



HAL
open science

AQP5 , a second gene at play with CFTR in aquagenic palmoplantar keratoderma

B. Sperelakis-Beedham, M. Lopez, E. Bourrat, N. Gaitch, F. Houriez, B. Martinez, I. Fajac, Pierre-Régis Burgel, G. Hickman, Marie-Pierre Audrézet, et al.

► To cite this version:

B. Sperelakis-Beedham, M. Lopez, E. Bourrat, N. Gaitch, F. Houriez, et al.. AQP5 , a second gene at play with CFTR in aquagenic palmoplantar keratoderma. *Journal of the European Academy of Dermatology and Venereology*, 2023, 37 (5), 10.1111/jdv.18869 . hal-03942390

HAL Id: hal-03942390

<https://hal.science/hal-03942390>

Submitted on 14 Oct 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

AQP5, a second gene at play with CFTR in aquagenic palmoplantar keratoderma

Keywords: Aquagenic palmoplantar keratoderma, Aquagenic wrinkling, CFTR, Aquaporin 5, AQP5

Manuscript word count: 599, 1 table, 1 figure

B. Sperelakis-Beedham^{a#}, M. Lopez^{a#}, E. Bourrat^b, N. Gaitch^a, F. Houriez^a, B. Martinez^a, I. Fajac^c, PR. Burgel^d, G. Hickman^b, MP. Audrézet^e, D. Gonde^f, F. Cabet^g, M. Gerfaud-Valentin^h, R. Nove-Josserandⁱ, C. Raynal^j, A. Pagine^k, MP. Reboul^l, A. de Becdelièvre^m, T. Bienvenu^a, I. Callebautⁿ, E. Girodon^a

Author e-mails :

brian.sperelakis-beedham@aphp.fr

maureen.lopez@aphp.fr

emmanuelle.bourrat@aphp.fr

natacha.gaitch@aphp.fr

florence.houriez@aphp.fr

brigitte.martinez@aphp.fr

isabelle.fajac@aphp.fr

pierre-regis.burgel@aphp.fr

geoffroy.hickman@aphp.fr

marie-pierre.audrezet@chu-brest.fr

delphine.gonde@chu-rouen.fr

faiza.cabet@chu-lyon.fr

mathieu.gerfaud-valentin@chu-lyon.fr

raphaele.nove-josserand@chu-lyon.fr

caroline.raynal@inserm.fr

adrien.pagin@chru-lille.fr

marie-pierre.reboul@chu-bordeaux.fr

alix.debecdelievre@aphp.fr

thierry.bienvenu@aphp.fr

isabelle.callebaut@sorbonne-universite.fr

emmanuelle.girodon@aphp.fr

^a APHP.Centre-Université de Paris Cité, Service de Médecine Génomique des Maladies de Système et d'Organe, Hôpital Cochin, Paris, France

^b APHP, Service de Dermatologie, CRM Magec Nord St Louis, Hôpital-Saint Louis, Paris, France

^c APHP.Centre-Université de Paris Cité, Physiologie-Explorations Fonctionnelles, Hôpital Cochin, Paris, France

^d APHP.Centre-Université de Paris Cité, Respiratory Medicine and Cystic Fibrosis National Reference center, Hôpital Cochin; Inserm U1016 ; Institut Cochin, Paris, France

^e Laboratoire de Génétique Moléculaire, CHRU de Brest, Brest, France

^f Department of Genetics and Reference Center for Developmental Disorders, Normandie Univ, UNIROUEN, CHU de Rouen, Inserm U1245, FHU G4 Génomique, F-76000, Rouen, France

^g Service de Biochimie Biologie Moléculaire Grand Est, Hospices Civils de Lyon, Groupement Hospitalier Est, CBPE, Lyon, France

^h Service de Médecine Interne, Hospices Civils de Lyon, Hôpital de la Croix Rousse, Lyon, France

ⁱ Service de Médecine Interne, CRCM, Centre Hospitalier Lyon Sud, Pierre-Benite, France

^j Laboratoire de Génétique Moléculaire, CHU de Montpellier, PhyMedExp, INSERM U1046, Montpellier, France

^k Service de Toxicologie et Génopathies, CHRU de Lille, Lille, France

^l Laboratoire de Génétique Moléculaire, Groupe Hospitalier Pellegrin, C.H.U. de Bordeaux, Bordeaux, France

^m AP-HP, Laboratoire de Génétique, Hôpital Henri Mondor, Université Paris Est Créteil, INSERM, IMRB, F-94010, Créteil, France

ⁿ IMPMC, Sorbonne Université, UMR7590 CNRS, Muséum National d'Histoire Naturelle, Paris, France

Correspondence: E. Girodon

Phone: +33 1 58 41 19 24

Fax: +33 1 58 41 15 80

E-mail: emmanuelle.girodon@aphp.fr

B. Sperelakis-Beedham and M. Lopez have contributed equally to this work as first authors

Funding sources: none to declare

Conflict of interest: none to declare

Each author has provided a disclosure statement.

