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Kidney Medicine

# Precision Medicine Diagnostics for Rare Kidney Disease: Twitter as a Tool in Clinical Genomic Translation

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New technologies such as genomics present opportunities to deliver precision medicine, including in the diagnosis of rare kidney disorders. Simultaneously, social media platforms such as Twitter can provide rapid and wide-reaching information dissemination in health care and science. We present 2 cases in which the reporting of a novel genetic cause for human kidney disease was communicated through Twitter and then subsequently noted by treating clinicians, thereby resulting in rapid clinical diagnostic translation. In 1 family, this involved the reporting of heterozygous variants in *GREB1L* relating to autosomal dominant unilateral or bilateral renal agenesis, and in the other family, this involved biallelic variants in *CLDN10* relating to autosomal recessive hypokalemic renal tubular phenotypes. The times from Twitter notification to clinical diagnostic genetic report for these families were 111 and 200 days, respectively. Although caution is required, these cases show that social media platforms can contribute to rapid and accessible academic communication that may benefit clinicians, genomics-based researchers, and patients and families affected by rare kidney diseases.



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## INTRODUCTION

Where previously study of human genes, including their diagnostic interrogation, was relatively limited to their singular and sequential sequencing and analysis, technological advances have heralded the field of genomics, in which many or all genes are sequenced and analyzed concurrently, which enables speed, efficiency, and new understanding of gene-phenotype relationships.[1] Genomics and its clinical applications have begun to affect health care, specifically with regard to the diagnosis of rare and undiagnosed diseases,[2] including in nephrology.[3] Genomic discovery in nephrology continues to progress at an increasing pace,[4] resulting in challenges for translation into diagnosis and therapy,[5] the iterative addressing of which is generating tangible clinical impact.[6,7] Patients and families with rare kidney disorders have great potential to clinically benefit, although many previous genomic efforts have focused on genetic discovery rather than clinical translation for many rare and ultrarare kidney disorders. Simultaneously, platforms are emerging that may enable unexpected innovation and increased opportunity for patient-level benefits to be realized.

One such platform is Twitter, which is already having a positive effect in several areas of nephrology.[8,9] This platform enables perusal of information shared rapidly and widely between individuals, groups, and institutions that are able to form networks with similar interests. The development of such co-interested and aligned networks maximizes benefit and productivity that might be derived across clinical research,[10] different stakeholders,[11] journal clubs,[12] and health care broadly.[13] Although there are facilities with individual journals or interest groups to enroll in for targeted and regular updates on topics of interest, the large number of relevant journals and individual disorders within a field such as genetic kidney disease may make this challenging. A single platform such as Twitter can leverage the combined capacities of journals, interest groups, academic and clinical institutions, and individuals to disseminate information of interest within networks of common interest and thus may minimize such challenges and maximize visibility of relevant content while strengthening interdisciplinary care. The local protocol for genomic evaluation of rare phenotypes has been published previously[14] and is described in Item S1.

We present 2 cases that support our hypothesis that social media can play an important role in increasing dissemination of medical knowledge, global communication, and opportunities for serendipity to occur, particularly within the fields of human genetics and rare disease. Reflecting this, the Tweets referred to below were identified by the treating clinician and study lead at random without use of a targeted search strategy, notification method, or other platform.

## CASE REPORT

The first family (RG_0080) presented in 2013 after 3 pregnancies affected by bilateral renal agenesis in the context of asymptomatic 3-generation unilateral renal agenesis (Fig 1A). After diagnostic genetic testing for known forms of congenital abnormalities of the kidney and urinary tract returned negative, the family enrolled in a research genomics study. Whole-exome sequencing of 5 affected family members across 3 generations revealed candidate heterozygous variants in 19 genes; none had a known relationship with kidney disease, development, or physiology.

