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Tenorio syndrome: Description of 14 novel cases and review of the clinical and molecular features

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Abstract

Tenorio syndrome (TNORS) (OMIM #616260) is a relatively recent disorder with very few cases described so far. Clinical features included macrocephaly, intellectual

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disability, hypotonia, enlarged ventricles and autoimmune diseases. Molecular underlying mechanism demonstrated missense variants and a large deletion encompassing *RNF125*, a gene that encodes for an U3 ubiquitin ligase protein. Since the initial description of the disorder in six patients from four families, several new patients were diagnosed, adding more evidence to the clinical spectrum. In this article, we described 14 additional cases with deep phenotyping and make an overall review of all the cases with pathogenic variants in *RNF125*. Not all patients presented with overgrowth, but instead, most patients showed a common pattern of neurodevelopmental disease, macrocephaly and/or large forehead. Segregation analysis showed that, though the variant was inherited in some patients from an apparently asymptomatic parent, deep phenotyping suggested a mild form of the disease in some of them. The mechanism underlying the development of this disease is not well understood yet and the report of further cases will help to a better understanding and clinical characterization of the syndrome.

KEYWORDS
genomic medicine, macrocephaly, neurodevelopmental, overgrowth, ring-finger, RNF125, Tenorio syndrome, ubiquitin ligase

1 | INTRODUCTION

Clinical and molecular characterization of human genetic conditions is extremely useful not only to confirm the suspected clinical diagnosis, but also to perform an appropriate follow up and management of the affected patients and their families. Overgrowth disorders/syndromes (OGD/OGS) represent a heterogeneous group of diseases, all of them characterized by an increase of head circumference, weight and/or height above 97th centile or +2 *SD* above the mean.[1] Most OGS includes additional findings, especially neurodevelopmental abnormalities, which are present in the majority of the affected patients. Thus, identification and deep clinical characterization of patients with OGS represent a major challenge in daily clinical practice.

Tenorio syndrome (TNORS; MIM #616260) is one of the most recently described OGS syndromes. In the original publication in 2014,[2] we reported on six patients from families who had overgrowth, intellectual disability (mild to moderate), inflammatory disorders, ventriculomegaly and hypoglycemia. The observation of overgrowth in the patients described in the original publication might be a selection bias because all patients came from the Spanish Overgrowth Registry.[2] In all of them–except for one patient with a large deletion encompassing *RNF125*- a pathogenic missense variant was/identified in *RNF125*, a gene that encodes for an E3 ubiquitin ligase mainly involved in protein–protein binding processes that regulate protein expression and degradation through the proteasome system. Functional assays in patient-derived fibroblasts with RNF125 and its main target protein, RIG-1, suggested a haploinsufficiency mechanism of RNF125 that might lead to the dysregulation of the RIG1-IPS1-MDA5 pathway, which may also have an effect on the PI3K-AKT pathway, in which IPS-1 is involved as well. The specific mechanism from which variants in *RNF125* may lead to clinical features of the syndrome has not been fully elucidated yet. PI3K-AKT represent one of the major pathways associated with OGS, many of which are caused by pathogenic activating variants in genes that encode proteins related to this pathway, that is, Proteus syndrome caused by *AKT1*,[3] *PIK3CA* Overgrowth Related Disorders or PROS[4] and Smith-Kingsmore syndrome caused by pathogenic variants in *MTOR*.[5] In many of these disorders and others caused by pathogenic variants in genes within the same pathway, similar clinical features were reported, including intellectual disability, autism spectrum disorder and seizures, among other.[6–8]

Here, we described fourteen additional patients with RNF125 variants. TNORS should be classified as a neurodevelopmental disorder rather than an overgrowth syndrome, due to the relevant additional findings presented herein, which showed a variable degree of expression and incomplete penetrance. Our work provides an updated clinical phenotype of patients with this syndrome, presents fourteen additional patients and discuss its molecular mechanism of inheritance.

