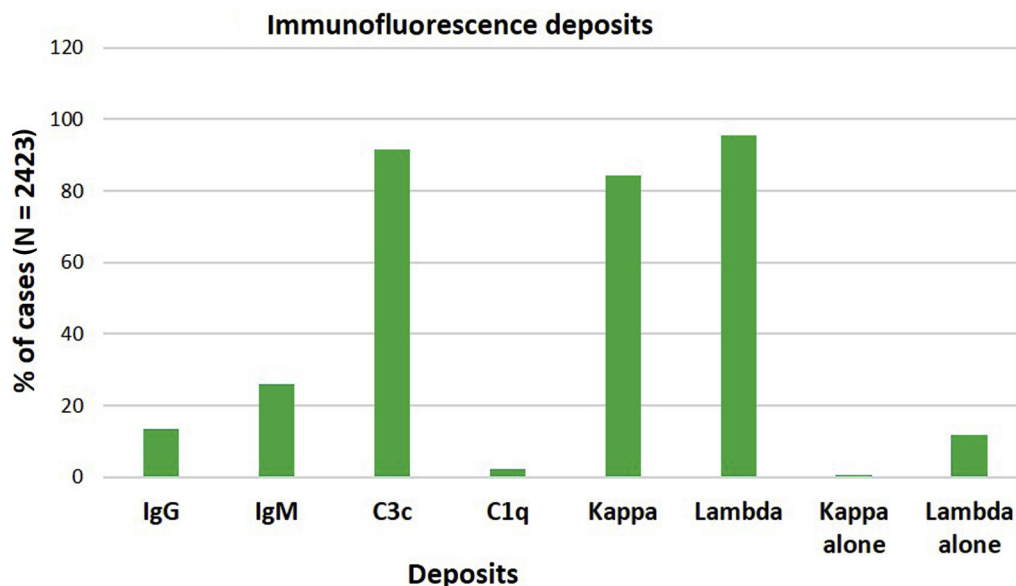

Figure 3. Immunofluorescence distribution.

Table 3. IgA nephropathy studies in India

Author	Year	No.	Mean age (yr)	Hypertension (%)	Proteinuria nephrotic range (%)	Hematuria (%)	High serum creatinine (%)
Bhuyan et al.[8]	1992	83	–	39	24	–	34
Muthukumar et al.[S20]	2002	98	25.7	9.2	25.6	5.1	13.5
Chacko et al.[S21]	2005	478	32	58	55	16	60
Chandrika et al.[S1]	2007	227	30	35	36.7	18.9	5.7
Mittal et al.[S22]	2012	66	29.9	78.8	23.1	81	–
Bhagchi et al.[S23]	2016	103	28.8	39.4	63.1	91	16.5

microscopic hematuria, defined as red blood cell count ≥2/high-power field, was seen in 80% of cases. Macroscopic hematuria, defined as "plenty" of red blood cells or >100/high-power field of microscopy, was seen in only 3.9% of our cases.

IgAN is a disease with varying degrees of progression and varying presentation, and the reasons for this, be they genetic, racial, and/or environmental, are not clear. In a Canadian-based study of a large multiracial cohort of IgAN with over 600 patients, it was observed that individuals of Pacific-Asian origin had a higher risk of progression to end-stage renal disease.[S17] The studies differ in their definition of a high level of serum creatinine and hence cannot be compared directly. However, "raised" levels of serum creatinine have varied from as low as 2%, in the study by Alamartine et al.,[S18] to as high as 36% in the report from Japan by Katafuchi et al.[S16] The studies from India, however, have reported high creatinine levels in as low as 5.6% of cases[S11] to as high as 60%.[S18] A serum creatinine level of >1 mg/dl was seen in 78.9% of our cases, and of >3 mg/dl in 36.4%. IgAN in South India is being detected at a more advanced stage than it is in other parts of the world.

The Oxford MEST-C scores proposed by the International IgA Nephropathy Network and the Renal Pathology Society proposed 4 scores—mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental sclerosis (S), and tubular atrophy/interstitial fibrosis (T), all of which had good interobserver correlation—to be independently associated with renal outcome in renal biopsies of IgAN with >8 glomeruli.[S3] Subsequently, the crescent (C) score was added as an independent predictive factor.[S4] In a systematic meta-analysis of 16 studies with 3893 cases of IgAN,[S19] the M-, S-, T- and C-scores were strongly associated with progression to renal failure, with hazard ratios of 0.6, 1.8, 3.2, and 2.3, respectively, without evidence of heterogeneity. E lesions, in contrast, were not associated with renal failure in this analysis, with a hazard ratio of 2.3, and with evidence of heterogeneity. E lesions have been proposed as a pathologic indicator for immunosuppression, but this was confirmed in only small cohorts in this analysis. In our study, we attempted a correlation of the 5 scores with serum creatinine, proteinuria, and hematuria (red blood cells/hpf) at the time of biopsy (Table 2). The mean serum creatinine level in all groups was higher in score 1 compared with score 0 but reached statistical significance ($P < 0.05$) in only the T-score. The mean proteinuria level was again higher in score 1 in the M, S, and T categories, with a statistically significant value in the latter. Hematuria, as expected, was significantly higher in the E1, T2, and C2 groups, compared with the

