Diabetic nephropathy : pathology, genetics and carnosine metabolism

Mooyaart, A.L.

A

Online supplements

Contents

Chapter 2 – Figure 1. Scoring form for glomerular lesions, extraglomerular lesions and other features.

Chapter 3 – ESM Table 2 - Details of the articles which were included in this meta-analysis study
(ESM Table 1 and ESM figure 1-36 can be found online on the Diabetologia website)

Chapter 5 – Hardy-Weinberg equilibrium, Sensitivity analysis, Permutation

Figure 1. Scoring form for glomerular lesions, extraglomerular lesions and other features.

RPS DN Working Group score sheet

Case Number	
Pathologist	
Date	
Stainings evaluated	

EM Avg GBM size (nm) ☐

A. Glomerular lesions	*Tally mark*	*no.*
Total # of evaluated glomeruli		
Normal glomeruli		
Global glomerulosclerosis		
Nodular lesions		
Mesangial expansion		
Mild		
Severe		

Name	#	*Criteria*	**Classify into glomerular class:** ?
EM proven DN	I	GBM > 395 nM (female), > 430 (male)	
Mild Mesangial Expansion	II A	Mild mesangial expansion in >25%	
Severe Mesangial Expansion	II B	Severe mesangial expansion in >25%	
Nodular Sclerosis	III	At least one convincing nodular lesion	
Glomerosclerosis with signs	IV	Global glomerular sclerosis in >50% of	
of DN		glomeruli in proven DN	

EM, electronmicroscopy; TA, tubular atrophy; IF, interstitial fibrosis

B. Extraglomerular Lesions		*Circle score*
Tubular atrophy (%)	< 25 % tubular atrophy	0
	25-50 % tubular atrophy	1
	>50 % tubular atrophy	2
Interstitial fibrosis (%)	< 25 % interstitial fibrosis	0
	25-50 % interstitial fibrosis	1
	>50 % interstitial fibrosis	2
Interstitial inflammation		
	absent	0
	Infiltration only in relation to IF or TA	1
	Infiltration in areas without IF or TA	2
Large vessels present?		Y / N
Arteriosclerosis (score worst artery)		
	No intimal thickening	0
	intima thickened and < thickness of media	1
	intima thickened and > thickness of media	2
Arteriolar hyalinosis	absent	0
	at least one case of arteriolar hyalinosis	1
	>1 case of arteriolar hyalinosis	2

C. Other features

Capsular drop present / absent

Fibrin cap present / absent

Chapter 3

Electronic supplementary material

ESM Table 2 Details of the articles which were included in this meta-analysis study

Variants	Article	Definitions		Cases of DN or controls (*n*)				Study details			OR[a]
		Cases	Controls	Total	EDN[b]	ADN[c]	Controls	Design	Country	TD	Allele level
ACE											
rs179975	Ahluwalia et al., 2009 (1)	EDN[b]+ADN[c]	Normoalb[d] ≥10 years of diabetes	240			255	Case–control	India	2	1.57 (1.21– 2.04)
	Araz et al., 2001 (2)	EDN	Normoalb	62			123	Case–control	Turkey	2	1.00 (0.64–1.54)
	Arfa et al., 2008 (3)	EDN	Normoalb ≥10 years of diabetes	54			51	Case–control	Tunisia	2	1.24 (0.70–2.21)
	Canani et al., 2005 (4)	EDN+ADN	Normoalb	203			609	Case–control	Brazil	2	1.22 (0.97–1.53)
	Chowdhury et al., 1996 (5)	EDN	Normo-/microalb[e] >15 years of diabetes (no proteinuria)	242			166	Case–control	UK	1	1.04 (0.78–1.38)
	Demurov et al., 1997 (6)	EDN	Normoalb (diabetes without complications)	56			76	Case–control	Russia	1	1.98 (1.19–3.30)
	Doi et al., 1996 (7)	EDN+ADN	Normoalb >10 years of diabetes	100			124	Case–control	Japan	2	1.55 (1.05–2.28)
	Fradin et al., 2002 (8)	EDN	Normoalb	39			118	Case–control	France	2	0.86 (0.51–1.44)
	Gohda et al., 2001 (9)	EDN+ADN	Normoalb >15 years of diabetes	416	289	127	212	Case–control	Japan	2	1.09 (0.86–1.39)
	Grzeszczak et al., 1998 (10)	EDN+ADN	Normoalb ≥10 years of diabetes	127			254	Case–control	Poland	2	0.91 (0.67–1.23)
	Guitterez et al., 1997 (11)	EDN	Normoalb	20			100	Case–control	Spain	2	1.27 (0.62–2.62)
	Ha et al., 2003 (12)	ADN	Stable kidney function >15 years	140			99	Follow-up	Korea	2	1.84 (1.27–2.66)
	Hadjadj et al., 2001 (13)	EDN+ADN	Normoalb ≥3 years of diabetes	24	18	6	251	Case–control	France	1	0.84 (0.46–1.52)
	Hadjadj et al., 2007 (14)	EDN+ADN	Normoalb ≥15 years of diabetes (without anti-hypertensiva)	380			382	Case–control	Denmark	1	1.04 (0.85–1.27)

Variants	Article	Definitions		Cases of DN or controls (*n*)				Study details			OR[a]
		Cases	Controls	Total	EDN[b]	ADN[c]	Controls	Design	Country	TD	Allele level
		EDN+ADN	Normoalb ≥15 years of diabetes (without anti-hypertensiva)	385			468	Case–control	Finland	1	1.09 (0.90–1.32)
		EDN+ADN	Normoalb ≥15 years of diabetes (without anti-hypertensiva)	277			273	Case–control	France	1	1.45 (1.14–1.84)
	Hibberd et al., 1997 (15)	EDN+Ret[f]	Normoalb ≥20 years of diabetes	72			86	Case–control	UK	1	0.69 (0.44–1.10)
	Kimura et al., 1998 (16)	EDN+ADN+Ret	Normo-/microalb >15 years of diabetes	98			110	Case–control	Japan	2	0.96 (0.65–1.43)
	Marre et al., 1997 (17)	EDN+ADN	Normoalb	233	126	107	157	Case–control	France	1	1.41 (1.06–1.88)
	Miura et al., 1999 (18)	EDN	Normoalb >10 years of diabetes	32			103	Case–control	Japan	1	0.98 (0.55–1.76)
	Mollsten et al., 2008 (19)	EDN+ADN	Normoalb ≥20 years of diabetes (without anti-hypertensiva)	48			197	Case–control	Sweden	1	0.81 (0.52–1.27)
	Nakajima et al., 1996 (20)	EDN+Ret	Normoalb	54			41	Case–control	Japan	2	1.25 (0.68–2.28)
	Naresh et al., 2009 (21)	EDN+Ret	No nephropathy	30			30	Case–control	India	2	3.02 (1.43–6.38)
	Ng et al., 2006 (22)	EDN+ADN	Normoalb; 6 years of diabetes	291			167	Case–control	USA	2	1.10 (0.84–1.45)
	Nikzamir et al., 2009 (23)	EDN	Normoalb	48			145	Case–control	Iran	2	4.33 (2.54–7.41)
	Ohno et al., 1996 (24)	EDN	Normoalb	25			53	Case–control	Japan	2	2.55 (1.24–5.21)
	Ortega-Pierres et al., 2007 (25)	EDN	Normoalb	45			116	Case–control	Mexico	2	3.20 (1.89–5.43)
	Park et al., 2005 (26)	ADN	Normoalb >15 years of diabetes	103			88	Case–control	Korea	2	1.71 (1.13–2.57)
	Prasad et al., 2006 (27)	ADN+Ret	Normoalb ≥10 years of diabetes	196			225	Case–control	India	2	1.36 (1.03–1.79)
	Shestakova et al., 2006 (28)	EDN	Normoalb >20 years of diabetes	63			66	Case–control	Russia	1	1.36 (0.83–2.22)
	Shin Shin et al., 2004 (29)	EDN	Normoalb	82			50	Case–control	Korea	2	0.68 (0.41–1.11)
	So et al., 2006 (30)	EDN	Normoalb	421			1225	Case–control	Hong Kong	2	0.97 (0.82–1.14)

Variants	Article	Definitions		Cases of DN or controls (*n*)				Study details			OR[a]
		Cases	Controls	Total	EDN[b]	ADN[c]	Controls	Design	Country	TD	Allele level
	Taniwaki et al., 2001 (31)	EDN+ADN	Normoalb	42	22	20	69	Case–control	Japan	2	1.03 (0.59–1.81)
	Tarnow et al., 1995 (32)	EDN+Ret	Normoalb	198			190	Case–control	Denmark	1	1.01 (0.76–1.34)
	Thomas et al., 2001 (33)	EDN	Normoalb	51			255	Case–control	China (Han)	2	0.88 (0.55–1.40)
	Tomino et al., 1999 (34)	EDN	Normoalb >10 years of diabetes	414			407	Case–control	Japan	2	0.96 (0.79–1.18)
	van Ittersum et al., 2000 (35)	EDN	Normoalb	30			188	Case–control	Netherlands	1	0.85 (0.49–1.48)
	Viswanathan et al., 2001 (36)	EDN	Normoalb+no Ret	86			23	Case–control	USA	2	1.83 (0.94–3.56)
	Vleming et al., 1998 (37)	EDN	Normoalb >15 years of diabetes	96			82	Case–control	Netherlands	1	1.41 (0.97–2.05)
	Vleming et al., 1999 (38)	ADN	Normoalb >15 years of diabetes	79			82	Case–control	Netherlands	1	*
	Wu et al., 2000 (39)	EDN+ADN	Normoalb	27			41	Case–control	China	2	2.60 (1.27–5.32)
	Yoshida et al., 1996 (40)	ADN	Normoalb	72			60	Case–control	Japan	2	1.76 (1.06–2.91)
	Young et al., 1998 (41)	EDN	Normoalb	20			54	Case–control	China (Han)	2	0.96 (0.44–2.09)
AKR1B1											
rs759853	Fanelli et al., 2002 (42)	EDN+ADN	Normoalb	231	126	105	157	Case–control	France	1	0.90 (0.67–1.21)
	Gosek et al., 2005 (43)	EDN	Normoalb	129			162	Case–control	Poland	2	0.96 (0.68–1.34)
	Moczulski et al., 2000 (44)	EDN+ADN	Normoalb ≥15 years of diabetes (without anti-hypertensiva)	221			193	Case–control	USA	1	1.43 (1.07–1.90)
	Neamat-allah et al., 2001 (45)	EDN	Normoalb	85			146	Case–control	England	2	1.56 (1.07–2.29)
		EDN	Normoalb >10 years of diabetes	181			154	Case–control	USA (Pima Indians)	2	1.42 (0.95–2.11)
		EDN	Normoalb >20 years of diabetes	107			102	Case–control	Ireland	1	2.47 (1.61–3.79)
		EDN	Normoalb >15 years of diabetes	77			85	Case–control	England	1	2.15 (1.37–3.37)
	Sivenius et al., 2004 (46)	EDN	Normoalb	4			68	Case–control	Finland	2	2.05 (0.39–10.93)
	So et al., 2008 (47)	ADN	Stable kidney function (8 years follow-up)	208			866	Follow-up	China	2	1.25 (0.97–1.61)
CA-repeat	Chistyakov et al., 1997 (48)	EDN	Normoalb >20 years of diabetes	10			15	Case–control	Russia	1	1.05 (0.28–3.93)
	Dyer et al., 1999 (49)	EDN	Normo-/microalb (long-term)	211			129	Case–control	UK	1	0.93 (0.67–1.28)