2 | MATERIAL AND METHODS

2.1 | Patients

All patients were recruited based upon the clinical defect in *RNF125*. Patients were identified through the GeneMatcher platform (https://genematcher.org/). Informed consent and authorization for the

publication of photographs were obtained by the referral centers. Clinical characterization was done at the referral centers where the patients were followed up. The craniofacial phenotype of all available patients is shown in Figure 1. This project was approved by the ethical committee of our Institution (CEIC-PI1543). Intellectual disability has been measured using tests and IQ calculations. Anxiety has been diagnosed by a psychiatrist using clinical interviews and specific scales and tests (ISRA and similar).

2.2 | Molecular analysis

All cases were analyzed by different NGS platforms including WES and specific custom panels, covering the entire exons and intron-exon boundaries of the *RNF125* gene. Variants were classified according to ACMG guidelines.[9]

3 | RESULTS

Networking scientific connections have allowed the identification of fourteen additional individuals with pathogenic variants in *RNF125*, and a presumptive clinical diagnosis of TNORS. Segregation analysis showed that 53% of the probands inherited the variant from one of their parents, who were either asymptomatic or had mild forms of the syndrome.

With the advances in massive paralleled sequencing technologies and by means of scientific network platforms such as GeneMatcher,[10] we have identified fourteen additional patients with TNORS based on their molecular findings. Moreover, some of their clinical findings expand the phenotype of the syndrome and guide clinicians that not all the patients show overgrowth but the most common findings are macrocephaly and a neurodevelopmental disorder (Table 2).

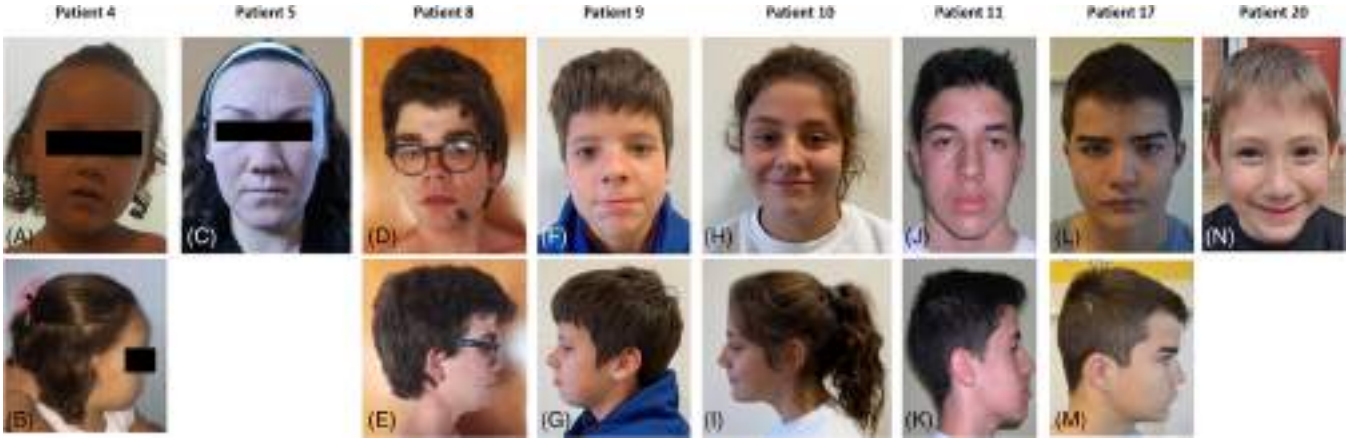

FIGURE 1 Craniofacial phenotypes of patients with Tenorio syndrome. Patient 17 (L-M) was included in the first publication in 2014 [Colour figure can be viewed at wileyonlinelibrary.com]

