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## Diagnosis and Risk Factors for Intracranial Aneurysms in Autosomal Polycystic Kidney Disease: A cross-sectional study from the Genkyst Cohort

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## Diagnosis and Risk Factors for Intracranial Aneurysms in Autosomal Polycystic Kidney Disease:

### A cross-sectional study from the Genkyst Cohort

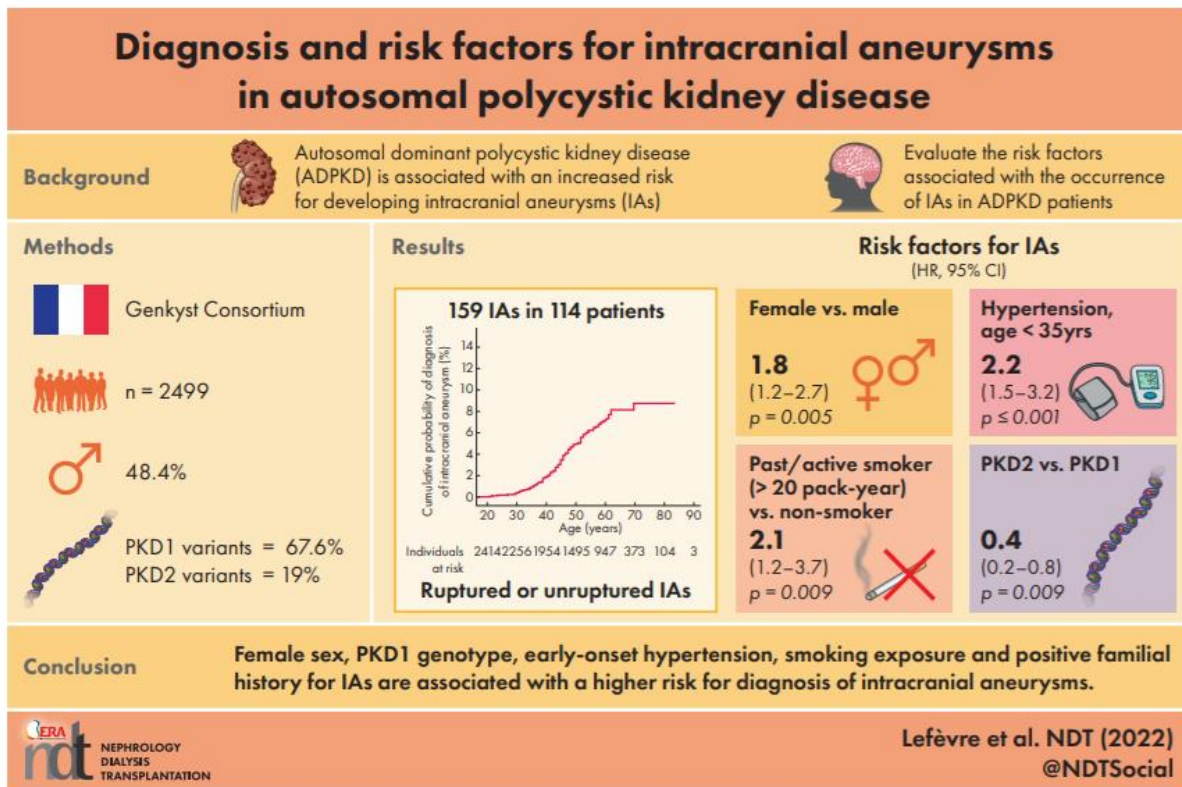
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Running title : Intracranial Aneurysms in ADPKD

## GRAPHICAL ABSTRACT



## ABSTRACT

**Background.** Autosomal dominant polycystic kidney disease (ADPKD) is associated with an increased risk for developing intracranial aneurysms (IAs). We aimed to evaluate the frequency of diagnosis of IAs in the cross-sectional, population-based, Genkyst cohort, to describe ADPKD-associated IAs and to analyze the risk factors associated with the occurrence of IAs in ADPKD patients.

**Methods.** Cross-sectional study performed in 26 nephrology centers from the Western part of France. All patients underwent genetic testing for *PKD1*/*PKD2* and other cystogenes.

**Results.** Among the 2449 Genkyst participants, 114 (4.65%) had a previous diagnosis of ruptured or unruptured IAs at inclusion, and ~47% of them had a positive familial history for IAs. Most aneurysms were small and saccular and located in the anterior circulation; 26.3% of the patients had multiple IAs. The cumulative probabilities of a previous diagnosis of IAs were 3.9, 6.2 and 8.1% at 50, 60 and 70 y, respectively. While this risk appeared to be similar in male and female individuals <50 y, after

that age, the risk continued to increase more markedly in female patients, reaching 10.8% vs 5.4% at 70 y. The diagnosis rate of IAs was more than twofold higher in PKD1 compared to PKD2 with no influence of *PKD1* mutation type or location. In multivariate analysis, female sex, hypertension <35 y, smoking and *PKD1* genotype were associated with an increased risk for diagnosis of IAs.

**Conclusions.** This study presents epidemiological data reflecting real-life clinical practice. The increased risk for IAs in postmenopausal women suggests a possible protective role of estrogen.

**Keywords:** autosomal dominant polycystic kidney disease (ADPKD), genetics, intracranial aneurysms, PKD1, PKD2, risk factors, subarachnoid hemorrhage

ORIGINAL UNEDITED MANUSCRIPT

## KEY LEARNING POINTS

### What is already known about this subject?

- The most frequent and severe vascular feature in ADPKD is the development of intracranial aneurysm (IA).
- IA prevalence is fivefold higher in ADPKD than in the general population, with estimates ranging from 9 to 12%.
- The only identified risk factor is the presence of a familial history of unruptured or ruptured IA.