Data availability statement: *AQP5* variants identified in this study have been deposited in the Leiden Open Variation Databases (<http://www.lovd.nl/3.0/home>).

Ethics statement: the study was in accordance with the ethical standards in France and all patients gave their written informed consent to the genetic study.

CRedit author statement

B. Sperelakis-Beedham: Investigation, Writing- Original draft preparation, Writing- Reviewing and Editing

M. Lopez: Methodology, Formal analysis

E. Bourrat: Conceptualization, Resources, Supervision

N. Gaitch: Investigation

F. Houriez: Investigation

B. Martinez: Investigation

I. Fajac: Resources, Writing- Reviewing and Editing

PR. Burgel: Resources, Writing- Reviewing and Editing

G. Hickman: Resources

MP. Audrézet: Investigation

D. Gonde: Resources

F. Cabet: Investigation

M. Gerfaud-Valentin: Resources

R. Nove-Josserand: Resources

C. Raynal: Investigation

A. Pagin: Investigation

MP. Reboul: Investigation

A. de Becdelièvre: Investigation, Writing- Reviewing and Editing,

T. Bienvenu: Conceptualization, Methodology, Writing- Reviewing and Editing

I. Callebaut: Methodology, Formal analysis, Writing- Original draft preparation, Writing- Reviewing and Editing

E. Girodon: Conceptualization, Methodology, Formal analysis Writing- Original draft preparation, Writing- Reviewing and Editing, Supervision

All authors have reviewed the manuscript and approved its submission.

Aquagenic palmoplantar keratoderma (APPK), also known as Aquagenic Wrinkling, is a rare skin disease characterized by transient skin wrinkling with oedema and whitish papules mostly on the palms, rarely on the soles, after water immersion¹. It is frequently observed in patients with cystic fibrosis (CF)² but also occurs sporadically, often in young women. An excess of carriers of variants in the Cystic Fibrosis Transmembrane conductance Regulator (*CFTR*) gene has been observed in patients and a mild phenotype such as a *CFTR*-related disorder (*CFTR*-RD) could be unmasked³. Other genes might be at play, such as the Aquaporin 5 (*AQP5*) gene, involved in Non-Epidermolytic Bothnian-type palmoplantar keratoderma (NEPPK), which is a permanent condition worsened by water immersion⁴.

We investigated the involvement of *AQP5* in 198 patients with an isolated APPK (86.9% of women, 92% of Caucasian ethnicity), including those from our previously published cohort³. Diagnosis was based on clinical examination by a dermatologist and familial data were collected, along with sweat test results when available (Table 1). All patients gave their written informed consent to the genetic studies and had an in-depth *CFTR* gene study, leading to unmask CF in one and a *CFTR*-RD in 13. Massive parallel sequencing of the *AQP5* coding regions led to identify an *AQP5* variant in six patients (3.0%), of whom two also carried a heterozygous *CFTR* variant (Table 1). Five *AQP5* variants are clustered in the cytoplasmic C-terminal tail, where variants implicated in NEPPK are absent from. These C-terminal variants could correspond to a mild form of NEPPK, mimicking APPK. Indeed, NEPPK-causing variants are located in the extracellular end of the water channel or in extracellular loops, thus the mechanism for NEPPK seems to be water conductance dysregulation⁴. On the contrary, the C-terminal *AQP5* variants found in this study are expected to moderately impact the 3D structure of *AQP5* but they could significantly impair the ability of *AQP5* to interact with partners, as well as its subcellular trafficking or stability at the membrane (Fig. 1). Recent studies revealed that *AQP5*'s C-terminal tail is compulsory for *AQP5* to pass protein quality controls⁵. Specific interactions between this region and multiple junctional proteins also suggest an influence on cell-to-cell adhesion regulation⁶. Hence, differences in variant location may cause different pathological processes and explain differences in the PPK phenotype. Epidemiological data also support the role of C-terminal *AQP5* variants, which are significantly more frequent in patients with APPK than in a control population taken from the GnomAD database⁷ (OR:10.0, 95% CI 4.1 to 24.4, $p < 0.0001$).

