

# Living Related Donor Kidney Transplantation in Atypical HUS: When Should It Be Considered?

Meghna Kurup, Didier Mandelbrot, Neetika Garg, and Tripti Singh 

KIDNEY360 2: 524–527, 2021. doi: <https://doi.org/10.34067/KID.0007112020>

## Key Points

- We recommend genetic testing in all patients with ESKD and aHUS to determine if there is a genetic mutation leading to aHUS.
- For related living donor, we also recommend genetic testing of donors as part of workup for eligibility for them being a donor.
- Recipients should undergo functional complement testing along with genetic testing to prevent recurrent disease.

## Introduction

Atypical hemolytic uremic syndrome (aHUS) is a thrombotic microangiopathy that manifests as hemolytic anemia, thrombocytopenia, and AKI. aHUS has been linked to the dysregulation of the alternative pathway of complement (1). In up to 60% of patients with aHUS, a genetic mutation known to cause dysregulation of complement system is found (2). Mutations in complement factor H (CFH), CD46 (membrane cofactor protein), complement factor I (CFI), thrombomodulin/CD141 (THBD), complement factor B (CFB), and C3 have been previously reported in patients with aHUS (3). People with mutations may not develop aHUS until adulthood (4). This incomplete penetrance indicates that a genetic mutation alone is insufficient to cause aHUS; instead, carriers of complement mutations require an additional trigger, such as pregnancy, viral infection, cancer, surgery, or medications, to progress to clinical disease of aHUS (5). As the type of mutation can influence both phenotype and rates of recurrence, genetic screening is advised pretransplant in patients with aHUS-related ESKD (2). However, there is no clear guidance for the genetic screening of family members who are potential living related donors. Historically, living related transplantation is actively discouraged in cases of aHUS due to increased risk of disease recurrence in recipients and risk of *de novo* disease in the donors (3,6). The recent advancement in genetics of aHUS challenges the recommendation against living related kidney transplantation. We present three patients with aHUS to explore whether living related kidney transplant can be considered as an option.

Department of Medicine, School of Medicine and Public Health, University of Wisconsin, Madison, Wisconsin

**Correspondence:** Dr. Tripti Singh, 1685 Highland Avenue, Medical Foundation Centennial Building, Madison, WI 53705. Email: [tsingh@medicine.wisc.edu](mailto:tsingh@medicine.wisc.edu)

## Statement of Ethics

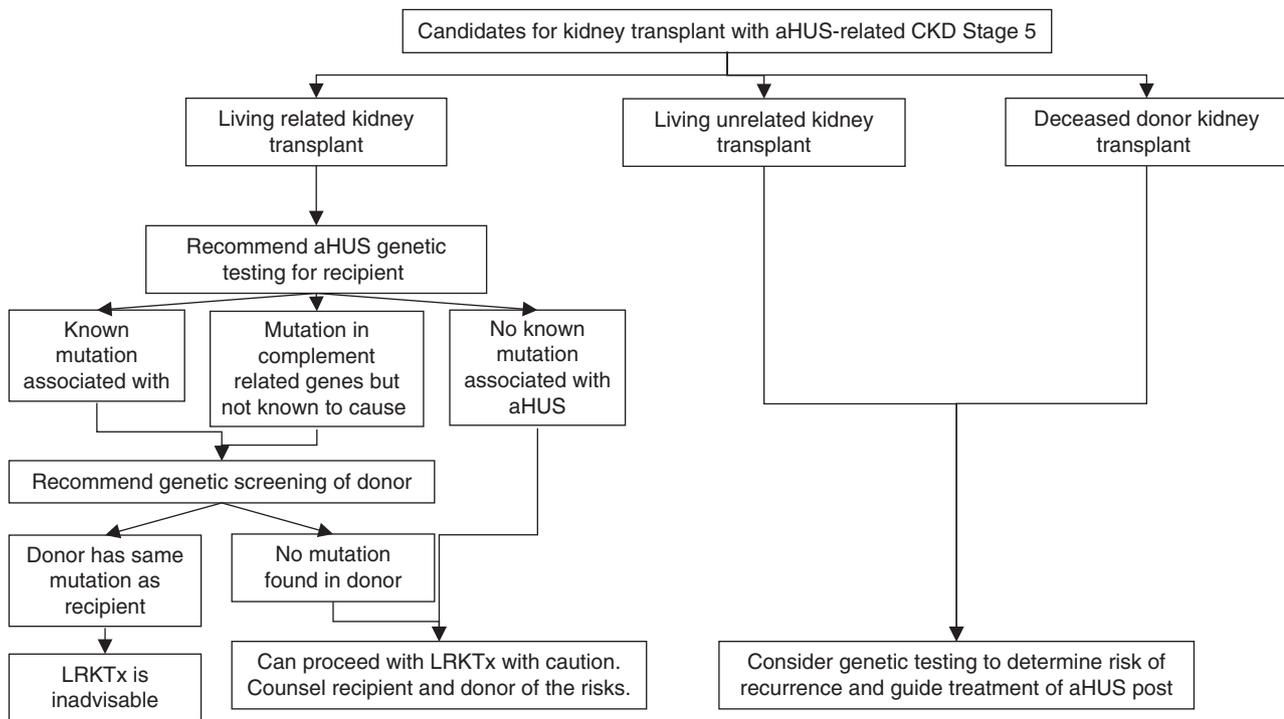
The ethical standards of the committee on human experimentation at our institution are in accord with the Declaration of Helsinki and its revisions. Institutional review board approval for patient reports is not needed at our institution. Informed consent from the patient or next of kin is required for patient reports. Informed consent was obtained from all of the patients in this manuscript.

