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SHORT REPORT

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Expanding the novel *MAPKAPK5*–related developmental disorder's genotype–phenotype correlation: Patient report and 19 months of follow-up

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Abstract

This study aimed to widen the knowledge of a recently identified, autosomal-recessive, multiple congenital anomalies syndrome to date observed in only other three children. This is the second report of biallelic mutations in *MAPKAPK5* whose impairment during human development has been associated with neurological, cardiac, and facial anomalies combined with fingers and toes malformations. Through the affected patients' genetic and phenotypic features overlap, this report confirms *MAPKAPK5* as causative gene and adds unique neurodevelopmental characterization. Moreover, based on the complex congenital genitourinary anomalies reported and *MAPKAPK5* literature review, we also propose kidney and external genitalia involvement as a key syndromic feature whose expressivity may be more severe in males.

KEYWORDS
ambiguous genitalia, CAKUT, congenital heart defects, *MAPKAPK5* gene, MK5 developmental disorder, nails dysplasia, olfactory bulbs

1 | INTRODUCTION

The mitogen-activated protein kinase (MAPK) cascades are evolutionary conserved intracellular signal transduction pathways that respond to various extracellular stimuli and control a large number of fundamental cellular processes.[1,2] Mammalian cells have been described with four well characterized canonical MAPK pathways, each consisting of three distinct protein kinase units: MAPK, MAPK kinase (MAPKK), and MAPK kinase kinase (MAPKKK), which operate by phosphorylating/interacting with a broad range of additional upstream and downstream components and/or other substrates.[2–4] In the last decade, while these pathways have been extensively investigated and linked to a wide spectrum of human diseases, the downstream MAPK-activated protein kinases' (MAPKAPKs) role remains poorly understood.[5–7] MAPKAPKs include the p90 ribosomal-S6-kinases (RSK1-3), the mitogen- and stress-activated protein kinases MSK1/2,

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the MAPK-interacting kinases MNK1/2 and the MAPKAP kinases: MK2, MK3, and MK5/PRAK.[7] To the best of our knowledge only constitutive *RSK2* (MIM 300075) deleterious variants had been recognized responsible for Coffin-Lowry syndrome (MIM 303600),[8] and recently Horn et al. first identified biallelic truncating variants in *MAPKAPK5* (MIM 606723), also designated as PRAK or MK5 whose locus lies on 12q24.12-q24.1 chromosome,[9] leading to a novel autosomal recessive developmental disorder.[3] Here, we report on an additional affected child whose features and life-long medical follow-up get new insights on this new rare condition.

2 | MATERIAL AND METHODS

2.1 | Subjects

All subjects or their legal representatives gave written informed consent to the molecular genetic analyses and the publication of the results. Written parental informed consent was obtained for the participation of the children in this study and for the publication of clinical photographs.

2.2 | Whole exome sequencing

WES was performed on proband, sibling and parents' DNA using the Twist Human Core Exome Kit (Twist Bioscience), according to the manufacturer's protocol and sequenced on the Illumina NovaSeq 6000 platform. The BaseSpace pipeline and the Geneyx software LifeMap Sciences were respectively used for the variant calling and annotating variants. Sequencing data were aligned to the hg19 human reference genome. The variants were filtered analyzed in silico by using Combined Annotation Dependent Depletion (CADD), Sorting Intolerant from Tolerant (SIFT), Polymorphism Phenotyping v2 (PolyPhen-2) and Mutation Taster for the prediction of deleterious non-synonymous SNVs for human diseases. Global minor allele frequency (MAF) for analyzed variants was calculated according Genome Aggregation Database (gnomAD). Based on the guidelines of the American College of Medical Genetics and Genomics (ACMG), a minimum depth coverage of 30× was considered suitable for analysis. Variants were also examined for Qscore and visualized by the Integrative Genome Viewer (IGV).