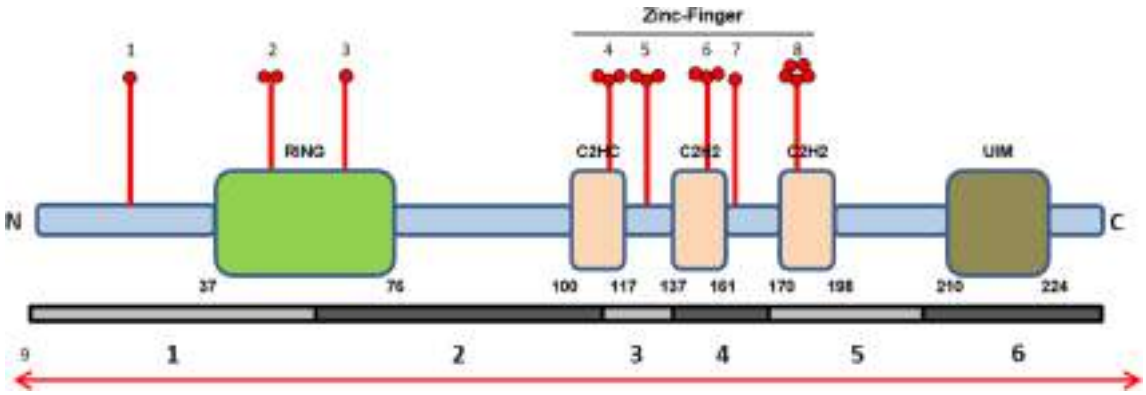

FIGURE 2 Protein domain organization of RNF125. This protein has three functional domains, RING, Zinc-finger and UIM. All variants detected in the 15 individuals are represented in red–including the patient with entire gene deletion- and the lower panels shows the correlation between exons of the gene and the protein sequence. All detected pathogenic variants falls within the zinc-finger region. Legend: 1- RNF125 (NM_017831.4):c.47C>G:p.Ser16Cys 2- RNF125(NM_017831.4):c.146G>C:p.Arg49Pro 3- RNF125(NM_017831.4):c.181A>T:p.Ile61Phe 4- RNF125(NM_017831.4):c.336G>A:p.Met112Ile; 5- RNF125(NM_017831.4):c.371A>G:p.Asp124Gly; 6- RNF125(NM_017831.4):c.472A>G:p.Ile158Val; 7- RNF125(NM_017831.4):c.488C>T:p.Ser163Leu; 8- RNF125(NM_017831.4):c.520C>T:(p.Arg174Cys); 8- (RNF125(NM_017831.4)) x1 [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Pathogenicity in silico analysis of *RNF125* variants. All variants are absent or with extremely low frequency in the pseudocontrol databases. A specific database for pseudocontrols in Spanish population have been also added. Pathogenicity prediction was applied by many in silico predictors from the dbNSFP. Classification of the pathogenicity of the variants was done according the ACMG guidelines described in Richards et al.[9] Genomic coordinates were annotated according to human genome reference hg19

Variant (cDNA and protein) **Genomic Coordinate (hg19)** **Mutation type**	**RNF125 (NM_017831.4): c.47C > G:p. Ser16Cys** **chr18:29598873C > G** ***missense***	**RNF125 (NM_017831.4): c.146G > C:p. Arg49Pro** **chr18:29598972G > C** ***missense***	**RNF125 (NM_017831.4): c.181A > T:p. Ile61Phe** **chr18:29617095A > T** ***missense***	***RNF125* (NM_017831.4): c.336G > A:p. Met112Ile** **chr18:29622159G > A** ***missense***	***RNF125* (NM_017831.4): c.371A > G:p. Asp124Gly** **chr18:29622194A > G** ***missense***	***RNF125* (NM_017831.4): c.472A > G:p. Ile158Val** **chr18:29625663A > G** ***missense***	***RNF125* (NM_017831.4): c.488C > T:p. Ser163Leu** **chr18:29625679C > T** ***missense***	***RNF125*(NM_017831.4): c.520C > T:p.Arg174Cys** **chr18:29645880C > T** ***missense***
1000 Genomes Database	0	0	0	0	0	0	0/1000	0/1000
Spanish population (300 patients; 600 chromosomes)	N/A	N/A	N/A	0	0	0	0/600	0/600
Spanish Exomes (BIER) (n = 350)	N/A	N/A	N/A	0	0	0	0/350	0/350
gnomAD exomes (ExAc)	0.0000383	0	0	0	0	0	0.0000398	0.0000199
gnomAD genomes	0.0000318	0	0	0	0	0	0	0
Beacon network	0	0	0	0	0	0	0	0
Bravo	0	0	0	0	0	0	0	0
Pathogenicity tools[a]	3/21	11/21	13/21	15/21	7/21	1/21	12/21	7/21
ACMG classification	VUS	Likely pathogenic	Likely pathogenic	Pathogenic	Likely pathogenic	Likely pathogenic	Likely pathogenic	Likely pathogenic
Reference	This study	This study	This study	2	This study	This study	2	2