### What this study adds?

- This study provides information about prevalence of detected IAs in one of the largest population-based cohorts of ADPKD patients. The cumulative probabilities of a previous diagnosis of IAs in the Genkyst cohort were 3.9, 6.2 and 8.1% at 50, 60 and 70 y.
- The risk of diagnosis of ruptured or unruptured IAs appear to be higher in women, especially after 50 y. This parallels observations made in the non-ADPKD population and suggests a possible protective role of estrogens.
- Multivariate analysis shows that female sex, age at diagnosis of hypertension <35y, smoking exposure and *PKD1* genotype are associated with an increased risk for diagnosis of IAs.

### What impact this may have on practice or policy?

- This study provides a real-life picture of diagnosis of IAs in ADPKD and may increase awareness and knowledge regarding prevalence and risk factors for IAs in ADPKD patients.
- Policies regarding screening for IAs in ADPKD patients differ accross countries and centers, and no clear recomandations have been made. Our study suggests that in at-risk women, screening should be probably repeated later in life than in men.

ORIGINAL UNEDITED MANUSCRIPT

## INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) affects ~39 to 68 individuals in 10000.[1, 2] Mutations in *PKD1* and *PKD2*, which encode polycystin 1 (PC1) and polycystin 2 (PC2), respectively, account for ~75% and ~18% of the ADPKD pedigrees.[3] Four other genes, *GANAB*, *DNAJB11*, *ALG8* and *ALG9*, involved in protein biogenesis, have been more recently described in atypical forms of ADPKD and/or autosomal dominant polycystic liver disease (ADPLD).[4-8]

In addition to the relentless development of renal and hepatic cysts, ADPKD is characterized by a wide spectrum of vascular complications, the most frequent and serious of which are intracranial aneurysms (IAs). In the non-ADPKD population, unruptured IAs are detected in 1.8 to 3.2% of the individuals screened by cerebral imaging, whereas the prevalence of IAs in ADPKD patients is nearly fivefold higher, ranging from 9.3% to 12.4% when systematic screening strategies are employed.[9-12] IA rupture, leading to subarachnoid hemorrhage (SAH), is associated with significant morbidity and mortality and occurs approximately ten years earlier in the ADPKD population than in the general population, with respective median ages of 41 versus 51 y.[13-15] In the United States, the early mortality rate associated with SAH is estimated to be ~20-30%.[16-19] Long-term complications of SAH include neurocognitive dysfunction, epilepsy, and other focal neurologic deficits.

This susceptibility to IAs in ADPKD is thought to be mediated by a maladaptive response of the vascular wall to hemodynamic stress, resulting from defects in PC1 and PC2, which are abundantly expressed in vascular smooth muscle cells and the endothelium and likely act as pressure sensors.[20-24] Until now, the main risk factor identified for IA occurrence in ADPKD patients has been the presence of a positive personal or family history of unruptured or ruptured IAs, suggesting a predominant role of genetic determinants.[9, 12] Indeed, the prevalence of IAs is nearly four times higher in ADPKD patients with a family history of IAs (~22%) than in those without such a family history (~6%).[9, 12] Previous studies in the early 2000s suggested an association of the localization of *PKD1* mutations in the 5' half of the gene with an increased risk for vascular complications.[25]

However, *PKD1* gene sequencing analysis is highly complex and was often incomplete at that time.[26] Compared to the general population, where nonmodifiable (e.g., female sex) and modifiable risk factors (such as smoking, hypertension and possibly dyslipidemia) are well identified, limited information is available in the ADPKD population.[27-29]

Screening for IA using cerebral magnetic resonance imaging is currently recommended only for patients with a family history of IAs or SAH, patients with a high-risk profession (e.g., airline pilots), and patients who demand screening despite adequate information.[30] These recommendations relate to the cost associated with unnecessary screening and the risk of identifying IAs at low risk of rupture that are ineligible for treatment, causing anxiety to patients and their families. However, recent cost-effectiveness studies suggest a benefit of systematic screening strategies.[31, 32] It should be noted that the annual aneurysm rupture rates employed in these models were higher than in other ADPKD cohorts.[29]

This study aimed to evaluate the frequency of diagnosis of ruptured and unruptured IAs in the large population-based Genkyst ADPKD cohort, to describe ADPKD-associated IAs and to analyze the risk factors associated with the occurrence of IAs in ADPKD patients.

## MATERIALS AND METHODS

### Patients

This is a cross-sectional study involving 26 centers from the Genkyst Consortium in western France.[33-35] ADPKD patients over 16 years of age were recruited from January 2010 to June 2019. ADPKD diagnosis was made by abdominal imaging, by employing the Pei criteria in the presence of a family history of ADPKD,[36] or following the identification of a proven pathogenic *PKD1* or *PKD2* mutation. In the absence of familial history or mutation identification, diagnosis required the presence of at least 10 bilateral kidney cysts. The patients' clinical data obtained during medical interviews at the time of their inclusion and from medical records were entered in a standardized clinical report form (CRF). For participants in whom previous history of IAs was reported in the CRF, medical records were reviewed on study sites to confirm the previous history of IAs and to collect additional information regarding aneurysm size (in millimeters), type (saccular versus fusiform), localization (anterior or posterior circulation) and management (monitoring, neurosurgical or neuro-radiointerventional treatment). The screening strategy for detecting unruptured IAs was, in most cases, a targeted screening strategy, in accordance with the current Kidney Disease Improving Global Outcomes (KDIGO) guidelines, i.e., by performing magnetic resonance imaging on patients with a positive family history of IAs, patients with at-risk occupations, and patients requesting screening after comprehensive information. All participants provided informed consent, and the local ethics committee approved the study (CCTIRS 10.385).

### Molecular analysis

All consenting patients underwent molecular genetic testing by Sanger sequencing for the *PKD1* and *PKD2* genes (patients included before March 2017) and/or targeted next-generation sequencing (NGS) of the *PKD1*, *PKD2*, *GANAB*, *DNAJB11*, *HNF1B*, *PKHD1*, *SEC63*, *PKRKCSH* and *UMOD* genes (patients included after March 2017 or before 2017 with no pathogenic variant detected by Sanger sequencing) in the Department of Molecular Genetics at Brest University Hospital, France.



