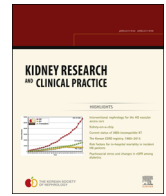




# Kidney Research and Clinical Practice

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## Letter and Reply

# A new water channel aquaporin-11: extension to renal transplantation



### To the Editor:

The aquaporins (AQPs) are a family of membrane water channel proteins, and they play a central role in water homeostasis. The seven isoforms, namely AQP1, AQP2, AQP3, AQP4, AQP6, AQP7 and AQP11, are expressed in the kidney [1]. Many studies have been carried out in animal models to prove the relationship between various pathologic renal conditions and AQPs. For instance, a decrease in the expression of renal AQP2 was described in nephrogenic diabetes insipidus and bilateral ureteral obstruction. In addition, lower levels of AQP1 and AQP2 were reported in ischemia–reperfusion injury and chronic kidney disease induced by renal mass reduction [2,3]. However, few experiments have focused on AQP11, and AQP expression has rarely been explored in human kidney samples and in the area of renal transplantation.

AQP11 is a member of the new AQP subgroup, and previous publications have indicated that AQP11 is a membrane-bound protein of the endoplasmic reticulum (ER), suggestive of an important role for AQP11 in ER homeostasis. The study by Park et al [4] investigated whether the donor AQP11 polymorphism had a genetic influence on allograft outcomes. The authors demonstrated that the minor allele rs2276415 (GA+AA) of AQP11 from donors had a harmful effect on graft survival compared with the wild-type donor (GG). They also performed AQP11 immunohistochemical analysis in graft biopsy samples and showed that AQP11 expression was significantly higher in the graft from donors with the wild-type genotype than in the graft from donors with the GA genotype or AA genotype. Furthermore, donor AQP polymorphism was an independent predictor for allograft survival, whereas recipient polymorphism did not have an effect. These findings suggest another predisposing condition that makes transplant kidneys susceptible to various injuries. ER stress may be induced by altered renal salt and water homeostasis, allograft rejection, ischemia–reperfusion, denervation, and tubular necrosis after transplantation, and it might be more disastrous if the proximal tubules are deficient in AQP11.

In addition to these meaningful findings, this study raised some questions. The authors very briefly described the pathology of renal allograft specimens using immunohistochemical staining. Is there any difference in AQP11 staining between normal samples and borderline changes? It is thought that

AQP11 in immunohistochemistry might be affected by renal pathology when it was associated with tubular dysfunction. The authors also demonstrated that AQP11 expression was prominently detected in the proximal tubules. Is there any difference in the incidence of delayed graft function according to AQP11 genotypes? Because the proximal tubule is highly vulnerable to ischemic injury, the relationship between ischemic injury and AQP11 polymorphism would be worthy of investigation.

### Conflicts of interest

The author declares no conflicts of interest.

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### In Reply:

We appreciate your interest in our recent article entitled “Genetic predisposition of donors affects the allograft outcome in kidney transplantation: single-nucleotide polymorphism of

aquaporin-11” [1]. Aquaporin-11 (AQP11) is a new member of the aquaporin family which was revealed with the completion of the human genome project and was first reported in 2000. In the field of kidney research, AQP11 has received attention because AQP11-null mice were proved to die from advanced renal failure with polycystic kidneys [2]. AQP11 is known to be localized to proximal tubule cells, and maintaining endoplasmic reticulum homeostasis might be an important physiologic function of AQP11 as a water channel [3]. The currently studied site, AQP11 rs2276415 (G→A) polymorphism, has its significance because it is located just next to the N-terminal Niemann-Pick C-protein (asparagine–proline–cysteine) motif, which is essential for AQP11 function [3]. First, we investigated the effect of the AQP11 polymorphism in the field of kidney transplantation and revealed that donors' AQP11 rs2276415 polymorphism was associated with an increased risk of graft loss. Our results suggested that the graft with a low expression of AQP11 due to the donor's polymorphism might be susceptible to endoplasmic reticulum stress in the course of kidney transplantation and finally be associated with its survival.

We agree with your opinion regarding the possible connection between tubular dysfunction and the expression of AQP11. According to your recommendation, we compared the expression of AQP11 resulting from immunohistochemistry in a total of 9 biopsy samples (3 diagnosed as normal vs. 6 with borderline changes or acute rejection). The AQP11-positive areas (%) were not significantly different between the groups (normal  $1.5 \pm 1.0$  vs. borderline changes or acute rejection  $2.2 \pm 2.1$ ,  $P=0.589$ ). However, the number of analyzed samples was too small. The 15 samples described in the article consisted of 3 normal, five borderline changes, one acute rejection, and 6 with other heterogeneous diagnoses (e.g., chronic allograft nephropathy, immunoglobulin A nephropathy). During our study, we tried to include as many samples as possible without pathology, but most of them were biopsied considering rejection in the early 2000s when protocol biopsy was not popular.

The answer to your second question was described in the article. The delayed graft function occurred in three patients in the GG group and no patients in the GA+AA group ( $P=0.267$ ).

These results might be due to the small sample size and low incidence of delayed graft function.

Unfortunately, we could not observe any tendency as you expected because of the small-sized and incomplete data. We hope that further study will follow to answer the questions and clearly demonstrate the role of AQP11 in kidney transplantation on the basis of our study.

#### Conflicts of interest

The author declares no conflicts of interest.

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