3 | RESULTS

The proband is a male, second child of healthy non-consanguineous parents whose family history was not informative for any genetic diseases. The 20 weeks of gestation (WG) fetal scan showed prefrontal edema, nasal bone hypoplasia, increased nuchal translucency, suspicious of aortic coarctation and ambiguous genitalia. Standard karyotype obtained from amniotic fluid cells' culture and CGH Array analysis tested normal. Due to premature rupture of membranes, the proband was born preterm by cesarean section at 34.6 WG. At birth several dysmorphic features were noted (Figure 1A,B): brachyturricephaly, round face; sparse hair and eyebrows; strabismus; short, narrow, and slightly downslanted palpebral fissures; hypoplastic nasal root; bulbous overhanging nasal tip; posteriorly rotated, low-set ears with folded helix; Pierre-Robin sequence and gingival hypertrophy; long philtrum; small mouth with thin lips; short neck; hands with short fingers; feet with wide first toes and marked nails hypo−/dysplasia (Figure 1C–F). Moreover, the ambiguous genitalia were characterized as follows: right cryptorchidism with ipsilateral hemiscrotum's hypoplasia, penoscrotal transposition and coronal hypospadias (Figure 1G). His birth parameters were weight 1980 g (13°C), head circumference 30.5 cm (10°C), length 42 cm (4°C). The infant's Apgar scores were 8 at 1 min and 5 at 5 min. He first needed oxygen supplementation (FIO2: 0.30) followed by nasal continuous positive airways pressure treatment up to the 5th day of life. During the first week of life, total parenteral nutrition was undertaken; then enteral support through gavage was established. At the age of 3 months, he was subjected to percutaneous gastrostomy. During the following hospitalizations, the child required a multispecialistic approach. The cardiological surveillance showed over the time a stable framework of partially fused bicuspid aortic valve, slight ascending aorta's dilation and dysmorphic aortic arch with mild acceleration flow. Regarding the central nervous system, a magnetic resonance imaging (MRI) of the brain was performed at the age of 14 months. This examination revealed several anomalies including corpus callosum hypoplasia, dilated fourth ventricle communicating with the cisterna magna, mild vermian and ventral pons hypoplasia (Figure S1A,B), absence of olfactory bulbs associated with left olfactory sulcus (OS) aplasia and hyperplasic appearance of the right (Figure S1C). Reduced thickness of cerebral white matter was also detected (Figure S1D,E). To further investigate his neurophenotype, we performed visual and auditory evoked potentials, which tested normal. Electroencephalographic analyses highlighted slow posterior activity and poor representation of NREM sleep graph-elements. To date, at the age of 19-month, the patient has not developed seizures, but he presents a global severe developmental delay. A whole body skeletal X-rays examination did not show segmental and/or appendicular anomalies. At age of 9 months, the patient was subjected to a renal scintigraphy reveling a separate uptake fraction due to left kidney functional impairment (Figure S1F). In addition, right orchidopexy was carried out at the age of 17 months as the first reconstruction step of the perineal malformation showed. Thus, we performed a WES analysis on proband, sibling and parents' DNA which revealed the homozygous nonsense variant in *MAPKAPK5* gene, NM_003668.4: c.1180C > T, p.(Arg394Ter) inherited from the heterozygous carrier parents and identified in the unaffected sibling in heterozygous state (Figure S2). The deleterious variant p.(Arg394Ter) has never been reported before, it is predicted disease causing by Mutation Taster with a global minor allele frequency of 0.000004304 in gnomAD, it is predicted deleterious due to a CADD score of 38 and can be classified as pathogenic according to the ACMG criteria (PVS1, PM2, and PP3).[10]