[a]Pathogenicity tools: BayesDel addAF, BayesDel noAF, DANN, EIGEN, EIGEN PC, FATHMM, FATHMM-MKL, LRT, MVP, MetaLR, MetaSVM, MutPred, MutationTaster, PROVEAN, REVEL, SIFT4G, DEOGEN2, FATHMM-XF, LIST-S2, Mutation assessor, PrimateAI, SIFT. The equation represented in the rows of 1000 Genomes Database, Spanish population (300 patients; 600 chromosomes), Spanish Exomes (BIER) (n = 350), represent the number of individuals identified with the same variant as any of those detected in the patients described to date, with respect to the total number of individuals included in that database. In addition, the value of the pathogenicity tools row represents the number of in silico bioinformatic predictors that predict a harmful effect of the variant, with respect to the total number of predictors consulted and mentioned above.

TABLE 2 Clinical features in Tenorio syndrome. Percentage of the clinical features identified in the 20 patients described so far

HPO	Trait	%	n
VERY FREQUENT (≥75%)			
HP:0000256	Macrocephaly	85%	17/20
FREQUENT (50–74%)			
HP:0001263	Developmental delay	60%	12/20
HP:0002003	Large forehead	60%	12/20
HP:0001249	Intellectual disability	55%	11/20
HP:0000750	Speech delay/problems	50%	10/20
INFREQUENT (26–49%)			
HP:0000445	Wide nose	45%	9/20
HP:0000708	Behavioral issues	45%	9/20
HP:0001548	Overgrowth	45%	9/20
HP:0000574	Thick eyebrow	40%	8/20
HP:0000739	Anxiety	35%	7/20
HP:0002312	Clumsiness	35%	7/20
HP:0000158	Macroglossia	30%	6/20
HP:0002342	Intellectual disability, moderate	30%	6/20
RARE (≤25%)			
HP:0001256	Intellectual disability, mild	25%	5/20
HP:0011968	Feeding or other issues	25%	5/20
HP:0000998	Hypertrichosis	25%	5/20
HP:0000506	Telecanthus	20%	4/20
HP:0002090	Pneumonia	20%	4/20
HP:0000717	Autism	15%	3/20
HP:0001943	Hypoglycemia	15%	3/20
HP:0030880	Raynaud phenomenon	15%	3/20
HP:0002104	Apnea	15%	3/20
HP:0000491	Keratitis	15%	3/20
HP:0001250	Seizures	10%	2/20
HP:0002389	Cavum septum pellucidum	10%	2/20
HP:0000509	Conjunctivitis	10%	2/20
HP:0002020	Gastroesophageal reflux	10%	2/20
HP:0000388	Otitis media	10%	2/20
HP:0000938	Osteopenia	10%	2/20
HP:0010280	Stomatitis	10%	2/20
HP:0011107	Recurrent aphthous stomatitis	10%	2/20
HP:0001096	Keratoconjunctivitis	10%	2/20
HP:0100021	Cerebral palsy	5%	1/20
HP:0001528	Hemihypertrophy	5%	1/20
HP:0002650	Scoliosis	5%	1/20
HP:0001279	Syncope	5%	1/20
HP:0040216	Hypoinsulinemia	5%	1/20

Abbreviations: N, number of individuals with the specific feature among all described; N/A: not applicable.

Clinical deep phenotyping and a review of the novel and published individuals revealed that the most common findings among all patients were: mild to moderate neurodevelopmental delay, behavioral problems (anxiety), clumsiness, speech delay (sometimes severe), macrocephaly and facial dysmorphic features including large forehead, thick eyebrows, wide nose and macroglossia (Figure 1).

Most patients identified in the present study had the same pathogenic variants that were identified by us in 2014: p.Met112Ile (x3), p.Asp124Gly (x3), p.Ile158Val (x2), p.Arg174Cys (x5) (Figure 2), suggesting that these are common changes in the disorder (Table 1).