The latest version of the targeted NGS panel, in addition to the above-mentioned genes, also includes *ALG8*, *ALG9*, *OFD1*, *COL4A1*, *DZIP1L*, *LRP5*, *PMM2*, *REN*, *SEC61B*, *SEC61A1*, *TSC1*, *TSC2* and *VHL* and was used after September 2019 for reanalysis of genetically unresolved patients. Patients with no clear pathogenic variant detected after Sanger sequencing or targeted NGS were screened for large rearrangements using multiplex ligation-dependent probe amplification and array-based comparative genomic hybridization. Mutations were classified as truncating (frameshift, indels, nonsense mutations, canonical splicing changes and in-frame indels  $\geq 5$  amino acids) or nontruncating (missense, in-frame  $\leq 4$  amino acids, noncanonical splicing events).

### **Statistical analyses**

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, N.Y., USA). The frequency of IAs detected in our cohort was estimated and reported with a 95% confidence interval (CI) constructed for the estimate. Baseline data are expressed as the median and standard deviation (SD) or range. Quantitative data were compared using the nonparametric Mann-Whitney test or Kruskal-Wallis test, depending on the number of groups. Qualitative data were compared using a t test or the chi-squared test.

Survival without a diagnosis of IA and survival without ruptured IAs were analyzed using the Kaplan-Meier method. The differences between the survival curves were assessed using a log-rank test with a 0.05 significance level.

Univariate Cox proportional hazards regression analysis was used to identify variables associated with IA diagnosis. Variables were entered into the Cox multivariate analysis when they were associated with ruptured or unruptured IA diagnosis in the univariate analysis at a conservative threshold of 20%. Complete observations were entered in the Cox multivariate analysis.

## RESULTS

### Baseline clinical parameters in the Genkyst cohort and genetic analyses

Two thousand four hundred forty-nine ADPKD patients (1185 males) from 1810 pedigrees were included. The median age at inclusion was 55.1 y [range 16.2-94.3]. The characteristics of the patients at inclusion are presented in Table 1. The results of genetic analysis were available in 2386 patients. *PKD1* pathogenic variants were identified in 67.6% of the participants (n=1612; truncating variants 44.1% (n=1052), nontruncating variants 23.5% (n=560)), while *PKD2* pathogenic variants were identified in 19% (n=454). In 11.8% of cases (n=281), no mutation was identified. Genetic analysis led to a differential diagnosis in 1.6% of the cases (n=39: *GANAB* (n=4), *DNAJB11* (n=5), *HNF1B* (n=8), *PKHD1* (n=1), *SEC63* (n=2), *PRKCSH* (n=3), *OFD1* (n=4), *UMOD* (n=2), *ALG8* (n=6), *ALG9* (n=1), *COL4A4* (n=2), *COL4A1* (n=1)).

### Diagnosis of ruptured or unruptured IA

A total of 114 patients from 107 pedigrees had a previous diagnosis of ruptured or unruptured IAs (4.65%, 95% CI: 3.56-5.74) (Figure 1). First diagnosis of IA was made at the time of IA rupture in 48 individuals, at the median age of 43.5 y [range: 21-69], while unruptured IAs were detected in 66 individuals, at a median age of 49 y [range: 24-78], leading to subsequent neurosurgical or radiointerventional treatment in 34 of them. Presymptomatic screening was mostly performed by magnetic resonance angiography (MRA), with diagnosis of unruptured IA made by MRA in 55 patients, and by computed tomography angiography in 11 patients. The reasons for screening included a positive family history of IAs (n=32, 48.5%), atypical headaches (n=16, 24.2%), systematic screening despite a negative family history (n=14, 21.2%), and evaluation before kidney transplantation (n=4, 6.1%).

The cumulative probability of diagnosis of ruptured or unruptured IAs was 1.3% at 40 y (95% CI, 0.9-1.7), 3.9% at 50 y (95% CI, 2.9-4.9), and 6.2% at 60 y (95% CI, 5-7.4) and reached 8.1% at 70 y (95% CI, 6.5-9.7) (Figure 2a). The cumulative probability of diagnosis of ruptured aneurysm was 0.9%

at 40 y (95% CI, 0.5-1.3), 1.8% at 50 y (95% CI, 1.2-2.4), 2.6% at 60 y (95% CI, 1.8-3.4) and 3.2% at 70 y (95% CI, 2.2-4.2) (Figure 2b).

Patients with IA were more frequently female patients (61.4% versus (vs) 51.1%,  $P=0.013$ ), of *PKD1* genotype (77.2% vs 63.8%,  $P=0.001$ ) and those being treated for hypertension (96.5% vs 76.1%,  $P=0.007$ ). Although nonsignificant, there were more smokers with exposure > 20 pack-years in the IA group than in the non-IA group (15% versus 8.8%,  $P=0.095$ ) (Table 1). IAs were diagnosed at all chronic kidney disease (CKD) stages. Family history of IAs was positive in 47.4% of the individuals with a diagnosis of ruptured or unruptured IAs.

### **Imaging characteristics of the aneurysms**

One hundred fifty-nine IAs were detected in 114 patients. Multiple aneurysms were found in 30 patients; either diagnosed simultaneously ( $n=16$ ), or successively (i.e. recurrent diagnoses of different IAs, prior inclusion in the Genkyst cohort) ( $n=14$ ). Amongst these 30 patients, 22 had two IAs, 3 had three IAs, 4 had three IAs, and 2 had five IAs. A large majority of the 159 aneurysms were saccular (~98%), and originated from the anterior circulation (89.3%) (Table 2). Size was available for 104/159 IAs (size was missing for 31 IAs diagnosed at rupture, and 24 unruptured IAs, mostly diagnosed before <2000). Most of these IAs were small, measuring less than 7 mm ( $n=85$ , 81.2%), including 47 IAs measuring less than 3 mm (45.2%). Only five patients were diagnosed with giant IAs (e.g., >10 mm, 3.6%). Of the 62 ruptured IAs in 48 patients, 49 were in the anterior circulation (87.5%), and 25 were <7mm.