The sixth *AQP5* variant found in this study, p.Asn125del, located in the membrane-spanning domain, could lead to disturb the overall conformation of the extracellular C-loop, which is

important for optimizing water transport⁸. An effect on the stability of the tetramer could also be expected, as the extremities of the C-loop interact with each other in the neighboring monomers.

This study eventually raises the hypothesis of a multifactorial aetiology of APPK, given the role of CFTR and AQP5 in fluid homeodynamics. Heterozygous *CFTR* and *AQP5* variants may therefore be risk factors predisposing to APPK. An oligogenic model could account for the absence of family history of APPK in patients carrying inherited *AQP5* variants. It compels us to consider *AQP5* variants, even frequent ones, as potential risk factors, especially when combined with *CFTR* variants. Our results prompt searching for permanent PPK, even if discrete, as well as other cases of PPK in the patients' families. Ultimately, our study underlines the interest of genetic exploration of APPK, including *AQP5* alongside *CFTR*, for medical care, genetic counselling of CF and a better understanding of the mechanisms underlying APPK.

Acknowledgements: The authors are indebted to all clinicians who referred the patients for genetic analysis.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interests: none to declare

Declaration of interest: none

References

1. English JC, McCollough ML. Transient reactive papulotranslucent acrokeratoderma. *J Am Acad Dermatol* 1996;**34**:686–7.
2. Arkin LM, Flory JH, Shin DB, *et al.* High prevalence of aquagenic wrinkling of the palms in patients with cystic fibrosis and association with measurable increases in transepidermal water loss. *Pediatr Dermatol* 2012;**29**:560–6.
3. Raynal C, Girodon E, Audrezet M p., *et al.* CFTR gene variants: a predisposition factor to aquagenic palmoplantar keratoderma. *Br J of Dermatol* 2019;**181**:1097–9.
4. Blyndon DC, Lind LK, Plagnol V, *et al.* Mutations in AQP5, Encoding a Water-Channel Protein, Cause Autosomal-Dominant Diffuse Nonepidermolytic Palmoplantar Keratoderma. *Am J Hum Genet* 2013;**93**:330–5.

5. Muroi S-I, Isohama Y. C-Terminal Domain of Aquaporin-5 Is Required to Pass Its Protein Quality Control and Ensure Its Trafficking to Plasma Membrane. *Int J Mol Sci* 2021;**22**:13461.
6. Login FH, Palmfeldt J, Cheah JS, Yamada S, Nejsum LN. Aquaporin-5 regulation of cell–cell adhesion proteins: an elusive “tail” story. *Am J Physiol Cell Physiol*. 2021;**320**:C282–92.
7. Karczewski KJ, Francioli LC, Tiao G, *et al*. The mutational constraint spectrum quantified from variation in 141,456 humans. *Nature* 2020;**581**:434–43.
8. Dingwell DA, Brown LS, Ladizhansky V. Structure of the Functionally Important Extracellular Loop C of Human Aquaporin 1 Obtained by Solid-State NMR under Nearly Physiological Conditions. *J Phys Chem B* 2019;**123**:7700–10.
9. Varadi M, Anyango S, Deshpande M, *et al*. AlphaFold Protein Structure Database: massively expanding the structural coverage of protein–sequence space with high-accuracy models. *Nucleic Acids Research* 2022;**50**:D439–44.
10. Lomize MA, Pogozheva ID, Joo H, Mosberg HI, Lomize AL. OPM database and PPM web server: resources for positioning of proteins in membranes. *Nucleic Acids Res* 2012;**40** Database issue:D370-376.
11. Horsefield R, Nordén K, Fellert M, *et al*. High-resolution x-ray structure of human aquaporin 5. *Proc Natl Acad Sci U S A* 2008;**105**:13327–32.

Figure legend

Fig 1. AQP5 variants found in patients referred for aquagenic palmoplantar keratoderma. 3D structure coordinates were taken from the Protein Data Bank (<http://www.rcsb.org/>) and from the AlphaFold database (<https://alphafold.ebi.ac.uk/>) and were visualized using Chimera (<https://www.cgl.ucsf.edu/chimera/>).

