RESEARCH LETTER

blood advances

TO THE EDITOR:

Unraveling facets of MECOM-associated syndrome: somatic genetic rescue, clonal hematopoiesis, and phenotype expansion

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Pathogenic germ line heterozygous variants in *MECOM* (myelodysplastic syndrome[MDS]1 and EVI1 complex locus) are associated with an autosomal dominant bone marrow failure (BMF) disorder characterized by radioulnar synostosis (RUS) often accompanied by amegakaryocytic thrombocytopenia (RUSAT2; Mendelian Inheritance in Man number 616738). MECOM is a transcription factor that is essential for hematopoietic stem cell self-renewal, and the loss of MECOM decreases absolute long-term hematopoietic stem cell numbers.[1] Several differentially spliced transcripts are encoded by the *MECOM* locus resulting in MDS1, MDS1-EVI1, and EVI1 isoforms. It has been demonstrated that these isoforms are involved in their own transcriptional regulation through distinct promoter regions and have an effect on the maintenance and transformation of hematopoietic stem and progenitor cell populations.[2]

Individuals with MECOM-associated syndrome display variable clinical presentations ranging from no hematological manifestations to severe BMF with or without skeletal abnormalities.[1,3] Other features

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The full-text version of this article contains a data supplement.

include clinodactyly, cardiac and renal malformations, hearing loss, and B-cell deficiency. Most individuals eventually progress to pancytopenia and require hematopoietic stem cell transplants at relatively young ages.[3-5] Skeletal abnormalities, particularly RUS, are seen predominantly in individuals with missense variants within the eighth and ninth zinc finger motifs of MECOM.[4,6] However, there are reports of affected individuals with premature termination variants or constitutional deletions with skeletal involvement.[7,8]

Clinical and genomics data from germ line *MECOM* variant carriers were collected from the Centre for Cancer Biology (Adelaide, Australia), Peter MacCallum Cancer Centre (Melbourne, Australia), Radboud University Medical Center (Radboud, The Netherlands). All procedures in this study involving human participants were performed in accordance with the Declaration of Helsinki. Studies were approved by institutional human research ethics committees and/or institutional research boards. All participants signed an informed consent form to share genomics and protected health information.

Here we report 15 cases (3 families and 5 de novo) of MECOM-associated syndrome, with onset of symptoms varying from in utero to late adulthood (Figure 1A-F). Our cohort represents the spectrum of this syndrome with individuals presenting with (1) classical RUSAT, (2) BMF (ranging from mild to severe) without RUS, and (3) RUS without hematological manifestations. Detailed information on clinical history and classification of germ line *MECOM* variants as per the American College of Medical Genetics guidelines are included in supplemental Information, Table 1, and supplemental Table 1.

Herein, we show that part of the variability in hematological presentation may be attributable to spontaneous reversion of germ line variants observed in some affected individuals. Our study identifies 7 of 15 affected individuals who show spontaneous resolution, alleviation of hematological symptoms, or late onset of hematological manifestation of MECOM-associated syndrome. For 4 of 6 individuals (3-II-4, 4-II-4, 5-II-1, and patient 11), amelioration of symptoms appears associated with somatic genetic rescue, in the form of copy neutral loss of heterozygosity of chromosome 3q encompassing *MECOM* (Figure 1H; supplemental Figures 2-4; supplemental Information), thereby duplicating the residual wild-type allele in an expanding clone. A chromosomal rearrangement involving the *MECOM* locus was detected by fluorescence in situ hybridization in a small subset of cells in 7-II-1. However, the consequence of this event at the cell differentiation/fitness level remains to be established. For 2 of 6 individuals, an explanation for mild presentation or symptom resolution remains enigmatic: 2-II-6 displayed spontaneous resolution of hematopoietic symptoms, whereas 4-II-1 has been free of hematological symptoms for most of her life. Longitudinal analysis of variant allele fractions in both these individuals showed no evidence of allelic imbalance (supplemental Figures 5 and 6). Somatic genetic rescue has been reported in several genetic diseases including skin disorders (eg, ichthyosis with confetti[9] and epidermolysis bullosa[10]) and BMF syndromes (eg, Fanconi anemia,[11] Diamond Blackfan anemia,[12] Wiskott-Aldrich syndrome,[13] and dyskeratosis congenita[14]), with only 1 report in MECOM-associated syndrome.[15] Spontaneous normalization of blood counts and absent/mild hematopoietic involvement in carriers have been described in the literature; however, there has been limited information/follow-up as to the mechanism.[3,6,16,17]

