Année 2017/2018

Thèse

Pour le

DOCTORAT EN MEDECINE

Diplôme d'État

par

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Née le 10 avril 1989, à Paris (75019)

Polykystose rénale autosomique dominante et cancers cutanés non-mélanomateux post-transplantation rénale : les mutations non troncantes du gène *PKD1* comme facteur de risque génétique

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Présentée et soutenue publiquement le **21 septembre 2018** devant un jury composé de :

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Résumé

Polykystose rénale autosomique dominante et cancers cutanés non-mélanomateux post-transplantation rénale : les mutations non troncantes du gène *PKD1* comme facteur de risque génétique

C Geneste, B Sautenet, A Bretagnol, E Chevallier, F Von Tokarski, L Machet, JM Halimi, M Büchler

La polykystose rénale autosomique dominante (PKRAD) est la première cause génétique d'insuffisance rénale, avec principalement des mutations des gènes *PKD1* (75%) et *PKD2* (15%). Elle mène dans de nombreux cas à une transplantation rénale. Plusieurs études ont montré que les patients présentant une mutation de *PKD1* présentaient une insuffisance rénale terminale 20 ans plus tôt que ceux présentant une mutation de *PKD2*. Par ailleurs, le traitement immunosuppresseur au long cours, nécessaire après une transplantation, est connu pour favoriser la survenue de cancers cutané non mélanomateux (CCNM). Dans plusieurs cohortes, la PKRAD est un facteur de risque indépendant de développement de CCNM après transplantation rénale. Jusqu'à présent, il n'existe aucune cause connue, y compris génétique, permettant d'expliquer l'association entre l'ADPKD et l'incidence des CCNM après transplantation. L'objectif de cette étude est d'évaluer si un type de mutation de *PKD1* ou *PKD2* est associé à un risque accru d'apparition de CCNM.

Nous avons mené une étude rétrospective monocentrique incluant tous les patients atteints de PKRAD transplantés rénaux au CHU de Tours de 1987 à 2016. Nous avons utilisé notre base de données clinico-biologique, comprenant des études génétiques, et effectué des analyses multivariées avec ajustement sur les facteurs de risque de CCNM.

Nous avons inclus 245 polykystiques transplantés rénaux: 206 (84,1%) avaient une mutation de *PKD1* et 19 (7,8%) de PKD2. La durée moyenne de suivi était de 10,8 ± 6,3 ans. Au total, 162 cas de CCNM ont été diagnostiqués pendant la période de suivi, chez 69 patients (28,2%). L'incidence des CCNM à 20 ans en cas de mutation de *PKD1* était de 48,9%. Le risque de CCNM était plus faible en cas de mutation de *PKD1* troncante par rapport aux non troncantes (p=0,023). Ce risque restait significatif en analyse multivariée après ajustement sur l'âge, le sexe, le phototype et le traitement immunosuppresseur d'induction (risque relatif à 0,37 IC 95% [0,21-0,68], p<0,01). Une mutation PKD1 non troncante était également un facteur de risque de multiple CCNM après transplantation en anlyse multivariée [Odds ratio pour chaque CCNM supplémentaire: 2,08 IC 95% (1,45-2,94), P<0,001]. Nos résultats montre qu'être porteur d'une mutation non troncante de *PKD1* est un facteur de risque indépendant du développement de CCNM après une transplantation rénale.

Mots-clés:
- Polykystose rénale autosomique dominante
- Cancer cutané non-mélanomateux
- Transplantation rénale
- Mutation de *PKD1*

Abstract

Autosomal dominant polycystic kidney disease and nonmelanoma skin cancer after kidney transplantation: a genetic influence of nontruncating *PKD1* mutations

C Geneste, B Sautenet, A Bretagnol, E Chevallier, F Von Tokarski, L Machet, JM Halimi, M Büchler

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited cause of kidney failure in adults, with predominantly *PKD1* (75%) and *PKD2* (15%) mutations, leading to renal transplantation. Several studies showed that patients with *PKD1* mutation had end-stage renal disease onset 20 years earlier than those with PKD2 mutation. Furthermore, the long-term immunosuppressive treatment needed after kidney transplantation can facilitate the occurrence of nonmelanoma skin cancer (NMSC). In various cohorts, kidney graft recipients with ADPKD have a higher risk of NMSC than renal recipients with other causes. To date, there is no known cause, including genetic, to explain the association between ADPKD and the incidence of NMSC after transplantation. We investigated whether the increase in risk of NMSC after transplantation is due to a specific type of mutation in *PKD1* or *PKD2.*

We conducted a retrospective monocenter study including all renal graft recipients with ADPKD who underwent transplantation at our institution between 1987 and 2016. Given the clinico-biological database, including genetics studies, we performed multivariate analysis with adjustment on risk factors for NMSC.

We included 245 renal graft recipients with ADPKD: 206 (84.1%) with a *PKD1* mutation and 19 (7.8%) a *PKD2* mutation. The mean duration of follow-up was 10.8 ± 6.3 years. Overall, 162 cases of NMSC were diagnosed during the follow-up period in 69 patients (28.2%). The incidence of NMSC at 20 years with a *PKD1* mutation was 48.9%. In this population, the risk of NMSC was reduced with a truncating versus nontruncating mutation (p=0.023). The risk remained significant after adjustments for age, sex, phototype and immunosuppressive induction therapy on multivariate analysis (HR 0.37, CI 95% [0.21–0.68], p<0.01). A nontruncating *PKD1* mutation was a predictor of multiple skin cancer after transplantation [odds ratio for each additional skin cancer: 2.08, CI 95% (1.45–2.94), P < 0.001]. Our findings suggest that a nontruncating PKD1 mutation is an independent risk factor for NMSC developing after kidney transplantation.

Keywords:
- Autosomal dominant polycystic kidney disease
- Nonmelanoma skin cancer
- Renal transplantation
- *PKD1* mutation

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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent,
et n'exigerai jamais un salaire au-dessus de mon travail.

Admise dans l'intérieur des maisons, mes yeux
ne verront pas ce qui s'y passe, ma langue taira
les secrets qui me seront confiés et mon état ne servira pas
à corrompre les mœurs ni à favoriser le crime.

Respectueuse et reconnaissante envers mes Maîtres,
je rendrai à leurs enfants
l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime
si je suis fidèle à mes promesses.
Que je sois couverte d'opprobre
et méprisée de mes confrères
si j'y manque.

Remerciements

A Monsieur le Professeur Jean-Michel HALIMI, auprès de qui j'apprends sans cesse. En travaillant à tes côtés, j'ai pu apprécier tes qualités professionnelles, humaines, et d'enseignement. Merci pour la confiance en moi dont tu fais preuve pour l'année à venir.

A Monsieur le Professeur Laurent MACHET, je vous suis très reconnaissante d'avoir très rapidement accepté de juger ce travail, et ce, avec beaucoup d'enthousiasme je crois.

A Monsieur le Professeur Matthias BÜCHLER, pour m'avoir proposée puis accompagnée dans ce projet. Merci pour cette dernière ligne droite, pour les appels te réveillant la nuit qu'on ne compte plus et pour l'apprentissage d'une médecine sensitive !

Au Docteur Bénédicte SAUTENET, pour ta capacité à faire qu'une rédaction de thèse ou de mémoire devienne un plaisir, pour ton aide précieuse, ton encadrement en tant que chef de clinique, ton soutien et ton écoute. Merci d'avoir accepté de travailler avec moi.

A Monsieur le Docteur Eloi CHEVALLIER. « Docteur », un titre que tu portes depuis peu mais déjà fort bien. Merci d'avoir accepté de faire parti de mon jury de thèse malgré la probable angoisse que cela génère en toi, merci pour la considération que tu m'as toujours apportée, pour les heures passées ensemble auprès des familles et des patients, et pour cette complicité qui englobe bien des choses que je ne puis détailler ici!

A l'encadrement que j'ai reçu dans le service de néphrologie de Tours, une famille d'une réelle bienveillance au sein de laquelle j'ai plaisir à travailler : merci à Christelle, toujours dispo!, à Maud pour ton humanité, à Hélène ou l'agréable efficace, à Nolwenn pour tous tes conseils avisés, à Elodie M pour ton soutien, à Sylvie pour tes robes qui volent, à Anne pour ta sérénité, à Louis, encore pardon pour ton téléphone et à Philippe.

A Christelle Guillerm-Regost et Bernadette, des ARC en or. A Lise Binet pour son travail et à Chantal qu'on ne peut oublier.

Aux *Blanc manger coco* et aux *ivrognes* biensûr : Johan, ce brave Moles, Mélanie, Alex, Rouf, Mathieu. Pourvu que ça dure… A mes co-internes, amis à la vie et au labeur : Annabelle, Caro, Pauline, Louis-Marie, Elodie, mon pti Moret ♥, une co-interne au top, Floflo, merci encore pout ton aide et pas que, Juliette, les 3 Charlotte's, Margaux et Mathieu, j'ai hâte de travailler avec vous, JB, Nico, Martin, et les petits derniers Léa et Alex qui ont tenu leur rang avec brio, et aux SNO, CUEN et autres réjouissances!!

A l'équipe de Néphropédiatrie qui me supporte actuellement, et m'a supporté en pleine rédaction de thèse, mémoire, et enceinte!

Au personnel du service, votre présence et vos soins permettent d'adoucir les moments difficiles des malades, j'apprécie l'esprit d'équipe que vous partagé et qui est indispensable à la réalisation quotidienne de notre travail ; et tout spécialement à Jenny, Faby, Marie, Audrey Cocu, Lucie, Clém, William, Isa et Marion.