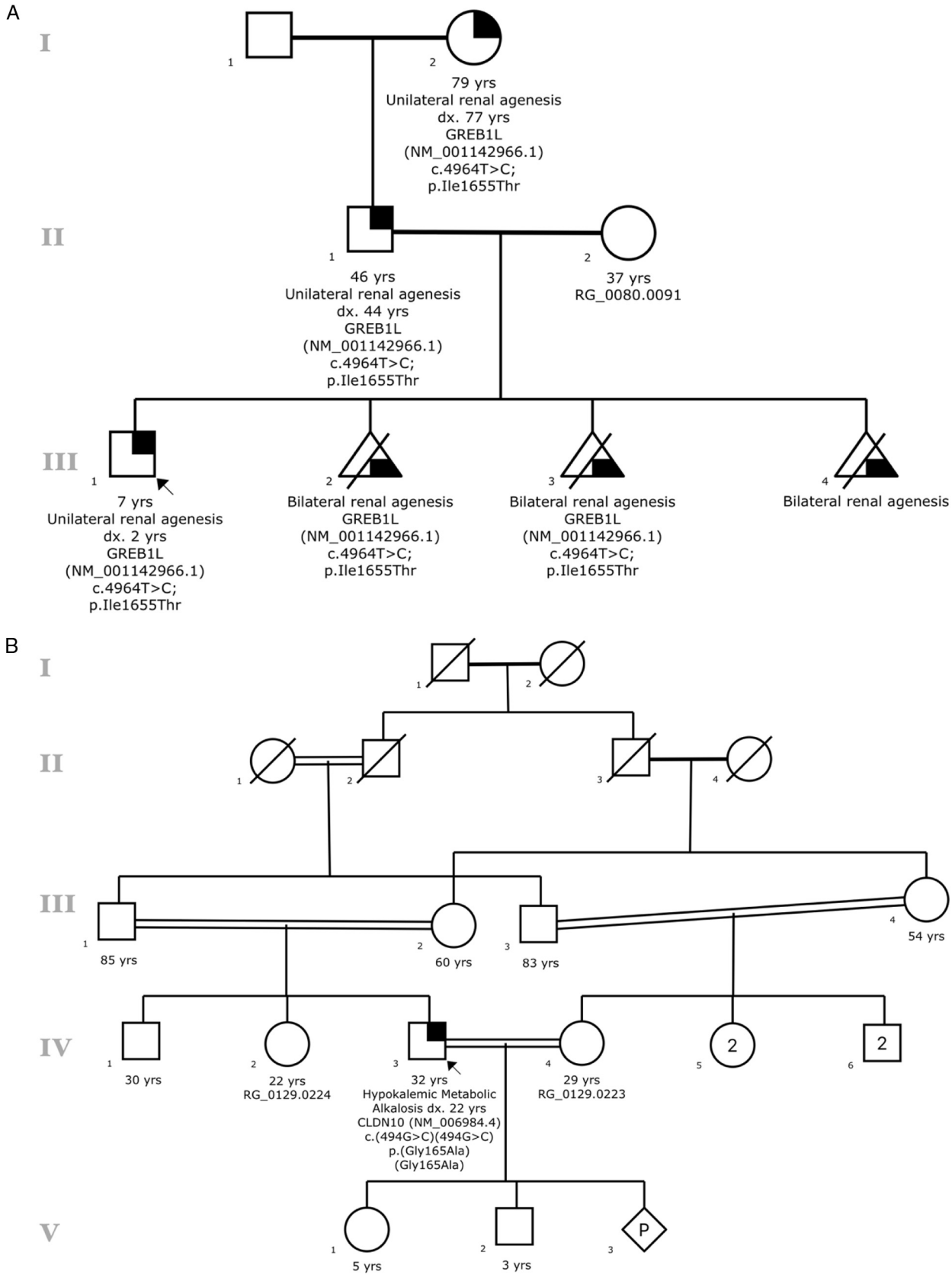


**Figure 1.** Family pedigrees and genomic outcomes. (A) Family RG_0080, unilateral and bilateral renal agenesis, and (B) family RG_0129, hypokalemic metabolic alkalosis. Abbreviation: dx, diagnosis.

At 5:00 AM AEST on Saturday, September 9, 2017, a Twitter post by a clinician-researcher of the recent report of heterozygous *GREB1L* variants associated with unilateral renal agenesis/bilateral renal agenesis[15] was seen.[16] The reporting of *GREB1L* was important because there are a limited number of known genes with a consistent and monogenic relationship to this phenotype. By 5:30 AM, the heterozygous candidate variant list for this unresolved family was reviewed and a segregating candidate *GREB1L* variant was identified from among the family's existing 19 gene candidate list. In concert with 2 subsequent reports of humans,[17,18] including an unrelated affected family with the same variant as this family, diagnostic confirmation and reporting in an accredited laboratory was enabled and progressed, with a diagnostic result returned on December 29, 2017.