### **Sex and diagnosis of IA**

The diagnosis rates of ruptured and unruptured IAs were 3.71% and 5.54% in male ( $n=44$ ) and female ( $n=70$ ) patients, respectively. The cumulative probability of diagnosis of ruptured or unruptured IAs was higher in female patients ( $p=0.012$ , Figure 3A). Interestingly, while cumulative probabilities for IA diagnosis appeared to be similar in individuals <50 y, after 50 y, probabilities continued to increase more markedly in female than in male patients. The cumulative probabilities of

IAs in male and female patients were hence 1.2% (95% CI, 0.6-1.8) vs 1.4% (95% CI, 0.6-2.2) at age 40, 3.6% (95% CI, 2.4-4.8) vs 4.2% (95% CI, 2.8-5.6) at age 50, 5.1% (95% CI, 3.5-6.7) vs 7.3% (95% CI, 5.3-9.3) at age 60, and 5.4% (95% CI, 3.8-7) vs 10.8% (95% CI, 8-13.6) at age 70. The cumulative probability of diagnosis of ruptured IAs was also higher in the female group ( $p=0.041$ ): 3.2% (95% CI, 2-4.4) vs 1.9% (95% CI, 0.9-2.9) at age 60 and 4.5% (95% CI, 2.7-6.3) vs 1.9% (95% CI, 0.9-2.9) at age 70 (Figure 3B).

### Genotype of patients with IA

The respective diagnosis rates of ruptured or unruptured IAs were 5.46% and 2.64% in *PKD1* ( $n=88/1612$ ) and *PKD2* ( $n=12/454$ ) mutation carriers. No cases of IAs were reported in patients with *GANAB* ( $n=4$ ) or *DNAJB11* ( $n=5$ ) mutations or patients harboring pathogenic mutations in other genes screened on the panel ( $n=30$ ). The cumulative probability of diagnosis of ruptured or unruptured IAs was higher in *PKD1* mutation carriers ( $p=0.001$ ; Figure 3C and 3D). The cumulative probabilities of IAs in *PKD1* and *PKD2* mutation carriers were indeed 1.7% (95% CI, 1.4-2) vs 0.5% (95% CI, 0.2-0.8) at age 40, 4.9% (95% CI, 3.6-4.8) vs 1.9% (95% CI, 1.2-2.8) at age 50, and 8.1% (95% CI, 7.2-9) vs 2.8% (95% CI, 1.1-3.8) at age 60 (Figure 3C). The cumulative probabilities of diagnosis of ruptured IAs were also significantly higher in the *PKD1* group ( $p=0.008$ ), reaching 3.6% (95% CI, 3-4.3) vs 0.7% (95% CI, 0.2-1.2) at age 60 (Figure 3D).

The distribution of *PKD1* mutations along the *PKD1* gene did not differ in patients with and without IAs, and the median amino acid position did not differ between groups ( $p=0.057$ ) (Figure 4). We did not observe recurring mutation of *PKD1* or *PKD2* among unrelated individuals with IAs. Furthermore, there was no association between *PKD1* mutation type (truncating vs nontruncating) and IA occurrence ( $p=0.957$ ) (Table 3).

### Risk factors associated with diagnosis of IAs

To evaluate the association between the different clinical and genetic factors and the diagnosis of ruptured or unruptured IAs, univariate and multivariate cox regression analyses were

performed. In the univariate analysis, female sex, hypertension before age 35 y, and *PKD1* genotype were associated with an increased risk for the diagnosis of IA (Table 3). After the multivariate Cox regression that included 1737 subjects, these three variables remained independent predictors of diagnosis of ruptured or unruptured IAs. In addition, smoking status, particularly when >20 PY, was also independently associated with diagnosis of IAs ( $p=0.009$ ) (Table 3).

## DISCUSSION

Widespread screening of IAs in ADPKD patients is currently not recommended, and presymptomatic screening was therefore conducted here only in patients with a positive family or personal history of IAs or SAH, before major elective surgeries, or upon specific request after adequate information.[30] While these recommendations might change in the future, our study reflects current real-life clinical practice. We report here a prevalence of detected IAs in the Genkyst cohort, one of the largest population-based cohorts of ADPKD patients, of 4.65% (95% CI: 3.56-5.74). As expected, this prevalence is therefore lower than that in systematic screening studies.[9, 12] Two recent studies, conducted at expert referral centers—Mayo Clinic, Rochester Minnesota, US and Necker Hospital, Paris, France—and possibly reflecting more severely affected patients, report IA detection rates of ~9.2% ( $n=75$ ) and ~12.7% ( $n=23$ ) in 812 and 181 patients who underwent presymptomatic screening (presymptomatic screening was performed in ~27 and 35% of the Mayo and Necker cohorts).[29, 31]

We confirm here that a large majority of IAs in ADPKD patients are small and saccular and located in the anterior circulation.[9, 12, 29] Approximately 26% of IA patients had multiple aneurysms. The median age at aneurysm rupture was 41.5 y, which is ten years earlier than in the non-ADPKD population and consistent with previous studies.[13, 15] While IAs from the anterior circulation are considered at lower risk of rupture in non-ADPKD patients, ~87% of the ruptured IAs in our cohort originated from the anterior circulation.

Cumulative probabilities of diagnosis of IA in this population-based cohort provide new and interesting information, which should, however, be interpreted with caution, as individuals with ruptured IAs, particularly at younger ages, might be underrepresented. At 70 y, the cumulative probabilities for diagnosis of IA or past history of ruptured IAs were 8.1 and 3.2%, respectively. Strikingly, cumulative probabilities of diagnosis of IA and ruptured IAs appear to be higher in women, especially after 50 y, which was not reported in ADPKD patients until now. This parallels observations made in the non-ADPKD population and suggests a possible protective role of estrogens.[11] Several former studies support a role for estrogen deficiency, causing a reduction in the collagen content of tissues, which might contribute to aneurysm development in postmenopausal women, similar to patients with connective tissue disorders. In the non-ADPKD population, an earlier age at menopause is associated with a higher risk for IAs, and animal and clinical studies have suggested a protective role of hormone replacement therapy (HRT) against SAH.[37-39] Whether HRT should be recommended for women with ADPKD at increased risk for IAs, i.e., with a positive familial history for IAs will require further studies.

