‘No causative variants found’: an unusual presentation of PAX2-related disorder not detected on rapid whole exome sequencing testing

Patricia A Wells [1], Anna P Basu [2,3], Laura M Yates [1,4]

[1]Northern Genetics Service, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
[2]Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, UK
[3]Paediatric Neurology, Great North Childrens Hospital, Newcastle upon Tyne, Tyne and Wear, UK
[4]Transitional and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK

Correspondence to
Dr Anna P Basu;
anna.basu@newcastle.ac.uk

Accepted 30 December 2024

To cite: Wells PA, Basu AP, Yates LM. *BMJ Case Rep* 2025;**18**:e263723. doi:10.1136/bcr-2024-263723

SUMMARY

Paired box 2 (*PAX2*)-related disorder, also known as renal coloboma syndrome, is a variably penetrant autosomal dominant condition, associated with renal and ophthalmological abnormalities. We report a child with *PAX2*-related disorder who presented atypically with acute ataxia on a background of stage 3 chronic kidney disease. Extensive biochemical, radiological and gene agnostic rapid trio exome sequencing was non-diagnostic. Identification of bilateral optic disc colobomas in the proband and his father raised the suspicion of an inherited *PAX2*-related disorder. No causative variants were identified on a focused review of the filtered genomic data. Given the strong suspicion of an inherited monogenic disorder, whole genome trio sequencing was requested. Analysis assuming incomplete penetrance identified a paternally inherited *PAX2* microdeletion encompassing exon 4. This case adds to evidence of a broader *PAX2*-associated phenotype. It highlights the importance of a clinical genetics and mainstream interface when navigating and interpreting genetic testing.

BACKGROUND

Paired box 2 (PAX2)-related disorder is a rare autosomal dominant condition also referred to as renal coloboma syndrome. It was first described in 1988 and is classically associated with renal abnormalities and optic disc coloboma.[1] There can be significant variability in phenotype, even within the same family.[2–6] The renal abnormalities described are highly variable including renal hypodysplasia, renal cysts, focal segmental glomerulosclerosis and vesicoureteral reflux.[3–7] Ophthalmological abnormalities include optic disc coloboma, dysplasia and chorioretinopathy.[2–8] There are occasional cases reported in the literature describing a variable wider system involvement. These reports include neurodevelopmental disorders, sensorineural hearing loss, short stature and inguinal hernia.[3–6]

The NHS England Genetic Test Directory includes rapid agnostic genome sequencing, known as R14.[9] This is available for acutely unwell children with a likely monogenic disorder. Its bioinformatic pipeline is designed to identify genetic diagnoses in cases when the parents are unaffected.[10] Secondary analysis of the sequencing data using virtual gene panels can be initiated by the analysing scientist. The scenarios for this are limited but include when a single gene is specifically implicated or incomplete penetrance is suspected.[10]

We report a case of a child with PAX2-related disorder where renal impairment was followed by acute ataxia and developmental regression. The typical ocular phenotype was subsequently diagnosed. Familial variability and ‘negative’ agnostic trio exome sequencing prolonged the diagnostic odyssey. Multidisciplinary team discussions including the clinical genetics team and clinical scientists were important in appreciating the limitations of genetic testing and guiding onwards testing strategies. This case also highlights the importance of trusting a clinical diagnosis when there is a strong suspicion of this.

CASE PRESENTATION

At toddler age, this male proband had an episode of acute ataxia leading to urgent, tertiary centre, paediatric neurology assessment. The episode evolved over the course of hours resulting in an inability to sit upright. The parents reported that 4 months previously there had been a rapid developmental regression of speech and social skills over a period of days. His speech regressed from multiple words with meaning to becoming non-verbal. His social skills regressed from making interactions in group play to having limited eye contact and not being responsive to his name. An MRI of the brain completed shortly after this regression was normal.

