Myeloid blast phase of chronic myeloid leukemia with co-occurring t(11;12)(p15;q13)/*NUP98::HOXC12*: a novel *NUP98* fusion partner

NUP98 on 11p15.4 encodes nucleoporin 98 protein that is involved in nuclear-cytoplasmic trafficking, chromatin remodeling, and transcriptional regulation. *NUP98* translocations are predominantly linked to myeloid malignancies, most often acute myeloid leukemia (AML), and encompass more than 30 fusion partners, most commonly, *NSD1* (at 5q35.3) and *HOXA9* (at 7p15.2) in adult case studies.[1-4] Rarely, *NUP98* fusions occur in chronic myeloid leukemia (CML) patients who underwent myeloid blast crisis, with identified fusion partners of *HOXA9*, *DDX10*, *PMX1*, and *PSIP1* (*LEDGF*).[2,5,6]

Here, we report a CML case in myeloid blast phase (BP) in a poorly managed patient with acquisition of *NUP98* rearrangement (*NUP98*-R). The patient was a 58-year-old man with a 4-year history of CML, chronic-phase, diagnosed on a bone marrow biopsy in June 2020. Conventional karyotyping was performed at diagnosis and showed no additional cytogenetic abnormalities. He had been treated initially with imatinib followed by bosutinib and dasatinib but these medications were intermittently discontinued due to side effects, non-compliance, and/or an insurance issue, and he was off medication for 3 months before presentation. In November 2024, the patient sought medical attention for extreme fatigue and dyspnea. At presentation, his complete blood count showed leukocytosis (17.2×10^9/L), anemia (9.0 g/dL), and marked thrombocytopenia (26×10^9/L) along with 56% circulating blasts (Figure 1A, B). Bone marrow aspiration and biopsy showed hypercellular (>95%) marrow with left-shifted granulopoiesis and 35% blasts on aspirate smears (Figure 1C-E). Flow cytometric immunophenotyping showed the blasts had a myeloid immunophenotype, positive for CD13, CD45 (dim), CD117 (increased), CD123 (increased), HLA-DR (decreased to absent), and myeloperoxidase, without co-expression

