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Letter to the Editor

LETTER TO THE EDITOR

Genetic screening in thrombotic microangiopathy: a plea for methylmalonic aciduria with cobalamine C deficiency detection

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The recent reviews by Knoers *et al.* [1] highlights the opportunities afforded by massively parallel sequencing (MPS) and lays the groundwork for empowerment of the clinician in his day-to-day exploration of kidney disease.

Atypical hemolytic uremic syndrome (aHUS) is an obvious application of MPS given the involvement of complement genetics which have paved the way for specific anti-C5-based treatments [2]. Accordingly, the authors recommend that genetic explorations should include *CFH*, *CD46*, *CFI*, *C3*, *CFB*, *THBD* and *DGKE* as part of a targeted gene panel sequencing strategy (TGPS).

We suggest that: (i) *MMACHC*, responsible for the processing and intracellular trafficking of vitamin B12, and *PRDX1*, a flanking gene involved in the regulation of *MMACHC* transcription, are known to cause autosomal recessive disease termed methylmalonic aciduria with cobalamin C deficiency (cblC) (OMIM #277 400). They represent genes worthy of first-line genetic investigation. (ii) It follows from this example that whole-exome sequencing or whole-genome sequencing (ES/GS) may represent a reasonable alternative to the TGPS approach.

In addition to HUS (Table 1), cblC is known for causing a wide range of (i) neurological, visual and neuropsychiatric manifestations, (ii) hematopoietic disorders, and (iii) pulmonary hypertension and thromboembolic complications, primarily in the neonatal period and early years. Numerous reports of adult-onset cblC have demonstrated that the disease spans the age spectrum [3, 4] with 45 recent cases of adult-onset cblC [5]. Adult patients display fewer features specific to cblC, thus making genotype predictions based solely on the phenotype challenging [3, 4]. Adult-onset cblC remains a rare disease, but is more common than, for instance, *DKGE*-related aHUS diagnosed in this age range, with a prevalence of 1:46 000 compared with 0.0015/million/year.

The diagnosis of cblC should not be postponed, as expeditious initiation of hydroxycobalamin has been demonstrated to partly reverse kidney failure and neurological impairment [5, 6]. Conversely, failure to recognize cblC carries a poor prognosis, including end-stage kidney disease, neurological disability, cardiovascular complications and death [3, 5]. Patients with undiagnosed cblC may be started on unnecessary antiC5 treatment trial or plasmatherapy within the traditional framework of HUS with negative genetic investigations, or unwarranted inclusion in clinical studies. Recently, the PanelApp consortium, an organization designed to adjudicate on the relevance of a

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Table 1: Summary of cases of adult-onset cblC with thrombotic microangiopathy.

Case	Age at onset (years)	Gender	Kidney function at diagnosis: eGFR (mL/min/1.73 m²)	Nadir hemoglobin (g/dL)/platelets (G/L)	LDH (UI/L)	Homocysteinemia upon diagnosis (µmol/l) (N < 15 µmol/L)	Kidney histological findings	Extra-renal features	Disease course and final eGFR (mL/min/1.73 m²)	Genotype		Reference
1	26	F	18	7.0/74	3000	230	Arteriolar and glomerular TMA	No	Control of TMA, persisting kidney graft dysfunction	c.271dupA	c.389A > G	[3]
2	18	M	Dialysis	7.8/141	787	73	Arteriolar and glomerular TMA	Delayed language acquisition at 3 years old	Dialysis discontinuation 5 months after treatment initiation; eGFR: 58	c.271dupA	c.82–9_12delTTTC	[6]
3	18	M	Dialysis	12.5/191	444	NA	Arteriolar and glomerular TMA	Pulmonary hypertension	Death (autopsic diagnosis)	c.271dupA	c.82–9_12delTTTC	[4]
4	20	M	Dialysis	11.6/101	1044	185	Arteriolar and glomerular TMA	No	Dialysis discontinuation 3 months after treatment initiation; eGFR: 32	c.271dupA	c.389A > G	[7]
5	28	F	Dialysis	6.2/83	635	75	TMA (no specification)	Coma, pulmonary hypertension	Neurological recovery, no kidney function improvement	c.565C > A	c.565C > A	[8]
6	23	M	Dialysis	7.3/88	NA	250	NA	Attention deficit in childhood, depressive episode at 20 years old	Improved psychosocial status, no renal function improvement	c.565C > A	c.565C > A	[8]
7	18	F	Dialysis	6.7/50	NA	344	NA	Epilepsy	Dialysis discontinuation after several months; eGFR: 50	c.271dupA	c.565C > A	[9]
8	34	F	34	8.2/NA	NA	100	Arteriolar and glomerular TMA	Pregnancy loss at 20 weeks	Normalization of kidney function, second pregnancy with healthy baby	c.388T > C	c.666C > A	[10]
9	19	F	7	8.9/151	700	285	Arteriolar and glomerular TMA	No	Control of TMA and normalization of kidney function	c.566G > A	c.271dupA	[11]
10	45	M	Dialysis	12.6/87	557	130	Arteriolar and glomerular TMA	Psychiatric symptoms and cognitive decline	Improvement of neurological symptoms; dialysis discontinuation; eGFR: 20	c.220delA	c.395_397delGAC	[12]
11	22 onset; 29 flare	M	Dialysis	6.0/83	297	175	Arteriolar and glomerular TMA	No	Control of TMA, no kidney function improvement	c.271dupA	c.389A > G	UP
12	26	M	49	12.4/207	352	346	Arteriolar and glomerular TMA	High blood pressure at 22 years old	Improvement of kidney function (eGFR: 83) and blood pressure control	c.566G > A	*PRDX1* c.515–1G > T	UP

N: normal; TMA: thrombotic microangiopathy; F: female; M: male; eGFR: estimated glomerular filtration rate; LDH: lactate dehydrogenase; NA: not available; UP: unpublished (personal communication).

given gene, has integrated *MMACHC* as a gene involved in HUS (https://panelapp.genomicsengland.co.uk/). Patients with *cblC* are prone to exhibit hyperhomocysteinemia. Nevertheless, this useful marker for routine screening is not infallible as its interpretation may be obscured by kidney failure and reciprocally patients with cblC may exhibit only mild levels of hyperhomocysteinemia. Ultimately, the diagnosis rests on genetic testing. This example also showcases the arbitrary character of TGPS gene selection. Simply incorporating *MMACHC* alongside the other genes indicated is not an lasting solution since a steady stream of novel genes has been incriminated in the pathogenesis of aHUS, including *PLG*, *VTN*, *IFN2* and *CLU* [2]. Any sequencing approach based on a predetermined list of genes may be hindered from the outset since it fails to capture new gene variants in a fast-changing field. Adjusting TGPS so that it integrates new findings comes at a cost, including crafting and validating a new panel [1]. ES/GS also have their own share of drawbacks, namely management of secondary findings, a reliance on powerful bioinformatic tools and failure to recognize complex *CFH/CFRH* rearrangements, whilst its cost-effectiveness has yet to be proven superior. Other hybrid strategies such as *in silico* panel and the so-called "mendeliome" may prove useful by meshing the benefits of TGPS and ES/GS while mitigating their flaws. Irrespective of the MPS utilized, *MMACHC/PRDX1* should rank among the genes analyzed. An etiological diagnosis requires the meticulous integration of clinical, biological and genetic investigations.

CONFLICT OF INTEREST STATEMENT

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