Importantly, our study allows revisiting the influence of genetics on IA development in ADPKD in light of modern genomics tools in a large cohort of patients. The diagnosis rate of ruptured and unruptured IAs was more than twofold higher in carriers of mutations in *PKD1* than in *PKD2*, with respective cumulative probabilities of 8.1 vs 2.8% at age 60. *PKD1* genotype remained significantly associated with diagnosis of IAs after the multivariate analysis. Confounding factors may partially account for this observation: first, early IA rupture, before the diagnosis of ADPKD, might occur in some *PKD2* mutation carriers. Second, presymptomatic screening might be more frequently conducted in *PKD1* mutation carriers who generally have more significant family histories and more severe renal disease, resulting in earlier ADPKD diagnosis and closer medical follow-up.[35] However, the consistent observation of a higher rate of diagnosis of ruptured IAs in *PKD1* mutation carriers and the results of the multivariate Cox analyses, showing that this association is independent from age at hypertension diagnosis, suggest that *PKD1* mutation carriers might be more at-risk of developing IAs.

Severe vascular phenotypes have been described in both *Pkd1* and *Pkd2* murine models.[20-23, 40] The reasons of this apparent higher risk for IAs in PKD1 patients remain to be understood. In contrast with a study from the early 2000s, we did not identify any correlation between the occurrence of IAs and the localization of mutations along the *PKD1* gene.[25] While truncating pathogenic variants of *PKD1* are known to be associated with poorer renal prognosis, no association between *PKD1* mutation type and diagnosis of IAs was identified.[33] We did not identify any recurring *PKD1* or *PKD2* mutations among individuals with IAs. Former studies reported IAs in unrelated families harboring a two base-pair deletion in PKD1 (c.5014\_5015delAG), suggesting an association with this specific mutation, but more systematic genetic testing in ADPKD patients has now established that this variant is in fact the most common pathogenic variant of *PKD1* (~1-2%).[25, 41] In the small subgroup of 39 patients harboring mutations in other genes, no diagnosis of IA was reported. However, IAs were occasionally reported in *GANAB* pedigrees, and various vascular phenotypes, including IAs, dilatation of the thoracic aorta and dissection of a carotid artery, were recently described in a cohort of *DNAJB11* mutation carriers.[42]

Studies in the non-ADPKD population have identified risk factors associated with IAs. These include nonmodifiable factors such as female sex, ethnicity and personal or family history (FH) of ruptured or unruptured aneurysm and modifiable factors such as smoking exposure and hypertension.[11, 27, 43-45] In a recent study conducted in the Mayo Clinic cohort, hypertension and smoking history were significantly more frequent in ADPKD patients with IAs.[29] In our study, after multivariate Cox analysis, four factors remained independently associated with the diagnosis of IA: female sex, hypertension before age 35, smoking status and *PKD1* genotype.

Because IA diagnosis was made by targeted screening in the context of a positive familial history in a majority of the IA subjects, this risk factor could not be entered in the multivariate analysis. However, the importance of a positive family history should be stressed. The observation of pedigrees with a strong familial clustering of IAs in our cohort and others suggests the role of genetic

modifiers hitherto unidentified. Using genome-wide association studies, whole-exome sequencing and/or RNA sequencing, some candidate genes involved in the development of IAs have already been identified in the general population.[44, 46] Similar strategies might be successful in identifying such modifiers in ADPKD but will require the enrollment of large numbers of participants and international collaborative efforts.

This study has some limitations. Data on the number of ADPKD-affected individuals who underwent screening for IAs and in whom no IA was detected are lacking, and this information could not be collected retrospectively. Because targeted screening was employed, the number of IAs may have been underestimated. However, the data presented here reflect real-life practice and are hence likely to be of interest in clinical practice.

In conclusion, the determinants of the development of IAs in ADPKD patients are complex and multifactorial. Female sex, *PKD1* genotype, early-onset hypertension, smoking exposure and positive familial history for IAs are associated with a higher risk for diagnosis of IA



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## CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this paper have not been published previously in whole or part, except in abstract format (ERA EDTA 2019).

