Single-Nucleotide Polymorphisms of Tight Junction Component Claudin-5 and Leukoaraiosis

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Background

BBB: brain microvascular endothelium cells (BMVEC), astrocytes, basement membrane, and pericytes and neuron

Claudins play a significant role in TJ formation and integrity at the BBB. therefore, a good candidate gene for LA.

- periventricular white matter (PVWM)**
0 = absent
1 = “caps” or pencil-thin lining
2 = smooth “halo”
3 = irregular periventricular signal extending into the DWM
- deep white matter (DWM)**
0 = absent
1 = punctate foci
2 = beginning confluence
3 = large confluent areas

Method

- Study population
Total of 339 LA cases (LA-PVWM, 183; LA-DWM 156) vs controls (LA-PVWM, 202; LA-DWM 229)
- Genotyping
Three single-nucleotide polymorphisms, rs1548359, rs10314 and rs739371, were genotyped by RT-PCR with LightCycler 2.0 RT-PCR (Roche, Germany).

Results

Table 1. Demographic and clinical characteristics in control and patients with LA

Characteristics	Control (n = 202)	LA-PVWM (n = 183)	p	Control (n = 229)	LA-DWM (n =156)	p
Age	61.66 ± 13.01	74.46 ± 7.76	< 0.001	63.86 ± 13.25	73.44 ± 8.87	<0.001
Gender (male), n (%)	127 (62.6%)	91 (49.7%)	0.009	143 (62.2%)	75 (48.1%)	0.006
Hypertension, n (%)	112 (55.4%)	134 (73.2%)	<0.001	133 (58.1%)	113 (72.4%)	0.004
Diabetes, n (%)	58 (28.7%)	65 (35.5%)	0.153	71 (31.0%)	52 (33.3%)	0.63
Cholesterol (mg %)	166.13 ± 43.51	169.21 ± 41.13	0.477	166.66 ± 43.15	168.97 ± 41.25	0.62
Triglyceride (mg %)	147.12 ± 130.59	134.62 ± 104.08	0.201	148.80 ± 130.52	126.46 ± 98.13	0.07
HDL-Chol (mg %)	40.40 ± 10.88	41.26 ± 12.02	0.459	40.43 ± 10.75	41.36 ± 12.37	0.43
LDL-Chol (mg %)	98.43 ± 34.89	97.92 ± 31.90	0.881	98.08 ± 34.65	98.36 ± 31.47	0.93
Chol/HDL	4.28 ± 1.21	4.31 ± 1.28	0.802	4.29 ± 1.23	4.30 ± 1.26	0.96
LDL/HDL	2.54 ± 0.95	2.51 ± 0.93	0.747	2.53 ± 0.95	2.51 ± 0.93	0.89
ApoA1 (mg %)	1.23 ± 0.78	1.19 ± 0.26	0.56	1.21 ± 0.72	1.20 ± 0.27	0.81
ApoB (mg %)	0.97 ± 0.29	0.93 ± 0.25	0.301	0.96 ± 0.28	0.92 ± 0.26	0.23
ApoA1/ApoB	0.84 ± 0.31	0.81 ± 0.27	0.367	0.85 ± 0.30	0.79 ± 0.27	0.06
Lp(a) (mg %)	30.42 ± 26.09	28.23 ± 26.13	0.46	31.12 ± 28.39	26.65 ± 21.86	0.14
Glucose (mg %)	144.80 ± 65.91	141.78 ± 81.78	0.693	145.28 ± 65.27	140.51 ± 85.08	0.54
HbA1C (%)	6.36 ± 3.53	6.21 ± 1.38	0.595	6.35 ± 3.34	6.19 ± 1.40	0.58
tHcy (μmol/L)	13.26 ± 6.30	14.34 ± 5.78	0.081	13.29 ± 6.30	14.48 ± 5.67	0.06

Table 2. Comparison of genetic frequency of Claudin 5 polymorphisms in the control and LA-PVWM