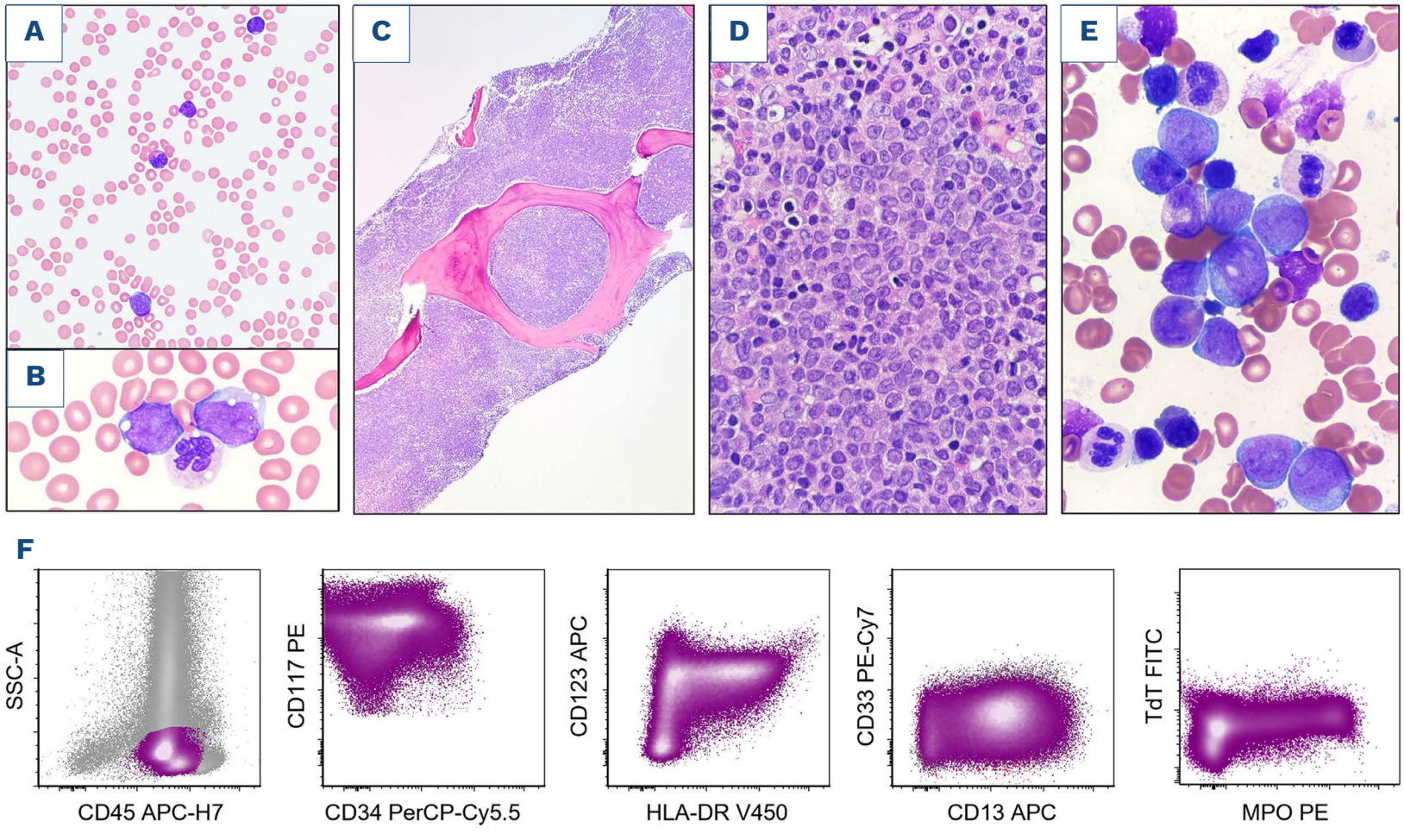


Figure 1. Morphological and immunophenotypic features. (A, B) Peripheral blood smear shows mild leukocytosis and increased circulating blasts (Wright-Giemsa; A, 400x; B, 1,000x), (C, D) Bone marrow trephine biopsy specimen shows a hypercellular marrow (~ 100%) with increased immature myeloid cells and blasts (hematoxylin-eosin; C, 40x; D, 500x). (E) Bone marrow aspirate smears show increased blasts (Wright-Giemsa, 1,000x). (F) Flow cytometric immunophenotyping showed that the myeloblasts express CD13 (major subset), CD45 (dim), CD117 (increased), CD123 (increased), HLA-DR (variably decreased to absent), and myeloperoxidase (MPO, subset) without co-expression of CD33, CD34, or TdT.

of CD33, CD34, TdT, T-cell, B-cell, or additional monocytic markers (Figure 1F). Chromosomal analysis revealed an abnormal karyotype: 46,XY,t(9;22)(q34;q11.2),t(11;12)(p15;q13)[20] (Figure 2A). Fluorescence *in situ* hybridization (FISH) showed that the concurrent t(11;12)(p15;q13) resulted in *NUP98*-R in 92% of the interphase cells analyzed using a break-apart probe (Figure 2B). Real-time reverse transcription polymerase chain reaction (RT-PCR) confirmed a b2a2 fusion transcript encoding a p210 isoform. RNA-sequencing analysis detected a *NUP98::HOXC12* in-frame fusion transcript consisting of *NUP98* (exons 1-12) on chromosome 11 and *HOXC12* (exon 2) containing intact Homeobox (HOX) domain on chromosome 12, confirmed by RT-PCR followed by Sanger sequencing (Figure 2C). No somatic mutations including *FLT3* and *WT1* were detected by next generation sequencing analysis. No mutations in the *ABL1* kinase domain were identified. A diagnosis of myeloid blast phase of CML, with *NUP98*-R, was rendered.

