Diabetic nephropathy : pathology, genetics and carnosine metabolism

Mooyaart, A.L.

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Online supplements

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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		

Classify into glomerular class: ?

Name	*#*	*Criteria*	
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 of DN	IV	Global glomerular sclerosis in >50% of 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

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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)

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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)

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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)

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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)

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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)

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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)

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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

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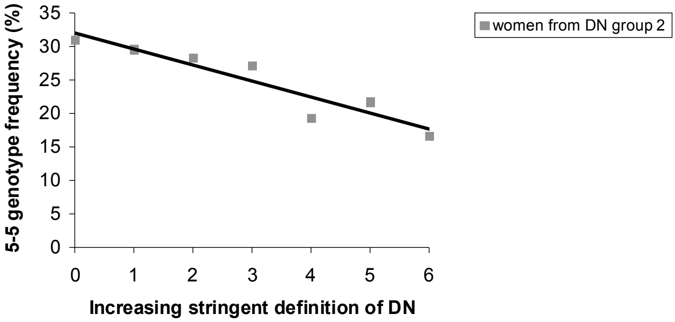
Hardy-Weinberg equilibrium

	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

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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

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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

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