Au CHU de Grenoble pour son excellente formation de 2ème cycle et pour le fait de faire de l'équité entre les étudiants une priorité. J'espère réussir à rendre à mes externes le temps et l'enseignement qu'on a bien voulu m'accorder lorsque j'étais à leur place.

Aux meilleurs externes qui iront loin! Juliette, Antoine, Paul, Clément et Elise

Aux filles du labo pour leur aide dans cette année parfois compliquée, CDG power!

A ces magnifiques rencontres Tourangelles : Céline et William, Julien LM, Marie, Anthony, best colocs ever, David, Caro, Célia. Les Mud Guys Léna, Hanna, Mathilde, Romain. Amandine et Jérôme. Les amis de Julien que je compte désormais parmi les miens avec une grande fierté : ces couples en « on », les Anon, les Rochon, les Dumont, les Bichons, j'ai à chaque nouvelle occasion plaisir à vous découvrir de mieux en mieux. Pierre et Margot, Julie et Thibaut, LMT.

Aux amitiés grenobloises et à celles antérieures. Elles perdurent pour le meilleur et pour le pire: Fanny et Lucie, Tom et Nab, Laura, Claire, Titi, Laura, Steven, Boris, Sarah, Annabelle, Tiphaine.

Aux patients, pour leur courage et parfois leur spontanéité qui nous ramène aux choses simples.

A ma nouvelle famille : à Nathalie, pour être toujours aussi attentionnée, à André pour ta bienveillance, à Marie-Claude, tu m'as demandé tellement de fois « Alors, ça avance cette thèse ? », la voilà enfin. Tu nous manques… Et à tata Po, Pascal et Fredo !

A tata Ro, merci d'être là quand j'en ai besoin. A Marguerite, pour être toi tout court, rien que le fait de t'entendre me donne le sourire. A Olive et 22 pour me faire sans cesse découvrir le meilleur, mais toujours 2 ans avant tout le monde. A Michèle et Jacques qui m'ont vu pleurer le jour des résultats de P1. A Catherine et Fanny pour leur soutien lors de cette première année. A mamie, la meilleure de toute, tu as intérêt à prendre soin de toi encore longtemps. Et à mes parents biensûr, fidèles au poste, je vous dois absolument tout, ce chemin parcouru n'aurait pu se faire sans vous.

A Julien, pour tout ce que tu sais m'apporter, pour les années passées, les aventures vécues, les difficultés parcourues et surtout à celles à venir, merci de me supporter chaque jour.

Au futur bébé, même si franchement, il ne m'a pas beaucoup aidé sur ce coup là! Mais il n'y est pour rien.

A nous, à notre terreau, qu'il soit fertile, à nos voyages, qu'ils soient nombreux, à nos futures vies, qu'elles soient généreuses, épanouissantes et audacieuses.

Je dédicace ce manuscrit à mon parrain, que j'ai toujours admiré et qui m'a toujours apaisé de bien des manières. J'ai encore souvent la sensation de t'avoir à mes côtés…

Abréviations

CCNM : cancer cutané non mélanomateux

PKRAD : polykystose rénale autosomique dominante

Abbreviations

ADPKD : autosomal dominant polycystic kidney disease

Aza : azathioprine

BCC : basal cell carcinoma

CI : confidence interval

CREBBP : c-AMP response element-binding protein

CsA : cyclosporine A

EGF : epidermal growth factor

ESRD : end-stage renal disease

FK : tacrolimus

HR : hazard ratio

IL-2 : interleukin-2

LFA1 : anti-leukocyte function-associated antigen 1

MMF : mycophenolate mofetil

MSG : mutation strength group

mTOR : mammalian target of rapamycin

NMD : no mutation detected

NMSC : nonmelanoma skin cancer

PTLD : post-transplantation lymphoproliferative disease

SCC : squamous cell carcinoma

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited cause of kidney failure in adults, with prevalence ranging from 1:500 to 1:4000. Inactivating somatic mutations of a *PKD* gene, which lead to loss of function of the corresponding polycystin, cause clonal expansion of kidney cyst epithelium and cyst formation. The typical phenotype is progressive kidney cyst development and expansion leading to end-stage kidney disease (ESRD) in middle age, with a risk of 50%[1,2]. ADPKD is classically inherited as an autosomal dominant disease resulting from heterozygous mutations in *PKD1* or *PKD2.*

Heterozygous germ-line mutations, predominantly in *PKD1* (on the short arm of chromosome 16, Fig 1.) in 77% of cases or in *PKD2* (on the long arm of chromosome 4) in 13% of cases, are responsible for ADPKD, with a penetrance of nearly 100%. In 10% of patients, no mutation in *PKD1* or *PKD2* is found with current testing methodologies[3].

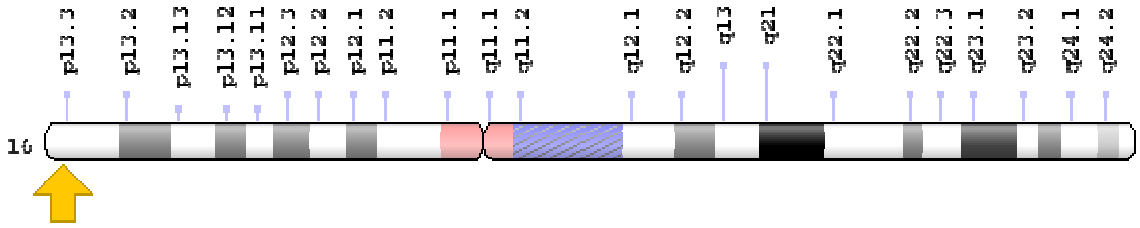


Figure 1. ***PKD1*** **cytogenetic Location:** 16p13.3, which is the short (p) arm of chromosome 16 at position 13.3. Molecular Location: base pairs 2,088,708 to 2,135,898 on chromosome 16 (Homo sapiens Annotation Release 109, GRCh38.p12, 47 190 base pairs – 15730 aa)

The severity of disease, even in mutation characterized cases, is variable and inversely correlated with the level of polycystin 1 function[4]. In recent years, the Genkyst cohort (a regional cohort involving all private and public nephrology centers in the west of France) described the largest mutation screening in patients with ADPKD, to link the type of mutation to clinical outcome. The authors showed that patients with *PKD1* mutation had ESRD onset 21.6 years earlier than those with *PKD2* mutation[5–7]. Similarly, the same applies to patients with *PKD1* truncating mutation compared to patients with *PKD1* nontruncating mutation[8].

After renal transplantation, the need to maintain a long-term immunosuppressive treatment increases the risk of some types of cancer, including skin cancer. Nonmelanoma skin cancers (NMSC), including basal cell carcinoma (BCC) and squamous cell carcinoma

(SCC), are the most common, with an incidence of up to 40% to 80% at 20 years post-kidney transplantation[9].

Several studies have shown that kidney graft recipients with ADPKD have a higher risk of NMSC than renal recipients with other causes. This difference has been observed in different populations, US and European[10,11]. To date, there is no known cause, including genetic, to explain the association between ADPKD and the incidence of NMSC after transplantation.

Here, we investigated whether the increase in risk of NMSC after transplantation is due to a specific type of mutation in the *PKD1* or *PKD2* gene. We conducted a retrospective monocenter study including all renal graft recipients with ADPKD who underwent transplantation at our institution between 1987 and 2016. Given the clinico-biological database, including genetics studies, we performed multivariate analysis with adjustment on risk factors for NMSC.

PATIENTS AND METHODS

Study population

This was a retrospective observational study performed in a French University Hospital from January 1987 to July 2016. All renal graft recipients with ADPKD who were followed for at least 3 months at our institution were included.

Induction immunosuppressive therapy was administrered in almost all cases, whether with antithymocyte globulins or interleukin-2 (IL-2) receptor antagonists (Beyong 1999). Maintenance immunosuppressive therapy, included cyclosporine, tacrolimus or, more recently, mammalian target of rapamycin (mTOR) inhibitors, mycophenolate mofetil (starting at 2 g/day) or azathioprine (2 mg/kg/day). Prednisone (1 mg/kg/day for the first 2 weeks) was progressively decreased and withdrawn within the first year after transplantation in patients with low immunological risk. Patients with acute rejection episodes received methylprednisolone for 3 to 5 days, followed by oral prednisone. With steroid-resistant rejection, polyclonal antibodies were prescribed.

Ambulatory follow-up was performed once a month during the first year post-transplantation and further once a year in most cases. Patients were referred annually to a dermatologist for cutaneous examination, according to the current recommendations.

Diagnosis of ADPKD and genetic status

The diagnosis of ADPKD was based on a personal history of progressive renal failure associated with a suggestive family history of ADPKD and typical ultrasonography[12], tomodensitometry or MRI evidence of polycystic kidneys. These patients or family members were included when possible in the Genkyst cohort. Genkyst is a cross-sectional study involving >70 nephrologist investigators working in France. Patients with ADPKD from the Genkyst cohort were recruited from dialysis centers and by nephrology and transplant consultations between 2009 and January 2015. This study involved a genetic testing with mutation screening for the coding regions of *PKD1, PKD2, neutral α-glucosidase AB* (*GANAB*)*, hepatocyte nuclear factor 1 β* (*HNF1B*)*, uromoduline* (*UMOD*)*, secretory* 63 (SEC63)*, protein kinase C subtrate 80K-H* (*PRKCSH*) and *LDL-R-related protein* 5 *(LRP5).* For *PKD1*, the mutation effect (truncating versus nontruncating) was also reported.