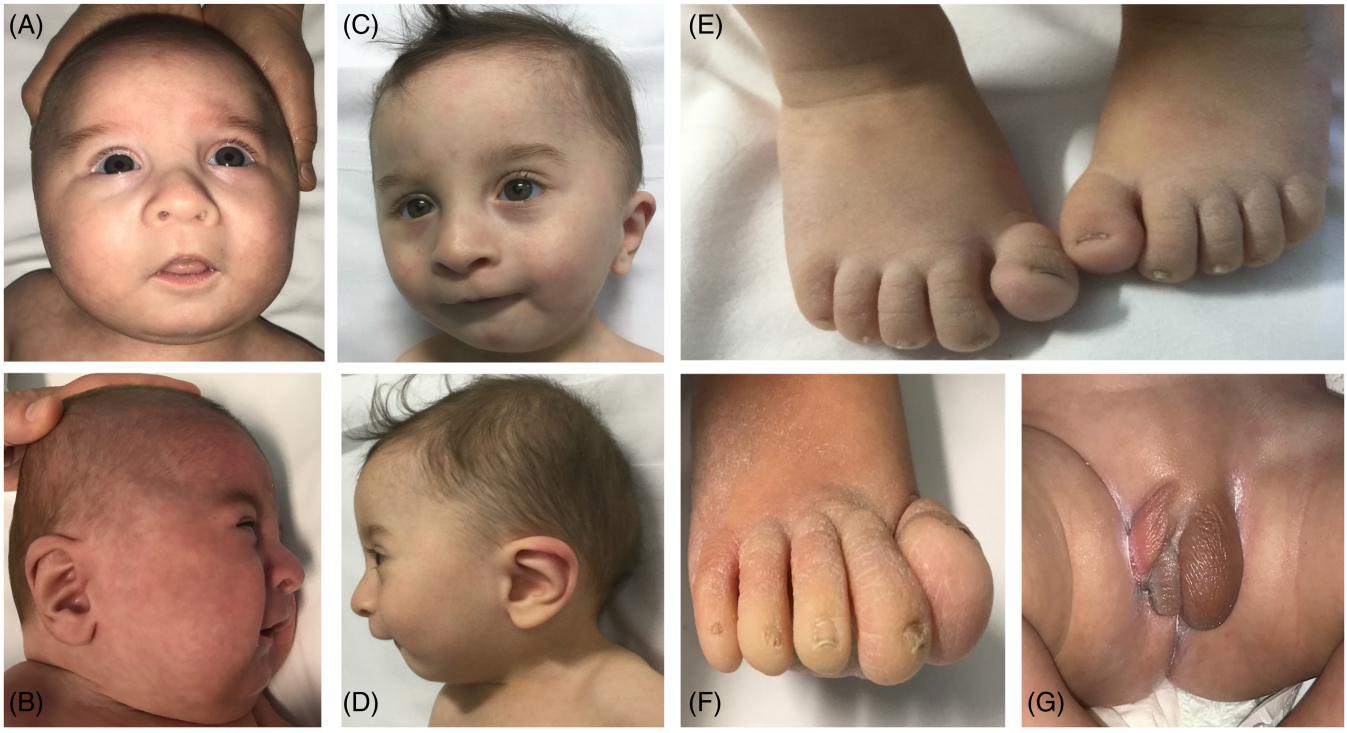

FIGURE 1 Clinical picture and patient's dysmorphisms (detailed in text) of the face at birth (A,B), at 15 months (C,D); of the feet (E) with right foot in magnification panel (F); and of urogenital system (G) [Colour figure can be viewed at wileyonlinelibrary.com]