Variants	Article	Definitions		Cases of DN or controls (*n*)				Study details			OR[a]
		Cases	Controls	Total	EDN[b]	ADN[c]	Controls	Design	Country	TD	Allele level
	Fanelli et al., 2002 (42)	EDN+ADN	Normoalb	231	126	105	157	Case–control	France	1	1.04 (0.77–1.40)
	Heesom et al.,1997 (50)	EDN	Normoalb 20 years of diabetes (without complications)	75			43	Case–control	UK	1	1.91 (1.02–3.59)
	Ichikawa et al., 1999 (51)	EDN	Normoalb (no nephropathy)	26			46	Case–control	Japan	2	0.84 (0.40–1.79)
	Lajer et al., 2004 (52)	EDN	Normoalb >15 years of diabetes	431			468	Case–control	Denmark	1	1.11 (0.92–1.35)
	Liu et al., 2002 (53)	EDN	Normoalb	52			128	Case–control	China	2	1.41 (0.80–2.46)
	Maeda et al., 1999 (54)	EDN	Normoalb	63			123	Case–control	Japan	2	0.68 (0.40–1.14)
	Moczulski et al., 2000 (44)	EDN+ADN	Normoalb ≥15 years of diabetes (without antihypertensiva)	221			193	Case–control	USA	1	0.95 (0.63–1.44)
	Moczulski et al., 1999 (55)	EDN	Normoalb	70			179	Case–control	Poland	2	1.52 (1.13–2.03)
	Neamat-allah et al., 2001(45)	EDN	Normoalb	81			137	Case–control	England	2	1.06 (0.71–1.58)
		EDN	Normoalb >10 years of diabetes	174			141	Case–control	USA (Pima Indian)	2	1.25 (0.87–1.79)
		EDN	Normoalb >20 years of diabetes	101			110	Case–control	Ireland	1	0.94 (0.63–1.39)
		EDN	Normoalb >15 years of diabetes	67			78	Case–control	England	1	0.83 (0.51–1.35)
	Ng et al., 2001 (56)	EDN	Normoalb >15 years of diabetes (without complications)	15			49	Case–control	Australia	1	1.19 (0.48–2.92)
	Park et al., 2002 (57)	EDN+Ret	Normoalb >10 years of diabetes (without complications)	48			38	Case–control	Korea	2	1.43 (0.73–2.80)
	So et al., 2008 (47)	ADN	Stable kidney function (8 years follow-up)	208			866	Follow-up	China	2	1.39 (1.09–1.77)
	Yamamoto et al., 2003 (58)	EDN	Normoalb	19			67	Case–control	Japan	1	1.08 (0.40–2.90)
	Zhao et al., 2004 (59)	autopsy proven DN	Normal biopsy	135			51	Case–control	China	2	0.96 (0.59–1.58)

Variants	Article	Definitions		Cases of DN or controls (*n*)				Study details			OR[a]
		Cases	Controls	Total	EDN[b]	ADN[c]	Controls	Design	Country	TD	Allele level
APOC1											
rs4420638	McKnight et al., 2009 (60)	EDN+Ret	Normoalb >15 years of diabetes (without complications, without anti-hypertensiva)	590			494	Case–control	UK	1	1.53 (1.23–1.90)
		EDN+Ret	Normoalb 15 years (without complications, without anti-hypertensiva)	267			441	Case–control	Ireland	1	1.56 (1.18–2.07)
APOE											
E2, E3, E4	Araki et al., 2000 (61)	EDN+ADN	Normoalb >15 years of diabetes	223			196	Case–control	USA	1	3.74 (2.06–6.79)
	Chowdhury et al., 1998 (62)	EDN	Normo-/microalb (>50 years of diabetes)	252			197	Case–control	UK	1	3.05 (1.22–7.62)
	Eto et al., 1995 (63)	EDN+ADN	Normoalb	100	43	57	135	Case–control	Japan	2	3.08 (1.30–7.30)
	Ha et al., 1999 (64)	EDN	Normoalb (normal renal function)	74			93	Case–control	Korea	2	1.20 (0.62–2.30)
	Hadjadj et al., 2000 (65)	EDN+ADN	Normoalb (normal renal function)	114			77	Case–control	France	1	3.29 (1.57–6.89)
	Horita et al., 1994 (66)	ADN	Normoalb	57			398	Case–control	Japan	2	0.83 (0.31–2.22)
	Kimura et al., 1998 (67)	ADN	Normoalb	81			97	Case–control	Japan	2	0.51 (0.03–8.36)
	Leiva et al., 2007 (68)	ADN	Normoalb (without complications)	56			29	Case–control	Chili	2	3.03 (1.60–5.73)
	Onuma et al., 1996 (69)	EDN+ADN	Normoalb >10 years of diabetes	41			74	Case–control	USA	1	0.76 (0.28–2.05)
	Tarnow et al., 2000 (70)	EDN+no Ret	Normoalb >15 years of diabetes	197			192	Case–control	Denmark	1	1.25 (0.76–2.05)
	Yakunina et al., 2005 (71)	EDN	Normo-/microalb ≥20 years of diabetes	62			68	Case–control	Russia	1	0.66 (0.33–1.30)
CCR5											
rs1799987	Ahluwalia et al., 2009 (72)	EDN	Normoalb ≥10 years of diabetes	240			255	Case–control	North India	2	0.46 (0.35–0.59)
		EDN	Normoalb ≥10 years of diabetes	96			92	Case–control	South India	2	0.46 (0.30–0.70)

Variants	Article	Definitions		Cases of DN or controls (*n*)				Study details			OR[a]
		Cases	Controls	Total	EDN[b]	ADN[c]	Controls	Design	Country	TD	Allele level
	Mlynarski et al., 2005 (73)	EDN+ADN	Normoalb ≥15 years of diabetes (without antihypertensiva)	496			298	Case–control	USA	1	1.19 (0.97–1.46)
	Nakajima et al., 2003 (74)	EDN	Normoalb	95			355	Case–control	Japan	2	0.85 (0.61–1.17)
	Pettigrew et al., 2010 (75)	EDN+Ret	Normoalb 15 years (without complications, without anti-hypertensiva)	263			437	Case–control	Ireland	1	0.98 (0.79–1.22)
	Prasad et al., 2007 (76)	ADN	Normoalb ≥10 years of diabetes	196			205	Case–control	India	2	0.61 (0.46–0.80)
	Tregouet et al., 2008 (77)	EDN+ADN	Normoalb ≥5 years of diabetes (without anti-hypertensiva)	489			463	Case–control	Denmark	1	1.00 (0.83–1.20)
		EDN+ADN	Normoalb ≥5 years of diabetes (without anti-hypertensiva)	387			391	Case–control	France	1	1.00 (0.83–1.21)
		EDN+ADN	Normoalb ≥5 years of diabetes (without anti-hypertensiva)	300			469	Case–control	Finland	1	1.00 (0.81–1.24)
CNDP1											
D18S880	Freedman et al., 2007 (78)	ADN	No nephropathy	165			258	Case–control	USA	2	0.77 (0.58–1.01)
	Janssen et al., 2005 (79)	EDN+ADN	Normoalb ≥15 years (without anti-hypertensiva)	114			71	Case–control	Germany	2	0.78 (0.52–1.17)
		EDN+ADN	Normoalb ≥15 years (without anti-hypertensiva)	21			36	Case–control	Germany	1	0.37 (0.17–0.81)
	Mooyaart et al., 2010 (80)	ADN	Normoalb ≥15 years	65			93	Case–control	Netherlands/ Germany	2	**
	Tregouet et al., 2008 (77)	EDN+ADN	Normoalb ≥5 years of diabetes (without anti-hypertensiva)	489			463	Case–control	Denmark	1	0.94 (0.82–1.07)
		EDN+ADN	Normoalb ≥5 years of diabetes (without anti-hypertensiva)	387			391	Case–control	France	1	1.01 (0.84–1.21)

