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CORRESPONDENCE

Association of microsatellite markers on chromosomes 6q27 region and 10p15 region with end-stage renal disease in a UK renal transplant population

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The incidence and prevalence of end-stage renal disease (ESRD) has increased significantly in the United Kingdom over the past 10 years, and it is predicted that more than 1000 persons per million population will be receiving renal replacement therapy (dialysis or transplantation) by 2010.[1] There is considerable evidence for a genetic susceptibility to ESRD, reflected in the familial clustering of renal failure and different prevalence rates in distinct ethnic populations.[2,3] ESRD is usually preceded by a progressive renal function decline, by persistent proteinuria and frequent histological findings of glomerular and interstitial fibrosis.[4] Quantitative markers of renal function, such as glomerular filtration rate and urinary albumin/creatinine ratio, also demonstrate a high degree of heritability.[5]

A genome-wide screen (n=6000 microsatellites) highlighted several markers associated with advanced renal failure secondary to diabetic nephropathy in an Irish case–control population.[6] We have subsequently investigated the top three microsatellite markers (D10S1435, $P_{uncorrected}$=0.000003, $P_{corrected}$=0.016; D10S558, $P_{uncorrected}$=0.000001, $P_{corrected}$=0.005; and D6S281, $P_{uncorrected}$=0.00007, $P_{corrected}$=not significant) for association with the development of ESRD in a UK population of renal transplant patients.

Ethical approval (www.orecni.org.uk) was obtained before conducting this study. Genomic DNA was accurately quantified to facilitate a case–control design testing for association with ESRD. Transplant recipients with ESRD (n=652) were defined as cases, and deceased kidney donors (n=607) were defined as controls. The cohort was consecutively assembled between 30th May 1986 and 30th April 2005. All recipients had a primary cause of renal disease recorded and classified according to the European Dialysis and Transplant Association (EDTA) coding system (www.era-edta.org). The renal transplant recipient group (62% male) had a mean age of 42 (s.d. 17) years, recipients included 11% of patients with diabetic nephropathy, and the deceased donor group (58% male) had a mean age of 37 (s.d. 17.0) years. Genotyping was conducted using fluorescent fragment analysis on an ABI PRISM 3730 Genetic Analyser (Applied Biosystems, Warrington, UK). Alleles were sized in uniquely mapped PCR products using a LIZ size standard (Applied Biosystems) and confirmed by dideoxy sequencing of homozygotes on the ABI PRISM 3730 Genetic Analyser. Experimental quality controls generated consistent results as determined by two independent personnel. A genotype completeness of more than 95% was achieved for each microsatellite assay. The frequency of alleles in cases and controls was compared using the T2 statistic in CLUMP, and corrected for multiple comparisons using the Bonferroni approach. Odds ratios (ORs) were derived on the basis of the T4 statistic from Clump and in accordance with that described earlier.[6]

We observed further evidence that markers at chromosomes 6q27 and 10p15 are associated with an increased risk of ESRD in a UK population (Tables 1 and 2). Similar outcomes were observed when comparing allelic distributions between diabetic and nondiabetic ESRD cases (D10S1435 $P_{uncorrected}$=0.01 and D6S281 $P_{uncorrected}$=0.0003 for nondiabetic ESRD case group). There is biological and genetic evidence suggesting that common genetic determinants modify kidney disease progression to ESRD, independent of the primary renal disorder. For example, polymorphisms in the *NOS3*[7,8] and *ITGA8*[9] genes are reported to influence progression to ESRD in individuals with autosomal dominant polycystic kidney disease. Our results support the possibility that genetic factors influencing risk of ESRD are located within chromosomes 6q27 and 10p15. The latter has emerged as a strong candidate genomic region that may harbor genetic risk factors for kidney disease. D10S1435 was first linked to nondiabetic ESRD in Black individuals (n=129 affected sib pairs, P=0.035). Subsequent studies have supported linkage with ESRD in African Americans (n=356 affected sib pairs; P=0.02), with diabetic nephropathy in Americans (n=59 affected sib pairs, 72 discordant sib pairs, P=0.04) and with diabetic nephropathy in the multiethnic Family Investigation of Nephropathy and Diabetes group (n=397 sib pairs, P=0.00004).[5]

Potential biological and positional candidate genes in these two regions include *GTPBP4* (10p15) and *SMOC2* (6q27). *GTPBP4* (previously known as 'chronic renal failure gene') is from a family known as GTP-binding proteins. These are regulatory proteins found in all cells, which form a type of molecular switch that is used in the control of a wide range of biological processes, such as protein synthesis, signal-transduction pathways, growth and differentiation.[10] *SMOC2* is a glycoprotein with a calcium-dependent conformation and has been shown to be expressed in many human tissues.[11]

In summary, we have replicated our original finding[6] of association between microsatellite markers at 6q27 and 10p15 with renal failure in an independent cohort of Caucasian

Table 1 Individual genotyping and candidate genes for each marker in case and control DNAs

Marker	*Chromosome*	$P_{uncorrected}$[a]/$P_{corrected}$[b]	*Candidate gene names*
D10S558	10p15	NS/NS	GTP-binding protein 4 (*GTPBP4*)
D10S1435	10p15	0.007/0.02	GTP-binding protein 4 (*GTPBP4*), RNA-editing deaminase-2 (*ADARB2*)
D6S281	6q27	0.0005/0.0015	Thrombospondin II (*THBS2*), Tata box-binding protein (*TBP*), Secreted modular calcium-binding protein 2 (*SMOC2*)

[a]Significance was assessed using a χ^2 test to compare allele counts in cases and controls; *P* values were obtained from the T2 statistic in CLUMP (http://www.smd.qmul.ac.uk/statgen/dcurtis/software.html).
[b]*P* values were corrected for the number of markers investigated in this case–control collection using the Bonferroni approach.

Table 2 Comparison of allele distributions for the three markers under investigation

	Size[a]											
D10S558	188	190	192	194	196	198	200	202	204	206	208	Odds ratio ($\geqslant$198 versus $\leqslant$196)
Case	312	30	1	1	3	95	317	165	242	86	18	0.96 (95% CI: 0.80–1.15)
Control	278	26	1	1	1	81	296	144	250	72	10	
D10S1435	251	255	259	263	267	271	275	Odds ratio[b] (255+271 versus others)				
Case	23	432	497	223	115	13	1	1.34 (95% CI: 1.13–1.59)				
Control	26	327	465	263	116	10	1					
D6S281	201	203	205	207	209	211	213	215	217	Odds ratio (215+217 versus others)		
Case	362	63	649	126	14	1	9	5	19	0.38 (95% CI: 0.23–0.62)		
Control	306	71	635	111	16	1	14	28	32			

[a]Sized (base pairs for individual alleles) referenced to 500 LIZ size standard on 3730 GA (Applied Biosystems).
[b]Odds ratio calculated for the corresponding allele described earlier[6]; 263 *versus* others=0.74 (95% confidence interval (CI) 0.60 to 0.91).

individuals. Further informative studies in these chromosomal regions are required to enhance our knowledge and understanding of chronic kidney disease.

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