Most reported *MECOM* cases have had allogeneic bone marrow transplants at relatively young ages, which could explain relatively low frequency of progression to myeloid malignancy in 5% of patients (3 adult MDS cases and 1 pediatric acute myeloid leukemia of 80 individuals[18]).[3,5,8] The findings of aplasia with dysplastic features in 1-II-5 and MDS in 5-II-1 adds 2 more cases of myeloid dysplasia in MECOM-associated syndrome. Notably, all 3 older individuals within our cohort (4-II-1, 4-II-4, and 5-II-1) displayed somatic variants in known age–related clonal hematopoiesis genes (supplemental Figure 7). Acquisition of somatic variants in genes such as *ASXL1, DNMT3A*, and *TET2* have been linked with improved hematopoietic stem cell fitness and self-renewal.[19] Both 3-II-4 and 4-II-4 also had transient 20q loss events (a common karyotypic abnormality observed in myeloid disorders and aging population[20]) in their surveillance marrows. Intriguingly, 4-II-1 and 5-II-1 also have somatic *ETV6* variants, which is not usually reported in an age-related context. Although the presence of such somatic alterations likely improves hematopoietic output, it may also signify an elevated risk of myeloid malignancy development, particularly with advancing age. Consistent with this, in addition to clonal haematopoiesis, 4-II-4 is beginning to exhibit dysplastic features in >1 lineage (supplemental Figure 2).

In the dynamic hematopoietic environment, demand-adapted hematopoiesis can drive mosaicism down 2 roads: clonal evolution through the acquisition of deleterious variants leading to cancer; or alternatively, revertant mosaicism resulting in partial/complete rescue of phenotype. Somatic genetic rescue is an important factor to consider in scenarios such as carriers with mild phenotype, selection of tissue sources for identification of causative lesion in individuals in remission, and use of patient-derived cell lines for drug screening. Understanding the mechanisms of revertant clonal selection in vivo and in vitro will open windows for rational correction and selection protocols for effective therapeutic intervention in inherited BMF disorders such as MECOM-associated syndrome.

Strikingly, there were 12 pregnancy losses of a total of 16 pregnancies in 5 mothers for whom detailed information regarding pregnancies was available (supplemental Table 2) within our cohort. This is a higher rate of loss (75%) than expected pregnancy outcomes in the general population (15%-25%) as well as other inherited BMF syndromes (12%-20%).[21,22] We observed recurrent pregnancy losses (including late losses) in 1-I-2, 4-II-1, and 5-II-1, all of whom are carriers of *MECOM* variants (Figure 1). 4-I-2, who tested negative for the *MECOM* variant and whose husband (4-I-1) displayed MECOM-associated phenotype, experienced stillbirth at 8.5 months of gestation (4-II-3), raising the possibility that pregnancy loss can also occur from MECOM-associated complications intrinsic to the developing fetus. Her remaining 3 children displayed symptoms of MECOM-associated syndrome with 2 testing positive for the variant, whereas the third could not be assessed due to unavailability of samples. However, we were unable to ascertain the *MECOM* status for the fetus. It is also worth noting that 2-I-2 and 3-I-2 (both wild-type for *MECOM*) have also experienced pregnancy losses. We cannot comment on whether ≥1 individuals are gonadal mosaics for the *MECOM* variants because we are unable to determine the *MECOM* status of the fetuses due to unavailability of material for genetic testing.