Variants	Article	Definitions		Cases of DN or controls (*n*)				Study details			OR[a]
		Cases	Controls	Total	EDN[b]	ADN[c]	Controls	Design	Country	TD	Allele level
		EDN+ADN	Normoalb ≥5 years of diabetes (without anti-hypertensiva)	300			469	Case–control	Finland	1	0.99 (0.82–1.20)
	Wanic et al., 2008 (81)	EDN+ADN	Normoalb ≥15 years of diabetes (without anti-hypertensiva)	656	445	221	613	Case–control	USA	1	1.03 (0.83–1.28)
ELMO1											
rs741301	Shimazaki et al., 2005 (82)	EDN+ADN+Ret	Normoalb	87			92	Case–control	Japan	2	1.84 (1.18–2.86)
		EDN+ADN+Ret	Normoalb	459			242	Case–control	Japan	2	1.51 (1.19–1.91)
	Pezzolesi et al., 2009 (83)	EDN+ADN	Normoalb ≥15 years of diabetes	820			885	Case–control	USA	1	0.88 (0.76–1.01)
EPO											
rs1617640	Tong et al., 2008 (84)	EDN+ADN	Normoalb ≥15 years (without nephropathy or Ret)	374			239	Case–control	USA	2	0.69 (0.55–0.87)
		EDN+ADN	Normoalb ≥15 years (without nephropathy or Ret)	865			574	Case–control	USA	1	0.65 (0.56–0.76)
		EDN+ADN	Normoalb ≥15 years (without nephropathy or Ret)	379			141	Case–control	USA	1	0.72 (0.55–0.95)
GLUT1											
rs841853	Grzeszczak et al., 2001 (85)	EDN	Normoalb	132			162	Case–control	Poland	2	1.82 (1.13–2.93)
	Gutierrez et al., 1998 (86)	EDN	Normoalb	20			100	Case–control	Spain	2	0.57 (0.20–1.60)
	Hodgkinson et al., 2005 (87)	EDN	No complications ≥20 years of diabetes	101			56	Case–control	UK	1	1.17 (0.73–1.86)
	Liu et al., 1999 (88)	EDN	No nephropathy	64			45	Case–control	China (Han)	2	0.52 (0.29–0.93)
	Makni et al., 2008 (89)	EDN	Normoalbuminuria >10 years of diabetes	126			273	Case–control	Tunesia	2	1.05 (0.62–1.79)
	Ng et al., 2002 (90)	EDN+ADN	Normoalb ≥15 years of diabetes	249			207	Case–control	USA	1	0.81 (0.56–1.17)
	Tarnow et al., 2001 (91)	EDN	Normoalb	175			192	Case–control	Denmark	1	0.73 (0.48–1.10)

Variants	Article	Definitions		Cases of DN or controls (*n*)				Study details			OR[a]
		Cases	Controls	Total	EDN[b]	ADN[c]	Controls	Design	Country	TD	Allele level
GREM 1											
rs1129456	McKnight et al., 2010 (92)	EDN	Normoalb >15 years of diabetes (without complications and without anti-hypertensiva)	264			439	Case–control	Ireland	1	1.73 (1.24–2.41)
		EDN+ADN	Normoalb, ≥15 years of diabetes (without anti-hypertensiva)	595			501	Case–control	UK	1	1.42 (1.09–1.85)
HSPG2											
rs3767140	Fujita et al., 1999 (93)	EDN	Normoalb (without nephropathy)	102			64	Case–control	Japan	2	0.67 (0.43–1.05)
	Hansen et al., 1997 (94)	EDN	Normoalb >20 years	170			90	Case–control	Denmark	1	0.60 (0.39–0.92)
		EDN+Ret	Normoalb >20 years	247			150	Case–control	UK	1	0.68 (0.48–0.96)
	Liu et al., 2003 (95)	EDN+ADN	Normoalb ≥10 years	213	163	50	77	Case–control	China (Han)	2	0.91 (0.63–1.33)
VEGFA											
rs833061	McKnight et al., 2007 (96)	EDN+Ret	Normoalb >15 years of diabetes (without complications and without anti-hypertensiva)	153			184	Case–control	Ireland	1	0.46 (0.34–0.62)
		EDN+Ret	Normoalb 15 years (without complications of diabetes and without anti-hypertensiva)	89			117	Case–control	Ireland	1	0.51 (0.35–0.76)
FRMD3											
rs1888747	Pezzolezi et al., 2009 (97)	EDN+ADN	Normoalb ≥15 years (without anti-hypertensiva)	379 [g]			413 [g]	Case–control	USA	1	1.33 (1.01–1.75)
		EDN+ADN	Normoalb ≥15 years (without anti-hypertensiva)	441 [h]			472 [h]	Case–control	USA	1	1.47 (1.20–1.80)
		EDN+ADN	Normo-/microalb (diabetes 16–22 years)	132			1172	Follow-up			1.27 (1.02–1.58)

Variants	Article	Definitions		Cases of DN or controls (*n*)				Study details			OR[a]
		Cases	Controls	Total	EDN[b]	ADN[c]	Controls	Design	Country	TD	Allele level
rs10868025	Pezzolezi et al., 2009 (97)	EDN+ADN	Normoalb ≥15 years of diabetes (without anti-hypertensiva)	379 [g]			413 [g]	Case–control	USA	1	1.23 (0.96–1.58)
		EDN+ADN	Normoalb ≥15 years (without anti-hypertensiva)	441 [h]			472 [h]	Case–control	USA	1	1.52 (1.26–1.83)
		EDN+ADN	Normo-/microalb (diabetes 16–22 years)	132			1172	Follow-up			1.35 (1.10–1.66)
CARS											
rs451041	Pezzolezi et al., 2009 (97)	EDN+ADN	Normoalb ≥15 years (without anti-hypertensiva)	379 [g]			413 [g]	Case–control	USA	1	1.32 (1.03–1.69)
		EDN+ADN	Normoalb ≥15 years (without anti-hypertensiva)	441 [h]			472 [h]	Case–control	USA	1	1.38 (1.15–1.66)
		EDN+ADN	Normo-/microalb (diabetes 16–22 years)	132			1172	Follow-up			1.38 (1.13–1.69)
rs739401	Pezzolezi et al., 2009 (97)	EDN+ADN	Normoalb ≥15 years (without anti-hypertensiva)	379 [g]			413 [g]	Case–control	USA	1	1.38 (1.13–1.68)
		EDN+ADN	Normoalb ≥15 years (without anti-hypertensiva)	441 [h]			472 [h]	Case–control	USA	1	1.27 (1.06–1.53)
ACACB											
rs2268388	Maeda et al., 2010 (98)	EDN+Ret	Normoalb	737			552	Case–control	Japan	2	1.61 (1.33–1.96)
		ADN+Ret	Normoalb ≥15 years of diabetes (Ret)	177			196	Case–control	Korea	2	0.83 (0.59–1.17)
		EDN	Normoalb >7 years of diabetes	199			212	Case–control	Singapore (Han)	2	1.07 (0.78–1.48)
		EDN	Normoalb	428			425	Case–control	Denmark	1	0.99 (0.76–1.29)
		EDN+Ret	Normoalb >5 years of diabetes	473			415	Case–control	USA	2	1.61 (1.22–2.12)

Variants	Article	Definitions		Cases of DN or controls (*n*)				Study details			OR[a]
		Cases	Controls	Total	EDN[b]	ADN[c]	Controls	Design	Country	TD	Allele level
ADIPOQ											
rs17300539	Jorsal et al., 2008 (99)	EDN	Normoalb >15 years of diabetes	438			440	Case–control	Denmark	1	1.46 (1.03–2.08)
	Prior et al., 2008 (100)	EDN+Ret	Normoalb ≥50 years of diabetes	98			99	Case–control	UK	1	2.19 (1.16–4.12)
	Zhang et al., 2009 (101)	EDN+ADN	Normoalb ≥15 years of diabetes	578			599	Case–control	USA	1	1.02 (0.78–1.33)
HP											
Hp 1/2	Awadallah et al., 2008 (102)	EDN	Normoalb	37			89	Case–control	Jordan	2	1.47 (0.82–2.62)
	Bessa et al., 2007 (103)	EDN	Normoalb	20			20	Case–control	Egypt	2	0.24 (0.09–0.63)
	Conway et al., 2007 (104)	EDN+Ret	Normoalb ≥15 years (without anti-hypertensiva)	224			285	Case–control	Ireland	1	0.74 (0.57–0.96)
	Costacou et al., 2009 (105)	EDN	Normoalb	62			163	Case–control	USA	1	0.89 (0.58–1.38)
	Moczulski et al., 2001 (106)	EDN+ADN	Normoalb ≥15 years of diabetes	312			290	Case–control	USA	1	1.00 (0.80–1.26)
	Nakhoul et al., 2001 (107)	EDN	Normoalb	5			43	Case–control	Israel	1	0.11 (0.01–0.92)
		EDN	Normoalb	10			38	Case–control	Israel	2	0.31 (0.07–1.46)
	Wobeto et al., 2009 (108)	EDN	Normoalb	48			128	Case–control	Brazil	1, 2	0.96 (0.60–1.55)
PVT 1											
rs11993333	Hanson et al., 2007 (109)	ADN	Normoalb (>10 years of diabetes)	102			103	Case–control	USA (Pima Indians)	2	0.48 (0.31–0.74)
	Millis et al., 2007 (110)	EDN+ADN	Normoalb ≥15 years of diabetes	526			558	Case–control	USA	1	0.82 (0.69–0.97)
CPVL/CHN2											
rs39059	Pezzolezi et al., 2009 (97)	EDN+ADN	Normoalb ≥15 years (without anti-hypertensiva)	379 [g]			413 [g]	Case–control	USA	1	0.70 (0.57–0.87)
		EDN+ADN	Normoalb ≥15 years (without anti-hypertensiva)	441 [h]			472 [h]	Case–control	USA	1	0.77 (0.64–0.93)
rs39075	Pezzolezi et al., 2009 (97)	EDN+ADN	Normoalb ≥15 years (without anti-hypertensiva)	379 [g]			413 [g]	Case–control	USA	1	1.18 (0.93–1.50)