The mutation screening protocol consisted of extraction of DNA on magnetic beads, amplification of the sequences of interest, sequencing and comparison with the reference sequence [*PKD1* (NM_001009944.2), *PKD2* (NM_000297.2), *HNF1B* (NM_000458.1),

SEC63 (NM_007214.4), *PKRCSH* (NM_002743.2), *UMOD* (NM_003361.2), *LRP5* (NM_002335.2) and *GANAB* (NM_198335.3)]. Genetic analysis was performed in the laboratory of molecular genetics and histocompatibility of Brest University Hospital Center (consent form in Appendix 1, p.34).

Data collection

Data were extracted from the local database and individually collected in each hospital records. Patients were informed about the data collection and a signed consent was mandatory for genetic analysis.

Data collected on the day of transplantation were recipient characteristics (sex, age, skin phototype, history of cancers, dialysis duration before transplantation), number of grafts, donor characteristics (sex, age, deceased or living donor) and immunosuppressive induction therapy. For patients who underwent transplantation twice, the induction treatment of the graft preceding the appearance of a first NMSC (in case of NMSC) was retained; otherwise, the use of antithymocyte globulins was retained if it was used at least once.

Data collected after transplantation were immunosuppressive maintenance therapy at 3 months, acute rejection episodes, the use of rituximab and the occurrence of all types of histologically proven cancers.

Definition of phototype

The phototype of each patient was determined by a dermatologist based on the Fitzpatrick classification[13] and recorded in the file. When this information was missing, skin phototype was determined by two independent trained nephrologists who participated in the follow-up. In case of disagreement, the two physicians discussed their point of view and gave a final result.

Six stages were defined as follows:

- Phototype I: skin color ivory white; easily sunburned; no tanning
- Phototype II: skin color white; easily sunburned; minimal tanning with difficulty
- Phototype III: skin color white; moderate sunburning; moderate and uniform tanning
- Phototype IV: skin color beige/olive, light tanning; minimal sunburning; moderate and easy tanning
- Phototype V: skin color light brown or tanned; rare sunburning; profuse tanning
- Phototype VI: skin color dark brown or black; no sunburning; profuse tanning

Most of patients lived in a temperate climate in the Loire valley.

Definition of NMSC

NMSC included cases of biopsy-proven BCC, SCC and Bowen's disease (considered *in situ* SCC). Melanomas, cutaneous Kaposi's sarcomas, primary cutaneous lymphomas and other rare types of skin tumor, including adnexal skin tumors, were therefore excluded.

Statistical analysis

Continuous data are presented as mean ± SD and categorical data as proportions. Cox models were used in univariate and multivariate analyses to assess the association between mutation type (*PKD1*, truncating, nontruncationg, *PKD2* mutation or no mutation detected), age, sex, phototype, time on dialysis before transplantation, history of cancer before transplantation, number of grafts, immunosuppressive treatments, and the development of NMSC after transplantation. Results are expressed as hazard ratios (HR), 95% confidence intervals (CI) and P-values.

Multivariate analyses included the following variables: mutation type, age, sex, skin phototype and immunosuppressive induction by antithymocyte globulin antibodies. Poisson regression was used to assess whether the mutation effect on *PKD1* (truncating or not) was associated with multiple skin cancers after transplantation, estimating odds ratios (OR) and 95% CI. GraphPad Prism 5 and R v3.2.3 (R Foundation for Statistical Computing, Vienna, Austria) were used for analysis. $P < 0.05$ was considered statistically significant.

RESULTS

Overall, 309 ADPKD patients received a renal transplant and 245 were included in our cohort (Fig 2). Mean duration of follow-up (±SD) was 10.8 ± 6.3 years (median 9.9 years; range 0.4–31.3 years; total observation period 2641 patient-years).

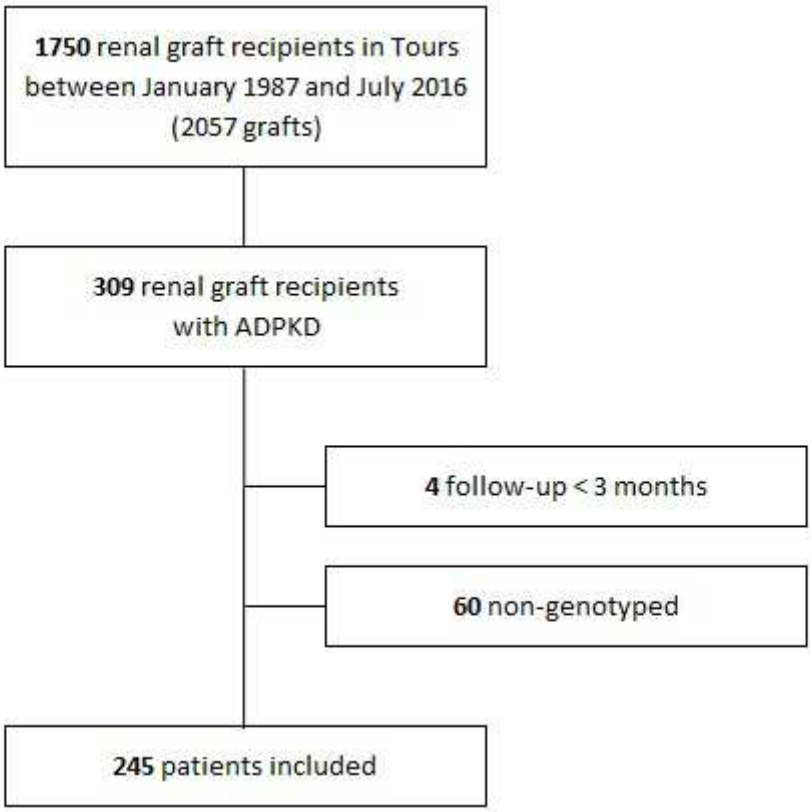


Figure 2. Flow chart (ADPKD : autosomal dominant polycystic kidney disease)

Baseline characteristics

PKD1 mutation was identified in 206 patients (84.1%) and *PKD2* mutation in 19 (7.8%); no mutation was detected in 20 patients (8.2%) (Table 1). Listing of the detected mutations (with genetic location, number of patients with the mutation and NMSC associated) is available in Appendix 3 (p.35).

Mean age at transplantation was 54.6 ± 9.9 years. The median length time on dialysis before transplantation was 16.5 months. Overall, 130 patients were men (53.1%). At the time of transplantation, patients with a *PKD2* mutation were older than those with a *PKD1* mutation (65.6 ± 8.3 vs 53.5 ± 9.1 years). Most patients had a phototype of II or III because they were of Caucasian origin. A history of cancer before transplantation was reported in 4.1% of all transplant recipients; at least 0.8% of these patients had an NMSC before transplantation, all with a PKD1 mutation.

Nearly 10% (9.8%) of the patients had a history of kidney transplantation. Immunosuppressive induction therapy included antithymocyte globulin antibodies for 45.7% and IL-2 receptor antagonists for 48.6% (mainly after 1999); 4.5% of patients had no induction therapy. Immunosuppressive maintenance therapy at 3 months included 45.7% on cyclosporine, 51.8% tacrolimus and 4.5% mTOR inhibitors (sirolimus or everolimus); 86.1% mycophenolate mofetil and 11.8% azathioprine. Nearly all patients (92.2%) were still receiving corticosteroids at 3 months after transplantation. Only 4.5% received a kidney from a living donor.

At least one acute rejection episode occurred in 26.8% of the patients; 35 (14.7%) had biopsy-proven solid cancer (excluding NMSC) or post-transplantation lymphoproliferative disease (PTLD) after transplantation.

Table 1. Population characteristics of renal graft recipients with autosomal dominant polycystic kidney disease (ADPKD) and PDK1 or PDK2 mutation or no mutation detected (NMD)

Characteristics	Renal graft recipients with ADPKD, *n* (%)		
	PKD1 mutation (n=206)	*PKD2* mutation (n=19)	NMD (n=20)
Sex			
Male	108 (52.4)	12 (63.2)	10 (50.0)
Female	98 (47.6)	7 (36.8)	10 (50.0)
Age at transplantation (year)			
18-50	63 (30.6)	0	6 (30.0)
> 50	143 (69.4)	19 (100)	14 (70.0)
mean ± SD	53.5 ± 9.1	65.6 ± 8.3	56.2 ± 12.6
Skin phototype			
1	2 (1.0)	1 (5.3)	0
2	84 (40.8)	8 (42.1)	8 (40.0)
3	92 (44.7)	9 (47.4)	7 (35.0)
4	21 (10.2)	1 (5.3)	3 (15.0)
5 or 6	3 (1.5)	0	1 (5.0)
History of NMSC	2 (1.0)	0	0
History of cancer (non-NMSC)	10 (4.9)	0	0
Time on dialysis before transplantation (month) (mean ± SD)	20.7 ± 20.6	15.3 ± 18.7	37.4 ± 53.3
Number of grafts			
1	184 (89.3)	18 (94.7)	19 (95.0)
2	22 (7.2)	1 (5.3)	1 (5.0)
Donor characteristics (1st graft)			
Male	129 (62.6)	13 (68.4)	15 (75.0)
Age (mean ± SD)	49.5 ± 15.7	68.5 ± 10.4	57.1 ± 15.5
Deceased donor	195 (94.7)	19 (100)	20 (100)
Immunosuppressive induction			
IL-2 receptor antagonists	95 (46.1)	15 (78.9)	9 (45.0)
Antithymocyte antibodies	97 (47.1)	4 (21.0)	11 (55.0)
Anti-LFA1 antibodies	3 (1.5)	0	0
No induction	11 (5.3)	0	0
Immunosuppressive medications (at 3 months after transplantation)			
Tacrolimus	100 (48.5)	13 (68.4)	14 (70.0)
Ciclosporine	101 (49.0)	5 (26.3)	6 (30.0)
MMF	173 (84.0)	19 (100)	19 (95.0)
mTOR inhibitors	9 (4.4)	1 (5,3)	1 (5.0)
Azathioprine	28 (13.6)	0	1 (5.0)
Corticosteroids	189 (91.7)	18 (94.7)	19 (95.0)
Use of rituximab	1 (0.5)	2 (10.5)	0
Acute rejection episode	61 (29.6)	4 (21.0)	5 (25.0)
Occurrence after transplantation			
Solid cancer (excluding NMSC)	23 (11.2)	2 (10.5)	3 (15.0)
PTLD	7 (3.4)	0	0