The proband was previously known to renal services following the diagnosis of stage 3 chronic kidney disease on a blood test requested for poor weight gain and food allergy. This diagnosis was made 6 months prior to his neurological presentation. Renal ultrasound demonstrated bilateral hypoplastic kidneys with increased cortical echogenicity and cysts. Micturating cystourethrogram demonstrated grade I vesico-ureteric reflux to the left kidney. Clinical genetic services had also recently reviewed and commenced baseline genetic investigations. Dysmorphic features including relative macrocephaly with frontal bossing had been noted. Other medical history included a unilateral inguinal hernia. Family history at the time of the assessment was unremarkable.

On admission to paediatric neurology, examination demonstrated an unsteady staggering gait. He was afebrile, alert and responsive. General system examination was normal and no other acute neurological defects were detected. His head circumference was on the 94th centile (z +1.64), height on the 7th centile (z −1.44) and weight on the 27th centile (z −0.60).

Table 1 Details of the paired box 2 (*PAX2*) gene variant identified

Genomic DNA nomenclature	Complementary DNA nomenclature	Zygosity	Inheritance	Classification
GRCh38(Chr10): g.100781017_100772675del	NM_003987.5 (*PAX2*) c.411-6823_c.497-229del	Heterozygous	Paternal	Pathogenic
Evidence for variant classification as per American College of Medical Genetics guidelines				
PVS1 PM2_Supporting PP4_Moderate	Single exon deletion disrupts the reading frame and is predicted to undergo nonsense-mediated decay. Exon is present in a biologically relevant transcript. Loss of function is an established disease mechanism. Clinical validity classification of gene is definitive Not reported in a population-based SNP study www.gnomad.broadinstitute.org Patient's phenotype is specific for a disease with a single genetic aetiology			
Variant interpretation was completed according to ACMG guidelines.[15]				

The child's ataxia improved over 48 hours and he was discharged. Investigations were non-diagnostic. In the months following, he was assessed by ophthalmology services due to an intermittent divergent squint. Bilateral optic nerve and retina abnormalities were identified in keeping with bilateral optic disc colobomata. His father had similar retinal findings.

INVESTIGATIONS

Blood investigations included a normal full blood count, electrolytes, thyroid function, ammonia, lactate, white cell enzymes, plasma amino acids, fatty acids and acylcarnitine profile, tripeptidyl peptidase, palmitoyl protein thioesterase and blood film microscopy. A COVID-19 RNA screen, urine microscopy, urine organic acids and mucopolysaccharides were also normal.

Electroencephalography and MRI of the brain were reported as normal. A CT of the head demonstrated delayed closure of the metopic suture and lambdoidal Wormian bones.

Single-nucleotide polymorphism (SNP) microarray testing requested prior to admission did not identify any significant copy number changes. An urgent agnostic trio whole exome sequencing (R14) request was accepted as per the NHS England Genetic Test Directory.[9] The case met testing criteria given acute neurological deterioration on the background of a suspected monogenic disorder. No pathogenic variants were detected.

The strong suspicion of a monogenic disorder prompted progression to non-urgent trio whole genome sequencing (WGS) testing. This was justified on the basis that the R14 exome does not cover intronic genetic code and may not have detected a variant inherited from a parent. Routine WGS trio testing in the NHS setting took 12 months at the time of request. The testing is not agnostic and virtual panels are applied. The following genomics medicine service gene panels were requested: R27 Paediatric disorders; R257 Unexplained young onset end stage renal disease; R193 Cystic renal disease and R55 Hereditary ataxia and cerebellar anomalies—childhood onset.[9] Analysis was requested using an incomplete penetrance filter, thereby allowing variants that are present in a parent to be reported.

DIFFERENTIAL DIAGNOSIS

The ophthalmological findings in the proband, identified after the R14 result, raised the clinical suspicion of a variant in the gene *PAX2*. The bioinformatically filtered R14 exomic data were reviewed with no variants identified in this gene. The paternal