Variants	Article	Definitions		Cases of DN or controls (*n*)				Study details			OR[a]
		Cases	Controls	Total	EDN[b]	ADN[c]	Controls	Design	Country	TD	Allele level
		EDN+ADN	Normoalb ≥15 years (without anti-hypertensiva)	441 [h]			472 [h]	Case–control	USA	1	0.75 (0.63–0.90)
		EDN+ADN	Normo-/microalb (diabetes 16–22 years)	132			1172	Follow-up	USA	1	0.68 (0.55–0.84)
AGT											
rs699	Ahluwalia et al., 2009 (1)	EDN+ADN	Normoalb ≥10 years of diabetes	240			255	Case–control	India	2	2.44 (1.89–3.16)
	Chowdhury et al., 1996 (5)	EDN+Ret	Normo-/microalb ≥20 years of diabetes	242			139	Case–control	UK	1	0.76 (0.38–1.51)
	Doria et al., 1996 (111)	EDN	Normoalb ≥15 years of diabetes	100			100	Case–control	USA	1	0.66 (0.31–1.38)
	Fogarty et al., 1996 (112)	EDN	Normoalb >20 years diabetes (without anti-hypertensiva)	95			100	Case–control	Ireland	1	0.81 (0.66–0.99)
	Fradin et al., 2002 (8)	EDN	Normoalb	39			118	Case–control	France	2	1.08 (0.82–1.41)
	Freire et al., 1998 (113)	EDN	Normoalb; 10 years of diabetes	115			118	Case–control	USA	2	0.86 (0.49–1.50)
	Guitterez et al., 1997 (11)	EDN	Normoalb	20			100	Case–control	Spain	2	1.04 (0.84–1.28)
	Marre et al., 1997 (17)	EDN+ADN	Normoalb	233	126	107	157	Case–control	France	1	2.71 (0.88–8.36)
	Miura et al., 1999 (18)	EDN	Normoalb >10 years of diabetes	32			103	Case–control	Japan	1	1.24 (0.92–1.69)
	Mollsten et al., 2008 (19)	EDN+ADN	Normoalb ≥20 years	48			197	Case–control	Sweden	1	1.37 (0.92–2.05)
	Ohno et al., 1996 (24)	EDN	Normoalb	25			53	Case–control	Japan	2	1.21 (0.80–1.83)
	Osawa et al., 2007 (114)	EDN+ADN	Normoalb+Ret	735			551	Case–control	Japan	2	1.05 (0.63–1.77)
	Prasad et al., 2006 (27)	ADN+Ret	Normoalb ≥10 years of diabetes	196			225	Case–control	India	2	1.20 (0.83–1.75)
	Tarnow et al., 1996 (115)	EDN	Normoalb >15 years of diabetes	195			185	Case–control	Denmark	1	1.15 (0.86–1.53)
	Thomas et al., 2001 (33)	EDN	Normoalb	51			255	Case–control	China (Han)	2	0.69 (0.44–1.10)
	Tregouet et al., 2008 (77)	EDN+ADN	Normoalb ≥5 years of diabetes (without anti-hypertensiva)	489			463	Case–control	Denmark	1	1.06 (0.88–1.27)

Variants	Article	Definitions		Cases of DN or controls (*n*)				Study details			OR[a]
		Cases	Controls	Total	EDN[b]	ADN[c]	Controls	Design	Country	TD	Allele level
		EDN+ADN	Normoalb ≥5 years of diabetes (without anti-hypertensiva)	387			391	Case–control	France	1	0.87 (0.72–1.06)
		EDN+ADN	Normoalb ≥5 years of diabetes (without anti-hypertensiva)	300			469	Case–control	Finland	1	1.22 (0.99–1.51)
	van Ittersum et al., 2000 (35)	EDN	Normoalb	30			188	Case–control	Netherlands	1	0.98 (0.73–1.32)
	Young et al., 1998 (41)	EDN	Normoalb	20			54	Case–control	China (Han)	2	1.61 (0.93–2.79)
	Zychma et al., 2000 (116)	EDN+ADN	Normoalb ≥10 years of diabetes	127			243	Case–control	Poland	2	0.90 (0.67–1.22)
AGTR1											
rs5186	Ahluwalia et al., 2009 (1)	EDN+ADN	Normoalb ≥10 years of diabetes	240			255	Case–control	India	2	0.68 (0.51–0.89)
	Chistyakov et al., 1999 (117)	EDN	Normo-/microalb ≥20 years of diabetes and no macroalbuminuria	27			41	Case–control	Russia	1	0.82 (0.38–1.76)
	Chowdhury et al., 1997 (118)	EDN+Ret	Normo-/microalb ≥20 years of diabetes	264			136	Case–control	UK	1	0.88 (0.64–1.22)
	Fradin et al., 2002 (8)	EDN	Normoalb	39			118	Case–control	France	2	1.78 (0.92–3.45)
	Mollsten et al., 2008 (19)	EDN+ADN	Normoalb ≥20 years of diabetes	48			197	Case–control	Sweden	1	1.14 (0.83–1.56)
	Marre et al., 1997 (17)	EDN+ADN	Normoalb	233	126	107	157	Case–control	France	1	1.55 (0.89–2.72)
	Osawa et al., 2007 (114)	EDN+ADN	Normoalb+Ret	735			551	Case–control	Japan	2	0.87 (0.65–1.16)
	Savage et al., 1999 (119)	EDN	Normoalb >20 years of diabetes	95			97	Case–control	UK	1	1.05 (0.67–1.63)
	Tarnow et al., 1996 (120)	EDN	Normoalb >15 years of diabetes	198			190	Case–control	Denmark	1	0.98 (0.72–1.34)
	Thomas et al., 2001 (33)	EDN	Normoalb	51			255	Case–control	China (Han)	2	1.02 (0.74–1.40)
	van Ittersum et al., 2000 (35)	EDN	Normoalb	30			188	Case–control	Nether-lands	1	1.84 (0.55–6.20)
	Vionnet et al., 2006 (121)	EDN+Ret	Normoalb ≥15 years of diabetes	390			385	Case–control	Den-mark	1	2.10 (1.10–4.01)
		EDN+Ret	Normoalb ≥15 years of diabetes	387			469	Case–control	Finland	1	1.06 (0.85–1.32)

Variants	Article	Definitions		Cases of DN or controls (*n*)				Study details			OR[a]
		Cases	Controls	Total	EDN[b]	ADN[c]	Controls	Design	Country	TD	Allele level
		EDN+Ret	Normoalb ≥15 years of diabetes	280			273	Case–control	France	1	0.85 (0.67–1.09)
	Young et al., 1998 (41)	EDN	Normoalb	20			54	Case–control	China (Han)	2	1.09 (0.84–1.42)
NOS3											
rs2070744	Ahluwalia et al., 2008 (122)	EDN	Normoalb ≥10 years (without anti-hypertensiva)	195			255	Case–control	India	2	1.27 (0.91–1.76)
	Zanchi et al., 2000 (123)	EDN+ADN	Normoalb ≥15 years of diabetes	152	74	78	195	Case–control	USA	1	1.57 (1.08–2.29)
rs3138808	Ahluwalia et al., 2008 (122)	EDN	Normoalb ≥10 years (without antihypertensiva)	195			255	Case–control	India	2	1.35 (0.94–1.94)
	Fujita et al., 2000 (124)	EDN	Normoalb	65			102	Case–control	Japan	2	0.73 (0.33–1.60)
	Neugebauer et al., 2000 (125)	EDN	Normoalb >5 years of diabetes	39			82	Case–control	Japan	2	3.02 (1.34–6.81)
	Rippin et al., 2003 (126)	EDN	Normoalb ≥50 years of diabetes	464			396	Case–control	UK	1	1.05 (0.80–1.38)
	Shestakova et al., 2006 (28)	EDN	Normoalb >20 years of diabetes	63			66	Case–control	Russia	1	1.97 (1.16–3.36)
	Shimizu et al., 2002 (127)	EDN+ADN	Normoalb ≥10 years of diabetes	230	107	123	203	Case–control	Japan	2	0.99 (0.66–1.48)
	Taniwaki et al., 2001 (31)	EDN+ADN	Normoalb	42	22	20	69	Case–control	Japan	2	0.94 (0.43–2.10)
	Zanchi et al., 2000 (123)	EDN+ADN	Normoalb ≥15 years of diabetes	152	74	78	195	Case–control	USA	1	1.69 (1.14–2.51)
PPARG											
rs1801282	Caramori et al., 2003 (128)	EDN	Normoalb ≥10 years diabetes	104			212	Case–control	Brazil	2	0.50 (0.26–0.97)
	Hermann et al., 2002 (129)	EDN+ADN	Normoalb (without complications)	241	197	44	203	Case–control	Germany	2	0.83 (0.57–1.21)
	Liu et al., 2010 (130)	EDN	Normoalb ≥10 years of diabetes (without antihypertensiva)	532			228	Case–control	Shanghai (China/Han)	2	1.16 (0.90–1.51)

Variants	Article	Definitions		Cases of DN or controls (*n*)				Study details			OR[a]
		Cases	Controls	Total	EDN[b]	ADN[c]	Controls	Design	Country	TD	Allele level
	Jorsal et al., 2008 (131)	EDN	Normoalb ≥15 years diabetes (geen antihypertensiva)	415			428	Case–control	Denmark	1	0.43 (0.30–0.63)
	Tregouet et al., 2008 (77)	EDN+ADN	Normoalb ≥5 years of diabetes	489			463	Case–control	Denmark	1	1.20 (0.94–1.54)
		EDN+ADN	Normoalb ≥5 years of diabetes	387			391	Case–control	France	1	0.97 (0.76–1.24)
		EDN+ADN	Normoalb ≥5 years of diabetes	300			469	Case–control	Finland	1	0.87 (0.61–1.25)
UNC13B											
rs13293564	Tregouet et al., 2008 (77)	EDN+ADN	Normoalb ≥5 years of diabetes (without anti-hypertensiva)	484	445	39	459	Case–control	Denmark	1	1.27 (1.05–1.53)
		EDN+ADN	Normoalb ≥5 years of diabetes (without anti-hypertensiva)	290	226	64	370	Case–control	France	1	1.05 (0.84–1.31)
		EDN+ADN	Normoalb ≥5 years of diabetes (without anti-hypertensiva)	386	264	122	467	Case–control	Finland	1	1.30 (1.07–1.58)
		EDN+ADN	Normoalb	412	269	143	314		Finland	1	1.25 (1.04–1.49)
No gene											
rs1041466	Pezzolezi et al., 2009 (97)	EDN+ADN	Normoalb ≥15 years of diabetes	379 [g]			413 [g]	Case–control	USA	1	1.22 (0.52–2.86)
		EDN+ADN	Normoalb ≥15 years of diabetes	441 [h]			472 [h]	Case–control	USA	1	1.38 (1.15–1.66)
		EDN+ADN	Normo-/microalb (diabetes 16–22 years)	132			1172	Follow-up	USA	1	1.39 (1.14–1.69)
rs1411766	Pezzolezi et al., 2009 (97)	EDN+ADN	Normoalb ≥15 years of diabetes	379 [g]			413 [g]	Case–control	USA	1	0.85 (0.66–1.10)
		EDN+ADN	Normoalb ≥15 years of diabetes	441 [h]			472 [h]	Case–control	USA	1	0.69 (0.57–0.83)
		EDN+ADN	Normo-/microalb (diabetes 16–22 years)	132			1172	Follow-up	USA	1	0.75 (0.62–0.91)