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## Tables

**Table 1. Clinical characteristics of the study participants at inclusion or at diagnosis of intracranial aneurysm**

Variable		Total cohort <sup>b</sup>	No past history of IAs <sup>b</sup>			
			All IAs	Past history of IAs <sup>c</sup> Unruptured IAs	Ruptured IAs	
Patients (number of pedigrees), n (n)		2449 (1810)	2335	114	66	48
Male		1185 (48.4%)	1141 (48.9%)	44 (35.6%)	27 (40.9%)	17 (35.4%)
Median age (years) <sup>b, c</sup>		55.1 [16.2-94.3]	55.2 [16.2-94.3]	48 [40.8-54.3]	49 [45-57]	43.5 [35.5-52.6]
CKD Stages <sup>a, b, c</sup>	1	456 (18.9%)	447 (19.4%)	20 (21.3%)	8 (13.3%)	12 (35.3%)
	2	394 (16.3%)	384 (16.7%)	21 (22.3%)	10 (16.7%)	11 (32.4%)
	3a	236 (9.8%)	230 (10%)	7 (7.4%)	4 (6.7%)	3 (8.8%)
	3b	256 (10.6%)	247 (10.7%)	15 (16%)	11 (18.3%)	4 (11.8%)
	4	211 (8.8%)	198 (8.6%)	15 (16%)	11 (18.3%)	4 (11.8%)
	5	859 (35.6%)	793 (34.5%)	16 (17%)	16 (26.7%)	0
	Requiring RRT	762 (31.6%)	700 (30.4%)	9 (9.6%)	9 (15%)	0
Missing		37 <sup>b</sup>	36 <sup>b</sup>	20 <sup>c</sup>	6 <sup>c</sup>	14 <sup>c</sup>
Hypertension	Yes	1873 (77%)	1763 (76.1%)	110 (96.5%)	64 (97%)	46 (95.8%)
	No	559 (23%)	555 (23.9%)	4 (3.5%)	2 (3%)	2 (4.2%)
	Missing	17	17	0	0	0
Hypertension before 35 y	Yes	535 (27.8%)	493 (27.2%)	42 (37.5%)	29 (43.9%)	13 (28.3%)
	No	1390 (72.2%)	1320 (72.8%)	70 (62.5%)	37 (56.1%)	33 (71.7%)
	Missing	326	325	1	0	1
	NA	198	197	1	0	1
Smoking status	Never smoker	1275 (56%)	1215 (56%)	60 (53.1%)	35 (53%)	25 (53.2%)
	Past or active <20PY	799 (35%)	763 (35.2%)	36 (31.9%)	24 (36.4%)	12 (25.5%)
	Past or active >20PY	207 (9%)	190 (8.8%)	17 (15%)	7 (10.6%)	10 (21.3%)
	Missing	168	167	1	0	1
Family history of IAs	No	2150 (87.8%)	2090 (89.5%)	60 (52.6%)	31 (53%)	19 (39.6%)
	Yes	299 (12.2%)	245 (10.5%)	54 (47.4%)	35 (47%)	29 (60.4%)
Genotype	<i>PKD1</i>	1612 (67.6%)	1524 (63.8%)	88 (77.2%)	50 (75.8%)	38 (82.6%)
	<i>truncating</i>	1052 (44.1%)	997 (41.8%)	55 (48.2%)	34 (51.5%)	21 (45.7%)
	<i>non-truncating</i>	560 (23.5%)	527 (22.1%)	33 (28.9%)	16 (24.2%)	17 (37%)
	<i>PKD2</i>	454 (19%)	442 (18.5%)	12 (10.5%)	10 (15.2%)	2 (4.3%)
	Unresolved	281 (11.8%)	269 (11.3%)	12 (10.5%)	6 (9.1%)	6 (13%)
	Other genes	39 (1.6%)	39 (1.6%)	2 (1.8%)	0	0
	Missing	63	61	0	0	2

Note: Values for categorical variables are given as number (percentage), and for continuous variables, as median [interquartile range].<sup>a</sup> According to estimated glomerular filtration rate (calculated using the CKD Epidemiology Collaboration creatinine equation) <sup>b</sup>Data at inclusion in the Genkyst cohort <sup>c</sup>Data at diagnosis of IA. Abbreviations: CKD, chronic kidney disease; IA, intracranial aneurysm, NA non applicable (corresponding to individuals <35y with no hypertension).

**Table 2. Characteristics of 159 IAs in 114 patients<sup>1</sup>**

Characteristics	All aneurysms N=159	Unruptured aneurysms N=97	Ruptured aneurysms N=62
<b>Type</b>			
Saccular	149 (98%)	93 (96.9%)	56 (100%)
Fusiform	3 (2%)	3 (3.1%)	0
<i>Missing</i>	7	1	6
<b>Location</b>			
Anterior circulation	135 (90%)	86 (91.5%)	49 (87.5%)
Internal carotid artery	21	13	8
Middle cerebral artery	74	51	23
Anterior communicating artery	39	22	17
Posterior communicating artery	1	0	1
Posterior circulation	15 (10%)	9 (8.5%)	7 (12.5%)
<i>Missing</i>	9	3	6
<b>Size<sup>2</sup></b>			
<7mm	85 (81.2%)	60 (82.2%)	25 (80.6%)
<3mm	47	31	16
≥7mm	19 (18.3%)	13 (17.8%)	6 (19.4%)
>10mm	5	3	2
<i>Missing</i>	55	24	31

**Notes:**

<sup>1</sup>Thirty patients (26.3%) had more than one intracranial aneurysm, either diagnosed simultaneously (n=16), or diagnosed successively (de novo formation of intracranial aneurysm) prior inclusion in Genkyst cohort (n=14).

Abbreviations: IA, intracranial aneurysm.

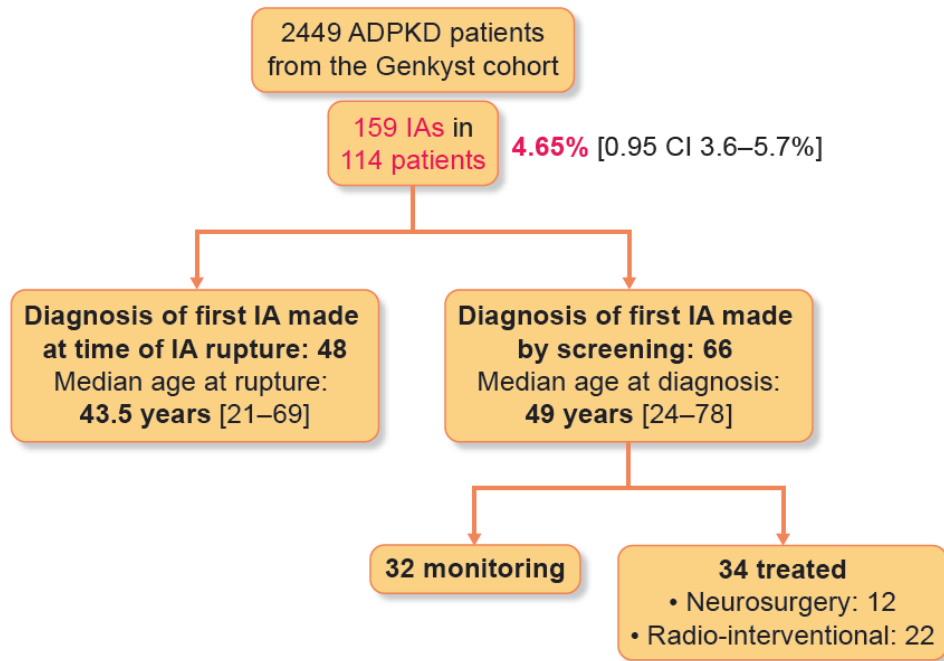
**Table 3. Effect of Clinical and Genetic variables on the occurrence of IAs**

