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The Genetics of Vascular Complications in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Abstract

The most important extra-renal manifestation of autosomal dominant polycystic kidney disease (ADPKD) in terms of debilitating injury and premature death is the development of intracranial aneurysms (IAs) and other vascular complications, resulting in subarachnoid hemorrhage (SAH). IAs are found at a rate approximately five times higher in ADPKD patients than in the general population and in patients with a family history of SAH/IAs the frequency is elevated further three to five times, indicating the importance of genetic factors in its etiology. Expression of the ADPKD gene products, polycystin-1 (*PKD1*) and polycystin-2 (*PKD2*), in vascular smooth muscle and the endothelium, and evidence that reduced levels of these proteins leads to IA development in mouse models, suggests a direct role of these proteins in the vascular disease. PKD1 and PKD2 patients seem equally likely to develop IAs, while patients with mutations to the 5' half of *PKD1* may more likely have vascular complications. Genome wide association and candidate studies of multiplex families with IAs without ADPKD have identified a number of genes/proteins that may be risk factors for the development of IAs. These candidate proteins largely have roles in the maintenance and remodeling of the arterial wall of small brain arteries. The development of the genetic methodologies of massively parallel sequencing mean it is now possible to test these and other candidates in ADPKD families with multiplex and singleton IA cases. Identifying strong modifiers of this phenotype will be important for prioritizing patients for presymptomatic screening and interventions.

Keywords

ADPKD; intracranial aneurysms; genetic modifiers; genotype/phenotype correlations

THE ADPKD DISEASE PHENOTYPE IS PLEIOTROPIC AND COMPLEX

The impressive advancements in human genetic methodologies in the last decade has led to the identification of a large number of Mendelian disease genes and pathogenic mutations that has enabled precise correlations with the clinically defined phenotypes. As a

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CONFLICT OF INTEREST
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consequence, there has been a muddying of the paradigm of mutation to a single gene causing a single clinical phenotype. Rather, a model has emerged where the Mendelian phenotype is modified allelically, by variants at other loci, and by environmental influences such that a rigid distinction between classical single gene conditions and complex traits has gradually shifted to one characterized by a continuum between the two extremes [1–3]. In reality, Mendelian conditions are complex in nature, with mutations to a single gene causative, but the precise clinical phenotypic spectrum and degree of severity modulated by modifying loci.

ADPKD is a striking example of a Mendelian condition characterized by phenotypic variability [4, 5]. This phenotypic variability includes the degree of kidney disease severity, ranging from severe *in utero* cases [6, 7] to mild phenotypes characterized by adequate kidney function into late life [8, 9]. The complexity of the phenotype is also evident by the presence of extra-renal clinical features [10] making ADPKD a truly pleiotropic condition, with vascular complications the one most associated with morbidity and mortality. Genetic heterogeneity, with two recognized loci, *PKD1* on chromosome 16 and *PKD2* on chromosome 4 [11,12], strongly influences renal disease severity; average age at end stage renal disease (ESRD) is ~54y for PKD1 and ~74y for PKD2 [5]. In addition, significant renal phenotypic variability is observed within each genic population indicating a role for the specific mutation (allelic effects) [13,14], as well as within families (intra-familial variability) that is presumed to be due to the influence of modifier loci and the environment [15,16]. The degree to which these factors influence the vascular phenotype is discussed below and the likely important of the various potential modifiers illustrated in Fig. (**1**).

CLINICAL SPECTRUM AND SCREENING RECOMMENDATIONS FOR VASCULAR COMPLICATIONS IN ADPKD

A wide spectrum of vascular abnormalities is seen in ADPKD patients. These include intracranial aneurysms (IAs) and dolichoectasias, thoracic aorta and cervicocephalic artery dissections and coronary artery aneurysms [17–21]. IAs are the most life-threatening phenotypic feature in ADPKD. In a recent study of 407 ADPKD patients presymptomatically screened by magnetic resonance angiography (MRA) [22], a prevalence of 9.3% was estimated for asymptomatic IAs. The estimated prevalence of unruptured IAs in ADPKD patients with a family history of IAs and/or subarachnoid hemorrhage was 21.2%, while the estimated prevalence of unruptured IAs in ADPKD patients without such a history was 6.3%. Another recent study of 355 patients estimated a prevalence of 12.4% of IAs in the general ADPKD population, with an age dependent increase of prevalence, with a peak of 23.3% in patients older than 60 years [23]. Familial clustering is observed [22, 24, 25], with the IA frequency five times higher in ADPKD pedigrees with a positive family history of ruptured IAs than in those without such a history [26].