Table 2 Details of phenotypic features present in proband and his father

	Proband	Father	Reported in association with paired box 2 in the literature?
Renal	Bilateral hypoplastic kidneys with increased cortical echogenicity and cysts. Chronic kidney disease stage 3b. Grade I unilateral vesicoureteral reflux	Normal renal ultrasound scan. eGFR 75, creatinine 111	Various: renal hypodysplasia, cystic kidney disease, focal segmental glomerulosclerosis and vesicoureteral reflux[3–7]
Ophthalmological	Intermittent divergent squint. Bilateral optic disc colobomas and optic nerve atrophy. Small volume optic chiasm	Bilateral central optic disc pits. Absent central retinal artery. Myopia. Superior binasal visual field defects	Various: dysplasia of the optic nerve, optic disc coloboma and chorioretinopathy. Strabismus is reported in a handful of cases[2–8]
Neurodevelopmental	Normal developmental profile until toddler years Rapid autistic regression of speech and social skills, subsequent developmental delay affecting multiple domains Avoidant restrictive food intake disorder diagnosis. Sensory processing disorder Acute ataxic episodes—longest duration 48 hours	No	A handful of cases in the literature where autism, developmental delay, or mild intellectual disability are reported[3 5 16]
Hearing	Frequent ear infection	Bilateral high-frequency SNHL, Right>Left	High-frequency hearing loss is reported in a number of cases[4 6 16]
Inguinal hernia	Unilateral inguinal hernia Supraumbilical hernia	Bilateral inguinal hernia	Inguinal hernia reported in a handful of cases[6]
Facial features	Dysmorphic facies, relative macrocephaly, frontal bossing	No	No consistent features described
Skeletal	Delayed closure of metopic suture, Wormian bones, sacral dimple	Not known	Handful of cases with skeletal features including short stature, scoliosis, metatarsal microsomia or micrognathia[3–5]
Metabolic	Raised fasting cholesterol profile	Normal profile	No
Skin	Lipoatrophy, x3 small 1–2 cm areas on the forehead, translucent skin with prominent veins	No	No

eGFR, estimated glomerular filtration rate; SNHL, sensorineural hearing loss.

ocular phenotype was not taken into account in communications with clinical scientists.

OUTCOME AND FOLLOW-UP

The numerous health concerns in the proband, alongside 'negative' results from whole exome testing, understandably led to ongoing anxiety within the family. Additional health concerns emerged while WGS was in progress, raising anxiety further. These included suspected lipoatrophy presenting as a non-inflammatory loss of subcutaneous tissue in two discrete areas on the forehead; frequent ear infections; and a raised fasting cholesterol. Parental fasting cholesterol levels were within the normal range. A formal autism spectrum diagnosis was made. Fine motor and gross motor skill attainment slowed subsequent to the episode of ataxia with reports of frequent falling. The proband has had several further ataxic episodes which have resolved within 24 hours. Investigations for non-genetic causes of ataxia on presentation to his local hospital were again non-diagnostic.

14 months after the initial presentation to neurology services, a result was received from the trio WGS testing. It identified a paternally inherited, pathogenic, *PAX2* microdeletion encompassing exon 4 (see table 1). The presence of the variant in the father prompted further assessment of family members. A review of the father's eyes by an ophthalmologist with expertise in genetic eye disorders demonstrated features consistent with PAX2-related disorder. This included bilateral central optic disc pits containing fibrotic material, an absent central retinal artery, myopia and superior binasal visual field defects. The proband's father was also identified to have bilateral high-frequency sensorineural hearing loss which did not require hearing aids. He reported having had bilateral inguinal hernia repairs in infancy. Renal ultrasound scanning was normal. Creatinine was 111 with an estimated glomerular filtration rate of 75. Blood pressure was normal. A paternal first-degree relative had a history of a renal cyst but was found not to carry the variant.

DISCUSSION

This case has multiple points of interest. It adds to the emerging evidence of a broader phenotype associated with pathogenic *PAX2* gene variants which remains to be systematically documented. As highlighted in table 2, some features observed in this case have not been previously described. Most notably, our patient has had episodes of acute ataxia as well as rapid autistic regression. While it is possible that there is a second diagnosis, the proband has had extensive genetic and biochemical testing with no additional diagnosis identified. Two recent cohort studies in the Japanese and Chinese populations have reported individuals with phenotypes including autism and developmental delay.[3 5 6] *PAX2* is a highly conserved gene and developmental biology studies have demonstrated expression throughout the central nervous system.[11 12] *PAX2* plays a role in transcriptional networks both suppressing and activating a large number of genes.[11 13] Heterozygous knockout of the *PAX2* gene alters behaviour in the murine model.[13 14] It is therefore plausible that PAX2-related disorder may have a neurodevelopmental and neurological phenotype. The absence of neurodevelopmental features in the proband's father would not exclude this given the known intrafamilial variability of PAX2-related disorder.[2–6] More work is required to establish the broader PAX2-related phenotype.