Variables	n	Univariate			Multivariate		
		HR	95% CI	P-value	HR	95% CI	P-value
<b>Sex</b>							
Male	1185						
Female	1264	1.6	1.1 to 2.4	<b>0.013</b>	1.8	1.2 to 2.7	<b>0.005</b>
<b>Hypertension before 35y</b>							
No	1390						
Yes	535	2.5	1.7 to 3.7	<b>&lt;0.001</b>	2.2	1.5 to 3.2	<b>&lt;0.001</b>
<b>Smoking status</b>							
Never	1275						
Past or active,<20PY	799	1.1	0.7 to 1.7	0.575	1.3	0.9 to 2.1	0.176
Past or active,>20PY	207	1.6	0.9 to 2.7	0.095	2.1	1.2 to 3.7	<b>0.009</b>
<b>Genotype</b>							
<i>PKD1</i>	1612						
<i>PKD2</i>	454	0.4	0.2 to 0.7	<b>0.002</b>	0.4	0.2 to 0.8	<b>0.009</b>
Unresolved	281	0.4	0.2 to 0.8	<b>0.005</b>	0.7	0.4 to 1.3	0.230
<b><i>PKD1</i> mutation type</b>							
Non truncating	560						
Truncating	1052	1	0.6 to 1.5	0.957			

Note: Univariate and multivariable cox regressions.

Abbreviations: CI, confidence interval; SE, standard error; PY, pack-years.

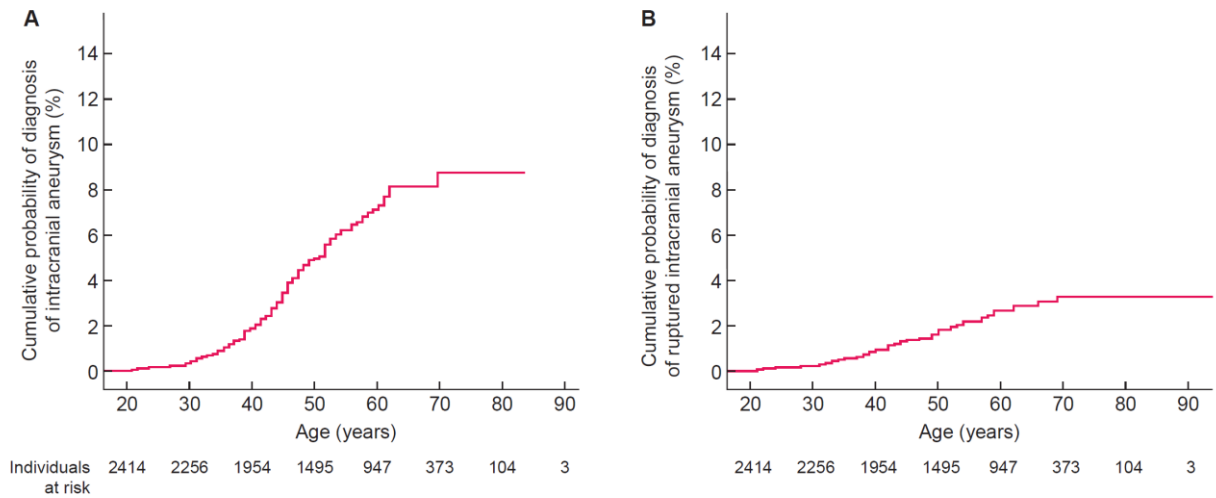
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**Figure 1. Flow diagram summarizing the diagnosis of ruptured and unruptured IAs in the Genkyst cohort.** Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; IAs, intracranial aneurysms.

