Fibromuscular dysplasia (FMD) is a common cause of renovascular hypertension in middle-aged women lacking cardiovascular risk factors. FMD is an intriguing group of non-inflammatory arterial deformations, which results in stenosis, and in some cases, aneurysms and dissections of medium-sized arteries. Mostly asymptomatic, the clinical manifestations of FMD depends on the arterial bed affected and is usually diagnosed in the context of resistant hypertension or after a stroke.\(^1\) We have previously established a complex genetic basis for FMD and reported a first genetic susceptibility locus on chromosome 6 involving rs9349379, a common genetic locus within the phosphatase and active regulatory 1 gene (\(PHACTR1\)).\(^2\) This pleiotropic genetic locus is also known to associate with several neurovascular diseases,\(^3\) atherosclerotic acute myocardial infarction,\(^4\) and spontaneous coronary artery dissection.\(^5\)

Here, we aimed to replicate the association between \(PHACTR1\) and FMD in a Polish case-control study and assess the effect of this locus on FMD, hypertension, and cardiac features among cases.

Patients were recruited through the ARCADIA-POL (Assessment of Renal and Cervical Artery Dysplasia - POLAND) study, a nation-wide Polish registry for FMD. Lesions in at least one vascular bed were confirmed in all patients using whole-body angio-computed tomography as previously described.\(^6\) We analyzed 129 patients for whom we excluded atherosclerotic stenosis and syndromes where FMD-like lesions are often observed (eg, Ehlers Danlos, Loeys-Dietz). Patients were 80.6% women, with a mean age at inclusion of 45.9±14.1 years, and a mean age at FMD diagnosis of 42.7±14.3 years. One hundred thirteen patients (87.6%) were hypertensive. The mean age at the diagnosis of hypertension was 36.5±14.3 years, and FMD was diagnosed on average 6.2±3.6 years later. Other most frequent FMD-related symptoms were headaches (38.8%), dizziness (37.2%), pulsatile tinnitus (15.5%), and stroke (9.3%). Among analyzed patients with FMD, 41.1% were current or ex-smokers. In this group of patients, FMD was identified in renal arteries in 109 (84.5%) patients, as well as in cerebrovascular, visceral, and lower extremities arteries in 34 (26.4%), 20 (15.5%), and 15 (11.6%) patients, respectively. Arterial dissection(s) or aneurysms in various vascular beds were present in 16 (12.4%) and in 31 (24%) patients, respectively. One hundred and ten (85.3%) patients presented multifocal FMD lesions. Multisite FMD was found in 42 patients (32.6%) and was defined as the presence of FMD stenosis, FMD-related aneurysms, FMD-related dissections, FMD-related S-shaped cervical arteries in 2 or more of the vascular beds. The median number of vascular beds affected was 1 (interquartile range 1–2, minimum =1, maximum =5). We extracted DNA using Chemagic (Perkin Elmer) and performed genotyping using direct sequencing (Applied Biosystems 3730XL) in cases and control.

From the Department of Hypertension (E.W.-C., A.P., E.F., K.J.-P., P.D., M.K., A.J.), Department of Epidemiology, Cardiovascular Disease Prevention and Health Promotion (W.S., W.D.), and Department of Interventional Cardiology and Angiography (J.K., A.W.), Institute of Cardiology, Warsaw, Poland; Université de Paris, PARCC, INSERM, F-75015 Paris, France (T.B., A.G., D.D., X.J., N.B.-N.); 2nd Department of Clinical Radiology, Medical University of Warsaw, Poland (M.J.); Institute of Cardiology, Warsaw, Poland National Institute of Cardiology, Warsaw, Poland. Unit of Demography and Social Gerontology, University of Lodz, Poland (W.S.); Department of Demography, University of Lodz, Poland (W.S.); Department of Preventive Medicine, Medical University of Lodz, Poland (W.D.); Department of Interventional Radiology and Neuroradiology, Medical University of Lublin, Poland (M.S.-T.); Pole de Cardiovascular Research, Institut de Recherche Expérimentale et Clinique and Division of Cardiology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium (M.P., A.P.); and Division of Internal Medicine and Hypertension Unit, Department of Medical Sciences, University of Turin, Italy (M.P.).

*These authors are joint first authors.
†These authors are joint last authors.
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controls, a randomly ascertained sample from the WOBASZ II (Multicentre National Population Health Examination Survey) study, a population-based Polish cohort.7

We confirmed the association between rs9349379 genotypes and FMD using logistic regression. We found 56% increased risk for FMD per A allele (odds ratio [OR]=1.56 [95% CI, 1.14–2.13]; P=5.5×10−3). We provide the estimated effect of this variant on FMD risk through an updated meta-analysis of the previously published data2 and the current case-control study using METAL.8 We confirmed the genome-wide significant association with FMD (OR=1.40 [95% CI, 1.27–1.55]; P=1.8×10−11) that now involves 1283 FMD cases and 4193 controls.

