CASE REPORT

Case Report: Making a diagnosis of familial renal disease – clinical and patient perspectives [version 1; peer review: 4 approved]

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Abstract

Background: A precise molecular genetic diagnosis has become the gold standard for the correct identification and management of many inherited renal diseases.

Methods: Here we describe a family with familial focal segmental glomerulosclerosis, and include a clinical and patient perspective on the diagnostic workup and relaying of genetic results following whole exome sequencing.

Results: Through next generation sequencing approaches, we identified a pathogenic mutation in *TRPC6*, the underlying cause of the phenotype. The identification of this mutation had important clinical consequences for the family, including allowing a living-unrelated kidney transplant to proceed in the index case. There are also wider ranging social and ethical dilemmas presented when reaching a genetic diagnosis like this one, which are explored here by both physicians and the index case.

Conclusions: Through physician and patient perspectives in a family with inherited renal failure we explore the implications and the magnitude of a molecular genetic diagnosis.

Keywords

focal segmental glomerulosclerosis, genetics, whole exome sequencing, TRPC6, podocyte, proteinuria, ethics

This article is included in the **Rare diseases** collection.

Open Peer Review

Approval Status ✓✓✓✓

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version 1	✓	✓	✓	✓
12 Apr 2017	view	view	view	view

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Any reports and responses or comments on the article can be found at the end of the article.

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Introduction

Familial renal disease is a challenging problem, in terms of diagnosis, treatment and ethical decisions. Here we describe a family affected by a familial form of focal segmental glomerulosclerosis (FSGS), which has resulted in end stage renal disease (ESRD) in two family members, with other family members at risk of the same disease. We wished to explore the significance of making a genetic diagnosis of familial ESRD and the impact of such a diagnosis on the index patient and their family. We therefore outline both the clinical and patient perspective of the index patient and her family.

Clinical case report

The index case presented in 2003 at the age of 30 years to renal services after her first pregnancy in 2003. She had developed heavy proteinuria and hypoalbuminemia during her pregnancy. After delivery of a healthy son at 40+2 weeks, her proteinuria reduced from a urine protein/creatinine ratio (uPCR) of 1200mg/mmol to 350mg/mmol at 6 months post-partum (Figure 1A). Her serum creatinine and blood pressure values remained normal during this pregnancy.

A positive family history of renal disease was known (Figure 1B). The index case's mother had presented similarly during her first pregnancy at age 30 in 1973. Her renal function steadily declined despite commencement of an ACE inhibitor and she reached ESRD in 2015 at the age of 70 years, and was commenced on peritoneal dialysis. In addition, a maternal grandmother had died in her 60s of "renal disease" but the exact diagnosis was unknown. The index case also had two maternal aunts who are not known to have renal disease. At this stage, no other family members had presented with symptoms consistent with renal disease.

In 2004, due to persistent proteinuria, 10 months after her first pregnancy, the index patient underwent a renal biopsy, which demonstrated FSGS. This was managed conservatively. At the age of 32 years and with careful pre-conception counselling, our patient conceived her second child. Her proteinuria again increased during this pregnancy. A healthy daughter was delivered successfully and post-partum, the proteinuria settled (uPCR = 650mg/mmol). During her third pregnancy aged 36, her proteinuria increased dramatically (uPCR = 1090mg/mmol at 20 weeks gestation and 1340mg/mmol at 33 weeks' gestation). This was associated with other features of nephrotic syndrome, including serum albumin of 20g/L and estimated Glomerular Filtration Rate (eGFR) declining to 45ml/min/1.73m² (Figure 1A). This prompted early delivery of her son at 36+5 weeks at a weight of 2.3kg, who then required a ten day stay at the specialist baby unit.

Following this third and final pregnancy, blood pressure was optimised with a combination of angiotensin receptor blockers and thiazide diuretic within the renal clinic. Despite these measures, her eGFR continued to progressively decline (Figure 1A) and she received counselling and information regarding the various methods of renal replacement therapy, opting for peritoneal dialysis when required. Her husband offered to be a living-unrelated kidney donor and pre-emptive renal transplantation work-up was commenced.