Rupture of an IA is associated with high morbidity and mortality, suggesting pre-symptomatic screening in ADPKD pedigrees as a preventive approach. However, the utility of pre-symptomatic screening depends on the tendency of IAs to grow and rupture and must take into consideration the not insignificant risk associated with clipping and other interventional procedures. The natural history of ADPKD-associated IAs was recently

studied in a follow-up of 38 ADPKD patients (36 pedigrees), where 45 saccular aneurysms were detected by presymptomatic screening by MRA [22]. Most of the IAs were small (less than 3.5mm in diameter) and 84% of them were in the anterior brain circulation. In this cohort, minimal change was observed in the evolution of the vascular lesions during the 243 years of cumulative follow-up. Only one *de novo* IA appeared, in two other patients the pre-existent IAs grew in size, but in the remainder no changes were observed and no IAs ruptured. This study, performed in a relatively young population of patients, suggested that the risk of IA enlargement and rupture is low. Other studies found that the only strong risk predictor for IAs enlargement [27–30] and rupture [29,31] is the IA size: an IA larger than 5mm has a higher risk of undergoing size increase, while the risk of rupture is higher for diameters larger than 7 [24] or 10 mm [31]. Hence, due to the significant mortality and morbidity associated with surgical intervention, screening for asymptomatic IAs is not recommended in ADPKD patients without a family history of SAH or aneurysmal rupture, unless undergoing major elective surgeries or in high-risk occupations, such as airline pilot or bus driver [22].

PATHOPHYSIOLOGY OF IAS IN ADPKD

Both the PKD1 and PKD2 proteins, polycystin-1 (PC-1) and polycystin-2 (PC-2), respectively, are expressed in the vasculature, particularly in smooth muscle cells of the tunica media and myofibroblasts [32, 33], but also in the endothelium [34]. A role has been suggested for the polycystin complex as a pressure sensor in the vasculature [35]. While the expression of PC-1 appears to be developmentally regulated, the expression of PC-2 is more constant [36]. Immunostaining of ruptured intracranial aneurysms in ADPKD patients shows expression of PC-1 and PC-2 in spindle-shaped cells on the wall of the aneurysm as well as in the smooth muscle cells of the tunica media of the parental arteries [32, 33, 36], suggesting a direct involvement of the two proteins in the maintenance of the arterial wall of the small arteries in the brain and the development of IAs in ADPKD patients. A similar pattern is observed in the arterial wall of ADPKD patients with aortic dissections or dolichoectatic intracranial arteries [32]. The localization of PC-1 and PC-2 in the proximity of smooth muscle cell dense plaques (structures similar to focal adhesions in epithelial cells) supports the involvement of these two proteins in the development and maintenance of the myoelastic wall of arteries.

The finding of lower levels of PC-2 expression in smooth muscle cells of *Pkd2*$^{+/-}$ mice suggests a direct involvement of PC-2 (a TRP-like calcium channel) in the regulation of intracellular calcium, and that *Pkd2* haploinsufficiency may be related to the development of the vascular phenotype in humans [37]. Furthermore, *Pkd2*$^{+/-}$ mice induced to develop hypertension form IAs at twice the level of wildtype controls [37]. Meanwhile, in the *Pkd1*$^{nl/nl}$ hypomorphic mouse model that expresses PC-1 at 26% of the normal level in the aorta, dissecting aortic aneurysms are common [38]. These were characterized by accumulation of matrix components between elastin lamella and a tear in the intima resulting in an intramural bleed. This data further emphasizes the importance of the level of PC-1 expression to maintain vascular integrity.

GENETICS OF IAs IN ADPKD: GENIC AND ALLELIC INFLUENCE

The association of IAs with *PKD1*- [39] or *PKD2*- [40] linked pedigrees has been known since the mapping of the two disease genes. However, it was only after the identification of the *PKD1* and *PKD2* genes [11,12], and the development of comprehensive assays [41–44] that genotype-phenotype correlations could be investigated.