Table 4. IgA nephropathy studies worldwide

Author, country	Year	No.	Mean age (yr)	HTN (%)	Proteinuria >3 gms/d (%)	Hematuria (%)	High serum creatinine (%)
Nicolls et al.,[S24] Australia	1984	244	32	23	6	39	36
D'Amico et al.,[S25] Italy	1986	365	29	36	7	55	24
Droz et al.,[S26] France	1984	280	–	6	10	37	–
Bogenschutz et al.,[S27] Germany	1990	239	–	19	–	26	34
Rekola et al.,[S28] Sweden	1990	209	25	11	1	64	16
Alamartine et al.,[S17] France	1991	282	28	9	3	39	2
Katafuchi,[S29] Japan	1994	225	32	22	16	20	36
Koyoma et al.,[5] Japan	1997	448	–	29	3	24	19
Roberts et al.,[S2] Oxford, multicentre	2009	265	30	31	1.7 gms (mean)	34	26 (CKD ≥3)
Zeng et al.,[S30] China	2011	1026	34	33	1.3 gms (mean)	27	24 (CKD ≥3)
Katafuchi et al.,[S15] Japan	2011	702	30		UPCR 0.9 (mean)		25 (CKD ≥3)
VALIGA cohort[S10]	2014	1147	36	65	21		37 (CKD ≥3)
Present study	2019	3345	35.8	60.4	37.4	79.9 (≥2/hpf) 3.9 (plenty)	78.9 (≥1 mg/dl) 36.4 (≥3 mg/dl)

CKD, chronic kidney disease; HTN, hypertension; UPCR, urine protein-to-creatinine ratio; VALIGA, Validation Study of the Oxford classification of IgAN.

0 group, and was marginally higher in the M1 group compared with the M0 group.

As IgAN in South India is being detected at an advanced stage, a direct correlation of the scores with creatinine level is not apparent. The T-score seems to be the most predictive of renal failure at the time of biopsy.

Even in the small cohort in this study of 199 cases of adequate biopsies, where all 5 scores were 0, the mean proteinuria level was 3.6 gm/day, and the serum creatinine level was 1.9 mg/dl. The group with "chronic" IgAN, defined as >50% sclerosed glomeruli and >50% tubular atrophy/interstitial fibrosis (213 cases), had a mean proteinuria of 4.2 gms/d and a serum creatinine level of 5.3 mg/dl. These 2 apparently polar groups seem similar in degree of proteinuria, a paradox that could be explained if IgAN is a heterogeneous disease within the renal parenchyma. This raises the question of whether a larger number of viable glomeruli is required for a valid scoring system.

There has been some concern over the interobserver concurrence in the scoring system, although the initial study arrived at the 4 scores after much discussion and also validated the scores. In addition, the group has provided an accurate description of each histologic marker that is easy to follow in routine practice. Analysis of the VALIGA cohort, however, has shown inconsistencies in the M and E identification.[S11,S20] As a part of this study, sets of glass slides with all stains from a total of 40 cases, 10 from each center, were circulated, and interobserver concurrence on the 5 scores, namely M, E, S, T, and C, was measured. The alpha reliability estimate in each of the 5 variable scores of the MEST-C was >0.7, indicating good interobserver correlation. The data obtained can thus be considered reliable. The correlation also may have been due to the fact that in all 4 centers, the pathologists were experienced in renal pathology, with a minimum of 10 years' experience and were implementing strict criteria for the scores. It would be worthwhile to study whether similar concordance is obtained among pathologists with less experience in renal biopsy reporting.

This study represents the largest cohort of biopsy-proven IgA nephropathy. Our patients, though young, have a greater prevalence of hypertension, significant proteinuria, and higher incidence of chronic kidney disease at presentation compared with the Western population.

The MEST-C scores show an association with clinical variables, notably hypertension with the S score, serum creatinine level and degree of hematuria with the E-, T-, and C-scores, and proteinuria with the T score, but their importance in prognostication and management is not clear. The emphasis therefore needs to be on community surveillance to recognize the disease at an early stage and implement measures to delay its progression.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)
Supplementary Methods.
Supplementary References.

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