Genotypes	Control (n=202, %)	LA-DWM (n=183, %)	OR (95%CI), p
rs1548359 P=0.509			
CC	137 (67.8)	124 (67.8)	1.0(Reference)
CG	59 (29.3)	50 (27.3)	0.93(0.59-1.46), 0.81
GG	6 (3.0)	9 (4.9)	1.65(0.57-0.479), 0.42
Dominant (CC vs CG+GG)	137/65	124/59	1.00(0.65-1.53), 1.00
Recessive (CC+CG vsGG)	196/6	174/9	1.69(0.58-4.84), 0.43
rs10314 P=0.294			
CC	29 (14.4)	17 (9.3)	1.0(Reference)
CG	103 (51.0)	96 (52.5)	1.59(0.82-3.077),0.19
GG	70 (34.7)	70 (38.3)	1.70(0.86-3.38),0.13
Dominant (CC vs CG+GG)	29/173	17/116	1.14(0.60-2.11),0.74
Recessive (CC+CG vs GG)	132/70	113/70	1.19(0.77-1.84),0.439
rs739371 P=0.838			
CC	63 (31.2)	52 (28.4)	1.0(Reference)
CG	100 (49.5)	94 (51.4)	1.13(0.71-1.80),0.63
GG	39 (19.3)	37 (20.2)	1.14(0.64-2.05),0.65
Dominant (CC vs CG+GG)	63/139	52/137	1.19(0.77-1.84),0.439

Table 3. Comparison of genetic frequency of Claudin 5 polymorphisms in the control and LA-DWM

Genotypes	Control (n=229, %)	LA-DWM (n=156, %)	OR (95%CI), p
rs1548359 P=0.406			
CC	157 (68.6)	104 (66.7)	1.0(Reference)
CG	61 (26.6)	48 (30.8)	1.18(0.75-1.86),0.48
GG	11 (4.8)	4 (2.6)	0.54(0.17-1.77),0.418
Dominant (CC vs CG+GG)	157/72	104/52	1.09(0.70-1.68),0.73
Recessive (CC+CG vsGG)	218/11	152/4	0.52(0.16-1.66),0.29
rs10314 P=0.817			
CC	29 (12.7)	17 (10.9)	1.0(Reference)
CG	119 (52.0)	80 (51.3)	1.14(0.59-2.24),0.74
GG	81 (35.4)	59 (37.8)	1.24(0.62-2.46),0.60
Dominant (CC vs CG+GG)	29/190	17/139	1.24(0.65-2.36),0.52
Recessive (CC+CG vs GG)	148/81	97/59	1.11(0.72-1.69),0.66
rs739371 P=0.653			
CC	65 (28.4)	50 (32.1)	1.0(Reference)
CG	116 (50.7)	78 (50.0)	0.87(0.54-1.39),0.633
GG	48 (21.0)	28 (17.9)	0.75(0.41-1.37),0.37
Dominant (CC vs CG+GG)	65/164	50/106	0.84(0.53-1.30),0.49

Table 4. Haplotype frequency of claudin 5 in control and LA

Genotype	Control	LA-PVWM	OR (95%CI)	p-value
SNP1/SNP2/SNP3				
C-C-C	0.3802	0.3374	0.82(0.61-1.10)	0.2
C-C-G	0.0098	0.01352	1.38(0.36-5.19)	0.74
C-G-C	0.1685	0.1962	1.21(0.83-1.74)	0.34
C-G-G	0.2658	0.2674	1.01(0.73-1.39)	0.93
G-C-C	0	0		
G-C-G	0.0086	0.0046	0.73(0.122-4.42)	1
G-G-C	0.0107	0.0073	0.82(0.18-3.71)	1
G-G-G	0.1565	0.1739	1.14(0.78-1.67)	0.49
SNP1/SNP2/SNP3				
C-C-C	0.3681	0.3488	0.91(0.68-1.24)	0.59
C-C-G	0.0078	0.0166	1.84(0.49-6.94)	0.49
C-G-C	0.1592	0.2135	1.44(0.99-2.08)	0.057
C-G-G	0.2837	0.2416	0.78(0.57-1.11)	0.188
G-C-C	0	0		
G-C-G	0.0105	0	0.13(0.007-2.39)	0.08
G-G-C	0.0098	0.0082	1.10(0.24-4.96)	1
G-G-G	0.1608	0.172	1.08(0.73-1.59)	0.69

Conclusion

This study provides weak evidence of genetic polymorphisms of claudin-5 associated with susceptibility of LA.