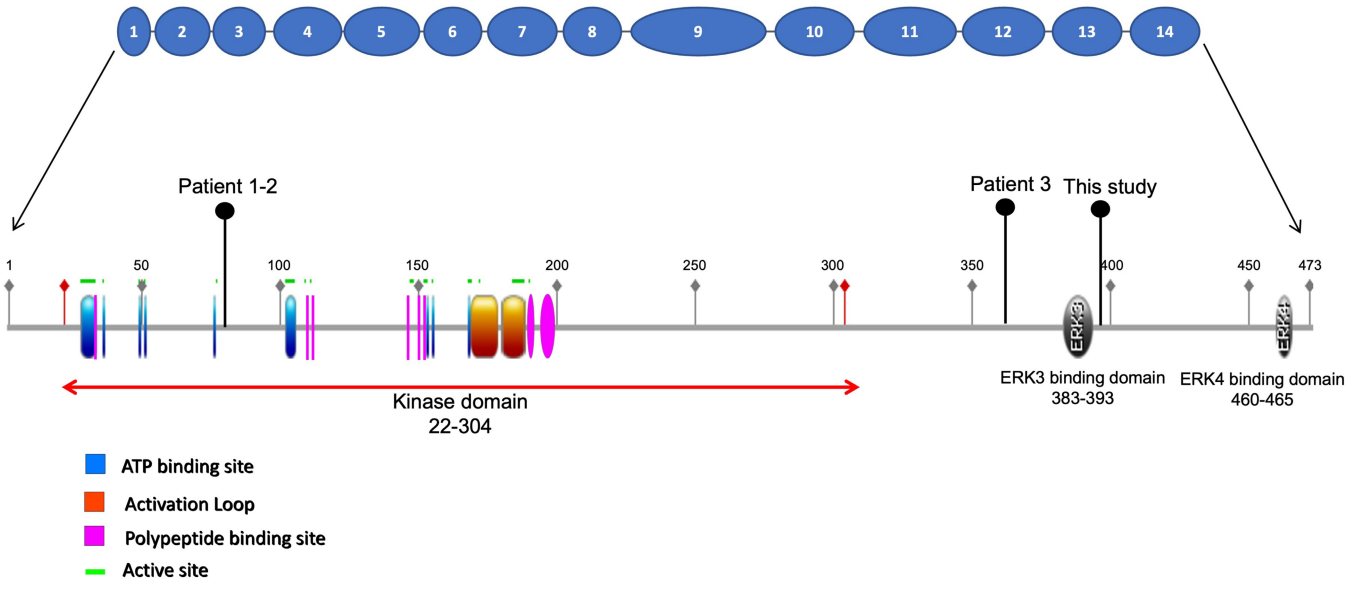

FIGURE 2 On the top: ideogrammatic representation of the *MAPKAPK5* gene; exons are depicted as blue boxes and introns as gray lines. Down (between arrows): MAPKAPK5 protein structural organization depicted by using ProteinPaint[11] showing the kinase domain and its subdomains (ATP-binding site, activation loop, and polypeptide binding site), active sites and binding sites (ERK3 and ERK4 marked in dark gray).[12,13] Known *MAPKAPK5* truncating variants are plotted as black dots across the protein. The numbers 1 and 473 represent the protein's first and last amino acid. [Colour figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

This study identifies a novel homozygous loss-of-function variant in *MAPKAPK5* in an additional child whose congenital anomalies broad the spectrum of the related clinical disorder. To date only truncating variants, both impinging MK5 functional domains and its interacting proteins' docking sites (Figure 2), have been identified in affected individuals.[3] This may also reflect a key genomic impairment underlying its etiology.

TABLE 1 Clinical characteristics of patients with *MAPKAPK5* pathogenic variants.

