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ARTICLE

Common variant in the *HMGA2* gene increases susceptibility to nephropathy in patients with type 2 diabetes

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Abstract
Aims/hypothesis Type 2 diabetes is a chronic metabolic disorder associated with devastating microvascular complications. Genome-wide association studies have identified more than 60 genetic variants associated with type 2 diabetes and/or glucose and insulin traits, but their role in the progression of diabetes is not established. The aim of this study was to explore whether these variants were also associated with the development of nephropathy in patients with type 2 diabetes.
Methods We studied 28 genetic variants in 2,229 patients with type 2 diabetes from the local Malmö Scania Diabetes Registry (SDR) published during 2007–2010. Diabetic nephropathy (DN) was defined as micro- or macroalbuminuria and/or end-stage renal disease. Estimated glomerular filtration rate (eGFR) was assessed using the MDRD-4 formula. Replication genotyping of rs1531343 was performed in diabetic (Steno type 2 diabetes [n=345], Genetics of Diabetes Audit and Research in Tayside Scotland [Go-DARTS] [n=784]) and non-diabetic (Malmö Preventive Project [n=2,523], Botnia study [n=2,247]) cohorts.
Results In the SDR, *HMGA2* single-nucleotide polymorphism rs1531343 was associated with DN (OR 1.50, 95% CI 1.20, 1.87, p=0.00035). In the combined analysis totalling 3,358 patients with type 2 diabetes (n=1,233 cases, n=2,125 controls), carriers of the C-allele had a 1.45-fold increased risk of developing nephropathy (95% CI 1.20, 1.75, p=0.00010). Furthermore, the risk C-allele was associated with lower eGFR in patients with type 2 diabetes (n=2,499, β±SEM, −3.7±1.2 ml/min, p=0.002) and also in non-diabetic individuals (n=17,602, β±SEM, −0.008± 0.003 ml/min ($\log_e$), p=0.006).
Conclusions/interpretation These data demonstrate that the *HMGA2* variant seems to be associated with increased risk of developing nephropathy in patients with type 2 diabetes and lower eGFR in both diabetic and non-diabetic individuals and could thus be a common denominator in the pathogenesis of type 2 diabetes and kidney complications.

Keywords Diabetes complications · *HMGA2* · Nephropathy · SNP · Type 2 diabetes

Abbreviations

ACR	Albumin–creatinine ratio
DN	Diabetic nephropathy
EMT	Epithelial–mesenchymal transition
ESRD	End-stage renal disease
eGFR	Estimated GFR

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Go-DARTS	Genetics of Diabetes Audit and Research in Tayside Scotland
GWAS	Genome-wide association study
HMG	High mobility group
MPP	Malmö Preventive Project
S-creatinine	Serum creatinine
SDR	Scania Diabetes Registry
SNP	Single-nucleotide polymorphism

Introduction

Type 2 diabetes is a metabolic disorder characterised by impaired insulin secretion and action that ultimately lead to chronic hyperglycaemia. Chronic hyperglycaemia is, in turn, associated with increased risk of progression to microvascular complications (nephropathy and retinopathy) of diabetes [1]. About 35% of patients with type 2 diabetes develop diabetic nephropathy (DN) [2]. Diabetes is also the most common cause of end-stage renal disease (ESRD) and the need for dialysis or kidney transplantation, which are associated with increased mortality [3, 4]. Several studies have demonstrated the preventive effect of controlling blood glucose on developing microvascular complications of diabetes [5–7].

DN is characterised by structural damage to the kidney, which results in leakage of albumin in urine. Both increased micro- (AER 20–200 μg/min or albumin/creatinine ratio >2.5 and >3.5 mg/mmol in men and women, respectively) and macroalbuminuria (AER >200 μg/min) are strongly associated with risk of morbidity and mortality from cardiovascular diseases [8, 9]. The GFR describes the flow rate of filtered fluid by the kidney and is used for assessment of renal function. Since direct measurements of GFR are tedious, the estimated GFR (eGFR) is often predicted from serum creatinine (S-creatinine), age, sex and ethnicity [10]. Clustering of DN within ethnic groups and families [11] indicates existing genetic predisposition to renal pathology [11]. Genome-wide associated studies (GWASs) have been shown to be an unbiased approach to identify genetic susceptibility loci for a number of diseases. Currently there are more than 60 common genetic variants that have been associated with type 2 diabetes and/or glucose or insulin levels using GWASs [12]. However, whether these variants also associated with the development of complications of diabetes is not established. In this study we explored whether variants influencing type 2 diabetes and/or glycaemic traits were also associated with the development of nephropathy in patients with type 2 diabetes.

