5.5. Confirmation that a polymorphism in the distal enhancer of the renin gene, REN-5312C/T, is associated with elevated blood pressure

C Vangjeli[1], N Clarke[1], U Quinn[1], P Dicker[1], O Tighe[1], C Ho[1], E O'Brien[2] and A Stanton[1]

[1]*Royal College of Surgeons in Ireland, Dublin, Ireland and* [2]*Beaumont Hospital, Dublin, Ireland*

Studies of knockout and transgenic mice have demonstrated key roles for genes encoding components of the Renin Angiotensin System (RAS) in blood pressure (BP) regulation. In contrast, most candidate gene studies examining for associations between RAS protein genetic variants and BP have not been replicated. Our strategy was to perform a gene centric experiment with dense tagging single nucleotide polymorphism (SNP) coverage including the promoter and untranslated regions of RAS genes in 2 large Irish populations. Both clinic and 24-h ambulatory BP measurements were available from population I ($n=387$), while only clinic BP was measured in population II ($n=1024$). Using modified TaqMan assays, we genotyped 22 Tag SNPs in 4 RAS genes, Angiotensinogen (AGT), renin (REN), angiotensin converting enzyme (ACE) and angiotensin converting enzyme 2 (ACE2). Association analyses were performed using Plink and Stata 8, with clinic and ambulatory BP measurements as quantitative traits.

Only REN-5312C/T polymorphism showed a consistent association with elevated BP. Carriage of one REN-5312T allele was associated with the following age and sex adjusted increments in systolic and diastolic pressures (mean [95% confidence intervals], mm Hg); Population 1, clinic 2.1[0.1–4.1]/1.5[0.3–2.8], daytime 2.0[0.6–3.4]/1.4[0.4–2.4], nighttime 3.6[0.9–2.3]/1.3[0.4–2.3], and Population 2, clinic 0.7[−1.1–2.6]/1.1[0.1–2.1]. Haplotypic analyses and multivariate analyses, including genetic variant-environment and gene-gene interactions, were in concordance with individual SNP analyses. In conclusion, we have shown, in two independent populations, that carriage of a REN-5312T allele is associated with elevated BP. Hence renin has been confirmed to be an important susceptibility gene for arterial hypertension in Caucasians.

Poster abstracts

PA.2. Blood pressure lowering efficacy of direct renin inhibition (aliskiren) in resistant hypertension – an observational study from UK primary care

B Williams, PS Lacy and AG Stanley

Department of Cardiovascular Sciences, University of Leicester School of Medicine, Leicester, United Kingdom

Background and Objective: The evidence-base for treatment of resistant hypertension (RH) is limited. Patients with RH, i.e. uncontrolled blood pressure (BP) despite treatment with an ACE-inhibitor or ARB (A) + CCB (C) + thiazide-type diuretic (D), i.e. A + C + D, are likely to have an activated renin system. Thus, this observational study evaluated the benefit of the direct renin inhibitor aliskiren in patients with RH.

Methods: We invited a sample of UK general practitioners to provide data on patients recently treated with aliskiren. Of 571 aliskiren-treated patients, 67 patients were identified who: (i) had uncontrolled BP (>140/90 mm Hg) despite treatment with A + C + D; (ii) were subsequently treated with aliskiren; (iii) had no other changes to medication that might have influenced BP during the aliskiren treatment period. Mean patient age was 59.5 ± 1.7 yrs, 41.8% were male and 97% Caucasian.

Results: Addition of aliskiren 150 mg daily to A + C + D reduced BP from baseline by 16.2/9.9 mm Hg over 12 weeks ($P<0.01$). For those titrated to 300 mg daily, the mean BP reduction from baseline was 22.4/9.6 mm Hg ($P<0.01$).

Aliskiren	Baseline (BL) BP	4 weeks BP	Δ BL to 4wks	12 weeks BP	Δ BL to 12wks
150mg					
Mean	166.1/93.1	153.2/86.4	12.8/6.7	146.2/81.7	16.2/9.9
SEM	1.3/1.3	2.2/1.2	2.2/1.0	2.7/2.3	2.3/1.3
300mg					
Mean	174.6/94.8	146.6/82.9	28.0/11.9	151.9/81.6	22.4/9.6
SEM	3.2/3.5	3.1/3.3	3.1/2.6	6.4/3.6	5.0/2.8

Conclusions: This observational study suggests aliskiren provides clinically significant BP reductions in RH, supporting the importance of renin in the development of RH. Limitations of observational studies are acknowledged but the magnitude of response suggests a novel treatment option for RH.