Given the likelihood of familial FSGS leading to ESRD, based on renal histology and the clinical course of the index case and her mother, genetic studies were initiated, following informed consent from the index case and her mother. Targeted genetic studies excluded mutations in *WT1* and *NPHS2* genes, and this was followed by whole exome sequencing which identified a known pathogenic variant in *TRPC6* (c.2683C>T; p.Arg895Cys) (Table 1), which segregated from the affected mother. The finding

Figure 1. Clinical progression of index case and family pedigree. A. Clinical progression of index case over time with serum albumin (solid line), urine protein/creatinine ratio (dashed line) and estimated Glomerular Filtration Rate (eGFR). Pregnancies marked with shaded area (P). **B.** Family tree with index case arrowed. Males are squares, females are circles. Heterozygously affected individuals are semi-shaded. Sibling with proteinuria marked with "?".

Table 1. *In silico* analysis of *TRPC6* variant.

Gene Variant	MutationTaster	Evolutionary Conservation	SIFT	ExAC database	PolyPhen-2	dbSNP	Ref
<i>TRPC6</i> c.2683C>T p.Arg895Cys	Disease causing	<i>D. rerio</i>	Damaging	Not found	Probably Damaging	rs121434394	Reiser <i>et al.</i> 2005

of a genetic mutation causing FSGS meant that the likelihood of recurrence of FSGS in a non-related donor was low and her living-unrelated transplant surgery was expedited. There have been no known recurrences of FSGS after renal transplants in patients with underlying mutations in *TRPC6*^{1,2}.

In 2014, at age 41, the index case received a pre-emptive living-unrelated renal transplant from her husband, which had immediate graft function. Her transplant function remains excellent with no evidence of recurrent FSGS.

More recently, the index case's brother was identified as having heavy proteinuria in 2016 at age 40, and is undergoing further investigations (Figure 1B). The three children of the index patient, who are fit and well, have not yet been tested for the disease causing variant.

Genetics and underlying mechanism of disease of familial FSGS

The first identification of human *TRPC6* mutations was reported in 2005. Here, a point mutation in *TRPC6* was identified in a family with autosomal dominant focal segmental glomerulosclerosis¹. Since then, several other mutations in *TRPC6* have been described. The *TRPC6* p.R895C heterozygous mutation that we report here has been described previously in a large Mexican family². Here, 9 of 25 family members were affected and presented between the ages of 18 and 46 years, and 6 of the family members reached ESRD. Of these, 2 had received renal transplants with no evidence of recurrent disease. *TRPC6* is a non-selective cation channel³ which is expressed in podocytes and glomerular endothelial cells². *TRPC6* channel activity at the slit diaphragm is required for the regulation of podocyte structure and function². Biophysical analysis of the p.R895C mutant *TRPC6* channel showed pathogenic changes in the current-voltage relationship which were suggestive of a gain-of-function², which *in vivo* would be predicted to increase calcium influx. Interestingly, podocytes express other TRPC channels, including *TRPC1*, *TRPC2* and *TRPC5*, and an overlap in function may account for the usual adult onset of glomerular disease. Another level of complexity is that *TRPC6* may also form heterotetramers with other TRPC channels². The fact that the p.R895C mutation causes a gain-of-function means that selective *TRPC6* inhibitors such as larixyl acetate may represent a pharmacological therapy for this form of FSGS⁴. More recently, a role for *TRPC6* in renal fibrosis has been identified, which may spur on efforts for the clinical use of *TRPC6* inhibition in other progressive renal diseases⁵.

Patient perspective

"Even though my mother had a history of renal disease, and I had presented with proteinuria during my first pregnancy, there had been no suggestion made to me, or present in my mind of a possible genetic renal condition. When following my biopsy in 1999, I received a probable diagnosis of familial FSGS, it came as a huge shock, not only to hear I had FSGS, but also the rarer familial form. Furthermore, knowing you have a rare chronic illness is one thing, but more significantly, I was devastated about what the future might hold for our children.

With this in mind, we began enquiries about how to find out which faulty gene had caused the FSGS and it was decided to undertake genetic tests including sequencing my whole exome. Whilst the result might not help in the short term, it would be useful in terms of being able to test other family members in the future.

I remember the consultant saying that finding the change in the faulty gene was like looking for 1 change in 6 billion pieces of genetic code and the expression 'needle in a haystack' was mentioned. Even after such detailed analysis I was told that the results are sometimes inconclusive. Not wanting to miss an opportunity, I flippantly mentioned screening for other faulty genes – by which I mean other non-renal conditions. I did not consider the possibility that our type of familial FSGS may be caused by more than one faulty gene and this is a serious and worrying consideration for patients waiting for the results of any genetic sequencing, notwithstanding the added complications it infers for future research and potential management or cure.