	Patient 1 (family 1 by Horn et al.[3])	Patient 2 (family 1 by Horn et al.[3])	Patient 3 (family 2 by Horn et al.[3])	This study
MAPKAPK5 pathogenic variant	Homozygous c.207_208dupTG; p.(Ala70Valfs*7)	Homozygous c.207_208dupTG; p.(Ala70Valfs*7)	Homozygous c.1077dupT; p.(Leu360Serfs*21)	Homozygous c.1180C > T, p.(Arg394Ter)
Gender	Female	Female	Male	Male
Measurements at birth	Low birth weight (2200 g at 40 weeks; −2.71 SD), normal length (48 cm; −0.65 SD) and OFC (32 cm; −1.9 SD)	Birth weight 2200 g at 36 weeks	Normal birth measurements at 38 weeks (weight 2600 g, −1.6 SD; length 53 cm, +0.8 SD; OFC 32.5 cm, −1.7 SD)	Normal birth measurements at 34,6 weeks (weight 1980 g, −1.12 SD; length 42 cm, −1.75 SD; OFC 30.5 cm, 0.1 SD)
Age of last assessment	9 years	2 years and 7 months	19 months	19 months
OFC	Normal: 51 cm; −0.68 SD	Microcephaly (HP 0000252): 44 cm; −2.71 SD	Microcephaly (HP 0000252): 43.5 cm; −4.3 SD	Microcephaly (HP 0000252): 46.5 cm; −1.76 SD
Length	Postnatal short stature (HP 0004322): 112.5 cm; −3.49 SD	Postnatal short stature (HP 0004322): 76 cm; −3.85 SD	Normal (82.5 cm; −0.4 SD)	Normal (80 cm, −1.03 SD)
Weight	Failure to thrive (HP 0001508): 16 kg; −7.03 SD	Failure to thrive (HP 0001508): 10 kg; −2.41 SD	Normal (10.8 kg; −0.6 SD)	Failure to thrive (HP 0001508): 8,33; −2.47 SD
Psychomotor developmental delay	Severe (HP 001134): no walking, one word	Severe (HP 001134): no head control and no speech	Severe (HP 001134): no sitting, no speech	Severe (HP 001134): no walking and no speech, only sitting position acquired
EEG abnormalities	Abnormal findings consistent with generalized epileptogenic discharge of left side origin (HP 0002353)	Generalized epileptiform discharges (HP 0011198)	Signs of increased seizure susceptibility in the left temporo-occipital region (HP 0002353)	Slow posterior activity and poor representation of the NREM sleep graph-elements (HP 0002353)
Heart defect	Tetralogy of Fallot (HP 0001636)	PDA (HP 0001643), ASD (HP 0001631)	Complex congenital heart defect (HP 0001627): double inlet left ventricle and malposition of great arteries, aortic arch tubular hypoplasia	Abnormal heart morphology (HP 0001627): intercoronary partially fused - bicuspid aortic valve, slight ascending aorta's dilation, hypertrabecular left ventricle and a dysmorphic aortic arch with mild acceleration flow
Brain anomalies	Small cerebellar hemispheres (HP 0001317), dilated fourth ventricle communicating with extra axial CSF, foramen of Luschka and cistern magna dilatation (HP 0010950), periventricular demyelination (HP 0007266)	Cavum septum pellucidum (HP 0002389), dilatation of lateral ventricles (HP 0006956), CC hypoplasia (HP 0007370), prominent cerebellar folia and mild vermian hypoplasia (HP 0001317), fourth ventricle communicating with extra axial CSF (HP 0010950)	CC hypoplasia (HP 0007370)	CC hypoplasia (HP 0007370), dilated fourth ventricle communicating with cistern magna (HP 0010950), mild vermian and ventral pons hypoplasia (HP 0001317), olfactory bulbs absence (HP 0001341), left olfactory OS absence and hyperplasic appearance of the right OS (HP 0006894), reduced thickness of cerebral white matter (HP 0007266), squared appearance of dilated lateral ventricle (HP 0006956).

(Continues)

TABLE 1 (Continued)

	Patient 1 (family 1 by Horn et al.[3])	Patient 2 (family 1 by Horn et al.[3])	Patient 3 (family 2 by Horn et al.[3])	This study
Eye abnormalities	Pallor optic disc (HP 0001085), postvisual pathway dysfunction (HP 0011514)	Nystagmus (HP 0006934)	Cataracts (HP 0000519), sclerocornea (HP 0000481), nystagmus (HP 0006934)	Mild strabismus (HP 0000486)
Hearing impairment	Moderate loss of hearing in high frequency range (HP 0012712)	–	Sensorineural hearing loss (HP 0008587)	–
Congenital anomalies of the kidney and urinary tract	–	Hydroureteronephrosis (HP 0000126), vescicoureteral reflux (HP 0000076)	Hypospadias (HP 0000047)	Left kidney hypoplasia (HP 0012210), right cryptorchidism (HP 0000028) with ipsilateral hemiscrotum's hypoplasia (HP 0000045), penoscrotal transposition (HP 0100600) and coronal hypospadias (HP 0000047)
Anomalies of the digits	Synpolydactyly (HP 0010442, HP 0001159) with an additional hypoplastic ray between the fourth and fifth digits, all extremities are affected	–	Synpolydactyly (HP 0010442, HP 0001159) with an additional hypoplastic ray between the fourth and fifth digit of the right foot	Short fingers (HP 0009803), wide first toes (HP 0001780) and marked toes' nails hypo−/dysplasia (HP 0008388)
Facial anomalies				
Skull	Bitemporal narrowing (HP 0000341), prominent forehead (HP 0011220)	Bitemporal narrowing (HP 0000341), prominent forehead (HP 0011220)	–	Brachyturricephaly (HP 0000244)
Hair and eyebrows	Sparse (HP 0000535)	Sparse (HP 0000535)	–	Sparse (HP 0000535)
Palpebral fissures	Narrow palpebral fissures (HP 0045025)	Narrow palpebral fissures (HP 0045025)	Narrow palpebral fissures (HP 0045025)	Narrow, and slightly downslanted (HP 0045024) narrow palpebral fissures (HP 0045025)
Nose	Prominent overhanging nasal tip (HP 0011833)	Prominent overhanging nasal tip (HP 0011833)	–	Hypoplastic nasal root (HP 0000422); bulbous prominent overhanging nasal tip (HP 0011833)
Mouth	Thin lips (HP 0000233)	Thin lips (HP 0000233)	Thin lips (HP 0000233), high arched palate (HP 0002705)	Small mouth (HP 0011337) with thin lips (HP 0000233), arched palate HP 0002705), glossoptosis (HP 000012)
Mandible	Retrognathia (HP 0000278)	Retrognathia (HP 0000278)	Retrognathia (HP 0000278)	Retrognathia (HP 0000278) in Pierre-Robin sequence (HP 0000201)