In a preliminary analysis of 35 ADPKD pedigrees [45] that included individuals with IAs and/or early onset disease, the *PKD1* region encompassing exons 11–21 was sequenced using locus-specific amplicons to overcome the problem of genomic duplication of the *PKD1* locus [11]. Five different frameshifting (c.3009_3012delCAAC, c.5014_5015delAG, c.5572delG, c.5813_5814insC, 7186_7187insTTGCCTCAATT) and two missense mutations (Arg2329Pro Ser2423Phe) [46] were found in eight pedigrees with ruptured or unruptured IAs. Notably, the frameshifting change c.5014_5015delAG was common to three pedigrees showing a vascular phenotype or early onset disease [45]. This suggested that this mutation could be a predisposing factor for developing more severe disease/vascular phenotype. However, this initial observation was not supported by mutation analysis on larger populations, and c.5014_5015delAG is now known to be the most common *PKD1* mutation (1–2% of total) [46, 47] and associated with a wide range of phenotypes. Recently the co-inheritance of an inactivating and hypomorphic *PKD1* allele has been associated with early onset ADPKD due to reduction in the level of functional PC-1 [13,14]. No evidence from human populations has yet shown if unusually low levels of functional PC-1 are associated with IA development, but studies from mouse models (see above) suggest that as a possibility (Fig. **1**) [37,38].

The relationship between the germline mutation and the risk of developing a vascular phenotype was further analyzed in a larger population of 58 ADPKD families where at least one individual developed a vascular phenotype, which was clinically well characterized [48]. Both the *PKD1* and *PKD2* genes were screened for mutation over the entire coding sequence of the two genes. Of the 58 pedigrees, 51 (88%) were PKD1 and seven PKD2 (12%), similar to their ratio in a typical ADPKD population (85% PKD1, 15% PKD2) [43], indicating that IAs are not less common in PKD2 populations, although they have milder kidney disease [5]. These 58 families contained 85 members with a vascular finding (46% males and 54% females) and 79% of the subjects had a ruptured IA, leading to death in half of them. The population was classed according to disease severity, including: individuals with rupture, individuals with rupture before 40y, and cases with familial clustering of IAs. No association was found with the mutation type in *PKD1*, truncating or in-frame change (including missense). However, a significant association was found with the mutation position in *PKD1*; the median position of the mutations was further 5’ (or N-terminal) in the vascular cohort as compared to the control cohort, which was most evident in the subgroups with rupture, early rupture and familial clustering (Fig. **1**). A receiver operating characteristics (ROC) analysis indicated an increased predictive ability from 7.5% in the control cohort to 12.6% in the cohort with mutation 5’ to the median position, and an increase from 2.5% to 7.1% in the sub-group with familial clustering. It is not clear why 5’ mutations may be more associated with IA development but it could be due to different roles of N-terminal and C-terminal GPS cleavage products in the vasculature [49, 50].

In a recent study of pre-symptomatic screening using MRA, a prevalence of 9.3% was found with a much higher prevalence in pedigrees with known IA history (21.1%) [22]. Molecular analysis of 26 pedigrees showed that 21 had a *PKD1* mutation (84%) and four a *PKD2* mutation (16%), while in the remaining family no mutation was identified. In this relatively small group the authors did not observe any specific genotype-phenotype correlation as to the size or location of the IAs, development of multiple IAs or presence of family history of rupture. As described above [48], PKD1 and PKD2 individuals appeared to be at equal risk of developing IAs.

GENETICS OF IAS IN THE GENERAL POPULATION

IAs occur in the general population with a prevalence between 0.5 and 1% [19, 51, 52], they are mainly located in the anterior circulation (80–85%), and are a common finding in post-mortem autopsies (1–6% in adults) [53–55]. Usually multiple IAs are found per patient, as many as 2–3 in 20–30% of the cases, and SAH is a major clinical problem associated with high morbidity and mortality [56–61]. Several lines of evidence suggest that genetics is an important risk factor for IAs in the general population, including the familial clustering observed in IAs pedigrees [62] and the association with Mendelian syndromes, particularly connective tissue disorders [63].

Familial clustering of IAs (not in association with a Mendelian syndrome) has been documented in hundreds of pedigrees [64]. It has been estimated that 7–20% of patients with IAs/SAH have a first or second degree relative with a confirmed IA [65–69]. Furthermore, the risk of IA rupture for a first-degree relative of an index patient is four times higher than for the general population [68–70]. However, no clear pattern of inheritance has been identified and so a high level of genetic heterogeneity with a low level of penetrance and environment input has been hypothesized [62]; it is a complex trait [71–74].