The screening process took a long time (over 6 months) and several clinic appointments passed before we received the results. Fortunately, the investigations were positive and as strange as it sounds, I was pleased to be told that I carried a variant in the *TRPC6* gene. No other faulty genes were identified. My mother was extremely interested in the diagnosis given her condition has been termed "nephrotic syndrome" for thirty years but this was tempered by an ill-founded sense of guilt that she had passed on her condition to her daughter. This is an emotion I can identify with in terms of my own children.

Consequently, the excitement about a positive result naively produced a sense of hope about a potential innovation in the near future, given we had a precise genetic cause. *TRPC6* encodes a calcium channel and based on current understanding the protein is expressed in the podocyte of the kidney, an area currently

undergoing a lot of research. Whilst the condition is extremely complex, this form of FSGS may well be a candidate for clinical trials aiming to modify the faulty channel.

As a patient, having something concrete to hold on to, such as the likely cause of our condition, provided some comfort and a sense of empowerment. Receiving the news that the cause of our FSGS was genetic meant it was much less likely for proteinuria to reoccur in a transplant, whereas the risk of recurrence is high in patients with other forms of FSGS. The prospect of immediate kidney rejection is daunting even without the added anxiety of the disease reoccurring and causing rejection, and having this information was an enormous relief for our family. In addition, awareness of this mutation now means that other family members (should the need arise) need only have a blood test rather than a kidney biopsy.

The sting in the tail, in our particular case, is that the pathogenic variant of *TRPC6* remains a very rare cause of familial FSGS, with only a small amount of published reports for doctors to refer to. The rate of deterioration in kidney function has been very different in myself and my mother, whose renal replacement therapy began at 70 years of age. In 2016, my brother presented with proteinuria and mildly raised blood pressure, and is awaiting the results of his genetic tests. He has two children and will no doubt have considered the possibility that they may also be vulnerable. We have all had unique experiences, and this does not make the analysis easier for the nephrologists, or give them the tools to predict future outcomes.

Identifying the variant in *TRPC6* contributing to our form of familial FSGS, does however open up the opportunity to support directed research studies and help further the knowledge about this condition. At this stage, we have decided with the support of the nephrologists, not to test our children, and will do so when the time is right. Yet whilst the threat of this condition hangs over their heads, we continue to fundraise and support renal research in the hope that one day a cure may be found."

Discussion and conclusions

Using a clinical case summary and a reflective patient perspective, we provide an example of how a molecular genetic diagnosis in a

life threatening inherited renal disease may provide an explanation of the underlying disease process and offer the ability for screening of other family members without the need for invasive tests such as renal biopsy. A genetic diagnosis, by its very nature, also raises issues within the patient and their family members, which may be far reaching. Importantly, a genetic diagnosis often furthers our knowledge of disease phenotypes in rare inherited disorders, and hopefully provides momentum for future research into precision medicine therapies. Engagement of patients and their families in the importance and value of genetic and genomic data for diagnostic, therapeutic and prognostic use should be actively encouraged. Mainstreaming of genomic medicine into medical specialties such as nephrology needs to be embraced by patients and their physicians.

Consent

Written informed consent was obtained from the patient and family for publication of this case report and any accompanying images and other details that could potentially reveal the family's identity.

Author contributions

The project was conceived and directed by JAS. ZI and JAS drafted the manuscript. All authors were involved in the revision of the draft manuscript and have agreed to the final content.

Competing interests

No competing interests were disclosed.

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgements

We recognise a valuable contribution from the index case who provided an insightful patient perspective which is quoted in full. We thank all family members who contributed to the information provided within this report.

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Beata S. Lipska-Ziętkiewicz

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The authors present the insidious course of an infrequent subtype of FSGS, the *TRPC6*-related glomerulopathy, that is an extremely rare renal disorder with ca.100 families diagnosed worldwide. Most likely an individual nephrologist will see no more than one-two such cases during his/her years of practice. The presented paper is an excellent source of information on how to comprehensively handle such patients, not only from medical but also emotional and ethical perspective.

The strong points of the work are 1) presenting the recent advances in diagnostics resulting from rapid improvements in genetic sequencing technologies making kidney biopsy (almost) obsolete; 2) including the patients perspective and highlighting their engagement not only in clinical management but also in research .