This case also highlights the importance of understanding the limitations of a genetic test and communication with clinical scientists. Detecting small microdeletions can be challenging. The resolution of an SNP microarray is dependent on the number of SNP calls for a given area of the genome. In the era of whole exome sequencing and WGS, different technologies and bioinformatic pipelines may be used. This can alter the type of variants detected. The rapid exome sequencing initially used in this case is designed to identify de novo autosomal dominant conditions.[10] On suspecting PAX2-related disorder, the clinical scientists reviewed the *PAX2* gene: adequate coverage of sequencing was confirmed with no variants flagged. However, the *PAX2* whole exon 4 deletion was inherited from a parent and could plausibly have been filtered out by the bioinformatic pipeline.[10] The break points of the microdeletion were deep intronic and were not visible on the exome sequencing data. When the clinical scientists reviewed the data, the paternal history was not known to them and would have altered the analysis strategy.[10] When the SNP microarray data were subsequently reviewed with the cytogeneticist, there was some evidence of a deletion in the *PAX2* gene at exon 4. However, this was not detected by the analysis software and required manual scientist review. The importance of exploration of family history and communication of evolving clinical suspicions to the clinical scientists is therefore highlighted. In this case, it may have reduced the time to a genetic diagnosis.

It is also important to note that genetic testing and bioinformatic pipelines evolve over time. R14 is now a genome-based test, and in specific circumstances, secondary analysis allowing for incomplete penetrance using virtual gene panels can be initiated.[10] However, no genetic test is perfect, and where there

Patient's perspective

As parents, the diagnostic journey has been unnerving, consuming and at many points overwhelming.

Because our son's genetic condition impacts multiple systems, he presented with various symptoms over a reasonably narrow timeframe and at a young age. This meant that as a family we received multiple discrete diagnoses simultaneously. Additionally, we had many different medical professionals raise concerns about the way that our son was presenting. At the time, we understood that an undiagnosed unifying genetic diagnosis was likely. Consequently, there remained a huge amount of uncertainty; we were often left wondering what was next. It felt like a race against time to get the diagnosis; in case there was a chance that the neurological differences could be halted or reversed in some way. We did have suspicions around a *PAX2* gene mutation however we believed this had been ruled out because of the R14 result. The whole genome sequencing took a substantial period of time to return results. During this period of waiting, we found ourselves researching our son's phenotypic presentation in the search for our own answers which often led to unnecessary worry about conditions that he didn't have but that presented similarly.

The diagnosis of PAX2 related disorder has given us a name for our son's condition and has confirmed a lot of what we had already learned prior to the diagnosis. However, we are left with unanswered questions about our son's wider phenotypic presentations. We hope to see more research on the condition going forward to help us better understand the wider phenotype that our son presents with. This could help confirm that our son's wider phenotype is due to PAX2 related disorder. It could also aid diagnosis and discussions around the condition with other affected families.

Learning points

- Paired box 2-related disorder may have a broader phenotype than the renal and ophthalmological findings classically described.
- All genetic tests have limitations; it is important to trust clinical acumen and not to discount a diagnosis based on a 'negative' genetic test result.
- A thorough family history can provide information which alters how genomic data are analysed.
- When a genetic diagnosis is strongly suspected, discussion with clinical genetics and the clinical scientists may help in reaching a diagnosis by reviewing existing data and guiding onwards testing.

is a strong clinical suspicion of a diagnosis, this should not be discounted when genetic testing is non-diagnostic. Discussion with clinical genetics services may assist in the navigation of genetic testing options.