Data are *n* (%) unless indicated. PKD (polycystic kidney disease), NMSC (nonmelanoma skin cancer), IL-2 (interleukin-2), LFA1 (leukocyte function-associated antigen 1), MMF (mycophenolate mofetil), mTOR (mammalian target of rapamycin), PTLD (post-transplant lymphoproliferative disease)

Among the 206 patients with a *PKD1* mutation, 150 (72.8%) had a truncating mutation and 56 (27.2%) a nontruncating mutation (Table 2). The mean age at transplantation was 52.9 ± 8.6 and 55.1 ± 10.3 years with a truncating and nontruncating mutation, respectively. Immunosuppressive induction treatment was based on antithymocyte antibodies for 46.7% of patients with a truncating mutation and 48.2% with a nontruncating mutation.

Table 2. Characteristics of renal graft recipients with truncating or nontruncating *PKD1* mutation

Characteristics	Truncating mutation (n=150)	Nontruncating mutation (n=56)
Sex		
Male	77 (51.3)	31 (55.4)
Female	73 (48.7)	25 (44.6)
Age at transplantation (year)		
18-50	48 (32)	15 (26.8)
>50	102 (68.0)	41 (27.3)
mean ± SD	52,9 ± 8.6	55,1 ± 10.3
Skin phototype		
1	1 (0.7)	1 (1.8)
2	60 (40.0)	24 (42.9)
3	72 (48.0)	20 (35.7)
4	13 (8.7)	8 (14.3)
5	1 (0.7)	2 (3.6)
Immunosuppressive induction		
IL-2 receptor antagonists	72 (48.0)	23 (41.1)
Antithymocyte antibodies	70 (46.7)	27 (48.2)
Anti-LFA1 antibodies	2 (1.3)	1 (1.8)
No induction	6 (4.0)	5 (8.9)

Data are n (%) unless indicated.
PKD (polycystic kidney disease), IL-2 (interleukin-2), LFA1 (leukocyte function-associated antigen 1)

Distribution of cases of nonmelanoma skin cancer

In total, 162 cases of NMSC were diagnosed during follow-up in 69 patients (28.2%); 57 patients with a *PKD1* mutation (27.7% of patients with a *PKD1* mutation), 8 with a *PKD2* mutation (42.1% of this population), and 4 with no mutation detected (20% of this population). At least one NMSC developed in 36 (24.0%) patients with a *PKD1* truncating mutation and 21 (37.5%) with a nontruncating mutation. A total of 18% of the patients had at least one case of BCC, 12.2% one case of SCC, and 6.9% one case of Bowen's disease (Table 3a); 6.9% had multiple types of NMSC. Nearly half of the patients with NMSC after transplantation (47.8%, n=99) had more than one NMSC during follow-up (Table 3b).

Table 3. Patients with ADPKD suffering from NMSC after renal transplantation

(a) Occurence of NMSC during follow-up: BCC, SCC and Bowen's disease

Genetic status	BCC	SCC	Bowen	Total
***PKD1* mutation (n=206)**	37 (18.0)	27 (13.1)	15 (7.3)	57 (27.7)
Truncating mutation (n=150)	25 (16.7)	15 (10.0)	8 (5.3)	36 (24.0)
Nontruncating mutation (n=56)	12 (21.4)	12 (21.4)	7 (12.5)	21 (37.5)
***PKD2* mutation (n=19)**	5 (26.3)	2 (10.5)	1 (5.3)	8 (42.1)
NMD (n=20)	2 (10.0)	1 (5.0)	1 (5.0)	4 (20.0)
Total (n=245)	44 (18.0)	30 (12.2)	17 (6.9)	69 (28.2)

(b) Number of NMSCs per patient during follow-up

Genetic status	1 NMSC	2 NMSCs	≥ 3 NMSCs
***PKD1* mutation (n=206)**	28 (13.6)	10 (4.9)	19 (9.2)
Truncating mutation (n=150)	20 (13.3)	7 (4.7)	9 (6.0)
Nontruncating mutation (n=56)	8 (14.3)	3 (5.4)	10 (17.9)
***PKD2* mutation (n=19)**	5 (26.3)	0	3 (15.8)
NMD (n=20)	3 (15.0)	0	1 (5.0)
Total (n=245)	36 (14.7)	10 (4.1)	23 (9.4)

Data are n patients (% of the genetic status population).
NMSC (nonmelanoma skin cancer), ADPKD (autosomal dominant polycystic kidney disease), NMD (no mutation detected), SCC (squamous cell carcinoma), BCC (basal cell carcinoma)

Incidence of NMSC during follow-up

At 10 years after transplantation, at least one NMSC occurred in 27.4% of patients with a *PKD1* mutation, 69.2% with a *PKD2* mutation and 15.5% with no mutation detected. The incidence of NMSC in the *PKD1* population was 48.9% at 20 years and 68.6% at 30 years (Fig. 3).

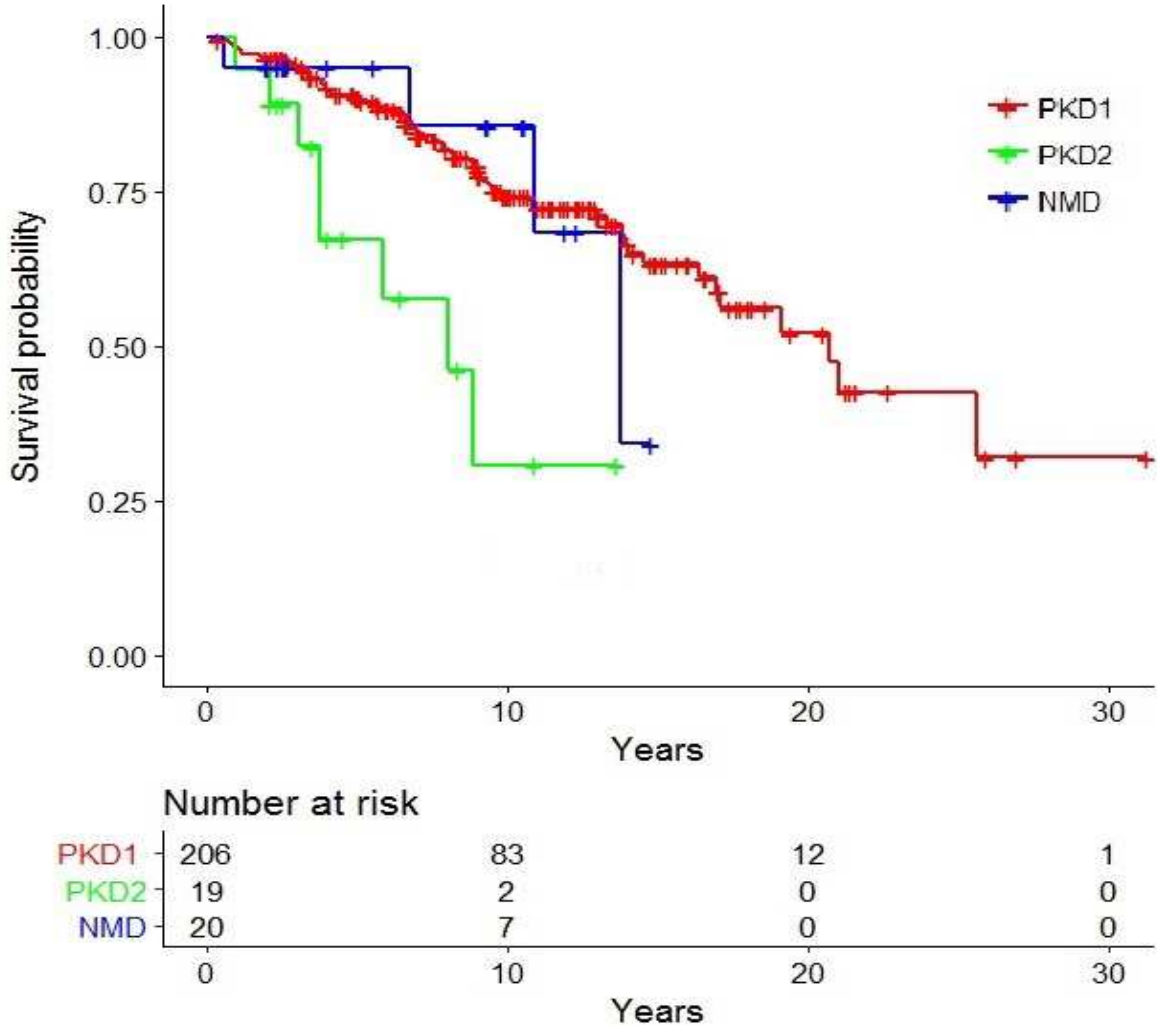


Figure 3. Survival without NMSC: Kaplan–Meier curves of time from transplantation to cancer diagnosis in 245 renal graft recipients with ADPKD (206 with *PKD1* mutation, 19 with *PKD2* mutation and 20 with no mutation detected [NMD]).