Given his extensive cardiovascular co-morbidities, the patient was treated initially with decitabine, venetoclax, and bosutinib. He also received prophylactic intrathecal chemotherapy with four doses of cytarabine. A follow-up bone marrow specimen on day 32 after one cycle of induction was 20-40% cellular with no increase in blasts by morphology and rare CD117^{+} immature cells by immunohistochemistry. However, FISH analysis showed persistent *BCR::ABL1* and *NUP98*-R in 55.5% and 48% of analyzed cells, respectively, including in segmented neutrophils.

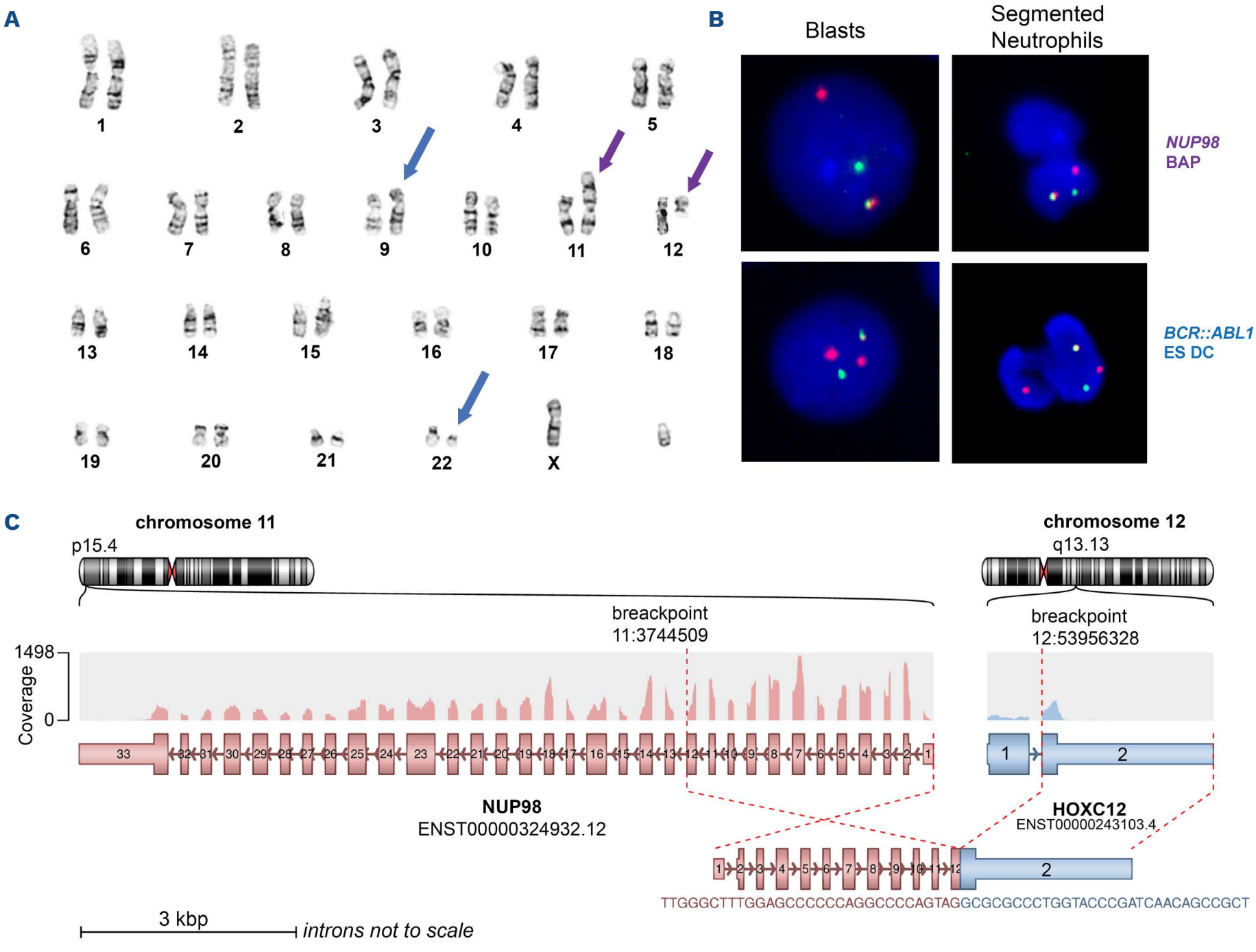


Figure 2. Cytogenetic and molecular characteristics. (A) Chromosomal analysis demonstrates an abnormal karyotype with co-occurring balanced t(9;22)(q34;q11.2) (blue arrows) and t(11;12)(p15;q13) (purple arrows). (B) Fluorescence *in situ* hybridization (FISH) analysis with a break-apart probe (BAP) for *NUP98* (top) shows a signal pattern of 1R1G1F, confirming *NUP98* rearrangement; the FISH analysis with an extra signal dual color *BCR::ABL1* probe (ES DC, bottom) shows a signal pattern of 2R1G1F, indicating the presence of major *BCR::ABL1* fusion product, corresponding to a *p210* isoform. Both fusion products are detected in both round (blasts) and segmented (neutrophils) cells. (C) RNA sequencing detected a *NUP98::HOXC12* in-frame fusion transcript consisting of *NUP98* (exons 1-12) from chromosome 11p15 and *HOXC12* (exon 2) from 12q13.

He was then transferred to local care due to the lack of insurance coverage in our system and lost to follow-up in our system thereafter.

Blast crisis (BP) of CML is associated with acquisition of additional chromosomal aberrations, gene mutations, decreased telomere activity, and epigenetic modifications.[7] *NUP98* rearrangement was one of the newly introduced leukemia-defining genetic aberrations in the 5th edition of the World Health Organization (WHO) Classification and International Consensus Classification (ICC) of myeloid neoplasms.