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ABSTRACT N. CO47

ALTERAZIONI DELLE PIASTRINE E CONDIZIONI GENETICHE

GENETIC CHARACTERIZATION OF THE KIV2 LPA POLYMORPHISM IN SUBJECTS WITH BICUSPID AORTIC VALVE WITH DIFFERENT CLINICAL COMPLICATIONS.

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Background and aims: The bicuspid aortic valve (BAV) is the most common congenital cardiopathy affecting 0.5 to 2.0% of the general population. This condition can cause secondary complications such as valvular aortic stenosis, calcification, aortic insufficiency and thoracic aortic aneurysm. Beyond hemodynamic valvular impairment, a frequent determinant of BAV natural history, dyslipidemia and elevated lipoprotein (a) [Lp(a)] levels also favour progression and complications of BAV disease. Lp(a) levels are known to be under a strict genetic control (heritability of the trait >90%) and are largely influenced by LPA Kringle IV type 2 (KIV2) size polymorphism: a lower number of KIV2 repeats is associated with higher levels of circulating Lp(a). In this study, we characterized LPA KIV2 repeats, using a digital droplet PCR (ddPCR) approach, in a cohort of BAV patients with different clinical settings.

Methods: One hundred nine subjects of Caucasian origin referred to the Regional Referral Center for Marfan syndrome and related disorders and to the Advanced Molecular Genetics Laboratory (Atherothrombotic Diseases Center, AOU-Careggi) were enrolled.

Patients were divided into two groups according to different clinical settings: 1) patients undergoing valve replacement surgery (VRS, n=68 subjects) and 2) patients not undergoing valve replacement surgery (NVRS, n=41 subjects). The genetic characterization of the LPA KIV2 polymorphism was carried out through ddPCR (Bio-Rad).

Results: NVRS and VRS patients showed, respectively, significant differences in median age (IQR) [45 (28-52) vs 66 (57–75), p<0.001], and in classical cardiovascular risk factors such as dyslipidaemia [11 (16.2%) vs 19 (46.3%), p=0.0009], hypertension [20 (29.4%) vs 26 (63.4%), p=0.0007], and smoking habit [7 (10.3%) vs 23 (56.1%), p=0.0001], as expected. The prevalences of aortic stenosis, calcification and aortic root/thoracic ascending aorta dilatation, according to different severity degree in both groups, are reported in the enclosed table. We also observed a significant difference in the median number of KIV2 repeats between the two groups [13 (8.1 – 22.6) in NVRS vs 33.6 (19.1 – 42.9) in VRS, p<0.001].

As concerns KIV2 repeat evaluation according to BAV clinical complications, NVRS patients with complications showed a trend towards reduction in the number of KIV2 repeats with respect to NVRS patients without complications [stenosis: 10,90 (7.1 – 19.9) vs 13.21 (9.2 – 24.4), p=0.341; calcification: 12.6 (7.2 – 20.3) vs 15 (9.88 – 24.5), p=0.319; root dilatation: 11.9 (6.9 – 18.6) vs 15.8 (10.4 – 24.0), p=0.165]. Moreover, we observed a statistically significant decrease in KIV2 repeats number in NVRS patients with thoracic ascending aorta dilatation with respect to those without dilatation [11.2 (6.7 – 17.6) vs 18.8 (11.8 – 25.9), p=0.016].

In VRS patients, instead, no significant difference in the distribution of the number of KIV2 repeats, according to the presence or absence of BAV clinical complications, was found.

Conclusions: Our analysis suggests that in NVRS patients, younger and with a lower prevalence of traditional cardiovascular risk factors than VRS ones, higher levels of genetically determined lipoprotein (a) might contribute to the development of BAV complications and in turn to a worse prognosis. Data observed in VRS patients might be likely due to the not negligible impact of cardiovascular risk factors burden in influencing the phenotype severity.

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Demographic, clinical and genetic characteristics of 109 BAV patients

	NVRS patients N=68	VRS patients N=41	*p*
Age, years*	45 (28 – 52)	66 (57 – 75)	<0.001
Male/Female	52/16	30/11	0.82
Smoking habit, N (%)	7 (10.3)	23 (56.1)	0.0001
Diabetes, N (%)	2 (2.9)	3 (7.3)	0.36
Hypertension, N (%)	20 (29.4)	26 (63.4)	0.0007
Dyslipidemia, N (%)	11 (16.2)	19 (46.3)	0.0009
BAV types			
RL, N (%)	55 (80.9)	11 (26.8)	
RN, N (%)	11 (16.2)	4 (9.8)	
Not available, N (%)	2 (2.9)	26 (63.4)	
BAV associated complications			
BAV calcification degree			
No calcifications, N (%)	41 (60.3)	10 (24.4)	
Mild calcifications, N (%)	17 (25)	6 (14.6)	
Moderato calcifications, N (%)	7 (10.3)	0 (0)	
Severe calcifications, N (%)	3 (4.4)	25 (61)	
BAV stenosis degree			
No stenosis, N (%)	55 (80.9)	10 (24.4)	
Mild stenosis, N (%)	3 (4.4)	3 (7.3)	
Moderate stenosis, N (%)	5 (7.4)	2 (4.9)	
Severe stenosis, N (%)	5 (7.4)	26 (63.4)	
Root dilatation N (%)	28 (41.2)	18 (43.9)	
Ascending aorta dilatation N (%)	38 (55.9)	27 (65.9)	
Both N (%)	21 (30.9)	16 (39.0)	
KIV2 repeat*	13.0 (8.1 – 22.6)	33.6 (19.1 – 42.9)	<0.001