X Anna P Basu @AnnaBasu1

Acknowledgements The authors would like to acknowledge the family and thank them for their support of the report and patient perspective. Furthermore the following all provided care for the patient and were involved in critical review of the case report: Tse, Y, Dept of Paediatric Nephrology, Great North Children's Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust; Browning, AC, Newcastle Eye Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust; Leech, S, Dermatology Department, Great North Children's Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust; Blackett, J, Northern Genetics Service, Newcastle upon Tyne Hospitals NHS Foundation Trust; Bowron, A, Department of Blood Sciences, Newcastle upon Tyne Hospitals NHS Foundation Trust.

Contributors PAW, APB and LMY were all involved in the provision of care for the family in this case. PAW was the submitting author contributing to the drafting and revision of the manuscript. LMY and APB provided critical revision of the manuscript and guidance. LMY is responsible for the overall content as the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained from parent(s)/guardian(s).

Provenance and peer review Not commissioned; externally peer reviewed.

Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

ORCID iDs
Patricia A Wells http://orcid.org/0000-0002-4838-888X
Anna P Basu http://orcid.org/0000-0002-1356-3027
Laura M Yates http://orcid.org/0000-0002-7963-625X

REFERENCES

1 Weaver RG, Cashwell LF, Lorentz W, *et al*. Optic nerve coloboma associated with renal disease. *Am J Med Genet* 1988;29:597–605.
2 Adam J, Browning AC, Vaideanu D, *et al*. A wide spectrum of phenotypes in a family with renal coloboma syndrome caused by a PAX2 mutation. *Clin Kidney J* 2013;6:410–3.
3 Deng H, Zhang Y, Xiao H, *et al*. Diverse phenotypes in children with PAX2-related disorder. *Mol Genet Genomic Med* 2019;7:e701.
4 Chang Y-M, Chen C-C, Lee N-C, *et al*. *PAX2* Mutation-Related Renal Hypodysplasia: Review of the Literature and Three Case Reports. *Front Pediatr* 2021;9:765929.
5 Rossanti R, Morisada N, Nozu K, *et al*. Clinical and genetic variability of PAX2-related disorder in the Japanese population. *J Hum Genet* 2020;65:541–9.
6 Yang X, Li Y, Fang Y, *et al*. Phenotypic spectrum and genetics of PAX2-related disorder in the Chinese cohort. *BMC Med Genomics* 2021;14:250.
7 Bower M, Salomon R, Allanson J, *et al*. Update of PAX2 mutations in renal coloboma syndrome and establishment of a locus-specific database. *Hum Mutat* 2012;33:457–66.
8 Benador-Shen CL, Reichel E, Reed D, *et al*. Ocular phenotype in a patient with *PAX2* gene mutation-associated papillorenal syndrome. *Ophthalmic Genet* 2022;43:385–8.
9 NHS England. The national genomic test directory. 2024. Available: https://www.england.nhs.uk/genomics/the-national-genomic-test-directory/
10 Exeter Clinical Laboratory International. R14 rapid genome sequencing service. 2024. Available: https://www.exeterlaboratory.com/genetics/genome-sequencing/
11 Lv N, Wang Y, Zhao M, *et al*. The Role of PAX2 in Neurodevelopment and Disease. *Neuropsychiatr Dis Treat* 2021;17:3559–67.
12 Namm A, Arend A, Aunapuu M. Expression of Pax2 protein during the formation of the central nervous system in human embryos. *Folia Morphol (Warsz)* 2014;73:272–8.
13 Wang Y, Wang Y, Tang J, *et al*. Impaired neural circuitry of hippocampus in *Pax2* nervous system-specific knockout mice leads to restricted repetitive behaviors . *CNS Neurosci Ther* 2024;30.
14 Lv N, Wang Y, Liu Y, *et al*. Decreased Microglia in *Pax2* Mutant Mice Leads to Impaired Learning and Memory. *ACS Chem Neurosci* 2022;13:2490–502.
15 Richards S, Aziz N, Bale S, *et al*. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;17:405–24.
16 Schimmenti LA, Cunliffe HE, McNoe LA, *et al*. Further delineation of renal-coloboma syndrome in patients with extreme variability of phenotype and identical PAX2 mutations. *Am J Hum Genet* 1997;60:869–78.