[8,9] *NUP98* fusions typically deregulate expression of HOX cluster genes in leukemogenesis, and are associated with treatment failure, high relapse rates, and poor prognosis.[10] Although uncommon, acquisition of *NUP98*-R in CML has been reported to associate with myeloid blast crisis in several case reports that show variable morphologic and phenotypic features.[2,5,6] *NUP98* fusions with *HOXC* partners in CML progression have not been previously documented. Homeodomain-containing *HOX* genes constitute one essential category of *NUP98* fusion partners and are composed of four gene clusters on chromosomes 7p15.2 (*HOXA*), 17q21.3 (*HOXB*), 12q13.3 (*HOXC*) and 2q21 (*HOXD*). To date, at least ten HOX clustered genes (*HOXA6, HOXA9, HOXA11, HOXA13, HOXC11, HOXC13, HOXD8, HOXD11, HOXD12,* and *HOXD13*) have been implicated in AML carrying *NUP98*-R.[1-3] Among these HOX genes, *HOXA9* was the first identified fusion partner for *NUP98*-R and the second most frequently detected *NUP98* fusion partner in adult AML.[1-3] In all instances, the C-terminal DNA-binding homeodomain of the HOX protein is retained in the fusion protein, and the transactivation domain is replaced by the FG and GLFG repeats of *NUP98*. Although most *NUP98*-R AML cases lack a consistent leukemic phenotype, specific fusion partner protein shows a preferential association with a particular leukemia subtype. For example, AML with *NUP98::RARG* showed features resembling acute promyelocytic leukemia.[11] A fusion partner at 12q13 in CML-BP has not been previously reported, and in cases of AML, reported fusion genes include the partners *HOXC11*, *HOXC13*, and *RARG*.[2,10] Here, we present a CML-BP case with acquisition of *NUP98*-R involving a novel partner gene *HOXC12* on 12q13, and with an unique immunophenotype that was $CD34^{-}$ $CD117^{+}$ differentiating towards basophilic lineage.