(a) : Variants (green balls) are mapped on the AlphaFold2 model of the AQP5 3D structure (AF-P55064-F1-model_v1⁹), colored according to the prediction confidence score (pLDDT>90: blue, 90≥pLDDT>70: cyan, 70≥pLDDT>50: yellow). The cytoplasmic C-terminal tail is predicted as an alpha-helix (yellow). The position of the membrane bilayer was predicted using the PPM server¹⁰. (b) : The monomeric model of the full length protein was superimposed on the experimental 3D structure of human AQP5, organized as a tetramer (in grey, pdb 3D9S¹¹, RMSD 0.67 Å). The position of the C-terminal, cytoplasmic helix (shown in yellow on the AlphaFold2 model and absent from the experimental 3D structures (3 other subunits in grey) is predicted to be variable, according to the position of its homologous sequence on the experimental 3D structure of human AQP2 (pdb 4OJ2, not shown).

Table 1: Genotype and clinical data of patients found to carry an *AQP5* variant

Patient				Genotype				Clinical data			
number	gender	age at diagnosis	age of onset	<i>AQP5</i> (NM_001651.4) *	maximum allele frequency in gnomAD v3 (population**)	<i>CFTR</i> (NM_000492.4)	class of <i>CFTR</i> variant***	persistant thickening outside of water immersion	symptoms evocative of <i>CFTR</i> dysfunction	family history	background therapy
1	F	30	24	c.739G>A, p.(Glu247Lys) +/-	0.01443 (AFR)	c.1521_1523del, p.Phe508del +/-	CF	yes	sinusitis, intermediate sweat test (33mmol/L)	no	none
2	M	33	18	c.704G>A p.(Arg235His) +/-	0.0009551 (Oth)	-	-	yes	recurrent bronchitis	first degree cousin suffering from APPK	antidepressants
3	M	25	-	c.767G>A, p.(Arg256Gln) +/-	0.02131 (ASJ)	c.1210-34_1210- 6TG[12]T[5] +/-	CFTR-RD	no	no	no	none
4	F	21	-	c.794G>A, p.(Arg265His)+/-	0.0004139 (SA)	-	-	no	no	no	none
5	F	-	26	c.374_376del, p.(Asn125del)+/-	absent	-	-	yes	no	- mother reports frequent chapping of the hands and had a pneumothorax - cousin suffers from asthma	nasal corticosteroids; sodium cromoglicate (eye drops)
6	F	-	-	c.728A>G, p.(Tyr243Cys)+/-	0.00005880 (NFE)	-	-	no	no	- testicular cancer (father), ovary cancer (sister), lymphoma (brother)	none

* All variants but c.372_374del, p.(Asn125del) are located in the C-terminal region.

** AFR : African/African American, Oth : Other (population not assigned), ASJ : Ashkenazi Jewish, SA : South Asian, NFE : Non-Finnish European

*** *CFTR* variants were classified according to the *CFTR*-France database (<https://cftr.iurc.montp.inserm.fr/cgi-bin/home.cgi?>)

+/-: heterozygous; CF: CF-causing; CFTR-RD: CFTR-RD causing

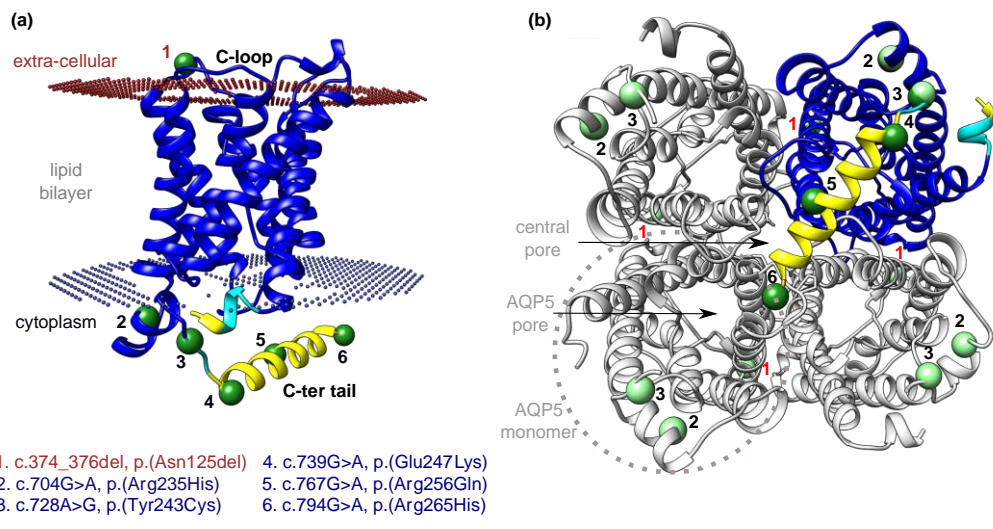


Figure 1