Analysis of the genetic variants revealed that some missense variants, were shared by several unrelated patients. The majority of the detected/identified variants fall within or between the zinc-finger domains (C2H2, C2HC) although three variants were located outside this region, two within the RING domain p.(Arg49Pro) and p(Ile61Phe) and one in the interdomain region p(Ser16Cys). Molecular analysis of the variants is presented in Table 1. None of the variants have been previously reported in control population databases (>200 000 pseudocontrol individuals) (gnomAD, Kaviar, Beacon, 1000G, ESP and Bravo), the majority of the in silico pathogenicity-prediction tools suggested a damaging effect of all variants. Moreover, based on our previous functional assays, some variants have been shown to disturb the function of RNF125.

4 | DISCUSSION

TNORS was first described in 2014 by Tenorio et al.[2] The main clinical findings included overgrowth (mainly characterized by a macrocephaly and enlarged ventricles), autoimmune disorders resembling Sjögren disease and/or Raynaud phenomenon, intellectual disability of variable degree, behavioral problems, speech delay, and craniofacial dysmorphic features such as large forehead, macroglossia, thick eyebrows and a wide nose. Since the description of the initial series of patients in 2014, no additional cases have been published.

In this article, we report fourteen new patients with TNORS, and include a full overall review of the clinical and molecular findings (Supplementary Table S1) of the total of eighteen cases. Macrocephaly was the most common feature, as it has been observed in 89% of individuals, with some of them manifesting hydrocephaly. Clinical features counting more than 50% of patients were: at neurological level, developmental delay (60%), intellectual disability (55%), speech delay/problems (50%) and craniofacial dysmorphic features such as large forehead (60%). Less frequent clinical characteristics were: mild to moderate intellectual disability, some behavioral problems including anxiety and psychotic episodes, speech delay/problems, clumsiness, macroglossia, thick eyebrows and wide nose (Table 2).

TNORS can be classified as a neurodevelopmental disorder that may include overgrowth (mainly macrocephaly). Patients with OGS such as Sotos, Malan, Weaver and Beckwith-Wiedemann syndrome show distinctive craniofacial features that may help to distinguish with TNORS. For instance, some patients who had macroglossia and large forehead were initially diagnosed with Beckwith-Wiedemann or Simpson-Golabi-Behmel syndrome. Differential diagnosis should also include: Sotos syndrome, Weaver syndrome, Tatton-Brown-Rahman

syndrome due to pathogenic variants in *DNMT3A*,[11] and intellectual disability due to pathogenic variants in *BRWD3*.[12]

RNF125 encodes for an E3 ubiquitin ligase protein, which is involved mainly in a redundant process of binding proteins and adding lysine residues to facilitate the degradation of those proteins through the proteasome. Other genes that encode for E3 ubiquitin and ligases and related to head size anomalies have been previously described by us and by other groups.[13,14] RNF125 has been also involved in the innate immune response by the action of either RIG-I or MDA5, depending on the activation pathway. In fact, RIG-1 has been found to be related to the PI3K-AKT pathway in which many of its genes have already been associated not only with overgrowth but also with neurodevelopmental disorders. Therefore, RNF125 might have an indirect effect on this molecular pathway. Moreover, recent studies have also associated RNF125 expression with the more aggressive forms of gallbladder cancer because it activates the TGF-β1-SMAD3-ID1 signaling pathway.[15]

Functional studies of RNF125, reported in our first paper demonstrated that the pathogenic variants identified prevented the degradation of RIG1 and, therefore, that this protein might accumulate in the cytoplasm, potentially overactivating some downstream pathways. Based on the findings mentioned above, haploinsufficiency is the most likely mechanism associated with the development of TNORS. Further experiments are necessary to explore the possible role of RIG-I in the PI3K-AKT pathway, and how this might contribute to the phenotype development associated with TNORS.

We found eight pathogenic missense variants and one entire deletion of the gene in 20 individuals, most of them located in the zinc-finger domains or in the regions linking these domains (Figure 2). Only two of the variants falls within the RING domain of the protein. The zinc/ring finger domains are present mainly in proteins whose functions include ubiquitination. They are domains that have a Cys(n) HisCys(n) type structure and that have the ability to bind to some substrates and/or enzymes in order to be degraded in the proteasome and thus regulating their expression.