Methods

Participants

Scania Diabetes Registry The Scania Diabetes Registry (SDR) was initiated in Malmö (south of Sweden) in 1996; the majority of patients regularly attended the Department of Endocrinology, Skåne University Hospital. The aim of the study was to find factors associationed with the development of complications using biomarkers and genetic markers [13]. Microalbuminuria was defined as at least two out of three consecutive measurements with AER ≥20<200 μg/min. Macroalbuminuria was defined as at least one measurement with AER ≥200 μg/min or ≥300 mg/24 h. ESRD was defined as eGFR ≤15 ml/min or dialysis or kidney transplantation. S-creatinine was determined using an enzymatic colorimetric method (Cobas NPU04998; Roche Diagnostic, Basel, Switzerland). Urine albumin was determined using immunonephelometry (Beckman Instruments, Brea, CA, USA) until 1998 and thereafter using an immunoturbimetric method (Beckman Coulter; Beckman Instruments, Brea, CA, USA) [14]. eGFR was estimated using the MDRD-4 formula. Nephropathy was defined as micro- or macroalbuminuria and/or ESRD.

Steno type 2 diabetes cohort In the Steno cohort patients with type 2 diabetes (n=345) were included as either cases with DN or controls without nephropathy collected as part of a European case–control study collaboration [15, 16]. The study design included nephropathy with inclusion criteria of albuminuria >300 mg/l and presence of diabetic retinopathy to ensure that albuminuria was the consequence of DN rather than a non-diabetic glomerulopathy [17]. Urinary albumin was determined using an enzyme immunoassay. S-creatinine was determined using a modified Jaffe's method.

Genetics of Diabetes Audit and Research in Tayside Scotland The Genetics of Diabetes Audit and Research in Tayside Scotland (Go-DARTS) database includes prescription and biochemistry information and clinical phenotypes of all patients with diabetes within Tayside, Scotland, from 1992 onwards. The Go-DARTS study is a joint initiative of the Department of Medicine and the Medicines Monitoring Unit (MEMO) at the University of Dundee. A total of 3,800 patients with type 2 diabetes from the Go-DARTS cohort were genotyped on the Affymetrix 6.0 single nucleotide polymorphism (SNP) array (Affymetrix, High Wycombe, UK) and linked with the Go-DARTS database. DN was defined as macroalbuminuria (albumin–creatinine ratio [ACR] ≥25 mg/mmol for men and ACR ≥35 for women) [18].

In all diabetic cohorts (SDR, Steno and Go-DARTS) controls were defined having normoalbuminuria.

Malmö Preventive Project The Malmö Preventive Project (MPP) is a population-based study from the city of Malmö in southern Sweden. The study started with 33,346 participants in total, of which 25,677 eligible persons participated in a health screening visit during 1974–1992 aiming at investigating large strata of the adult population to find high-risk individuals for preventive interventions. Blood samples were collected for measurements of fasting blood glucose and lipid concentrations. S-creatinine was determined with Jaffe's alkaline picrate method [19]. During 2002–2006, 17,284 persons participated in the re-screening visit and blood samples were taken for genetic analyses [20]. In our study we included 15,066 non-diabetic individuals with available baseline S-creatinine data, of them 2,536 with available S-creatinine data at follow-up.

Botnia Study The Botnia study is a family-based study from the western coast of Finland that started in 1990, aiming to identify genes that increase susceptibility to type 2 diabetes [21]. In the present study, we included 2,247 non-diabetic participants from the Botnia study with available eGFR measurements.