**PHACTRI** robust association with FMD is intriguing, as this variant also associates with risk for several neurovascular and cardiovascular diseases involving diverse risk factors. We sought to characterize the effects of this variant among FMD patients of the ARCADIA-POL who have benefited from extensive clinical phenotyping related to FMD, hypertension and cardiac morphology and function. To gain power, we analyzed AG and AA genotypes carriers under the same category (dominant model) using unconditional logistic regression for binary traits and linear regression or Mann-Whitney test for continuous traits, adjusted for sex and age whenever relevant (Tables 1 through 5).

Among the 129 Polish patients, we found equal distribution of rs9349379 genotypes in ever and nonsmokers (P=0.78) and for oral contraception treatment among women (P=0.92). No differences were found between mean age of FMD and hypertension diagnosis. We report a nonsignificant younger age at hypertension diagnosis (β=−3.32 years, P=0.17). Interestingly, patients with AG+AA genotypes tend to associate with an average of 5.61 years difference between hypertension and FMD diagnosis (P=0.01), which may reflect a milder hypertension phenotype, and thus discourage vascular imaging exploration overtime that is needed to reveal FMD lesions. Patients carrying the AG+AA genotypes tend to be more likely to present with multifocal versus focal FMD subtype (OR=4.82, P=0.15). We found a trend for a decreased odd among AG+AA genotype group for multisite lesions (OR=0.41, P=0.08), especially at both renal arteries (OR=0.37, P=0.05), supporting a potentially milder presentation. Systolic and diastolic blood pressure values were similar by genotype, as was hypertension status among patients. We found the risk allele for FMD to tend to associate with decreased levels of creatinine (β=−6.32, P=0.053), although renal function estimated by glomerular filtration rate did not differ by genotype (P=0.69).

FMD stenosis may evolve in aneurysm and dissections in the affected arteries. In our cohort, 13 patients presented...
The low number of dissections observed. Our study is probably lacking statistical power to confirm the previously reported association where the A allele associated with a higher risk for cervical dissection and coronary dissection. Larger samples are needed to address the specific association of rs9349379 with dissection events in FMD.

Patients with FMD from the ARCADIA-POL study underwent a series of echocardiographic measurements, including intraventricular septum thickness, posterior wall thickness, ankle-brachial index, left ventricular mass, ejection fraction, and diastolic function. The number of patients available for analysis is indicated for each trait. Binary variables are expressed as the number of patients (percentage) and quantitative variables as mean±SD. The P value for the association between the clinical trait and rs9349379 under the genetic dominant model adjusted for sex and age, except for GFR (CDK-Epi), is reported. For binary dependent variables odds ratio (95% CI) from unconditional logistic regression is reported. The P value for the association between the clinical trait and rs9349379 under the genetic dominant model adjusted for sex and age except for sex and glomerular filtration rate, which included these variables in the calculation formula. The P values and the analysis were not adjusted for sex and age. The P value for the association between genotype groups means and Mann-Whitney (nonparametric test) Δβ from linear regression is reported. *For this trait, we report the P value for the association between the clinical trait and rs9349379 under the genetic dominant model adjusted for sex and age. Effect for binary dependent variables odds ratio (95% CI) from unconditional logistic regression is reported and for quantitative dependent variable the β from linear regression is reported. Analysis was adjusted for sex and age except for sex and glomerular filtration rate, which included these variables in the calculation formula.
left ventricular mass, which were all comparable according to genotypes as were ejection fraction and global longitudinal strain (Tables 1 through 5). We noted nonsignificant trends for lower E-wave length during diastole \((\beta=-5.067, P=0.17)\) but not A-wave, resulting in a lower E- to A-wave ratio \((\beta=-0.146, P=0.09)\) in the AG+AA group.

Our study is limited by the small size of the cohort of patients and the low power to robustly estimate the genetic associations with a large number of the traits and lack of significance after multiple testing corrections. Except for the global association with FMD, additional exploration of PHACTR1 on hypertension and cardiac traits is needed in larger cohorts of patients with FMD to validate our results.

In summary, we provide confirmatory association between PHACTR1 locus and FMD in this first genetic study in a Polish case-control study and an updated global effect through the largest existing genetic meta-analysis for this vascular disease. Additional risk loci are expected to be revealed through ongoing genome-wide association studies. We found evidence for an association with delayed diagnosis for FMD among patients who present with HTN. These patients could be at higher risk for FMD misdiagnosis and less risk to present multisite lesions. We overall exclude a major genetic effect of this locus on blood pressure and cardiac morphology parameters among patients with FMD.

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Disclosures

None.

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