Two recent genome wide association studies (GWAS) were conducted on large cohorts with familial clustering of IAs and identified several critical intervals and a reproducible group of candidates. Study of a cohort of 2,100 cases and 8,000 controls from Finland, the Netherlands and Japan [75] identified loci on chromosomes 2q, 8q and 9p. The second larger study utilized 5,891 cases and 14,181 controls from Europe and Japan [76] and confirmed the two loci on 8q and 9p and identified three new loci on chromosomes 18q, 13q and 10q. Analysis in these intervals identified potential candidate genes: *RBBP8* at 18q (encoding the retinoblastoma binding protein 8); *STARD13* at 13q (the StAR-related lipid transfer (START) domain containing 13), with *KL* (klotho) close to this interval; *CNNM2* at 10q (encoding cyclin M2); *BOLL* and *PLCL1* at 2q (an RNA binding protein and a protein with high homology to phospholipase C, respectively); *SOX17* at 8q and *CDKN2A*, *CDKN2B* and *ANRIL* (a non-protein-coding transcript) at 9p. All these genes code for proteins putatively involved in cell cycle regulation and progression, cell proliferation and senescence of progenitor cells or regulate a balance between progenitor cells and terminally differentiated cells in the arterial wall [76]. In fact, *SOX17* is required for both endothelial formation and maintenance [77–80]; *CDKN2A* and *CDKN2B* encode for a cyclin-dependent kinase inhibitor and a regulator of p53 activity [81]; *RBBP8* influences the cell cycle by interacting with BRCA1 [82]; *STARD13* overexpression causes suppression of cell

proliferation [83]; and *KL* modulates the fibroblast growth factor receptor specificity [84] and its absence causes accelerated aging in mouse models [85]. All these functions merge into a unified model that defines the risk to develop IAs in the general population as a defect in the maintenance and remodeling of the arterial wall of the small brain arteries.

Interestingly, the 9p interval has also been associated with abdominal aortic aneurysms [86], myocardial infarction, abdominal aortic aneurysms and IAs [87], suggesting a wider influence for *CDKN2A*, *CDKN2B* and/or *ANRIL* [88]. Conversely, *DAB2IP*, an inhibitor of cell growth and survival, was identified as a candidate gene conferring susceptibility to abdominal aortic aneurysm [89] but not IAs, suggesting that in some cases different specific genetic susceptibility may exist for aneurysms in different arterial locations.

An alternative approach to identify susceptibility genes for IAs has utilized linkage analysis on large, multiplex families [90,91], a candidate approach [92–94]; or expression analysis of human arterial wall-associated genes [95]. Candidates have been tested in IA pedigrees that play a critical role in arterial wall maintenance and repair or are involved in Mendelian syndromes that include IAs as part of the phenotypic spectrum. A group of functional candidates has been defined based on knowledge of the structure and function of the arterial wall [91,96]. These include genes involved in the remodeling of the extracellular matrix (alpha 1 antitrypsin, elastases, metalloproteinases); basal membrane constituents (collagens, laminins, nidogen); and constituents of the tunica media (collagens, vitronectin, laminin, fibrillins and elastin). Some other obvious candidates include genes mutated in syndromic disorders that include the development of vascular aneurysms, or pathways known to influence vasculature remodeling. These include the TGF beta pathway [97–101] and collagen genes [102–107]. Overall, meta-analysis of all the published studies suggests a high level of genetic heterogeneity and polygenic inheritance [71,74,108].

GENETICS OF IAS IN ADPKD: GENETIC MODIFIERS

Although some genotype-phenotype correlation have been observed in ADPKD for the development of a vascular phenotype (see above) [22,48], strong intra-familial variability is observed, suggesting that other genetic variants are involved besides the *PKD1* or *PKD2* mutation (Fig. **1**). The task ahead is to identify and functionally evaluate genetic modifiers associated with the development of IAs and other vascular complications in ADPKD patients. The populations are too small to consider GWAS but the availability of next-generation sequencing technologies makes it possible to deeply scan the human genome, particularly the coding portion (exome), for disease-causing variants. A likely design of such studies will employ whole exome analysis in ADPKD pedigrees with multiple vascular cases with follow-up in singleton families. The other option, and one that might be attractive at this time, is employing a candidate-based approach analyzing genes identified from the familial IA studies and other candidates suggested from their involvement in the maintenance, integrity and function of the arterial wall of the small brain arteries (see above) in the multiplex and singleton vascular ADPKD pedigrees (Fig. **1**) [109]. However, segregation analysis and comprehensive comparison to an ADPKD population without IAs will be required, plus functional validation using *in vivo* testing and animal models, to definitely prove the disease-association of identified genes and variants.