The incidence of NMSC was higher with a nontruncating than truncating *PKD1* mutation (p=0.023) (Fig. 4). At 10 years after transplantation, 20.3% of patients with a truncating *PKD1* mutation and 39.9% with a nontruncating *PKD1* mutation had at least one NMSC. The incidence of NMSC at 20 years was 45.3% with a truncating mutation and 55.5% with a nontruncating mutation.

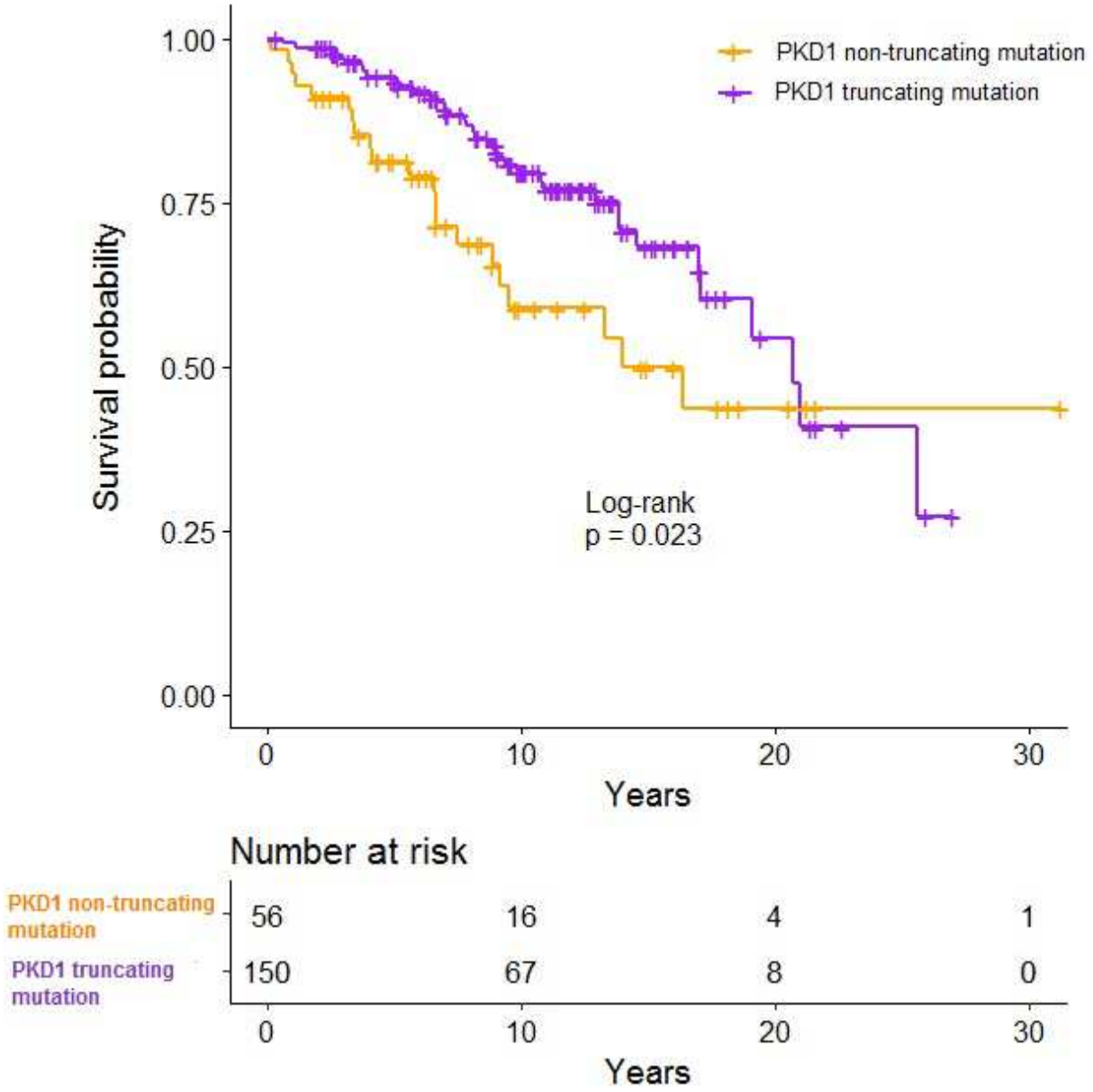


Figure 4. Survival without NMSC: Kaplan–Meier curves of time from transplantation to cancer diagnosis in 206 renal graft recipientswith *PKD1* mutation.

Risk factors for NMSC in renal graft recipients with ADPKD

Risk of developing NMSC after transplantation was increased with a PKD2 mutation and a PKD1 nontruncating mutation (Table 4). Risk of NMSC was increased with age and sex, and was reduced with induction with antithymocyte antibodies as immunosuppressive induction on univariate analysis. The length of time on dialysis before transplantation, number of grafts and immunosuppressive therapies did not significantly increase the risk of NMSC.

Table 4. Risk factors for nonmelanoma skin cancer during follow-up in autosomal dominant polycystic kidney disease: univariate analysis.

	NMSC		
	HR	95% CI	*P*-value
Genetic factors			
PKD1 (yes/no)	0.48	0.25 - 0.90	**0.023**
PKD1 truncating *vs* nontruncating mutation	0.54	0.31 - 0.93	**0.025**
PKD2 (yes/no)	3.62	1.70 - 7.72	**< 0.001**
NMD (yes/no)	1.02	0.37 - 2.81	0.97
Clinical parameters			
Age (per 10 years)	1.70	1.26 - 2.29	**< 0.001**
Sex (male *vs* female)	2.04	1.23 - 3.39	**0.006**
Skin phototype ≤ 3 (yes/no)	2.19	0.88 - 5.44	**0.09**
Time on dialysis (per year of dialysis)	0.89	0.75 - 1.06	0.19
History of cancer before transplantation (yes/no)	1.27	0.40 - 4.07	0.68
1 graft *vs* 2 grafts	1.31	0.70 - 2.46	0.40
Immunosuppressive medications			
Immunosuppressive induction (antithymocyte antibodies *vs* IL-2 receptor antagonists/anti-LFA1)	0.59	0.35 -0.98	**0.043**
Induction *vs* no induction	0.81	0.25 - 2.58	0.72
FK *vs* CsA	1.19	0.72 - 1.98	0.50
mTOR inhibitor (yes/no)	1.34	0.42 - 4.32	0.61
MMF *vs* Aza	1.38	0.77 - 2.47	0.27

NMSC (nonmelanoma skin cancer), PKD (polycystic kidney disease), NMD (No mutation detected), IL-2 (interleukin-2), LFA1 (leukocyte function-associated antigen 1), FK (tacrolimus), CsA (cyclosporine A), mTOR (mammalian target of rapamycin), MMF (mycophenolate mofetil), Aza (azathioprine), HR (hazard ratio), CI (confidence interval).

On univariate analysis, with a PKD1 mutation, risk of NMSC was increased with only age (HR 1.49, 95% CI [1.06-2.08], p=0.02) and sex (HR 2.70, 95% CI [1.50-4.88], p <0.001) (Table 5).

Table 5. Risk factors for nonmelanoma skin cancer during follow-up in patients with ADPKD and a *PKD1* mutation: univariate analysis.

	NMSC		
	HR	95% CI	*P*-value
PKD1 truncating *vs* nontruncating mutation	0.54	0.31 - 0.93	**0.025**
Genetic factors			
Age (per 10 years)	1.49	1.06 - 2.08	**0.020**
Sex (male *vs* female)	2.70	1.50 - 4.88	**< 0.001**
Skin phototype ≤ 3 (yes/no)	1.79	0.71 - 4.50	0.21
Time on dialysis (per year of dialysis)	0.88	0.72 - 1.08	0.24
History of cancer before transplantation (yes/no)	1.42	0.44 - 4.57	0.56
1 graft *vs* 2 grafts	1.28	0.64 - 2.54	0.49
Immunosuppressive medications			
Immunosuppressive induction (antithymocyte antibodies *vs* IL-2 receptor antagonists/anti-LFA1)	0.60	0.33 - 1.06	0.077
Induction *vs* no induction	0.89	0.28 - 2.86	0.85
FK *vs* CsA	1.38	0.77 - 2.46	0.28
mTOR inhibitor (yes/no)	0.49	0.07 - 3.58	0.49
MMF *vs* Aza	1,6	0.88 - 2.93	0.13

NMSC (nonmelanoma skin cancer), PKD (polycystic kidney disease), IL-2 (interleukin-2), LFA1 (leukocyte function-associated antigen 1), FK (tacrolimus), CsA (cyclosporine A), mTOR (mammalian target of rapamycin), MMF (mycophenolate mofetil), Aza (azathioprine), HR (hazard ratio), CI (confidence interval).