Notably, this case also illustrates the first-time observation of concurrent *NUP98* and *BCR::ABL1* translocations in both blasts and segmented neutrophils at diagnosis and after induction with resolution of BP. The detection of *NUP98*-R in neutrophils is unusual and may suggest either early acquisition of the fusion during CML evolution, or an unexpected biological behavior of *NUP98::HOXC12* fusion in perturbing myeloid proliferation and/or differentiation. A similar observation was noted in a recent study on longitudinal clonal evolution for adult AML with *NUP98*-R, in which seven of 12 patients were found to have more *NUP98*-rearranged cells than blast counts in follow-up samples, raising the possibility of a subset of maturing myeloid cells carrying *NUP98*-R.[12] Mechanistically, ectopic overexpression of *NUP98::HOXA9* delivered through retroviral or lentiviral transduction was previously demonstrated to be capable of enhancing myeloid cell proliferation in colony-forming assays,[13,14] inducing myeloproliferative disease in murine models,[13] and promoting CML progression in genetically engineered CML models.[14] In these disease models, enforced overproduction of NUP98::HOXA9 led to sustained upregulation of downstream transcripts including genes in the *HOXA* and *HOXB* clusters and their co-factors such as *MEIS1* and *PBX3*, while the leukemic transformation required co-expression or recruitment of cofactors such as KMT2A or MEIS1 following a latency period.[13,14]

HOXC12 has not been previously associated with hematologic malignancies. It belongs to the DNA-binding *HOX* gene family encoding hematopoietic transcription factors essential for promoting myeloid proliferation and/or differentiation. *HOXC12* represents one of the *HOXC* cluster genes on chromosome 12q13, with neighboring *HOXC11* and *HOXC13* genes. *HOXC12* in fusion with *NUP98* would likely derive from alternative splicing at intronic sites in response to HOX pathway deregulation. The identification of a novel *HOXC* family partner gene has biological and therapeutic impact, as the immunophenotype, transcriptome, and epigenome of HOX-activating fusion partners may offer targets for more effective therapies. Specifically, NUP98 fusion protein interactions such as HOXA/MEIS1 axis are vulnerable to menin inhibitors, offering an alternative therapeutic approach currently undergoing phase I clinical trial. Menin serves as the scaffold protein to interact with KMT2A and menin-KMT2A association is required for maintenance of *HOXA/MEIS1* upregulation, the critical leukemic transcription program in AML with *NUP98*-R and others. Although HOXC members share conserved sequence homology to *HOXA* genes, they exhibit distinct biological divergence in leukemogenesis with limited available studies on *HOXC* genes, such as less MEIS1 dependent, involvement of long non-coding RNA like *HOTAIR* within the *HOXC* cluster in epigenetic regulation and oncogenic activation, and promoting leukemic cell survival and proliferation.[15] The prognostic relevance of *NUP98*-R in CML is unknown but appears to have conferred imatinib resistance and contributed to leukemogenesis in one study with a *DDX10* fusion partner and a latency period of 4 months.[6] It remains unclear when *NUP98::HOXC12* emerged in this case, whether the resultant fusion confers resistance to tyrosine kinase inhibitors, and how *NUP98::HOXC12* facilitates clonal evolution and leukemic transformation of CML.

In summary, we present an unusual CML-BP case with a poorly controlled disease course and acquisition of *NUP98*-R involving a novel partner *HOXC12* at 12q13, which has not been previously associated with hematologic malignancies.

This case broadens the spectrum of HOX fusion partner genes in *NUP98* translocations and underscores the complex biology underlying the clonal evolution of CML progression. Further studies are needed to better understand the structural and functional properties of NUP98 fusion oncoproteins and partner-specific co-factors at a higher resolution level than ever before. We acknowledge the limitation of this single case study and the lack of single cell dissection of clonal architecture in the progressive course of CML.
This study was approved by the Institutional Review Board at the MD Anderson Cancer Center (2025-0535).

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Contributions
LQ collected, analyzed data, and wrote the manuscript. AK collected data and drafted the manuscript. JX, BT, GT, and LJM analyzed data and edited the manuscript. All authors read and approved the manuscript.

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Data-sharing statement
Data available on request from the corresponding author.

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