The second family (RG_0129), with significant consanguinity and a single proband with an established phenotype of hypokalemic metabolic alkalosis and variable normocalciuria without overt nephrocalcinosis approximating Bartter syndrome type 3 (Fig 1B), was referred in 2016. Diagnostic genetic testing for hypokalemic tubulopathies was negative. The family was enrolled in research genomics with whole-genome sequencing undertaken in 1 affected and 2 unaffected family members. A candidate homozygous variant in *CLDN10* was identified. A submission to GeneMatcher[19] on April 4, 2017, returned a single result related to a phenotype our patient did not have.

The existing literature relating *CLDN10* variants to kidney tubular physiology and dysfunction in preclinical models[20-22] resulted in embarking on variant-specific functional genomic modeling in a mouse model. The day after this mouse model was established, a report of a similar human renal tubular phenotype associated with biallelic *CLDN10* variants occured[23] and was noted in a Twitter post by the publishing journal at 7:00 AM AEST on Tuesday, July 4, 2017.[24] The reporting of *CLDN10* was significant because there were an already well-established number of genes that have a monogenic relationship to such hypokalemic metabolically alkalotic kidney phenotypes. In company with other reports of humans of similar though heterogeneous phenotypes,[25,26] diagnostic confirmation and reporting in an accredited laboratory was undertaken, enabling the return of a clinically meaningful result on January 19, 2018.

## DISCUSSION

In both families, reporting of new genetic causes for rare kidney disease played a significant and synergistic role with research genomics, clinical genomics, and patient care. The times from Twitter notification of the first online report to a clinical diagnostic genetic report for these families were 111 and 200 days, respectively. It is important to acknowledge the limitations of this information dissemination medium, such as the authenticity of individual Tweets and associated responses. Additionally, although there are alternative social media platforms such as Facebook or blogs that may have similar functions, the significant use of direct links to primary publications and contributions from academic journals themselves, as demonstrated in these 2 cases, potentially highlights the strengths and validity of information disseminated through Twitter.

Accordingly, we suggest appropriate critical review of information disseminated in Tweets, including verification of primary source information from journal websites, conference proceedings, and the published literature. This is important for all who might consume and propagate this information, including patients and families, in addition to clinicians and researchers who might all take part in social media networks due to common interests and focus.

In the first family, it is difficult to predict whether a clinical diagnostic report would have been possible in the absence of the publication by Brophy et al[15] (2017) and its online sharing. For the second family, diagnostic translation was expedited and resource-intensive in-depth functional genomic experimentation was avoided.

In the first instance, these 2 families demonstrate the diagnostic power afforded by genomic sequencing technologies, particularly in ultrarare and diagnostically unresolved instances of likely heritable kidney disease. Second, they highlight the meaningful acceleration of translation from gene discovery to clinical practice and real-world patient outcomes, including in sometimes novel, unexpected, and serendipitous ways. In both instances, missing the otherwise random opportunity that was afforded to access critical new academic information may have significantly further delayed translation and diagnosis. These instances also show how information disseminated by different sources, such as other clinician-researchers with similar interests and academic journals, demonstrate the value of social medial amplification.

Although anecdotal, we suggest that these examples demonstrate the promising and emerging role of Twitter as a rapid and accessible academic information platform that may benefit clinicians, genomics-based researchers, and most importantly, patients and families affected by rare and ultrarare kidney disease. Future initiatives incorporating machine learning and artificial intelligence approaches to amalgamate and monitor large amounts of data are indicated to leverage such promise. Ongoing and future progress will hinge upon global information exchange and collaboration across broadened multidisciplinary teams to deliver on the promise of genomics in nephrology.

## SUPPLEMENTARY MATERIAL

### Supplementary File (PDF)

**Item S1:** Protocol for genomic evaluation of rare phenotypes.

## ARTICLE INFORMATION

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