On multivariate analysis including the variables age at transplantation, sex, skin phototype and induction with antithymocyte antibodies (Tables 6 and 7), PKD2 mutation was no longer associated with the occurrence of NMSC (HR 1.76, 95% CI [0.77–4.02], p=0.18). However, risk of NMSC was reduced with a PKD1 truncating versus nontruncating mutation (HR 0.39, 95% CI [0.21–0.72], p<0.01).

Table 6. Genetic status in autosomal dominant polycystic kidney disease as a risk factor for nonmelanoma skin cancer after kidney transplantation: multivariate analysis

	NMSC		
	adjusted HR	95% CI	*P*-value
Genetic factors			
PKD1 *(ref)*	-	-	-
PKD2 (yes/no)	1.76	0.77 - 4.02	0.18
NMD (yes/no)	1.16	0.41 - 3.29	0.77
Adjustement criterias			
Age (per 10 years)	1.88	1.35 - 2.62	**< 0.001**
Sex (male *vs* female)	1.98	1.20 - 3.49	**0.012**
Skin phototype ≤ 3 (yes/no)	2.09	0.81 - 5.18	0.12
Antithymocyte antibodies (yes/no)	0.76	0.44 - 1.3	0.31

NMSC (nonmelanoma skin cancer), PKD (polycystic kidney disease), NMD (no mutation detected), ref (reference), HR (hazard ratio), CI (Confidence interval).

Table 7. PKD1 mutation effect as a risk factor for nonmelanoma skin cancer after kidney transplantation: multivariate analysis

	NMSC		
	adjusted HR	95% CI	*P*-value
PKD1 truncating mutation (yes/no)	0.39	0.21 - 0.72	**0.002**
Age (per 10 years)	1.85	1.26 - 2.71	**0.001**
Sex (male *vs* female)	3.68	1.95 - 6.95	**< 0.001**
Skin phototype ≤ 3 (yes/no)	1.70	0.67 - 4.33	0.26
Antithymocyte antibodies (yes/no)	0.58	0.32 - 1.06	0.076

NMSC (nonmelanoma skin cancer), PKD (polycystic kidney disease), HR (hazard ratio), CI (confidence interval).

Poisson regression was used to consider patients with more than one skin cancer. Despite adjustment for age, sex, skin phototype and induction with antithymocyte anibodies, *PKD1* nontruncating mutation was a predictor of multiple skin cancer after transplantation [OR for each additional skin cancer: 2.08, 95% CI (1.45–2.94), $P < 0.001$]. We did not adjust on the duration of follow-up because it was similar in the two groups (11.4 ± 6.2 years with a truncating mutation and 11.6 ± 6.9 years with a nontruncating mutation).

DISCUSSION

Our analysis indicates an increased risk of developing both NMSC and multiple NMSC after kidney transplantation in a specific population, patients with a *PKD1* nontruncating mutation. Indeed, this mutation effect remained a risk factor for the development of BCC, SCC and Bowen's disease, even after adjustments for age, sex, skin phototype and immunosuppressive induction[14,15]. Of note, a low CD4 lymphocyte count has been associated with skin cancers in kidney transplant recipients[16] but was not confirmed in all studies[17]. Our results did not reveal an increased risk for patients with a *PKD2* mutation or no mutation detected. Nonmelanoma skin cancers are a concern because they are the most common cancers after transplantation[14] and are associated with significant morbidity and mortality.

Our distribution of genetic status was consistent with that of other ADPKD cohorts[5,6,8] : 84% with *PKD1* mutation (72.8% truncating and 27.2% nontruncating), 7.8% *PKD2* mutation and 8.2% no mutation detected. Proportions and incidence of NMSC after transplantation agreed with other studies, also in polycystic cohorts[18], and concerning the increased risk in patients with ADPKD as compared with other kidney disease (20.1% *vs* 9.9% in all patients who underwent transplantation in Tours). This results have been showed in our cohort of renal graft recipient with ADPKD[10] and in two large retrospective american studies[11,19]. Finally, mean age at ESRD onset was 51.1 ± 8.4 years with a truncating mutation and 53.3 ± 10.4 years with a nontruncating mutation. This difference was less than in the Genkyst cohort, finding a median age at ESRD onset of 55.6 and 67.9 years, respectively[6].

Nevertheless, several works found a strong correlation between the type of *PKD1* mutation and renal survival[7]. Indeed, results of renal survival in patients with a truncating or nontruncating *PKD1* mutation were confirmed in a large study of 1120 patients[8]. Moreover, *PKD1* mutation types have been analysed in more detail. Truncating mutations (frameshifting indels, nonsense mutations, canonical splicing changes, and in-frame indels ≥ 5 amino acids) were defined as mutation strength group 1 (MSG1) and nontruncating mutations (missense, in-frame indels ≤ 4 amino acids and noncanonical splicing events) as strongly predicted (MSG2) and weakly predicted (MSG3) nontruncating by bioinformatics assay. Severe disease was associated more with strong than weak predicted nontruncating *PKD1* mutations[8].

The effect of the type of mutation in patients with ADPKD on the incidence of NMSC after transplantation has never been studied. This is the first study to reveal this finding. The underlying mechanisms linking *PKD1* nontruncating mutation and NMSC are not clear; however, genetic factors such as interleukine-10 genotype seem associated with skin cancer in renal transplant patients[20]. We therefore hypothesized that there might be candidate genes influencing cutaneous tumorogenesis. For instance, the *C-AMP response element (CREB)* gene is located in the short arm of chromosome 16 at position 13.3 as for the *PKD1* gene. Changes in the structure of chromosome 16 are associated with several types of cancer. An example is acute myeloid leukemia with chromosomal translocation disrupting the region of chromosome 16 containing *CREB*. CREB-binding protein plays a role in regulating cell growth and division, which helps prevent the development of cancers. The effect of mutation types of ADPKD patients on the incidence of NMSC could be related to a genetic local effect related to *CREB.* In fact, genomic analysis of lymph node metastases from primary SCC showed frequent (28%) CREBBP mutation[21]. The role of CREBBP in SCC is unclear, but a second study found CREBBP inactivation associated with tumor progression in SCC[22].

In the same way, dysregulation of the *epidermal growth factor (EGF)* gene, located on chromosome 4 near *PKD2*, has been associated with the growth and progression of certain cancers, and perhaps NMSC[23]. It could be a candidate gene. However, our results showed no difference in occurrence of NMSC with and without a *PKD2* mutation, perhaps because of the small number of patients.

Thus, the mutation position could be important (Appendix 2, p.35), so we separated *PKD1* mutations in two groups, 3' half versus 5' mutation position. Codon 2151 is the midpoint in the *PKD1* coding region. The two mutation groups did not differ in incidence of NMSC. The only reported allelic effect of ADPKD causing genes was a weak effect of PKD1 mutation position on the severity of renal disease[24] and the occurrence of intracranial aneurysms[25], with 5' mutations more severe than 3' mutations; analysis performed in a larger cohort showed no difference either[6].

Polycystin-1, the protein encoded by *PKD1* and underexpressed in the presence of *PKD1* mutation, has a role in cation transport, mechanosensitivity, cell–cell/matrix interactions and also regulation of the cell cycle. The neoplastic nature of renal cysts in ADPKD has been recognized for several years[26]. Zheng et al.[27] reported that in vitro overexpression of polycystin-1 induced apoptosis and cell cycle arrest in the Go/G1 phase in cancer cells. As the authors hypothesized, another explanation for our results could be a

potential suppressor tumor role of polycystin-1, which is expressed in many tissues, in particular the skin[28].

Finally, our findings suggest a genetic predisposition of developing NMSC after kidney transplantation. The two categories of nontruncating mutation (MSG2 and MSG3) may explain our results. Disease severity did not differ by mutation types or truncating and nontruncating *PKD2* mutations (but the frequency of nontruncating mutations was low). Pathophysiologic explanations remain to be demonstrated.

Of note, the incidence of solid cancers (excluding skin cancers) or PTLD after transplantation for patients with and without ADPKD was previously analysed and did not significantly differ in renal graft recipients who underwent transplantation at our institution[10]. Again, *PKD1* nontruncating mutation carriers are an exception in that they more frequently exhibited solid organ cancer than did other patients (data not shown).

Several study limitations must be considered. First, in our *PKD2* and NMD populations, the issue of allelic effect on the incidence of NMSC after transplantation was not addressed because of the small number of patients. These two populations were too different to be compared. Second, we could not test other risk factors for NMSC, such as sun exposure, HPV infection or tobacco consumption. Of note, nearly all the patients lived in the center of France and were of caucasian origin. Furthermore, this study was a retrospective analysis, and some information may not have been available. Finally, among the 305 patients with ADPKD who underwent transplantation in our institution, 60 could not be genotyped because of death and/or graft failure at the time of data collection.

In conclusion, we showed a significant association between the type of mutation and nonmelanoma skin cancer in renal graft recipient with ADPKD. We found a nontruncating *PKD1* mutation as an independent risk factor for developing NMSC after kidney transplantation. This is the first study of genetic predisposition of NMSC developing after kidney transplantation in these patients. Therefore, ADPKD genetic information can identify a population at increased risk that requires close clinical monitoring. Preventing skin cancer should be a major concern in these patients. Finally, the genetic mechanisms underlying these results need to be investigated in detail.

REFERENCES

1. Torres VE, Harris PC, Pirson Y. Autosomal dominant polycystic kidney disease. *Lancet Lond. Engl.* 2007;369(9569):1287–1301.