The weak point is too superficial presentation of the current standards of preemptive genetic testing in minors for late-onset conditions. I would recommend at least adding a reference to European Society of Human Genetics position on the issue (for details see: <https://www.eshg.org/eshgdocs.0.html>) and/or paragraph discussing the ethical, legal, and psychosocial implications of such genetic testing.

I would also suggest to modify Figure 1B (family pedigree). Currently it seems to report results of genetic testing in the entire family, but most of the family members were not subject to any genetic testing, the affected grandmother included. Therefore, I recommend that the graph reports on phenotype and not genotype, ie. the individuals with phenotype expressed should be marked as "fully filled-in" while the information re: mutational status is to be provided below where available.

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment

given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: clinical genetics, genomic disorders, hereditary kidney disease

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 22 May 2017

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Larissa Kerecuk

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Excellent case report highlighting an important area of genetic testing being very useful for managing the patient. The report shows the importance of taking a family history in any disease especially renal and exploring this further. Having the patient perspective adds a different angle which is very important for doctors to be aware of as lots of learning can happen from this.

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 19 May 2017

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Aoife M. Waters

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Familial cases of rare diseases provide a remarkable opportunity to delineate important biological processes relevant to human disease. Of particular importance, are the implications for future therapeutic strategies for refractory and progressive diseases such as focal segmental glomerulosclerosis.

Iqbal and Sayer through their report elegantly present the natural history of TRPC6-associated glomerulopathy arising as a result of the mutation c.2683C>T; p.Arg895Cys which concurs with previous reports of disease manifestation of the same genotype by Reiser et al in 2005. Presentation tends to have an insidious onset in mid-adulthood and despite intervention with ACEIs, patients with this genotype progress towards end-stage renal disease. Functional characterisation of the TRPC6 variant, p.Arg895Cys, utilising electrophysiological studies, revealed the likelihood that this variant represented a gain of function in the encoded mutant protein. Increased intracellular calcium influx as a result of gain of function mutations in TRPC6 have been shown to lead to increased podocyte apoptosis, a common pathogenetic mechanism of FSGS. Therefore, downstream inhibition of increased TRPC6 activation, represents a therapeutic strategy for patients with TRPC6-associated glomerulopathy. As highlighted by Iqbal and Sayer, without effective treatment for this disease, progression to end-stage renal disease and renal transplantation occurs. For this particular variant, the risk of recurrence post renal transplant is negligible.

Including the patient perspective is an innovative approach to the case reporting of interesting pedigrees of rare disease. By undertaking such a strategy, Iqbal and Sayer highlight the importance of patient engagement in genomics research by consent for testing of additional affected and unaffected family members to fully characterise the genotype-specific disease manifestations. Furthermore, it provides an answer for the affected patients and provides a rationale for clinical decisions relating to their care.

Importantly, this report also provided perspective with regards to future testing of prospective asymptomatic younger family members and whether to burden families with advance knowledge

of prospective disease susceptibility.

What this knowledge does offer, of course, is the possibility to influence the disease course prior to manifestation of overt disease symptoms and careful consideration of this prospect should be highlighted at time of consent.

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Molecular mechanisms of glomerulosclerosis utilising inducible transgenic mouse models and molecular genetic studies of human disease.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 02 May 2017

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Moin A. Saleem

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This is an interesting way of presenting a familial case of renal disease from the patient perspective. The case illustrates how a new diagnosis of monogenic (Mendelian) disease can impact on the family, by firstly clarifying the underlying cause, and being able to discuss in more detail the prognostic and genetic testing implications.

It also illustrates the powerful impact of the rapid improvements in genetic sequencing technologies, and how these have translated into clinical practice. It is worth emphasising that this will have impact on all clinicians treating renal (and other) diseases, who will need to keep up to date with the current screening technologies and interpretation/limitations of the data generated. In the UK routine whole genome sequencing of patients with rare diseases is being rolled out, so there will be more cases like this being uncovered and requiring counselling.

One key issue touched upon is the ethical implications of testing younger family members, who may (or may not) develop disease much later in life. The consensus at the moment is to wait until the young person is of an age to make the decision to test independently, unless there are treatment implications of knowing earlier in life. With this particular mutation this is unlikely to be the case, though cases of TRPC6 mutations have been reported to present with proteinuria as early as 6 years of age.

Another ethical consideration of whole exome or genome sequencing is of finding completely unrelated potentially pathogenic mutations. This needs careful pre-counselling before the test is done.

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Paediatric nephrology; glomerular biology; genetics; podocyte biology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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