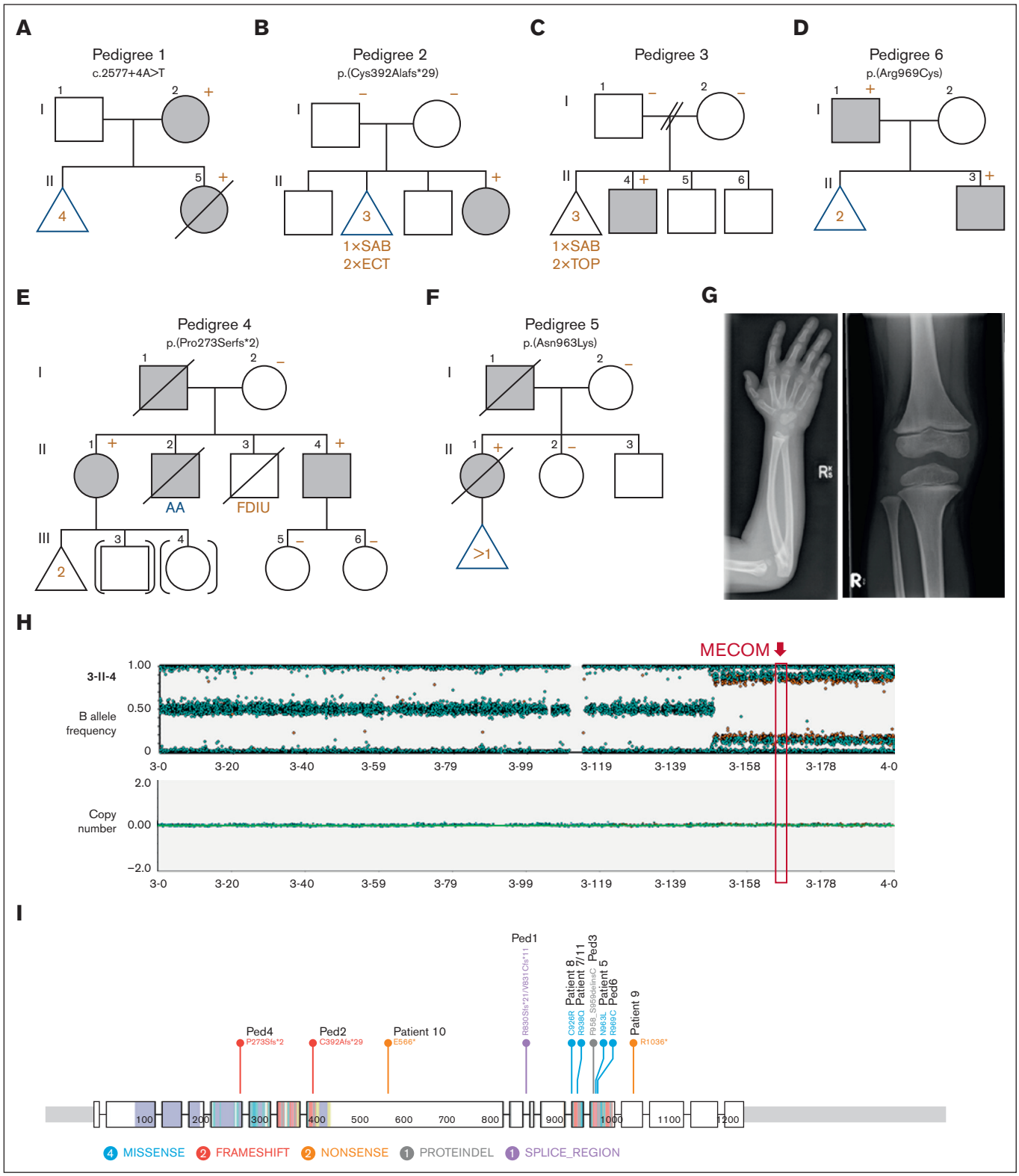

Figure 1. Pedigrees, phenotypes, and genotypes of families and individuals carrying rare germ line *MECOM* variants. (A-F) Pedigrees with germ line *MECOM* variants. Affected individuals (gray), *MECOM* mutation carriers (+), *MECOM* WT (–). (G) X-ray images from 3-II-4 demonstrating RUS and absent patella. (H) Copy neutral loss of heterozygosity in 3-II-4 across chromosome 3q encompassing the *MECOM* germ line variant and leading to somatic genetic rescue. (I) Distribution of germ line *MECOM* variants (NM_004991.4) visualized using ProteinPaint web application. AA, aplastic anemia; ECT, ectopic pregnancy; FDIU, fetal death in utero; SAB, spontaneous abortion; TOP, termination of pregnancy.

Table 1. Genotypes and phenotypes of affected individuals carrying rare germ line *MECOM* variants