2. Rangan GK, Alexander SI, Campbell KL, et al. KHA-CARI guideline recommendations for the diagnosis and management of autosomal dominant polycystic kidney disease. *Nephrol. Carlton Vic*. 2015;

3. Rossetti S, Consugar MB, Chapman AB, et al. Comprehensive Molecular Diagnostics in Autosomal Dominant Polycystic Kidney Disease. *J. Am. Soc. Nephrol.* 2007;18(7):2143–2160.

4. Hopp K, Ward CJ, Hommerding CJ, et al. Functional polycystin-1 dosage governs autosomal dominant polycystic kidney disease severity. *J. Clin. Invest.* 2012;122(11):4257–4273.

5. Audrézet M-P, Cornec-Le Gall E, Chen J-M, et al. Autosomal dominant polycystic kidney disease: comprehensive mutation analysis of PKD1 and PKD2 in 700 unrelated patients. *Hum. Mutat.* 2012;33(8):1239–1250.

6. Cornec-Le Gall E, Audrézet M-P, Chen J-M, et al. Type of PKD1 mutation influences renal outcome in ADPKD. *J. Am. Soc. Nephrol. JASN*. 2013;24(6):1006–1013.

7. Harris PC, Hopp K. The Mutation, a Key Determinant of Phenotype in ADPKD. *J. Am. Soc. Nephrol.* 2013;24(6):868–870.

8. Heyer CM, Sundsbak JL, Abebe KZ, et al. Predicted Mutation Strength of Nontruncating PKD1 Mutations Aids Genotype-Phenotype Correlations in Autosomal Dominant Polycystic Kidney Disease. *J. Am. Soc. Nephrol. JASN*. 2016;

9. Ho WL, Murphy GM. Update on the pathogenesis of post-transplant skin cancer in renal transplant recipients. *Br. J. Dermatol.* 2008;158(2):217–224.

10. Bretagnol A, Halimi JM, Roland M, et al. Autosomal dominant polycystic kidney disease: risk factor for nonmelanoma skin cancer following kidney transplantation. *Transpl. Int. Off. J. Eur. Soc. Organ Transplant.* 2010;23(9):878–886.

11. Otley CC, Cherikh WS, Salasche SJ, et al. Skin cancer in organ transplant recipients: effect of pretransplant end-organ disease. *J. Am. Acad. Dermatol.* 2005;53(5):783–790.

12. Pei Y, Obaji J, Dupuis A, et al. Unified criteria for ultrasonographic diagnosis of ADPKD. *J. Am. Soc. Nephrol. JASN*. 2009;20(1):205–212.

13. Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. *Arch. Dermatol.* 1988;124(6):869–871.

14. Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. *N. Engl. J. Med.* 2003;348(17):1681–1691.

15. Ramsay HM, Fryer AA, Reece S, Smith AG, Harden PN. Clinical risk factors associated with nonmelanoma skin cancer in renal transplant recipients. *Am. J. Kidney Dis. Off. J. Natl. Kidney Found.* 2000;36(1):167–176.

16. Ducloux D, Carron PL, Rebibou JM, et al. CD4 lymphocytopenia as a risk factor for skin cancers in renal transplant recipients. *Transplantation*. 1998;65(9):1270–1272.

17. Thibaudin D, Alamartine E, Mariat C, Absi L, Berthoux F. Long-term kinetic of T-lymphocyte subsets in kidney-transplant recipients: influence of anti-T-cell antibodies and association with posttransplant malignancies. *Transplantation*. 2005;80(10):1514–1517.

18. Jankowska M, DębskaŚlizień A, ImkoWalczuk B, et al. Skin cancer in kidney transplant recipients affected with autosomal dominant polycystic kidney disease. *Clin. Transplant.* 2016;30(4):339–343.

19. Kasiske BL, Snyder JJ, Gilbertson DT, Wang C. Cancer after kidney transplantation in the United States. *Am. J. Transplant. Off. J. Am. Soc. Transplant. Am. Soc. Transpl. Surg.* 2004;4(6):905–913.

20. Laing ME, Kay E, Conlon P, Murphy GM. Genetic factors associated with skin cancer in renal transplant patients. *Photodermatol. Photoimmunol. Photomed.* 2007;23(2–3):62–67.

21. Li YY, Hanna GJ, Laga AC, et al. Genomic analysis of metastatic cutaneous squamous cell carcinoma. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* 2015;21(6):1447–1456.

22. Watt SA, Purdie KJ, den Breems NY, et al. CREBBP mutation in human cutaneous squamous cell carcinoma. *Exp. Dermatol.* 2016;25(8):650–651.

23. Wollina U. Cetuximab in non-melanoma skin cancer. *Expert Opin. Biol. Ther.* 2012;12(7):949–956.

24. Rossetti S, Burton S, Strmecki L, et al. The position of the polycystic kidney disease 1 (PKD1) gene mutation correlates with the severity of renal disease. *J. Am. Soc. Nephrol. JASN*. 2002;13(5):1230–1237.

25. Rossetti S, Chauveau D, Kubly V, et al. Association of mutation position in polycystic kidney disease 1 (PKD1) gene and development of a vascular phenotype. *Lancet Lond. Engl.* 2003;361(9376):2196–2201.

26. Grantham JJ. Time to treat polycystic kidney diseases like the neoplastic disorders that they are. *Kidney Int.* 2000;57(1):339–340.

27. Zheng R, Zhang Z, Lv X, et al. Polycystin-1 induced apoptosis and cell cycle arrest in G0/G1 phase in cancer cells. *Cell Biol. Int.* 2008;32(4):427–435.

28. Geng L, Segal Y, Peissel B, et al. Identification and localization of polycystin, the PKD1 gene product. *J. Clin. Invest.* 1996;98(12):2674–2682.

APPENDICES

Appendix 1: Consent form for genetic testing

Formulaire de consentement.

Je soussigné Mr, Mme, Mlle né(e) le / / et demeurant

Certifie :

- Avoir été informé de la nature et des objectifs des analyses proposées par le Dr
- Accepter que le prélèvement de sang soit effectué pour l'analyse de l'ADN
  - A des fins de recherche (étude n°1)
  - A des fins médicales (étude n°2)
- Autoriser, à des fins de recherche le recueil, la saisie et l'analyse des données contenues dans mon dossier médical, dans le plus strict respect du secret médical. Le traitement informatique et statistique de ces données sera mené par l'investigateur de l'étude ou pour son compte en respect des informations prévues par la loi informatique et liberté (article 40)
- Avoir été informé que mon échantillon d'ADN sera stocké sous forme codée de manière à ce que mon identité reste confidentielle. La durée de stockage a été fixée à 10 ans, période au bout de laquelle mon échantillon sera détruit.
- Savoir que je peux à tout moment demander des informations complémentaires
- Savoir que je peux refuser de participer sans en indiquer les raisons, ou retirer ma participation à tout moment
- Savoir que je peux demander la destruction de mon échantillon d'ADN en contactant le Professeur Lebranchu et le laboratoire de biochimie et biologie moléculaire du CHRU de Tours.

Fait en quatre exemplaire (dossier, patient, un par laboratoire) à Tours le

Signature du patient Signature du médecin

Appendix 2. Gene structure of PKD1, showing the intron/exon structure. Exons are shown with solid box; introns are shown with thin line arrow heads; 3' and 5' UTR regions are indicated by open boxes. Some exons numbers are labelled above. This graph was generated by using UCSC genome browser.

Appendix 3: Listing of detected mutations, with genetic location, number of patients with the mutation and NMSC associated. (a) *PKD1* truncating mutations (x3), (b) *PKD1* nontruncating mutations, (c) *PKD2* mutations

(a)

PKD1 truncating mutations	Exon	Intron	Number of patients	Patient(s) with NMSC
c.74_75delinsT	1	-	1	-
c.74del	1	-	1	-
grande délétion	1	-	1	1
c.114del	1	-	**2**	**1**
c.1029del	5	-	**2**	**1**
c.1445del	7	-	2	-
p.E499X	7	-	1	-
c.1751_1757del	9	-	1	-
c.2444_2445del	11	-	1	-
c.2494dup	11	-	**2**	**1**
p.Q718X	11	-	2	-
c.2886_2887del	12	-	1	-
c.2901del	12	-	1	-
p.Glu1073*(c.3217G>T)	14	-	1	-
c.3423_3484del	15	-	1	-
c.3538_3539dup	15	-	1	-
c.3812_3813del	15	-	2	-
c.3920dup	15	-	1	-
c.4247_4248del	15	-	1	-
c.4375del	15	-	1	-
c.4580del	15	-	1	1
c.4924del	15	-	1	-
c.5014_5015del	15	-	**6**	**3**
c.5599_5600del	15	-	1	-
c.5778del	15	-	1	-
c.5968_5969del	15	-	**5**	**3**
c.5982_5994del	15	-	2	-

(a2)