Variants	Article	Definitions		Cases of DN or controls (*n*)				Study details			OR[a]
		Cases	Controls	Total	EDN[b]	ADN[c]	Controls	Design	Country	TD	Allele level
rs79899848	Pezzolezi et al., 2009 (97)	EDN+ADN	Normoalb ≥15 years	379 [g]			413 [g]	Case–control	USA	1	0.93 (0.72–1.20)
		EDN+ADN	Normoalb ≥15 years of diabetes	441 [h]			472 [h]	Case–control	USA	1	1.33 (1.10–1.61)
		EDN+ADN	Normo-/microalb (diabetes 16–22 years)	132			1172	Follow-up	USA	1	1.32 (1.08–1.61)
rs9521445	Pezzolezi et al., 2009 (97)	EDN+ADN	Normoalb ≥15 years of diabetes	379 [g]			413 [g]	Case–control	USA	1	1.32 (1.09–1.61)
		EDN+ADN	Normoalb ≥15 years of diabetes	441 [h]			472 [h]	Case–control	USA	1	1.38 (1.14–1.65)
rs6492208	Pezzolezi et al., 2009 (97)	EDN+ADN	Normoalb ≥15 years of diabetes	379 [g]			413 [g]	Case–control	USA	1	0.90 (0.70–1.16)
		EDN+ADN	Normoalb ≥15 years of diabetes	441 [h]			472 [h]	Case–control	USA	1	1.33 (1.10–1.61)
		EDN+ADN	Normo-/microalb (diabetes 16–22 years)	132			1172	Follow-up	USA	1	1.32 (1.08–1.61)

* Vleming 1999 and Vleming 1998 are considered as one dataset, as they use the same control group

** Mooyaart 2010 and Janssen 2005 are considered as one dataset, as they use the same control group

[a]OR (95% CI)

[b]EDN, established diabetic nephropathy; [c]ADN, advanced diabetic nephropathy; [d]Normoalb, normoalbuminuria; [e]microalb, microalbuminuia; [f]Ret, retinopathy; [g]GWU, George Washington University; [h]JDC, Joslin Diabetes Center

DN, diabetic nephropathy; TD, type of diabetes

Reference List

1. Ahluwalia TS, Ahuja M, Rai TS, et al (2009) ACE Variants Interact with the RAS Pathway to Confer Risk and Protection against Type 2 Diabetic Nephropathy. DNA Cell Biol. 28: 141-150
2. Araz M, Yilmaz N, Gungor K, Okan V, Kepekci Y, Sukru AA (2001) Angiotensin-converting enzyme gene polymorphism and microvascular complications in Turkish type 2 diabetic patients. Diabetes Res.Clin.Pract. 54: 95-104
3. Arfa I, Abid A, Nouira S, et al (2008) Lack of association between the angiotensin-converting enzyme gene (I/D) polymorphism and diabetic nephropathy in Tunisian type 2 diabetic patients. J.Renin.Angiotensin.Aldosterone.Syst. 9: 32-36
4. Canani LH, Costa LA, Crispim D, et al (2005) The presence of allele D of angiotensin-converting enzyme polymorphism is associated with diabetic nephropathy in patients with less than 10 years duration of Type 2 diabetes. Diabet.Med. 22: 1167-1172
5. Chowdhury TA, Dronsfield MJ, Kumar S, et al (1996) Examination of two genetic polymorphisms within the renin-angiotensin system: no evidence for an association with nephropathy in IDDM. Diabetologia 39: 1108-1114
6. Demurov LM, Chistyakov DA, Chugunova LA, et al (1997) Insertion/deletion polymorphism of the angiotensin-converting enzyme gene in normalcy and among diabetics with vascular complications. Molecular Biology 31: 49-52
7. Doi Y, Yoshizumi H, Yoshinari M, et al (1996) Association between a polymorphism in the angiotensin-converting enzyme gene and microvascular complications in Japanese patients with NIDDM. Diabetologia 39: 97-102
8. Fradin S, Goulet-Salmon B, Chantepie M, et al (2002) Relationship between polymorphisms in the renin-angiotensin system and nephropathy in type 2 diabetic patients. Diabetes Metab 28: 27-32
9. Gohda T, Makita Y, Shike T, et al (2001) Association of the DD genotype and development of Japanese type 2 diabetic nephropathy. Clin.Nephrol. 56: 475-480
10. Grzeszczak W, Zychma MJ, Lacka B, Zukowska-Szczechowska E (1998) Angiotensin I-converting enzyme gene polymorphisms: relationship to nephropathy in patients with non-insulin dependent diabetes mellitus. J.Am.Soc.Nephrol. 9: 1664-1669
11. Gutierrez C, Vendrell J, Pastor R, et al (1997) Angiotensin I-converting enzyme and angiotensinogen gene polymorphisms in non-insulin-dependent diabetes mellitus. Lack of relationship with diabetic nephropathy and retinopathy in a Caucasian Mediterranean population. Metabolism 46: 976-980
12. Ha SK, Park HC, Park HS, et al (2003) ACE gene polymorphism and progression of diabetic nephropathy in Korean type 2 diabetic patients: effect of ACE gene DD on the progression of diabetic nephropathy. Am.J.Kidney Dis. 41: 943-949

13. Hadjadj S, Belloum R, Bouhanick B, et al (2001) Prognostic value of angiotensin-I converting enzyme I/D polymorphism for nephropathy in type 1 diabetes mellitus: a prospective study. J.Am. Soc.Nephrol. 12: 541-549
14. Hadjadj S, Tarnow L, Forsblom C, et al (2007) Association between angiotensin-converting enzyme gene polymorphisms and diabetic nephropathy: case-control, haplotype, and family-based study in three European populations. J.Am.Soc.Nephrol. 18: 1284-1291
15. Hibberd ML, Millward BA, Demaine AG (1997) The angiotensin I-converting enzyme (ACE) locus is strongly associated with age and duration of diabetes in patients with type I diabetes. J.Diabetes Complications 11: 2-8
16. Kimura H, Gejyo F, Suzuki Y, Suzuki S, Miyazaki R, Arakawa M (1998) Polymorphisms of angiotensin converting enzyme and plasminogen activator inhibitor-1 genes in diabetes and macroangiopathy1. Kidney Int. 54: 1659-1669
17. Marre M, Jeunemaitre X, Gallois Y, et al (1997) Contribution of genetic polymorphism in the renin-angiotensin system to the development of renal complications in insulin-dependent diabetes: Genetique de la Nephropathie Diabetique (GENEDIAB) study group. J.Clin.Invest 99: 1585-1595
18. Miura J, Uchigata Y, Yokoyama H, Omori Y, Iwamoto Y (1999) Genetic polymorphism of renin-angiotensin system is not associated with diabetic vascular complications in Japanese subjects with long-term insulin dependent diabetes mellitus. Diabetes Res.Clin.Pract. 45: 41-49
19. Mollsten A, Kockum I, Svensson M, et al (2008) The effect of polymorphisms in the renin-angiotensin-aldosterone system on diabetic nephropathy risk. J.Diabetes Complications 22: 377-383
20. Nakajima S, Baba T, Yajima Y (1996) Is ACE gene polymorphism a useful marker for diabetic albuminuria in Japanese NIDDM patients? Diabetes Care 19: 1420-1422
21. Naresh VVS, Reddy ALK, Sivaramakrishna G, Sharma PVGK, Vardhan RV, Siva K, V (2009) Angiotensin converting enzyme gene polymorphism in type II diabetics with nephropathy. Indian Journal of Nephrology 19: 145-148
22. Ng DP, Placha G, Choo S, Chia KS, Warram JH, Krolewski AS (2006) A disease haplotype for advanced nephropathy in type 2 diabetes at the ACE locus. Diabetes 55: 2660-2663
23. Nikzamir A, Esteghamati A, Feghhi M, Nakhjavani M, Rashidi A, Reza JZ (2009) The insertion/deletion polymorphism of the angiotensin-converting enzyme gene is associated with progression, but not development, of albuminuria in Iranian patients with type 2 diabetes. J.Renin.Angiotensin. Aldosterone.Syst. 10: 109-114
24. Ohno T, Kawazu S, Tomono S (1996) Association analyses of the polymorphisms of angiotensin-converting enzyme and angiotensinogen genes with diabetic nephropathy in Japanese non-insulin-dependent diabetics. Metabolism 45: 218-222

25. Ortega-Pierres LE, Gomez GA, Rodriguez-Ayala E, et al (2007) [Angiotensin-1 converting enzyme insertion/deletion gene polymorphism in a Mexican population with diabetic nephropathy]. Med. Clin.(Barc.) 129: 6-10
26. Park HC, Choi SR, Kim BS, et al (2005) Polymorphism of the ACE Gene in dialysis patients: overexpression of DD genotype in type 2 diabetic end-stage renal failure patients. Yonsei Med.J. 46: 779-787
27. Prasad P, Tiwari AK, Kumar KM, et al (2006) Chronic renal insufficiency among Asian Indians with type 2 diabetes: I. Role of RAAS gene polymorphisms. BMC.Med.Genet. 7: 42
28. Shestakova MV, Vikulova OK, Gorashko NM, et al (2006) The relationship between genetic and haemodynamic factors in diabetic nephropathy (DN): Case-control study in type 1 diabetes mellitus (T1DM). Diabetes Research and Clinical Practice 74: S41-S50
29. Shin SY, Baek SH, Chang KY, et al (2004) Relations between eNOS Glu298Asp polymorphism and progression of diabetic nephropathy. Diabetes Res.Clin.Pract. 65: 257-265
30. So WY, Ma RC, Ozaki R, et al (2006) Angiotensin-converting enzyme (ACE) inhibition in type 2, diabetic patients-- interaction with ACE insertion/deletion polymorphism. Kidney Int. 69: 1438-1443
31. Taniwaki H, Ishimura E, Matsumoto N, Emoto M, Inaba M, Nishizawa Y (2001) Relations between ACE gene and ecNOS gene polymorphisms and resistive index in type 2 diabetic patients with nephropathy. Diabetes Care 24: 1653-1660
32. Tarnow L, Cambien F, Rossing P, et al (1995) Lack of relationship between an insertion/deletion polymorphism in the angiotensin I-converting enzyme gene and diabetic nephropathy and proliferative retinopathy in IDDM patients. Diabetes 44: 489-494
33. Thomas GN, Critchley JA, Tomlinson B, et al (2001) Albuminuria and the renin-angiotensin system gene polymorphisms in type-2-diabetic and in normoglycemic hypertensive Chinese. Clin.Nephrol. 55: 7-15
34. Tomino Y, Makita Y, Shike T, et al (1999) Relationship between polymorphism in the angiotensinogen, angiotensin-converting enzyme or angiotensin II receptor and renal progression in Japanese NIDDM patients. Nephron 82: 139-144
35. van Ittersum FJ, de Man AM, Thijssen S, et al (2000) Genetic polymorphisms of the renin-angiotensin system and complications of insulin-dependent diabetes mellitus. Nephrol.Dial.Transplant. 15: 1000-1007
36. Viswanathan V, Zhu Y, Bala K, et al (2001) Association between ACE gene polymorphism and diabetic nephropathy in South Indian patients. JOP. 2: 83-87
37. Vleming LJ, van Kooten C, van Dijk M, et al (1998) The D-allele of the ACE gene polymorphism predicts a stronger antiproteinuric response to ACE inhibitors. Nephrology 4: 143-149