For all studies the protocols were approved by local ethics committees, and informed consent was obtained from all participants.

Assessment of renal function

Morning ACR and/or overnight AER were used for classification of nephropathy in patients with type 2 diabetes. In addition, as a marker of renal function, we used eGFR calculated using the MDRD-4 formula: $\text{eGFR} = 186 \times \text{S-creatinine}^{-1.54} \times \text{Age}^{-0.203} \times (1.210 \text{ if black}) \times (0.742 \text{ if female sex})$ [16, 22].

Genotyping

We genotyped 28 known SNPs associated with type 2 diabetes/glycaemic traits published during 2006–2010 [23–27] in 2,229 patients with type 2 diabetes from SDR using the Mass Extend Mass ARRAY system (Sequenom, San Diego, CA, USA). Out of 28 SNPs 26 were in Hardy–Weinberg equilibrium with the call rate ranging from 90% to 100% (electronic supplementary material [ESM] Table 1). Replication of the *HMGA2* variants SNP rs1531343 in the Steno, MPP and Botnia cohorts was performed using the TaqMan allelic discrimination assay with an ABI 7900HT sequence detection system (Applied Biosystems, Foster City, CA, USA). In Go-DARTS the SNP rs1531343 was directly genotyped on the Affymetrix 6.0 SNP array.

Statistical analysis

The OR for developing nephropathy was analysed using logistic regression, adjusted for sex and diabetes duration as well as with and without HbA_{1c}. Univariate linear regression was used to study the association of SNP rs1531343 (genotypic additive model) with eGFR adjusted for sex, diabetes duration and HbA_{1c} in patients with type 2 diabetes (SDR and Steno) and with $\log_e$ transformed eGFR ($\log_e$ eGFR) adjusted for age, sex and BMI in non-diabetic individuals (MPP and Botnia). HbA_{1c} in SDR was calculated as mean value of HbA_{1c} during a mean follow-up period of 10.9 years. Diabetes duration was calculated from the age at onset of diabetes until development of nephropathy for cases and from age at onset of diabetes until last visit for controls. Bonferroni correction for multiple comparisons was used with an adjusted p level = 0.0018 (0.05/28). Statistical analyses were carried out using Statistical Package for the Social Sciences version 17.0 (SPSS, Chicago, IL, USA). Fixed-effects meta-analysis was performed by Meta-Analysis Package for R (Metafor 1.6-0; http://www.metafor-project.org/). Power calculations were performed using Quanto (Quanto Version 1.2.4; http://hydra.usc.edu/gxe).

Results

Clinical characteristics of the study participants are shown in Table 1. In the SDR, 947 (42%) patients progressed to nephropathy during a 10.2-year period. In the Steno study, there were 172 (50%) nephropathy cases with mean diabetes duration of 15.5 years. In the Go-DARTS cohort, 114 (15%) patients progressed to nephropathy during a 10.8-year period.

The prevalence and/or incidence of DN in men were significantly higher than in women (Table 1). In all studies, diabetic patients with nephropathy had higher HbA_{1c} (SDR, 7.1% [65.6 mmol/mol] vs 6.6% [60.47 mmol/mol], $p = 4.9 \times 10^{-24}$; Steno, 9.1% [76.6 mmol/mol] vs 8.6% [71.5 mmol/mol], $p = 0.009$; Go-DARTS, 8.0% [62.53 mmol/mol] vs 7.5% [56.07 mmol/mol], $p = 0.0002$) and in two of the studies patients with nephropathy were younger at onset of diabetes (SDR, 53.6±12 vs 54.6±12.1 years, $p = 0.021$; Steno, 45.7±12.4 vs 47.5±9.3 years, $p = 0.124$) compared with those without nephropathy.

