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Any symptom, in any organ, at any age: a case report of multiple genetic diagnoses mimicking mitochondrial disease in an adult with kidney disease.

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Unexplained clinical syndromes affecting multiple organ systems should raise suspicion for genetic disorders. Rarely, multiple genetic illnesses can coexist. Here, we present an older male who exhibited markers for Usher Syndrome as well as MYH9-related disorder.

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A 63-year-old gentleman was on maintenance hemodialysis after he developed renal failure following diabetes and hypertension. He had presented six years previously with proteinuria (urine albumin-to-creatinine ratio 92.6 mg/mmol), a bland urinary sediment and an estimated glomerular filtration rate of 43 mL/min/1.73m ^{2}. Other features included thrombocytopenia (with increased megakaryocytes in the bone marrow), bilateral sensorineural hearing loss, retinitis pigmentosa and early optic atrophy. His parents were first cousins. There was no kidney disease in the family.

The involvement of multiple organ systems raised the possibility of mitochondrial diseases (our patient scored 4 on the predictive Nijmegen Clinical Criteria [1]). He underwent Whole Genome Sequencing (WGS) after enrolment into the Australian Genomics Mitochondrial Disease Flagship study. While he did not have mitochondrial disease, variants for two other genetic conditions were seen – he was homozygous for a missense variant in *USH2A* (c.14453C>T, p.(Pro4818Leu)), associated with the autosomal recessive type IIa Usher syndrome, and heterozygous for a missense variant in *MHY9* (c.2114G>A, p.(Arg705His)), linked to the autosomal dominant MYH9-related disorder. Chromosomal microarray analysis showed a male pattern along with two copy number variants (CNVs) and findings consistent with parental consanguinity.

The co-occurrence of two genetic disorders, discovered for the first time in the seventh decade of life, is rare. Approximately 2% of patients with molecularly confirmed genetic kidney disease may have dual diagnoses; rates are similar with other organ systems too [2].

To our knowledge, this is the first reported co-occurrence of Usher syndrome and MYH9-related disorder. Usher syndrome, a ciliopathy, is not linked to renal disease, but is the most common genetic cause of combined deafness and blindness. MYH9-related disorder is associated with thrombocytopenia, giant platelets, sensorineural deafness and proteinuric glomerulonephritis. Polymorphisms in the *MYH9* gene have associations with diabetic kidney disease and HIV-associated nephropathy [3].

This case demonstrates that genetic diagnoses can be made at any age, not just in the young. Additionally, it illustrates that multiple molecular diagnoses may in fact be responsible for multisystem involvement. WGS is useful especially in such clinically heterogenous presentations, and since the technology adopts an unbiased approach to molecular diagnosis, it can sometimes reveal unexpected results. This case report demonstrates the pivotal role of WGS in providing a comprehensive analysis of the entire genome for unravelling complex genetic disorders.

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