38. Vleming LJ, van der Pijl JW, Lemkes HH, et al (1999) The DD genotype of the ACE gene polymorphism is associated with progression of diabetic nephropathy to end stage renal failure in IDDM. Clin. Nephrol. 51: 133-140
39. Wu S, Xiang K, Zheng T, et al (2000) Relationship between the renin-angiotensin system genes and diabetic nephropathy in the Chinese. Chin Med.J.(Engl.) 113: 437-441
40. Yoshida H, Kuriyama S, Atsumi Y, et al (1996) Angiotensin I converting enzyme gene polymorphism in non-insulin dependent diabetes mellitus. Kidney Int. 50: 657-664
41. Young RP, Chan JC, Critchley JA, Poon E, Nicholls G, Cockram CS (1998) Angiotensinogen T235 and ACE insertion/deletion polymorphisms associated with albuminuria in Chinese type 2 diabetic patients. Diabetes Care 21: 431-437
42. Fanelli A, Hadjadj S, Gallois Y, et al (2002) [Polymorphism of aldose reductase gene and susceptibility to retinopathy and nephropathy in Caucasians with type 1 diabetes]. Arch.Mal Coeur Vaiss. 95: 701-708
43. Gosek K, Moczulski D, Zukowska-Szczechowska E, Grzeszczak W (2005) C-106T polymorphism in promoter of aldose reductase gene is a risk factor for diabetic nephropathy in type 2 diabetes patients with poor glycaemic control. Nephron Exp.Nephrol. 99: e63-e67
44. Moczulski DK, Scott L, Antonellis A, et al (2000) Aldose reductase gene polymorphisms and susceptibility to diabetic nephropathy in Type 1 diabetes mellitus. Diabet.Med. 17: 111-118
45. Neamat-Allah M, Feeney SA, Savage DA, et al (2001) Analysis of the association between diabetic nephropathy and polymorphisms in the aldose reductase gene in Type 1 and Type 2 diabetes mellitus. Diabet.Med. 18: 906-914
46. Sivenius K, Niskanen L, Voutilainen-Kaunisto R, Laakso M, Uusitupa M (2004) Aldose reductase gene polymorphisms and susceptibility to microvascular complications in Type 2 diabetes. Diabet. Med. 21: 1325-1333
47. So WY, Wang Y, Ng MC, et al (2008) Aldose reductase genotypes and cardiorenal complications: an 8-year prospective analysis of 1,074 type 2 diabetic patients. Diabetes Care 31: 2148-2153
48. Chistyakov DA, Turakulov RI, Gorashko NM, et al (1997) Polymorphism of a dinucleotide repeat within the aldose reductase gene in normalcy and insulin-dependent diabetes with vascular complications. Molecular Biology 31: 660-664
49. Dyer PH, Chowdhury TA, Dronsfield MJ, Dunger D, Barnett AH, Bain SC (1999) The 5'-end polymorphism of the aldose reductase gene is not associated with diabetic nephropathy in Caucasian type I diabetic patients. Diabetologia 42: 1030-1031
50. Heesom AE, Hibberd ML, Millward A, Demaine AG (1997) Polymorphism in the 5'-end of the aldose reductase gene is strongly associated with the development of diabetic nephropathy in type I diabetes. Diabetes 46: 287-291

51. Ichikawa F, Yamada K, Ishiyama-Shigemoto S, Yuan X, Nonaka K (1999) Association of an (A-C) n dinucleotide repeat polymorphic marker at the 5'-region of the aldose reductase gene with retinopathy but not with nephropathy or neuropathy in Japanese patients with Type 2 diabetes mellitus. Diabet.Med. 16: 744-748
52. Lajer M, Tarnow L, Fleckner J, et al (2004) Association of aldose reductase gene Z+2 polymorphism with reduced susceptibility to diabetic nephropathy in Caucasian Type 1 diabetic patients. Diabet. Med. 21: 867-873
53. Liu YF, Wat NM, Chung SS, Ko BC, Lam KS (2002) Diabetic nephropathy is associated with the 5'-end dinucleotide repeat polymorphism of the aldose reductase gene in Chinese subjects with Type 2 diabetes. Diabet.Med. 19: 113-118
54. Maeda S, Haneda M, Yasuda H, et al (1999) Diabetic nephropathy is not associated with the dinucleotide repeat polymorphism upstream of the aldose reductase (ALR2) gene but with erythrocyte aldose reductase content in Japanese subjects with type 2 diabetes. Diabetes 48: 420-422
55. Moczulski DK, Burak W, Doria A, et al (1999) The role of aldose reductase gene in the susceptibility to diabetic nephropathy in Type II (non-insulin-dependent) diabetes mellitus. Diabetologia 42: 94-97
56. Ng DP, Conn J, Chung SS, Larkins RG (2001) Aldose reductase (AC)(n) microsatellite polymorphism and diabetic microvascular complications in Caucasian Type 1 diabetes mellitus. Diabetes Res.Clin. Pract. 52: 21-27
57. Park HK, Ahn CW, Lee GT, et al (2002) (AC)(n) polymorphism of aldose reductase gene and diabetic microvascular complications in type 2 diabetes mellitus. Diabetes Res.Clin.Pract. 55: 151-157
58. Yamamoto T, Sato T, Hosoi M, et al (2003) Aldose reductase gene polymorphism is associated with progression of diabetic nephropathy in Japanese patients with type 1 diabetes mellitus. Diabetes Obes.Metab 5: 51-57
59. Zhao HL, Tong PC, Lai FM, Tomlinson B, Chan JC (2004) Association of glomerulopathy with the 5'-end polymorphism of the aldose reductase gene and renal insufficiency in type 2 diabetic patients. Diabetes 53: 2984-2991
60. McKnight AJ, Maxwell AP, Fogarty DG, Sadlier D, Savage DA (2009) Genetic analysis of coronary artery disease single-nucleotide polymorphisms in diabetic nephropathy. Nephrol.Dial.Transplant. 24: 2473-2476
61. Araki S, Moczulski DK, Hanna L, Scott LJ, Warram JH, Krolewski AS (2000) APOE polymorphisms and the development of diabetic nephropathy in type 1 diabetes: results of case-control and family-based studies. Diabetes 49: 2190-2195

62. Chowdhury TA, Dyer PH, Kumar S, et al (1998) Association of apolipoprotein epsilon2 allele with diabetic nephropathy in Caucasian subjects with IDDM. Diabetes 47: 278-280
63. Eto M, Horita K, Morikawa A, et al (1995) Increased frequency of apolipoprotein epsilon 2 allele in non-insulin dependent diabetic (NIDDM) patients with nephropathy. Clin.Genet. 48: 288-292
64. Ha SK, Park HS, Kim KW, et al (1999) Association between apolipoprotein E polymorphism and macroalbuminuria in patients with non-insulin dependent diabetes mellitus. Nephrol.Dial. Transplant. 14: 2144-2149
65. Hadjadj S, Gallois Y, Simard G, et al (2000) Lack of relationship in long-term type 1 diabetic patients between diabetic nephropathy and polymorphisms in apolipoprotein epsilon, lipoprotein lipase and cholesteryl ester transfer protein. Genetique de la Nephropathie Diabetique Study Group. Donnees Epidemiologiques sur le Syndrome d'Insulino-Resistance Study Group. Nephrol.Dial.Transplant. 15: 1971-1976
66. Horita K, Eto M, Makino I (1994) Apolipoprotein E2, renal failure and lipid abnormalities in non-insulin-dependent diabetes mellitus. Atherosclerosis 107: 203-211
67. Kimura H, Suzuki Y, Gejyo F, et al (1998) Apolipoprotein E4 reduces risk of diabetic nephropathy in patients with NIDDM. Am.J.Kidney Dis. 31: 666-673
68. Leiva E, Mujica V, Elematore I, et al (2007) Relationship between Apolipoprotein E polymorphism and nephropathy in type-2 diabetic patients. Diabetes Res.Clin.Pract. 78: 196-201
69. Onuma T, Laffel LM, Angelico MC, Krolewski AS (1996) Apolipoprotein E genotypes and risk of diabetic nephropathy. J.Am.Soc.Nephrol. 7: 1075-1078
70. Tarnow L, Stehouwer CD, Emeis JJ, et al (2000) Plasminogen activator inhibitor-1 and apolipoprotein E gene polymorphisms and diabetic angiopathy. Nephrol.Dial.Transplant. 15: 625-630
71. Yakunina NY, Shestakova MV, Voron'ko OE, et al (2005) Polymorphic gene markers of lipid metabolism are associated with diabetic nephropathy in patients with type 1 diabetes mellitus. Russian Journal of Genetics 41: 760-765
72. Ahluwalia TS, Khullar M, Ahuja M, et al (2009) Common variants of inflammatory cytokine genes are associated with risk of nephropathy in type 2 diabetes among Asian Indians. PLoS ONE 4:
73. Mlynarski WM, Placha GP, Wolkow PP, Bochenski JP, Warram JH, Krolewski AS (2005) Risk of diabetic nephropathy in type 1 diabetes is associated with functional polymorphisms in RANTES receptor gene (CCR5): a sex-specific effect. Diabetes 54: 3331-3335
74. Nakajima K, Tanaka Y, Nomiyama T, et al (2003) RANTES promoter genotype is associated with diabetic nephropathy in type 2 diabetic subjects. Diabetes Care 26: 892-898
75. Pettigrew KA, McKnight AJ, Patterson CC, Kilner J, Sadlier DM, Maxwell AP (2010) Resequencing of the CCL5 and CCR5 genes and investigation of variants for association with diabetic nephropathy. J Hum.Genet.