In the SDR, out of the 28 genetic loci analysed, the *HMGA2* SNP rs1531343 was associated with increased risk of developing nephropathy after correction for multiple testing (ESM Table 2). The frequency of the minor C-allele of *HMGA2* rs1531343 was significantly higher in patients with type 2 diabetes who had nephropathy (10.2% vs 6.9%, $p = 9.8 \times 10^{-5}$) as compared with those who did not. This was translated into a 1.5-fold increased risk of developing nephropathy (95% CI, 1.20, 1.87, $p = 0.00035$) adjusted for sex, diabetes duration and HbA_{1c}. To replicate this finding, we validated this association in the additional available diabetic Steno and Go-DARTS cohorts. Although these cohorts had less power, similarly to SDR we observed that

Table 1 Clinical characteristics of the studied cohorts

Characteristic	SDR			Steno			Go-DARTS			MPP	Botnia
	DN+	DN−	*p*	DN+	DN−	*p*	DN+	DN−	*p*	Baseline	Baseline
n (% men)	947 (68)	1,282 (53)	2.2×10^{-12}	172 (60)	173 (58)	0.048	114 (70.1)	670 (53.5)	0.001	15,074 (62)	2,445 (46)
Age/age at onset of T2D, years	53.6±12	54.6±12.1	0.047	45.7±12.4	47.5±9.3	0.124	60±9.9	57.2±9.4	0.001	44.6±7.5	44.4±14.5
BMI, kg/m^2	30.5±5.4	30.0±9.9	0.538	29.9±5.3	26.9±4.4	2.0×10^{-7}	30.9±4.6	30.6±5.3	0.57	23.9±3.1	25.5±4.1
HbA_{1c}, % (mmol/mol)	7.1±1.1 (65.6± 12.3)	6.6±1.1 (60.47± 11.8)	1.6×10^{-24}	9.1±1.7 (76.6± 18.9)	8.6±1.3 (71.5± 13.9)	0.009	8.0±1.6 (62.53± 21.97)	7.5±1.3 (56.07± 17.07)	0.0002		
eGFR, ml min^{-1} (1.73 m)$^{-2}$	67.9±27.3	83.4±19.2	7.8×10^{-53}	58.4±21.6	76.6±17.9	1.2×10^{-12}				79.6 (17.8)	74.87 (18.3)
Duration of T2D, years	10.2±8.72	11.4±7.7	0.001	15.5±7.0	14.9±6.7	0.50	10.8±7.7	10.02±6.5	0.24		
Systolic BP, mm/Hg	144.3±21.0	138.58±19.7	0.023	157±24.4	148.3±20.4	0.0005	147.6±18.8	142.4±19.3	0.12	129.4± 15.3	128.6± 18.1
Diastolic BP, mm/Hg	80.9±10.0	79.8±10.4	0.38	80.8±12.0	78.6±10.18	0.072	75.3±11.1	76.5±10.5	0.27	84.2±9.1	78.3±10.8
Total cholesterol, mmol/l	5.6±1.30	5.69±1.2	0.19	5.8±1.3	5.28±1.08	0.004	4.23±1.01	4.39±0.12	0.12	5.6±1.0	5.5±1.16
HDL-cholesterol, mmol/l	1.04±0.28	1.18±0.35	2.98×10^{-12}	1.15±0.86	1.33±0.42	0.079	1.28±0.37	1.43±0.41	0.0007		1.4±0.33
LDL-cholesterol, mmol/l	2.62±1.62	2.85±1.58	0.0091	2.85±0.1.1	3.16±0.91	0.25	1.83±0.76	2.0±0.76	0.06		
Triacylglycerols (mmol/l)	2.0 (1.65)	1.83 (1.3)	7.26×10^{-5}	2.4 (2.4)	1.2 (0.95)	7.8×10^{-8}				1.1 (0.68)	1.1 (0.67)

Data are mean±SD or median (inter-quartile range)

DN+, diabetic patients with nephropathy; DN−, diabetic patients without nephropathy; T2D, type 2 diabetes; Duration, duration to onset of nephropathy

the frequency of the minor C-allele of *HMGA2* rs1531343 was significantly higher in Steno (11.3% vs 6.6%, p=0.031) and also tended to be higher in Go-DARTS (12.7% vs 10.9%, p=0.41) patients with type 2 diabetes who had nephropathy as compared with those who did not. The combined analysis of SDR, Steno and Go-DARTS cohorts showed that carriers of the C-allele had a 1.45-fold increased risk of DN (95% CI, 1.20, 1.75, p=0.00010) (Table 2). Additionally, we also explored whether *HMGA2* rs1531343 would influence eGFR in patients with type 2 diabetes. We found that the C-allele of rs1531343 was also associated with lower eGFR (β±SEM: −3.7±1.2 ml/min, p=0.002) (Table 3).