In that sense, given that most of the variants that have been identified in TNORS are missense, it is possible that they are preventing allosteric regulation, and therefore, binding to the proteins on which RNF125 acts, mainly RIG-I and MDA5. In turn, these two proteins accumulate in the cytoplasm and can overexpress their function on some pathways such as the PI3K-AKT pathway, of which we know that there are already other genes of the same pathway with gain-of-function mutations associated with the development of some pathologies (i.e., GOF pathogenic variants in *MTOR* associated with Smith-Kingsmore syndrome).

Other ring finger proteins belonging to the same family have been associated with neurodevelopmental disorders: RLIM in X-linked Tonne-Kalscheuer syndrome (MIM #300978),[16] *RNF216*- in Gordon-Holmes syndrome (also known as Cerebellar Ataxia and Hypogonadotropic Hypogonadism; MIM #212840),[17] homozygous pathogenic variants in *RNF268* in RIDDLE syndrome (MIM #611943)[18] and heterozygous pathogenic variants in *RNF13* in Developmental and Epileptic Encephalopathy 73 (MIM #618379), among others.[19] This information adds further evidence of the relationship between variants in ring-finger proteins and neurodevelopmental disorders.

Segregation analyses showed that most patients inherited the variant from one of their parents. In fact, approximately half of the patients with pathogenic or probably pathogenic variants in *RNF125* such variant was also present in one of their parents. Although in the initial examination of the transmitting parents showed no apparent clinical manifestations of the syndrome, deep phenotyping and cognitive screening revealed that some of them had borderline or mild intellectual disability, while others (e.g., mother of P5 in this report, P6 in the original paper from Tenorio et al.) showed some clinical features as well. Thus, confirmation of segregation is extremely important and, therefore, always recommended to identify relatives with milder forms of the syndrome, to whom it can be offered a proper management and a precise genetic counseling. Due to the overlap of TNORS with other overgrowth and neurodevelopmental disorders, molecular diagnosis must be carried out using massive parallel sequencing techniques, specifically whole exome sequencing (WES).

Thus, it is clear that the phenotype of TNORS is highly heterogeneous; ranging from patients with subtle or mild neuropsychological manifestations (mild forms) to individuals with moderate/severe manifestations. This is especially important for genetic counseling of families where only one member has been diagnosed with TNORS. In fact, we have found behavioral disturbances in three patients. Patient five suffered from severe postpartum depression with psychotic behavior, patient eight had severe behavior disturbances, including suicidal tendencies, refractory to pharmacological treatment, and finally, patient 14 suffered several years from severe depression, obsessions and anxiety that required multi-drug treatment.

Interestingly, patient seven had additional findings including eye anomalies (strabismus and mild enophthalmia), floppy ears, tapered hands, Meckel *diverticulum*, biliary lithiasis that required cholecystectomy, and subcortical–cortical atrophy and small corpus callosum. He had, besides the variant in *RNF125*, a likely pathogenic heterozygous variant in *MED13L* (p.Gln689*),[20] which could explain, at least in part, his complex phenotype (Table SS1).

In summary, we present fourteen additional patients with TNORS and review the clinical and molecular findings of the total 20 patients reported here, highlighting the wide heterogeneity of the syndrome even among members of the same family. The main clinical findings are the presence of a neurodevelopmental disorder with craniofacial dysmorphic features, especially macrocephaly with large forehead, in the majority of the patients. At the molecular level, we have demonstrated that most pathogenic variants cluster in a region of *RNF125*, with the majority located within the zinc-finger domain of the protein. Further studies are needed to elucidate the specific mechanism by which the haploinsufficiency of *RNF125* leads to the development of TNORS.

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CONFLICT OF INTEREST

Authors declared no conflict of interest.

AUTHOR CONTRIBUTION

JAT and PL designed the work and wrote the manuscript. PA performed all the sequencing techniques, NG, SR and JT, SA performed the molecular analyses, AFJ, GL, AB, LOF, JL, FTM, FSS, LP, FMM, GBL, FJR, and MMO identified additional patients and recorded clinical and molecular data.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/cge.14020.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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