## Patient 1

In 2016, a 27-year-old woman presented to the hospital with diarrhea, microangiopathic hemolytic anemia, and AKI requiring dialysis. On admission, laboratory data showed hemoglobin levels of 6.9 g/dl, platelet count of 71,000/ $\mu$ l, serum creatinine of 16.9 mg/dl, haptoglobin of <8 mg/dl, and lactate dehydrogenase of 1085 U/L. Renal biopsy showed thrombotic microangiopathy with focal crescents and severe interstitial fibrosis and tubular atrophy. She was diagnosed with aHUS; complement studies showed low C3 (69 mg/dl) and C4 (9 mg/dl); normal CD46 and Factors H, I, and B; and no autoantibodies to CFH. Genetic testing showed a mutation (c.1243delG, p.Ala415Profs\*39) on exon 9 (SCR7) of CFH that has been shown to cause aHUS as well as another variant (c.782G>A, p.Arg261His) on exon 7 of plasminogen (PLG), which is present in 0.3% of European Americans and may be pathogenic (7). She was initiated on eculizumab but progressed to ESKD. Ten months later, she was evaluated for a living related kidney transplant from her brother. Genetic testing of her brother as part of donor evaluation showed that he had the same mutation in CFH but not PLG. However, he did not have any clinical features of aHUS. The transplant was not approved because of increased risk of *de novo* aHUS in the donor and recurrence in the recipient. Genetic counseling was provided to the brother about his possible risk of aHUS. This patient has a calculated panel reactive antibody of 100% and remains active on the deceased donor waiting list.

## Patient 2

In 2011, a 24-year-old woman diagnosed with aHUS leading to ESKD received a living related kidney transplant from her mother. In 2017, she became pregnant,



**Figure 1. | Risk assessment for patients with atypical hemolytic uremic syndrome (aHUS) and CKD stage 5 to assess the candidacy for kidney transplantation.** Historically, living unrelated and deceased donor kidney transplants have been viewed as the treatment of choice for patients with aHUS. However, living related kidney transplants may also be available to these patients with proper genetic screening to determine the risk of recurrence in recipient and *de novo* aHUS in donor. We recommend that all recipients who are candidates for living related kidney transplant undergo genetic testing. When recipients are found to have mutations known to cause aHUS or mutations in complement-related genes with undetermined significance, donors should also be screened. Living related kidney transplant may be considered when the recipient and donor do not have mutations known to be associated with aHUS or when the donor is free of mutations. When the donor and recipient have the same mutation, living related kidney transplant is not. LRRKTx, living related kidney transplantation.

and during the last trimester of her pregnancy, she had recurrence of aHUS. Complement studies showed alternative pathway functional activity at 50%, normal C3 and C4 levels, normal Factor B, borderline soluble membrane attack complex levels, normal Factors H and I, and negative Factor H antibody. The hemolytic assay detected ongoing hemolysis due to compromised complement regulation on the cell surface. ADAMTS13 was normal. The patient was treated with eculizumab. Two months after the flare, she progressed to ESKD. A genetic panel done in 2017 showed complex rearrangement in her *complement factor H-related 5 (CFH-CFHR5)* region, which has been causally related to aHUS. Her father was a potential donor, and his genetic testing revealed that he had the same mutation as the patient. The father was disease free, but he was excluded as a donor due to increased risk of *de novo* aHUS in donor and recurrence in the patient. The patient's mother was not tested and remains disease free. In 2019, the patient received a living unrelated kidney from her husband. She remains in remission on ravilizumab, mycophenolate, tacrolimus, and prednisone.