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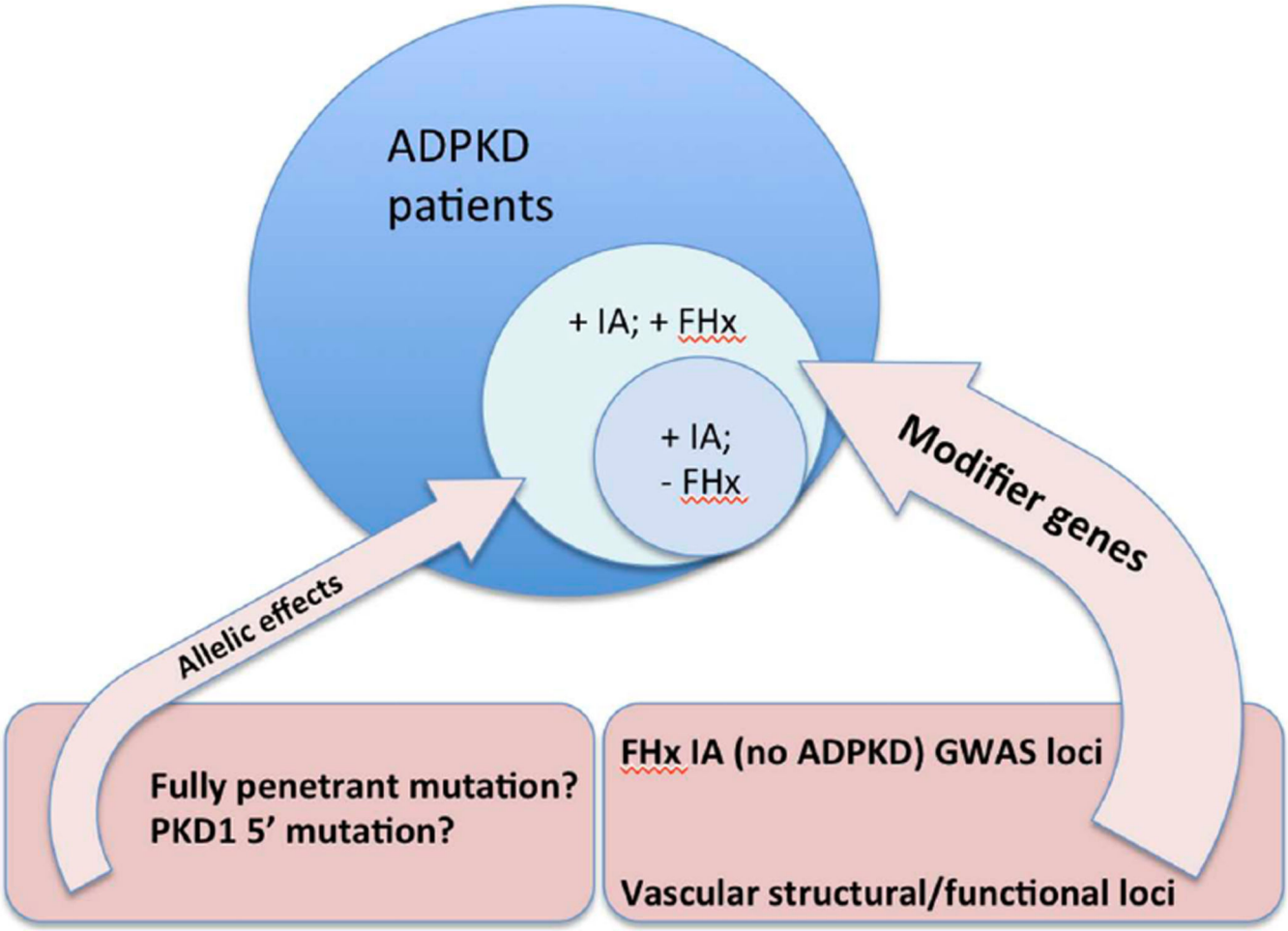

Fig. (1).

Factors influencing the development of IAs in ADPKD patients. Patients with IAs with (+) or without (−) a family history (FHx) are illustrated. Modifier genes are likely the major determinant whether a patient develops vascular complications and may include variants in genes encoding vascular proteins, with some candidates already identified by GWAS in multiplex families with IA, without ADPKD. *PKD1* and *PKD2* allelic effects are probably less important, with the changes most likely to be associated with IA development illustrated.