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Genotype and phenotype Alport syndrome differences in the same family

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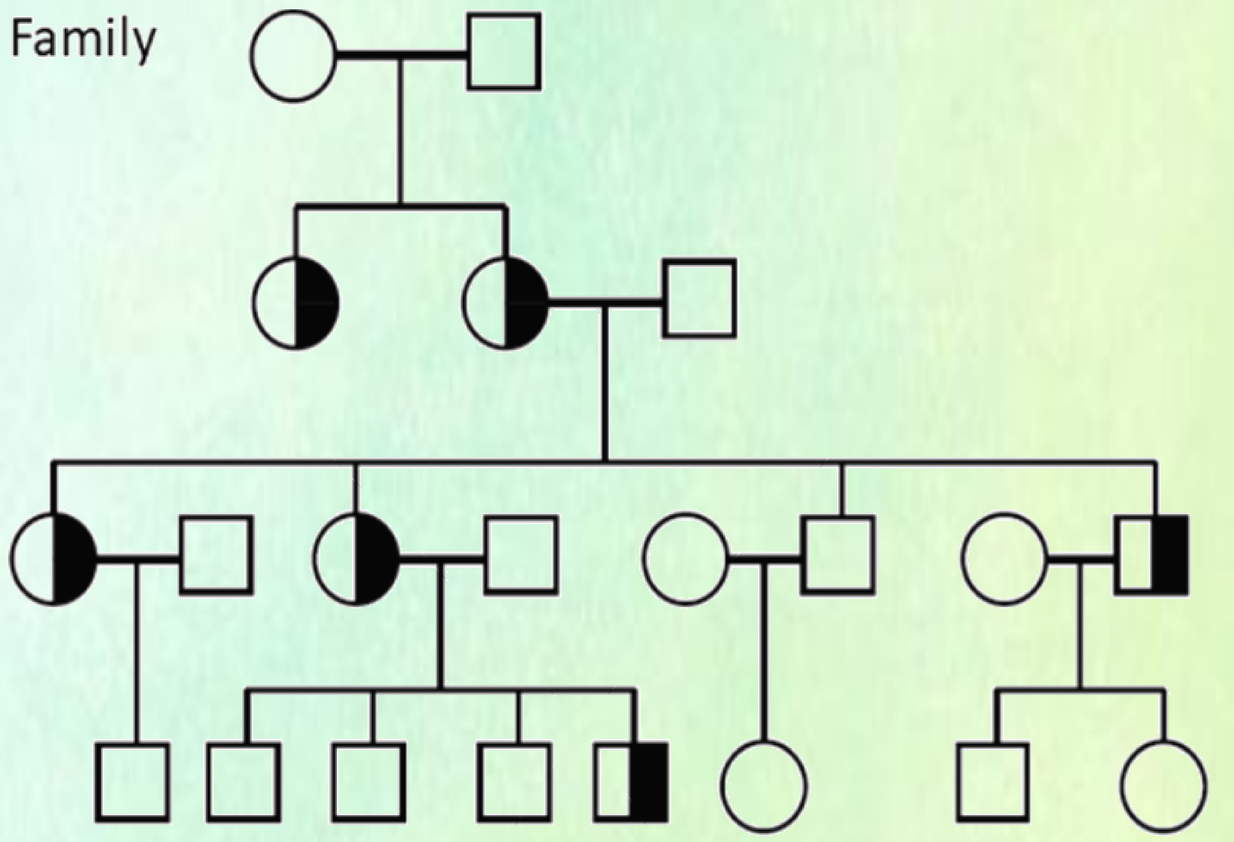
Alport syndrome is a hereditary disorder caused by variants in genes for chains of collagen type IV:COL4A3, COL4A4, and COL4A5.Variants inCOL4A3 andCOL4A4causean autosomal recessive type of disease, while inCOL4A5cause a classic, X-linked disease.

Methods

c.2881+1G>A in COL4A3 gene. The proband presented with end-stage renal disease(ESRD)and had a history of hematuria and renal injury (RI). We have made a family pedigree and gathered all family members for urinalysis and blood sampling for genetic analysis. Genetic testing was performed using NGS (next generation sequencing) for COL4A3, COL4A4 and COL4A5 genes.



Results

All patients tested positive for hematuria and proteinuria. Four patients underwent kidney biopsy. Mother had hematuria and non-nephrotic proteinuria, 2 children had ESRD, 3 had nephrotic proteinuria and 1 son had subnephrotic proteinuria. 3 children had sensorineural hearing loss, 3 were diagnosed with Alport syndrome on kidney biopsy specimen and a pathogenic 'splice site' variant c.2881+1G>A in COL4A3 gene was found in 3 children. Mother hasn't been tested.

Family members with the same variant, despite the same genotype, had different clinical presentation [Table 1.]It is not yet clear what causes phenotype variability. It is possible that some other, not detected variant in COL4 genes which is not pathogenic by itself, but in co-inheritance with the pathogenic variant contributes to more severe phenotype. Possible cause are also variants in other genes connected with the structure and function of the glomerular filtration barrier that were not sequenced by this method. Finally, environmental factors and diseases (smoking, obesity, hypertension) surely play the role in kidney damage and in accordance with that, contribute to severe phenotype and worse prognosis.

		Hematuria +/N	Proteinuria +/g	Creatinine/GFR	NGS	Renal biopsy	Ocular signs	Hearing loss Audiometric check-ups	Blood pressure over 140/90 mmHg
Mother	N ♀	+ 10	+ 0,51gr/24h	74 µmol/L 90 mL/min	No	No	No	No	✓
Child	M ♀	0	0	ESRD/Tx 2010/normal graft	COL4A3 c. 2881+1G> A	x2	No	Yes	✓
Child	P ♀	+ 20	++ 1.46gr/24h 3.5 gr/24h	114 µmol/L 80 mL/min	COL4A3 c. 2881+1G> A	x2	No	Yes	✓
Child	B ♂	+ 12	++ 4.64 gr/24h 8.31 gr/24h	CAPD 2020	COL4A3 c. 2881+1G> A	x3	No	Yes	✓
Child	L ♂	+ 4-6	+ 1.2 gr/24h	76 µmol/L 136.4 mL/min	COL4A3 c. 2881+1G> A	x1	No	0	✓

Table 1 Hematuria +/N (qualitatively/quantitatively), proteinuria +/g (qualitatively/quantitatively) creatinine/GFR (creatinine/glomerular filtration ratio)

Conclusion

Clinical and morphological differences among patients with the same variant point to the need for patients to be monitored more, early detection and prevention of the progression to ESRD