Next, we analysed 15,066 non-diabetic participants from the MPP study with available information on eGFR (Table 3). Notably, in the MPP the C-allele was associated with lower eGFR at baseline (β±SEM: −0.007±0.003 ml/min, p=0.038) and remained lower after a 6.4-year follow-up period (β±SEM: −0.021±0.008 ml/min, p=0.007). Similarly, in the non-diabetic participants of the Botnia study the risk C-allele was associated with lower eGFR (β±SEM: −0.024±0.012 ml/min, p=0.040). Combined analysis of the MPP and Botnia studies strengthened this association (β±SEM: −0.008±0.003 ml/min, p=0.006) (Table 3).

Table 3 Effect of *HMGA2* rs1531343 on eGFR

Study	*n*	β	SE	*p*
SDR	2,244	−3.68	1.27	0.004
Steno	255	−3.65	3.42	0.286
Meta-analysis	2,499	−3.7	1.2	0.002
MPP baseline[a]	15,066	−0.007	0.003	0.038
MPP follow-up[a]	2,536	−0.021	0.008	0.007
Botnia[a]	2,247	−0.024	0.012	0.040
Meta-analysis[a]	17,602	−0.008	0.003	0.006

Linear regression adjusted for sex, diabetes duration and HbA_{1c} in type 2 diabetes cohorts (SDR and Steno), and age, sex and BMI in non-diabetic cohorts (MPP and Botnia)

[a] Log_e transformed eGFR

Discussion

In this study, we demonstrated that the risk C-allele of the common variant (rs1531343) in the *HMGA2* loci predisposing to type 2 diabetes was also associated with progression to nephropathy in patients with type 2 diabetes and decline in renal function measured with eGFR in non-diabetic individuals.

Our observations are in line with a recently reported GWAS for kidney function (eGFR) [28]. The study included 67,093 participants of European ancestry from 20 predominantly population-based studies to identify new susceptibility loci for reduced renal function. The risk C-allele of SNP *HMGA2* rs1531343 was also negatively associated with eGFR (p=0.039) in this study, supporting our findings (https://intramural.nhlbi.nih.gov/labs/CF/Pages/CKDGenConsortium.aspx, accessed 08/08/2012) [28]. Notably, in a GWAS for DN in African-Americans, another variant (rs2358944), located 57 kb downstream of the *HMGA2* rs1531343, was one of the strongest signals associated with diabetic ESRD, but also to a lesser extent with non-diabetic ESRD [29].

The high mobility group (HMG) protein family includes HMGA, HMGB and HMGN [30]. HMGA proteins are transcribed from two genes, *HMGA1* and *HMGA2* [31]. HMGA

Table 2 Effect of *HMGA2* rs1531343 on nephropathy in patients with type 2 diabetes

Genotype	SDR		Steno		Go-DARTS	
	DN+	DN−	DN+	DN−	DN+	DN−
G/G, *n* (%)	768 (81)	1,111 (87)	136 (79)	152 (88)	88 (77)	533 (79)
G/C, *n* (%)	164 (17)	165 (13)	33 (19)	19 (11)	23 (20)	128 (19)
C/C, *n* (%)	15 (2)	6 (0.5)	3 (2)	2 (1)	3 (3)	9 (1)
RAF (C-allele), %	10.2	6.9	11.3	6.6	12.7	10.9
χ^2 *p* value	0.000098		0.041		0.29	
OR (95% CI)	1.47 (1.19, 1.82)		1.58 (0.92, 2.72)		1.21 (0.79, 1.84)	
p value	0.0004		0.099		0.37	
OR (95% CI)[a]	1.50 (1.20, 1.87)		1.56 (0.86, 2.82)		1.23 (0.80, 1.89)	
p value[a]	0.00035		0.14		0.34	
Meta-analysis OR (95% CI)	1.45 (1.20, 1.75)					
p value	0.00010					