### Patient 3

A 61-year-old woman with a past medical history of CKD of unknown etiology had a preemptive living related donor kidney transplant from her HLA-identical twin brother in

2015. Two months later, a kidney biopsy showed thrombotic microangiopathy. Subsequently, tacrolimus was stopped, and plasmapheresis was started in March 2016. A diagnosis of aHUS was made. She was initiated on eculizumab and continued on it for a duration of 2.5 years. Complement function testing was normal, although it was done after plasmapheresis. It showed normal CD46 levels; normal Factors H, I, and B; normal C3 (94 mg/dl); low C4 (14 mg/dl); and no Factor H antibody. Genetic testing revealed a mutation in the complement factor H-related 2 (CFHR2) gene, which is of unknown significance and has no known etiologic link to aHUS. Four years post-transplant, the patient's brother, who was the donor, remains healthy with no evidence of kidney disease.

### Discussion

The incidence of complement-mediated aHUS is rare (8), but up to 67% of adults died or reached ESKD (3). Kidney transplantation, especially living donor, is the best treatment for ESKD (9). However, there is debate in the literature over whether living related transplants should be offered for patients with aHUS (3,4,10). Living related transplant poses a risk of recurrence in the recipient and *de novo* disease in the donor if the donor possesses a predisposing genetic variant (11), although living donor transplant alone was not found to be a risk factor for recurrence (12). We present three

patients with aHUS where genetic screening of recipients and donors helped us guide the decision of pursuing living related kidney donation. With careful genetic testing and risk stratification on a patient by patient basis, living related kidney transplantation may be more accessible than previously thought.

Genetic testing may present any one of four scenarios— aHUS genetic susceptibility factors in donor and recipient, in neither, or solely in recipient (Figure 1). In our first and second patients, both the recipient and donor were found to have aHUS-predisposing mutations. When the donor and recipient share a genetic vulnerability to aHUS, living related donor transplantation is inadvisable (13). The post-transplant recurrence rate is worse for mutant circulating factors, such as CFH, but in the context of a living related transplant, membrane-bound factors like MCP whose expression is determined by the donor genome could be problematic if the donor has the same mutation as the recipient (14). The transplant was canceled in both patients. The risks with transplantation were shared with both the recipient and the donor, and the donor was counseled about the risk of *de novo* aHUS. In the third patient, the recipient did not have any known genetic risk factors associated with aHUS. The donor did not undergo genetic testing prior to transplant. The risk associated with living related donor transplantation is still moderate when no mutations have been identified in either the donor or recipient (15). This highlights that it is impossible to rule out recurrence or *de novo* disease because all genetic factors have not been discovered. The third scenario is when the recipient has a mutation known to cause aHUS and the donor does not. This is the safest compared with the former two. The fourth scenario, which is possible although we have not encountered it clinically, is that the recipient is not found to have a known mutation as cause for aHUS but the donor is found to have a known mutation for aHUS during the workup. We would recommend that transplant be cancelled in this scenario.

Although individual risk assessment with genetic analyses may pave the way for living related transplants in patients with aHUS, it is important to acknowledge the paucity of data to support the safety and reliability of this method. Another limitation is the cost of genetic testing and difficulty with getting insurance to cover the cost for both the recipient and the donor. However, there are now commercial companies offering genetic testing, which will hopefully make genetic testing easier and affordable. Genetic screening should be used in conjunction with functional complement testing for the recipient to determine eligibility for transplant.

Despite the limitations, personalized medicine aided by genetic testing will be the future of decision making in living related kidney transplant in patients with aHUS.

#### Disclosures

N. Garg reports honoraria from CareDx and scientific advisor or membership with *BMC Nephrology* as an associate editor and CareDx as an advisory board member. D. Mandelbrot reports scientific advisor or membership with CareDx and CSL Behring. All remaining authors have nothing to disclose.

#### Funding

None.

#### Author Contributions

T. Singh conceptualized the study; M. Kurup and T. Singh were responsible for data curation and investigation; M. Kurup was responsible for methodology; T. Singh was responsible for visualization; T. Singh provided supervision; M. Kurup wrote the original draft; and N. Garg, D. Mandelbrot, and T. Singh reviewed and edited the manuscript.

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**Received:** November 30, 2020 **Accepted:** January 14, 2021