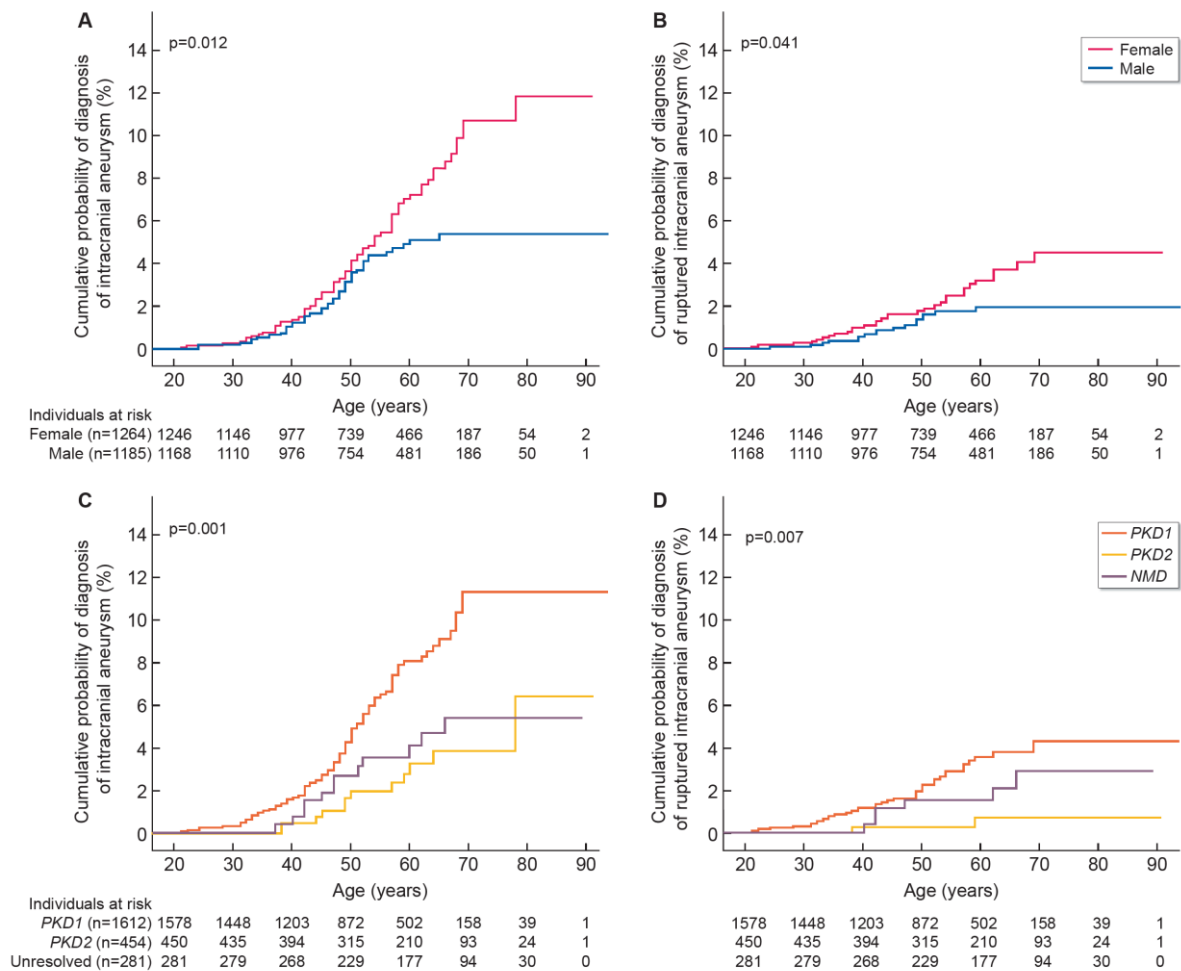
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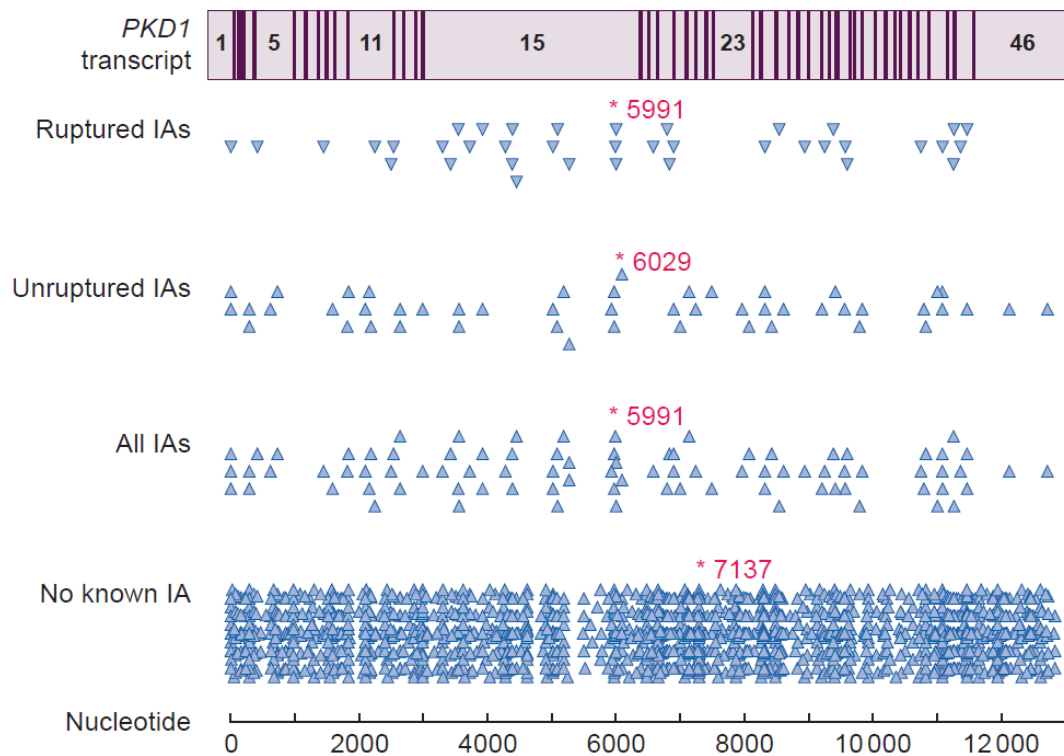
**Figure 2. Cumulative probabilities of diagnosis of IAs and ruptured IAs.** **A-** Kaplan survival curve representing the cumulative probability of diagnosis of ruptured or unruptured IAs in the Genkyst cohort. Cumulative probability of diagnosis of IA is 3.9% at 50 years, 6.2% at 60 years and reaches 8.1% at 70 years. **B-** Kaplan survival curve representing the cumulative probability of diagnosis of ruptured IA in the Genkyst cohort, which remains inferior to 4% at 70 years.

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**Figure 3. Higher probability of diagnosis of unruptured and ruptured IA in female patients and in PKD1 patients.**

- (A) Kaplan-Meier curves representing the cumulative probability of diagnosis of IAs in male and female patients. At age 60, cumulative probabilities of IA are 7.1% and 5.3% in female versus male patients, respectively.
- (B) Kaplan-Meier curves representing the cumulative probability of diagnosis of ruptured IAs in female versus male patients, respectively. At age 60, cumulative probabilities of ruptured IAs are 7.1% and 5.3% in female versus male patients, respectively.
- (C) Kaplan-Meier curves representing the cumulative probability of diagnosis of IAs in PKD1, PKD2, and genetically unresolved ADPKD patients. At age 50, cumulative probabilities of IAs are 4.9% and 1.9% in PKD1 versus PKD2 patients, respectively.
- (D) Kaplan-Meier curves representing the cumulative probability of diagnosis of ruptured IAs in PKD1, PKD2, and genetically unresolved ADPKD patients. At age 50, cumulative probabilities of ruptured IAs are 1.9% versus 0.3% in PKD1 versus PKD2 patients, respectively.



**Figure 4. Distribution of mutations identified along the *PKD1* gene in each of the three groups: no known intracranial aneurysm (IAs), all IAs, unruptured IAs and ruptured IAs.** The different *PKD1* pathogenic mutations are plotted against their respective nucleotide positions within *PKD1* coding sequence (cDNA designation, from 1 to 12912, indicated on the lower part of the figure). The median nucleotide position for each group is represented by a star. *PKD1* transcript is shown above. Abbreviations: IAs, intracranial aneurysms.

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