OR, 95% CI and *p* value are from logistic regression adjusted for sex and duration of diabetes

[a] Logistic regression adjusted for sex, duration of diabetes and HbA_{1c}

RAF, risk allele frequency

proteins are found in high levels in human embryonic stem cells and derived embryoid bodies in vitro [32]. HMGA2 is ascribed an important role in the control of stem-cell development and proliferation, and also high levels of HMGA2 is found in many benign, as well as malignant, tumours [33, 34]. HMG proteins are the most abundant non-histone DNA-binding chromatin factors in the eukaryotic nucleus involved in up- and downregulation of several genes [33].

Although the role of *HMGA2* in diabetes or DN is still not fully understood, it was demonstrated that overexpression of *HMGA2* was associated with formation of micropolycystic kidney suggesting involvement of *HMGA2* in kidney development [35].

Diabetic kidney abnormalities are characterised mainly by hypertrophy, thickening of the glomerular basement membrane, tubular atrophy and interstitial fibrosis, which have been shown to lead to increased loss of renal function [33]. Recently, epithelial–mesenchymal transition (EMT) has been suggested as a novel pathway playing a key role in the pathogenesis of tubulointerstitial fibrosis in DN and blockage of EMT has been shown to delay progression to DN [33, 34]. Of note, transcriptomic analyses of TGF-β-stimulated EMT in NAMRU mouse mammary gland (NMuMG) cells identified HMGA2 as a main target involved in the control of epithelial differentiation [36]. TGF-β is a pro-sclerotic cytokine strongly associated with the development of fibrosis in DN [34]. The induction of cytokines, chemokines and growth factors, particularly TGFβ1 and connective tissue growth factor (CTGF), leads to glomerular basement membrane thickening, podocyte injury and mesangial matrix expansion. Thus changes in *HMGA2* expression may ultimately increase the risk of development of irreversible glomerular sclerosis and tubulointerstitial fibrosis involved in the pathogenesis of DN. However, as for many genetic association studies, the observed phenotypic effect could be caused by one or several genetic variants in LD with the genotyped variant rather than the genotyped SNP itself. Thus, we cannot rule out that the effect is mediated by *cis*- or *trans*-regulatory genetic elements other than the *HMGA2* gene.

Although in this study we had 96% power to detect an association of *HMGA2* rs1531343 with nephropathy, the available replication cohorts were less powered. Also, the original discovery cohort still had limited power to detect an effect of other genetic loci with smaller effect sizes. Thus, we cannot exclude weaker associations and false-negative results. Larger studies will be needed to detect or exclude a role of these SNPs in DN. Additionally, given that long-term glycaemia and duration of diabetes are major determinants of progression to nephropathy, glycaemic control and longer duration of diabetes should be clearly applied, if available, to define patients without nephropathy in the design of future studies.

In conclusion, we demonstrate that an *HMGA2* variant seems to be associated with increased risk of developing nephropathy in patients with type 2 diabetes and with lower eGFR in both diabetic and non-diabetic individuals and thus could represent a common denominator in the pathogenesis of type 2 diabetes and kidney complications. However, the biology of most genetic determinants influencing type 2 diabetes/glycaemic traits is most likely different from those involved in progression to complications of diabetes.

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Duality of interest The authors declare there is no duality interest associated with the manuscript.

Contribution statement SA performed genotyping, participated in data analysis, interpretation, and manuscript writing. ML participated in data collection and manuscript writing. HD participated in data analysis and manuscript writing. HC participated in acquisition of data, conception and design of the Go-DARTS study. EA participated in data analysis of SDR. BI acquisition of data in the Botnia study. PR participated in acquisition of data, conception and design of the Steno study. LG participated in acquisition of data, conception and design of the Botnia study, participated in data interpretation. VL participated in the study design, data interpretation, manuscript writing and overall supervision of the study. All authors critically revised and approved the final version of the manuscript.

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