76. Prasad P, Tiwari AK, Kumar KM, et al (2007) Association of TGFbeta1, TNFalpha, CCR2 and CCR5 gene polymorphisms in type-2 diabetes and renal insufficiency among Asian Indians. BMC.Med. Genet. 8: 20
77. Tregouet DA, Groop PH, McGinn S, et al (2008) G/T substitution in intron 1 of the UNC13B gene is associated with increased risk of nephropathy in patients with type 1 diabetes. Diabetes 57: 2843-2850
78. Freedman BI, Hicks PJ, Sale MM, et al (2007) A leucine repeat in the carnosinase gene CNDP1 is associated with diabetic end-stage renal disease in European Americans. Nephrol.Dial.Transplant. 22: 1131-1135
79. Janssen B, Hohenadel D, Brinkkoetter P, et al (2005) Carnosine as a protective factor in diabetic nephropathy: association with a leucine repeat of the carnosinase gene CNDP1. Diabetes 54: 2320-2327
80. Mooyaart AL, Zutinic A, Bakker SJ, et al (2010) Association between CNDP1 genotype and diabetic nephropathy is sex-specific. Diabetes
81. Wanic K, Placha G, Dunn J, Smiles A, Warram JH, Krolewski AS (2008) Exclusion of polymorphisms in carnosinase genes (CNDP1 and CNDP2) as a cause of diabetic nephropathy in type 1 diabetes: results of large case-control and follow-up studies. Diabetes 57: 2547-2551
82. Shimazaki A, Kawamura Y, Kanazawa A, et al (2005) Genetic variations in the gene encoding ELMO1 are associated with susceptibility to diabetic nephropathy. Diabetes 54: 1171-1178
83. Pezzolesi MG, Katavetin P, Kure M, et al (2009) Confirmation of Genetic Associations at ELMO1 in the GoKinD Collection Support its Role as a Susceptibility Gene in Diabetic Nephropathy. Diabetes
84. Tong Z, Yang Z, Patel S, et al (2008) Promoter polymorphism of the erythropoietin gene in severe diabetic eye and kidney complications. Proc.Natl.Acad.Sci.U.S.A 105: 6998-7003
85. Grzeszczak W, Moczulski DK, Zychma M, Zukowska-Szczechowska E, Trautsolt W, Szydlowska I (2001) Role of GLUT1 gene in susceptibility to diabetic nephropathy in type 2 diabetes. Kidney Int. 59: 631-636
86. Gutierrez C, Vendrell J, Pastor R, et al (1998) GLUT1 gene polymorphism in non-insulin-dependent diabetes mellitus: genetic susceptibility relationship with cardiovascular risk factors and microangiopathic complications in a Mediterranean population. Diabetes Res.Clin.Pract. 41: 113-120
87. Hodgkinson AD, Page T, Millward BA, Demaine AG (2005) A novel polymorphism in the 5′ flanking region of the glucose transporter (GLUT1) gene is strongly associated with diabetic nephropathy in patients with Type 1 diabetes mellitus. J.Diabetes Complications 19: 65-69
88. Liu ZH, Guan TJ, Chen ZH, Li LS (1999) Glucose transporter (GLUT1) allele (XbaI-) associated with nephropathy in non-insulin-dependent diabetes mellitus. Kidney Int. 55: 1843-1848

89. Makni K, Jarraya F, Rebai M, et al (2008) Risk genotypes and haplotypes of the GLUT1 gene for type 2 diabetic nephropathy in the Tunisian population. Ann.Hum.Biol. 35: 490-498
90. Ng DP, Canani L, Araki S, et al (2002) Minor effect of GLUT1 polymorphisms on susceptibility to diabetic nephropathy in type 1 diabetes. Diabetes 51: 2264-2269
91. Tarnow L, Grarup N, Hansen T, Parving HH, Pedersen O (2001) Diabetic microvascular complications are not associated with two polymorphisms in the GLUT-1 and PC-1 genes regulating glucose metabolism in Caucasian type 1 diabetic patients. Nephrol.Dial.Transplant. 16: 1653-1656
92. McKnight AJ, Patterson CC, Pettigrew KA, et al (2010) A GREM1 Gene Variant Associates with Diabetic Nephropathy. J Am Soc Nephrol
93. Fujita H, Narita T, Meguro H, et al (1999) Lack of association between the heparan sulfate proteoglycan gene polymorphism and diabetic nephropathy in Japanese NIDDM with proliferative diabetic retinopathy. Ren Fail. 21: 659-664
94. Hansen PM, Chowdhury T, Deckert T, Hellgren A, Bain SC, Pociot F (1997) Genetic variation of the heparan sulfate proteoglycan gene (perlecan gene). Association with urinary albumin excretion in IDDM patients. Diabetes 46: 1658-1659
95. Liu L, Xiang K, Zheng T, et al (2003) The heparan sulfate proteoglycan gene polymorphism: association with type 2 diabetic nephropathy in Chinese. Mol.Cell Biochem. 245: 121-126
96. McKnight A-J, Maxwell AP, Patterson CC, Brady HR, Savage DA (2007) Association of VEGF-1499C[right arrow]T polymorphism with diabetic nephropathy in type 1 diabetes mellitus. Journal of Diabetes and its Complications 21: 242-245
97. Pezzolesi MG, Poznik GD, Mychaleckyj JC, et al (2009) Genome-wide association scan for diabetic nephropathy susceptibility genes in type 1 diabetes. Diabetes 58: 1403-1410
98. Maeda S, Kobayashi M, Araki S, et al (2010) A Single Nucleotide Polymorphism within the Acetyl-Coenzyme A Carboxylase Beta Gene Is Associated with Proteinuria in Patients with Type 2 Diabetes. Plos Genetics 6:
99. Jorsal A, Tarnow L, Frystyk J, et al (2008) Serum adiponectin predicts all-cause mortality and end stage renal disease in patients with type I diabetes and diabetic nephropathy. Kidney Int. 74: 649-654
100. Prior SL, Javid J, Gill GV, Bain SC, Stephens JW (2008) The adiponectin rs17300539 G>A variant and nephropathy risk. Kidney Int. 74: 1361
101. Zhang D, Ma J, Brismar K, Efendic S, Gu HF (2009) A single nucleotide polymorphism alters the sequence of SP1 binding site in the adiponectin promoter region and is associated with diabetic nephropathy among type 1 diabetic patients in the Genetics of Kidneys in Diabetes Study. J.Diabetes Complications 23: 265-272

102. Awadallah SM, Saleh SA, Abu Shaqra QM, Hilow H (2008) Association of haptoglobin phenotypes with markers of diabetic nephropathy in Type 2 diabetes mellitus. J.Diabetes Complications 22: 384-388
103. Bessa SS, Hamdy SM, Ali EM (2007) Haptoglobin gene polymorphism in type 2 diabetic patients with and without nephropathy: An Egyptian study. Eur.J.Intern.Med. 18: 489-495
104. Conway BR, Savage DA, Brady HR, Maxwell AP (2007) Association between haptoglobin gene variants and diabetic nephropathy: haptoglobin polymorphism in nephropathy susceptibility. Nephron Exp.Nephrol. 105: e75-e79
105. Costacou T, Ferrell RE, Ellis D, Orchard TJ (2009) Haptoglobin Genotype and Renal Function Decline in Type 1 Diabetes. Diabetes 58: 2904-2909
106. Moczulski DK, Rogus JJ, Krolewski AS, Levy AP (2001) -To: F.M. Nakhoul et al. (2001) Haptoglobin phenotype and diabetes. Diabetologia 44: 602-604 [1] (multiple letters). Diabetologia 44: 2237-2238
107. Nakhoul FM, Zoabi R, Kanter Y, et al (2001) Haptoglobin phenotype and diabetic nephropathy. Diabetologia 44: 602-604
108. Wobeto VP, Garcia PM, Zaccariotto TR, Sonati MF (2009) Haptoglobin polymorphism and diabetic nephropathy in Brazilian diabetic patients. Ann.Hum.Biol. 36: 437-441
109. Hanson RL, Craig DW, Millis MP, et al (2007) Identification of PVT1 as a candidate gene for end-stage renal disease in type 2 diabetes using a pooling-based genome-wide single nucleotide polymorphism association study. Diabetes 56: 975-983
110. Millis MP, Bowen D, Kingsley C, Watanabe RM, Wolford JK (2007) Variants in the plasmacytoma variant translocation gene (PVT1) are associated with end-stage renal disease attributed to type 1 diabetes. Diabetes 56: 3027-3032
111. Doria A, Onuma T, Gearin G, Freire MB, Warram JH, Krolewski AS (1996) Angiotensinogen polymorphism M235T, hypertension, and nephropathy in insulin-dependent diabetes. Hypertension 27: 1134-1139
112. Fogarty DG, Harron JC, Hughes AE, Nevin NC, Doherty CC, Maxwell AP (1996) A molecular variant of angiotensinogen is associated with diabetic nephropathy in IDDM. Diabetes 45: 1204-1208
113. Freire MB, Ji L, Onuma T, Orban T, Warram JH, Krolewski AS (1998) Gender-specific association of M235T polymorphism in angiotensinogen gene and diabetic nephropathy in NIDDM. Hypertension 31: 896-899
114. Osawa N, Koya D, Araki S, et al (2007) Combinational effect of genes for the renin-angiotensin system in conferring susceptibility to diabetic nephropathy. J.Hum.Genet. 52: 143-151