Abbreviations: ASD, atrial septal defect; CC, corpus callosum; CSF, cerebrospinal fluid; EEG, electroencephalogram; HP, human phenotype ontology term; OFC, occipitofrontal head circumference; OS, olfactory sulcus; PDA, patent ductus arteriosus.
Source: Adapted from Horn et al.[3]

Although our patient did not present postaxial polydactyly of hands and feet (that has been totally reported in two out of four patients), he showed hands with short fingers and feet with wide first toes and marked nails hypo⁻/dysplasia. All patients present congenital heart defects (CHDs) resulting in a complex condition in three out of four, as summarized in Table 1, but different from those CHDs mainly detected in 60%–90% of patients affected by RASopathies[14] and falling in its atypical subgroup (Atypical Cardiac Defects, ACDs).[15] While this evidence strongly suggests the need of ACDs careful investigation and longitudinal follow-up due to their possible impact on patients' clinical outcomes, it also confirms a limited degree of clinical overlap with the RASopathies' phenotypic spectrum.[15,16] Indeed, although affected individuals can show failure to thrive in both of these conditions, CHDs and/or ACDs, their dysmorphic features and congenital anomalies substantially diverge, and developmental delay appears severely compromised in *MAPKAPK5*–related ones. In this regard, all MK5 developmental disorder's affected patients share a common pattern of severe global hypotonia and psychomotor delay; three out of four showed microcephaly over the time, and all their neurophysiological examinations depicted EEG abnormalities (Table 1). Brain anomalies were constantly reported with a variable degree and intersection of dilated lateral ventricles, vermian and/or cerebellar hemispheres hypoplasia, and thin/hypoplasic corpus callosum. In addition, our patient also showed novel features of bilateral absence of olfactory bulbs associated with left OS aplasia and hypoplastic aspect of the right one. These malformations seem to be specific and to differ from other primary olfactory system's anomalies.[17,18] All these features, taken together, further confirm a role of MK5 in neuronal morphogenesis and plasticity as already characterized in a Mapkapk5$^{-/-}$ mice model.[19]

Finally, it is also worth of mention the overall role of the MAPK/ERK pathway in congenital anomalies of the kidney and urinary tract (CAKUT)'s onset.[20] Indeed, MAPK/ERK activity not only contributes to the regulation of ureteric bud (UB) branching morphogenesis (dictating kidney final size, shape, and nephron number), but it is also involved in nephric duct connection to cloaca, whereas inhibition of MEK proteins leads to a decrease in proliferation in the UB tip cells and abnormal branch formation.[21,22] To note three out of four reported patients showed a composite clinical picture of: kidney hypoplasia, hydroureteronephrosis and external genitalia malformation in males who both show hypospadias (Table 1). Thus, although MK5 involvement in CAKUT deserves to be further investigated, we suggest kidney and the genitourinary system's impairment as a prominent *MAPKAPK5*–related disorder's feature that may also help clinicians to better recognize, properly screen and manage this novel rare condition.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Sequence WES data have been deposited at the European Variation Archive (EVA) - EMBL-EBI.

with the following project number: PRJEB50475 and analyses number: ERZ4951485. All the unique materials and datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

Written informed consent of all participants or their legal representatives was obtained prior to participation in the study. All studies and investigations were performed according to the Declaration of Helsinki principles of medical research involving human subjects.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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