Patient ID	cDNA (NM_004991.4)	Protein (NP_004982.2)	Sex	Age at presentation	HSCT (age)	Somatic genetic rescue	Additional somatic genetic changes	Hematopoietic abnormalities (age at diagnosis)	Skeletal abnormalities	Cardiac/vascular abnormalities	Other abnormalities
1-I-2	c.2577+4A>T	p.(Arg830Serfs*21) p.(Val831Cysfs*11)	F	15 y	Haploidentical HSCT (36 y)	Not detected	None detected	Pancytopenia and anemia (15 y)	Short stature, brachydactyly, short toe, proximal placement of hallux, short proximal phalanx of hallux, short proximal phalanx of fifth finger, and cholelithiasis	Ventricular septal defect	
1-II-5	c.2577+4A>T	p.(Arg830Serfs*21) p.(Val831Cysfs*11)	F	In utero	NA	N	Not analyzed	Aplasia with dysplastic features (in utero)	Preaxial polydactyly, supernumerary ribs, and coronal cleft vertebrae	None reported	Fetal Hydrops, splenic hemosiderin deposition, and small placenta
2-II-6	c. 1174delT	p.(Cys392Alafs*29)	F	9 mo	N	Not detected	None detected	• Thrombocytopenia and transient low relative B-cell numbers (9 months) • Hypocellular bone marrow with complete absence of megakaryocytes, dyserythropoiesis and left shifted granulopoiesis with abnormal granulation • Spontaneous recovery (3 y)	Not present	Mild aortic root dilatation	Congenital hearing loss
3-II-4	c.2873_2875delTTA	p.(Phe958_Ser959delinsCys)	M	Birth	N	cnLOH chr3q	Transient del(20q)	• Neonatal thrombocytopenia managed with multiple platelet transfusions followed by spontaneous recovery • Subsequent mild pancytopenia and hypocellular bone marrow	Proximal RUS, hypoplastic thumbs, short, broad fingers, short fifth digits, and coalition of right capitate and hamate, and bilateral absent patellae	Mild mitral valve prolapse	
4-II-4	c.816dupT	p.(Pro273Serfs*2)	M	Birth	N	cnLOH chr3q	Transient del(20q) ASXL1 p.(Arg860Glufs*7) ASXL1 p.(Leu775*)	• Pancytopenia • Aplastic anemia (11 y)	Club foot and small patellae	Aortic root dilatation progressing to aortic aneurysm and mitral valve defect	
4-II-1	c.816dupT	p.(Pro273Serfs*2)	F	59 y	N	Not detected	DNMT3A p.(Leu504Trpfs*147) ETV6 p.(Ser139Tyrfs*14) TET2 p.(Cys973*) TP53 p.(Ala276Asp)	• Mild intermittent thrombocytopenia and neutropenia • Hypocellular bone marrow	Small patellae	Aortic root dilatation	Bicornuate uterus, mild sensorineural hearing loss, cataract (50 y), and bilateral scarring of kidneys with normal function
5-II-1	c.2889C>G	p.(Asn963Lys)	F	Childhood (exact age unknown)	N	cnLOH chr3q	ASXL1 p.(Gly646Trpfs*12) SETBP1 p.(Ser869Asn) EZH2 p.(Tyr733Phe) EZH2 p.(Cys609_Ser610delinsTyr) ETV6 p.(Arg369Trp)	• Aplastic anemia in childhood • Diagnosed with myelodysplastic syndrome (40 y)	Clinodactyly in fingers and toes	None reported	Hearing impairment, locally recurrent anal squamous cell carcinoma, gynecological warts, cataracts, and glaucoma

F, female; HSCT, haematopoietic stem cell transplant; M, male; MUD, matched unrelated donor; N, no; NA, not applicable; VSD, ventricular septal defect; Y, yes.

Table 1 (continued)