PKD1 truncating mutations	Exon	Intron	Number of patients	Patient(s) with NMSC
c.6247_6259dup	15	-	1	-
c.6549_6550del	15	-	1	1
c.6577_6583del	15	-	1	-
c.6720_6721del	15	-	2	-
c.6727_6728del	15	-	1	-
c.6994_7000del	15	-	1	-
p.5968-5969del	15	-	**2**	**1**
p.Gln1621*(c.4861C>T)	15	-	1	-
p.Gln2158*(c.6472C>T)	15	-	1	-
p.Q2011X	15	-	1	-
p.Q2158X	15	-	1	-
p.Tyr1693*(c.5079C>A)	15	-	1	-
c.74dup	15	-	1	-
p.Q1975X	15	-	1	-
c.5981_5994delinsG	15	-	1	-
c.6994_7000del	16	-	1	-
c.7113_7114del	17	-	1	-
c.7390del	18	-	1	-
p.Arg2430*(c.7288C>T)	18	-	**3**	**2**
p.R2430X (c.7288C>T)	18	-	1	-
c.7737_7747del	20	-	**3**	**1**
p.Q2602X	20	-	1	-
p.Q2606X	20	-	1	-
c.7870del	21	-	1	-
p.Gln2641*(c.7921C>T)	21	-	1	-
p.Y2622X	21	-	1	-
c.8070del	22	-	1	-
PKD1delE22	22	-	1	1
c.8420_8430del	23	-	1	-
c.8435del	23	-	1	-
p.Q2784X	23	-	1	1
p.Tyr2991*(c.8973C>G)	25	-	1	-
c.9202-2A>G	26	-	1	1
p.W3263X	29	-	1	-

(a3)

PKD1 truncating mutations	Exon	Intron	Number of patients	Patient(s) with NMSC
c.10073del	31	-	1	-
c.10215dup	32	-	2	-
c.10050+574_10499+392del	32,33	-	1	1
c10739del	36	-	1	-
c.10949_10950dup	37	-	1	-
c.11017-1G>C	38	-	1	-
p.Trp3726*(c.11177G>A)	39	-	1	-
p.W3726X	39	-	**2**	**1**
c.11314_11324del	40	-	**3**	**1**
c.11386dup	40	-	1	-
p.Q3821X	41	-	1	-
p.Q3821X	41	-	1	-
c.11554del	42	-	1	1
c.11792_11793dup	43	-	1	-
c.11923_11942del	43	-	**2**	**1**
p.W3939X	43	-	1	1
p.Q3955X	43	-	1	-
p.Gln4004*(c.12010C>T)	44	-	1	1
p.Q4042X	44	-	2	-
pGln4004*	44	-	2	-
p.R4021X	44	-	1	-
c.12253del	45	-	1	1
c.12440dup	45	-	**4**	**2**
c.12608_12635del	46	-	1	-
p.Q4241X	46	-	2	-
p.Arg4021*(c.12061C>T)	1/42-45	-	1	-
c.6831del - p.R4276W	15 - 46	-	1	-
PKD1Dele25-46	25 to 46	-	1	-
c.9397+744_10221-73del	27 to 32	-	**3**	**2**
c.10051-519_10499+338del	31 à 33	-	1	-
c.359+2T>G	-	3	1	1
c.1202-1G>C	-	5	1	-
c.1722+1_1722+3delinsAGT	-	8	**3**	**1**
c.2985+5G>C	-	13	1	1
c.3161+5G>T	-	13	1	-
c.3296-1G>T	-	14	2	-
c.6915+2T>C	-	15	1	-
c.8017-2A>G	-	21	2	-
c.10821+1G>A	-	36	**8**	**3**
c.12004-2A>G	-	43	**4**	**2**

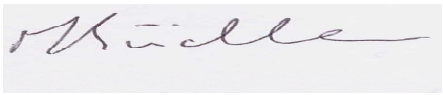
(b)

PKD1 nontruncating mutations	Exon	Intron	Number of patient	Patient(s) with NMSC
p.Leu56Pro	1	-	1	-
p.C155Y	4	-	1	-
variation p.L385R	5	-	**2**	**2**
p.A432V	6	-	1	-
p.Val460Asp	6	-	1	-
p.Arg611Trp (c.1831C>T)	9	-	1	-
p.Y698D (c.2092T>G)	10	-	**4**	**4**
p.Ala800Glu	11	-	1	1
p.Leu727Pro (c.2180T>C)	11	-	**3**	**1**
c.3719_3721del	15	-	1	1
p.W2298R	15	-	2	-
p.Y2028D	15	-	1	-
p.Cys2370Arg (c.7108T>C)	17	-	**2**	**1**
c.7236_7238delCCA	18	-	1	-
p.A2407P	18	-	1	-
p.T2422P	18	-	**3**	**3**
c.8284_8295del	23	-	1	1
c.8557_8562del	23	-	1	-
p.E2771K (c.8311G>A)	23	-	1	-
p.T3126I	26	-	1	-
c.9564_9566del	27	-	1	-
p.G3144E	27	-	2	-
p.G3144R	27	-	1	-
p.T3135M	27	-	1	-
p.Val3184Gly (c.9551T>G)	27	-	**2**	**1**
p.F3213L	28	-	1	-
c.9859_9861del	29	-	1	-
p.W3263S	29	-	1	-
p.Gly3651Asp (c.10952G>A)	37	-	**3**	**2**
p.L3667P	37	-	1	-
c.11249_11250delinsAA(p.R3750Q)	39	-	**2**	**1**
p.Leu3880Pro (c.11639T>C)	42	-	1	-
c.11980_11988dup	43	-	2	-
p.R4276W	46	-	1	1
p.N77S	2	-	**2**	**1**
variation p.Arg3835Pro(c.11504G>C)	41	-	1	-
p.K4147E	45	-	1	-
p.Y325C	5	-	1	1
c.1246_1248del	6	-	1	-

(c)

PKD2 mutations	Exon	Intron	Number of patient	Patient(s) with NMSC
p.Glu95*(c.283G>T)	1	-	1	1
c.817_818del	3	-	1	-
p.Gln255*(c.763C>T)	3	-	1	1
p.Arg306*(c.916C>T)	4	-	1	-
p.Arg325*(c.973>T)	4	-	1	1
c.1175_1177del	5	-	1	-
p.R464X	6	-	1	-
p.R592X	8	-	1	1
p.Arg654*(c.1960C>T)	9	-	1	1
p.R654X	9	-	1	1
p.K735X	11	-	1	-
p.Lys735*(c.2203A>T)	11	-	1	-
c.2568_2569del	14	-	**3**	**2**
p.Arg325Gln	14	-	1	-
del10-15 (g.88983145_g.89011203	10 à 15	-	1	-
c.2240+1G>A	-	11	1	-
DelPKD2	-	-	1	-

Vu, le Directeur de Thèse



Vu, le Doyen
De la Faculté de Médecine de Tours
Tours, le

Geneste Claire

42 pages – 7 tableaux – 4 figures – 3 annexes

Résumé : La polykystose rénale autosomique dominante (PKRAD) est la première cause génétique d'insuffisance rénale, avec principalement des mutations des gènes *PKD1* (75%) et *PKD2* (15%). Elle mène dans de nombreux cas à une transplantation rénale. Plusieurs études ont montré que les patients présentant une mutation de *PKD1* présentaient une insuffisance rénale terminale 20 ans plus tôt que ceux présentant une mutation de *PKD2*. Par ailleurs, le traitement immunosuppresseur au long cours, nécessaire après une transplantation, est connu pour favoriser la survenue de cancers cutané non mélanomateux (CCNM). Dans plusieurs cohortes, la PKRAD est un facteur de risque indépendant de développement de CCNM après transplantation rénale. Jusqu'à présent, il n'existe aucune cause connue, y compris génétique, permettant d'expliquer l'association entre l'ADPKD et l'incidence des CCNM après transplantation. L'objectif de cette étude est d'évaluer si un type de mutation de *PKD1* ou *PKD2* est associé à un risque accru d'apparition de CCNM.

Nous avons mené une étude rétrospective monocentrique incluant tous les patients atteints de PKRAD transplantés rénaux au CHU de Tours de 1987 à 2016. Nous avons utilisé notre base de données clinico-biologique, comprenant des études génétiques, et effectué des analyses multivariées avec ajustement sur les facteurs de risque de CCNM.

Nous avons inclus 245 polykystiques transplantés rénaux: 206 (84,1%) avaient une mutation de *PKD1* et 19 (7,8%) de PKD2. La durée moyenne de suivi était de 10,8 ± 6,3 ans. Au total, 162 cas de CCNM ont été diagnostiqués pendant la période de suivi, chez 69 patients (28,2%). L'incidence des CCNM à 20 ans en cas de mutation de *PKD1* était de 48,9%. Le risque de CCNM était plus faible en cas de mutation de *PKD1* troncante par rapport aux non troncantes (p=0,023). Ce risque restait significatif en analyse multivariée après ajustement sur l'âge, le sexe, le phototype et le traitement immunosuppresseur d'induction (risque relatif à 0,37 IC 95% [0,21-0,68], p<0,01). Une mutation PKD1 non troncante était également un facteur de risque de multiple CCNM après transplantation en anlyse multivariée [Odds ratio pour chaque CCNM supplémentaire: 2,08 IC 95% (1,45-2,94), P<0,001]. Nos résultats montre qu'être porteur d'une mutation non troncante de *PKD1* est un facteur de risque indépendant du développement de CCNM après une transplantation rénale.

Mots-clés:
- Polykystose rénale autosomique dominante
- Cancer cutané non-mélanomateux
- Transplantation rénale
- Mutation de *PKD1*

Jury :

Président du Jury : Professeur Jean-Michel HALIMI
Directeur de thèse : Professeur Matthias BUCHLER
Membres du Jury : Professeur Laurent MACHET
Docteur Bénédicte SAUTENET
Docteur Eloi CHEVALLIER

Date de soutenance : 21/09/18