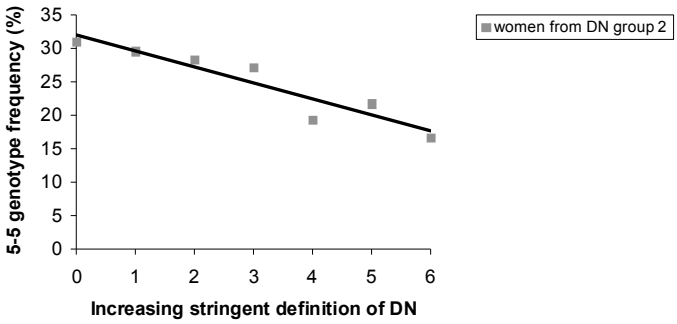
115. Tarnow L, Cambien F, Rossing P, et al (1996) Angiotensinogen gene polymorphisms in IDDM patients with diabetic nephropathy. Diabetes 45: 367-369
116. Zychma MJ, Zukowska-Szczechowska E, Lacka BI, Grzeszczak W (2000) Angiotensinogen M235T and chymase gene CMA/B polymorphisms are not associated with nephropathy in type II diabetes. Nephrol.Dial.Transplant. 15: 1965-1970
117. Chistyakov DA, Chugunova LA, Shamkhalova MS, et al (1999) Polymorphism of angiotensin II receptor gene and microangiopathies in patients with insulin-dependent diabetes mellitus. Russian Journal of Genetics 35: 1111-1115
118. Chowdhury TA, Dyer PH, Kumar S, et al (1997) Lack of association of angiotensin II type 1 receptor gene polymorphism with diabetic nephropathy in insulin-dependent diabetes mellitus. Diabet. Med. 14: 837-840
119. Savage DA, Feeney SA, Fogarty DG, Maxwell AP (1999) Risk of developing diabetic nephropathy is not associated with synergism between the angiotensin II (type 1) receptor C1166 allele and poor glycaemic control. Nephrol.Dial.Transplant. 14: 891-894
120. Tarnow L, Cambien F, Rossing P, et al (1996) Angiotensin-II type 1 receptor gene polymorphism and diabetic microangiopathy. Nephrology Dialysis Transplantation 11: 1019-1023
121. Vionnet N, Tregouet D, Kazeem G, et al (2006) Analysis of 14 candidate genes for diabetic nephropathy on chromosome 3q in European populations: strongest evidence for association with a variant in the promoter region of the adiponectin gene. Diabetes 55: 3166-3174
122. Ahluwalia TS, Ahuja M, Rai TS, et al (2008) Endothelial nitric oxide synthase gene haplotypes and diabetic nephropathy among Asian Indians. Mol.Cell Biochem. 314: 9-17
123. Zanchi A, Moczulski DK, Hanna LS, Wantman M, Warram JH, Krolewski AS (2000) Risk of advanced diabetic nephropathy in type 1 diabetes is associated with endothelial nitric oxide synthase gene polymorphism. Kidney Int. 57: 405-413
124. Fujita H, Narita T, Meguro H, et al (2000) Lack of association between an ecNOS gene polymorphism and diabetic nephropathy in type 2 diabetic patients with proliferative diabetic retinopathy. Horm. Metab Res. 32: 80-83
125. Neugebauer S, Baba T, Watanabe T (2000) Association of the nitric oxide synthase gene polymorphism with an increased risk for progression to diabetic nephropathy in type 2 diabetes. Diabetes 49: 500-503
126. Rippin JD, Patel A, Belyaev ND, Gill GV, Barnett AH, Bain SC (2003) Nitric oxide synthase gene polymorphisms and diabetic nephropathy. Diabetologia 46: 426-428
127. Shimizu T, Onuma T, Kawamori R, Makita Y, Tomino Y (2002) Endothelial nitric oxide synthase gene and the development of diabetic nephropathy. Diabetes Res.Clin.Pract. 58: 179-185

128. Caramori ML, Canani LH, Costa LA, Gross JL (2003) The human peroxisome proliferator-activated receptor gamma2 (PPARgamma2) Pro12Ala polymorphism is associated with decreased risk of diabetic nephropathy in patients with type 2 diabetes. Diabetes 52: 3010-3013
129. Herrmann SM, Ringel J, Wang JG, Staessen JA, Brand E (2002) Peroxisome proliferator-activated receptor-gamma2 polymorphism Pro12Ala is associated with nephropathy in type 2 diabetes: The Berlin Diabetes Mellitus (BeDiaM) Study. Diabetes 51: 2653-2657
130. Liu L, Zheng T, Wang F, et al (2010) Pro12Ala polymorphism in the PPARG gene contributes to the development of diabetic nephropathy in Chinese type 2 diabetic patients. Diabetes Care 33: 144-149
131. Jorsal A, Tarnow L, Lajer M, et al (2008) The PPAR gamma 2 Pro12Ala variant predicts ESRD and mortality in patients with type 1 diabetes and diabetic nephropathy. Mol.Genet.Metab 94: 347-351

Hardy-Weinberg equilibrium

	Population		Type 2 diabetes population		DN group 1		DN group 2		DN group 3		Diabetic non-nephropathy controls	
	N = 472		N = 562		N = 114		N = 90		N = 66		N = 93	
CNDP1 genotype	**Observed**	**Expected**	**Observed**	**Expected**	**Observed**	**Expected**	**Observed**	**Expected**	**Observed**	**Expected**	**Observed**	**Expected**
5-5	197	201.0	214	205.7	32	35.4	32	31.2	27	25.2	40	3508
5-6	194	186.0	230	243.8	58	52.3	39	38.9	23	27.4	34	52.8
5-7	28	28.1	22	24.8	4	2.8	3	4.7	4	3.1	1	208
6-6	40	43.0	79	72.7	17	19.3	11	12.1	10	7.4	15	19.3
6-7	11	13.0	15	14.7	1	2.1	5	2.9	1	1.7	1	2.1
7-7	2	1.0	2	0.7	0	0.1	0	0.2	0	0.1	0	0.1
P	0.57		0.24		0.50		0.50		0.50		0.43	

Sensitivity analysis



	Increasing stringent definition of DN:	women (n)	5-5 homozygous frequency (%)
0	MDRD < 60	220	31
1	MDRD < 60 and age < 70	88	30
2	DN as in manuscript	60	28
3	MDRD < 60 + microalbuminuria	59	27
4	MDRD < 45	52	19
5	MDRD < 45 + microalbuminuria	23	22
6	MDRD < 30	6	17

With increasing stringent definition of the diagnosis diabetic nephropathy the frequency of the 5-5 homozygous genotype decreases in women, suggesting that the protective effect will only be stronger with a more stringent definition of diabetic nephropathy.

Permutation studies

We first analyzed Hardy-Weinberg Equilibrium (HWE) for the total dataset and various subgroups (table 1) to see if there would be indications for population stratification. Stratification by sex and disease status does not reveal any deviation from HWE. Hence, HWE analysis does not give an indication on population strata.

Table 1. Tests for deviation from HWE in several subgroups of the data set. Subgroups are characterized by *Sex* (F=female, M=male) and disease status. P-values are given for the Chi-Square goodness of fit test. *N* denotes the sample size in the subgroups.

Sex	Disease status	p-value	N
F	no DN	0.53	44
M	no DN	0.90	47
Both	no DN	0.43	91
F	DN	0.56	139
M	DN	0.74	128
Both	DN	0.95	267
F	All	0.92	183
M	All	0.48	175
Both	All	0.85	358

As individual ethnicity is not known for all patients in this sample and the sample is in almost perfect HWE, it is difficult to construct a permutation scheme that incorporates population strata. We therefore first performed a permutation test without incorporating population strata by randomly permuting phenotype status across the whole data set. Such a procedure can primarily account for small sample size. The permuted P-values are lower than P-values based on the asymptotic Chi-Square distribution (table 2), indicating that small sample size cannot explain the P-values in our study. The asymptotic P-values behave conservative in this situation.

Table 2. P-values for genetic association of the 5-5 genotype in a recessive model. Column *Total* lists P-values for the combined sample (all cases are treated as a single group).

	Total	DN group 1	DN group 2	DN group 3
Asymptotic P-value	0.0000358	0.000542	0.00102	0.00689
Permuted P-value	0.0000073	0.000234	0.000444	0.00281

Sensitivity analysis of population stratification

We addressed the question of population stratification by a sensitivity analysis. The sensitivity analysis was performed in R version 2.10.0. For all Chi-Square tests a continuity correction was used leading to slightly different numeric results compared to the paper. The sensitivity analysis is based on the so-called inflation factor used in genome wide association studies (Biometrics, 55. p.997-1004, 1999), which assesses how much the average/median test statistic of single nucleotide polymorphisms, based on a Chi-Square distribution with one degree of freedom, deviates from the expectation. If the inflation factor is greater than 1, there is an indication that there might be population stratification. This inflation factor can be used to correct results from genome wide association studies by dividing the test statistic by the inflation factor, thereby assuring that a re-analysis is uninflated. We used this concept to determine how large the inflation factor could be in our study to still get significant results at a certain significance level (table 3).

For all groups an inflation of 1.1 is allowed to still achieve a significance of 0.01. An inflation factor of 1.1 is larger than the maximal inflation factor observed in the WTCCC study (Nature, 447. p.661-678, 2007). The maximal reported inflation factor for a genome wide association studies is 1.4 to our knowledge (BMC Proc, 3 Suppl 7. s.13, 2009) (NARAC study). Note, that group 2 and group 3 do not reach the significance

level of 10^{-3} but the combined sample is still significant and still exceeds the inflation factor 1.4 from the NARAC study. We have repeated the analysis with a permutation test in the individual groups and present these results in table 4.

In conclusion, there is no indication for a systematic error due to population stratification based on our sensitivity analysis.

Table 3. Sensitivity analysis for P-values of the study. For an assumed inflation factor the significance level would be precisely alpha for inflation factor > 1. For inflation factor = 1 the nominal p-value is greater than alpha.

	P-value	Alpha	Inflation factor
DN group 1	0.0005	0.050	3.11
DN group 2	0.0010	0.050	2.81
DN group 3	0.0070	0.050	1.89
All	<0.0001	0.050	4.45
DN group 1	0.0005	0.010	1.80
DN group 2	0.0010	0.010	1.63
DN group 3	0.0070	0.010	1.10
All	<0.0001	0.010	2.57
DN group 1	0.0005	0.001	1.10
DN group 2	0.0010	0.001	1.00
DN group 3	0.0070	0.001	1.00
All	<0.0001	0.001	1.58

Table 4. Sensitivity analysis for P-values using a permutation test. For an assumed inflation factor the significance level would be precisely alpha for inflation factor > 1. For inflation factor = 1 the nominal p-value is greater than alpha.

	P-value	Alpha	Inflation factor
DN group 1	0.0004	0.050	3.31
DN group 2	0.0070	0.050	3.03
DN group 3	0.0045	0.050	2.10
All	<0.0001	0.050	4.53
DN group 1	0.0004	0.010	1.92
DN group 2	0.0070	0.010	1.75
DN group 3	0.0045	0.010	1.22
All	<0.0001	0.010	2.63
DN group 1	0.0004	0.001	1.17
DN group 2	0.0070	0.001	1.07
DN group 3	0.0045	0.001	1.00
All	<0.0001	0.001	1.61

A