Patient ID	cDNA (NM_004991.4)	Protein (NP_004982.2)	Sex	Age at presentation	HSCT (age)	Somatic genetic rescue	Additional somatic genetic changes	Hematopoietic abnormalities (age at diagnosis)	Skeletal abnormalities	Cardiac/vascular abnormalities	Other abnormalities
6-I-1	c.2905C>T	p.(Arg969Cys)	M	4 y	N	Not detected	Not analyzed	No abnormalities	Bilateral RUS-surgically corrected at age 4	None reported	
6-II-1	c.2905C>T	p.(Arg969Cys)	M	2 y	N	Not detected	Not analyzed	No abnormalities	Bilateral RUS and clubfeet	Small patent ductus arteriosus/patent foramen ovale, hemodynamically not significant	Slightly cupped ears with borderline normal hearing
Patient 7	c.2813G>A	p.(Arg938Gln)	M	34 y	N	Y	None detected	• Thrombocytopenia diagnosed at birth • Mild thrombocytopenia and macrocytosis without anemia (33 y)	Presumed bilateral RUS (limited ability to pronate arms bilaterally), bilateral club foot, Perthes-like hip disease, endochondromata, and ecchondromata	None	Small kidneys without structural deficits, nonspecific punctate foci of T2/FLAIR hyperintensity in the peripheral/subcortical white matter slightly greater than expected for patient's age
Patient 8	c.2776T>C	p.(Cys926Arg)	F	27 y	N	Not detected	Not analyzed	Severe thrombocytopenia and mild leukopenia	Clinodactyly of the thumb, short toe, unfused vertebral arch L5, coxa valga, and cam deformity	None reported	
Patient 9	c.3106C>T	p.(Arg1036*)	M	19 y	N	Not detected	Not analyzed	Thrombocytopenia	Marfanoid habitus, tall spindly fingers, hypoplastic thumbs, and adducted toes	None reported	
Patient 10	c.1696G>T	p.(Glu566*)	F	Birth	MUD (11 mo)	Not detected	Not analyzed	• Thrombocytopenia diagnosed at birth • Progressive pancytopenia (9 mo) • Profoundly hypocellular marrow (9 mo)	Retrognathia	Patent foramen ovale and pulmonary branch stenosis (resolved without intervention at 2 y)	Congenital conductive hearing in loss both ears, with cleft palate (corrected at 7 mo)
Patient 11	c.2813G>A	p.(Arg938Gln)	F	17 y	N	Y	Not analyzed	• Mild leukopenia and thrombocytopenia • Hypocellular marrow with absence of megakaryocytes	Right-sided RUS, camptodactyly of the fifth fingers, brachydactyly of the first toes, and scoliosis	Bicuspid aortic valve	Congenital mixed hearing loss, bilateral relatively small kidneys without structural defects, from age 18 onwards, chronic mild renal insufficiency (stage 2)
Patient 12	Complete loss of MECOM gene		F	In utero	N	N	Not analyzed	Hypocellular bone marrow	Micrognathia	At autopsy: ductus arteriosus type II with VSD. Pericardial fluid and ascites	Generalized edema hygroma colli nuchal translucency cleft palate, simple ears, lung hypoplasia due to pleural fluid, and unilateral renal agenesis

F, female; HSCT, haematopoietic stem cell transplant; M, male; MUD, matched unrelated donor; N, no; NA, not applicable; VSD, ventricular septal defect; Y, yes.

Cardiac and vascular abnormalities including atrial septal defect, ventricular septal defect, and patent ductus arteriosis have been reported in MECOM-associated syndrome. However, there has only been 1 report each of aortic coarcatation and aortic root dilatation.[3,23] We have observed 3 cases of aortic dilatation, with 1 progressing to an aortic aneurysm reaching the threshold for surgical correction in our cohort of 15 cases.

Overall, this report adds to the breadth of disease presentations in MECOM-associated syndrome and expands age of onset varying from in utero to late adulthood with at least 1 individual being in relatively good health well into their sixties. It is becoming increasingly clear that the complex disease presentations of MECOM-associated syndrome are primarily driven by genomic location and the nature of the germ line variants, and these presentations are further complicated by mechanisms such as somatic genetic rescue and, possibly, somatic compensation by other genes. The clinical presentation and threshold of somatic genetic rescue required for phenotypic improvement/reversion is likely dictated by how severe the impact on protein function/output is in each affected individual. The prevalence of somatic genetic rescue provides a rationale for gene-corrected autologous transplantation or direct gene editing approaches as potential treatments for the hematopoietic phenotype of MECOM-associated syndrome in the absence of matched donors. The presence of clonal hematopoiesis of indeterminate potential in the older individuals, and the finding of additional cases of myeloid dysplasia in our cohort warrant consideration of surveillance particularly in older carriers. Given the high rate of pregnancy losses in these families, they should be considered for counseling for reproductive planning and the use of preimplantation genetic diagnosis to reduce the risk of future pregnancy losses. Moreover, the variability of presentation can make accurate genetic diagnosis challenging, and the notable prevalence of somatic genetic rescue reiterates the importance of using DNA from nonhematopoietic tissue such as hair follicles or skin fibroblasts for genetic testing.

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Conflict-of-interest disclosure: S.T.C. is a volunteer member of ClinGen Expert Panels: Muscular Dystrophies and Myopathies Gene Curation Expert Panel and Limb Girdle Muscular Dystrophy Variant Curation Expert Panel; is named inventor of intellectual property (IP) relating to novel methods to identify splicing variants (PCT/AU2019/000141; PCT/AU2020/050234), which is jointly owned by The University of Sydney and The Sydney Children's Hospitals Network; serves as the director of Frontier Genomics Pty (Sydney, Australia), which has licensed this IP; and performs this director role outside of her UniSydney position and currently receives no consultancy fees or other remuneration for it. Frontier Genomics has not traded and has no existing financial relationships that will benefit from publication of these data. The remaining authors declare no competing financial interests.

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