Egyptian Journal of Medical Human Genetics

REVIEW

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ADGRG1-related polymicrogyria syndrome: report on a large consanguineous family with a novel variant and review

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Abstract

Background Polymicrogyria is a spectrum of complex cortical malformations encompassing multiple subtypes. Of these, bilateral frontoparietal polymicrogyria (BFPP) has been associated with pathogenic variants in the *ADGRG1* gene, formerly known as *GPR56*. BFPP is characterized by cognitive impairment, motor delay, seizures, oculomotor findings, cerebellar, pyramidal signs, and brain malformations that consist of abnormal changes in the cortex, white matter, brainstem, and cerebellum.

Case presentation A large consanguineous Syrian family with five affected individuals exhibiting features of BFPP, is included in this study. These patients presented with cognitive impairment, psychomotor delay, epileptic episodes, cerebellar signs, oculomotor findings, and brain malformations. Through whole exome sequencing, a novel homozygous pathogenic variant in the *ADGRG1* gene (NM_201525.4: c.308T > C; p.Leu103Pro) was identified.

Conclusion Here, we report a thorough literature review of cases with BFPP, and we discuss the importance of genetic counseling in families with genetic disorders, especially in underdeveloped countries.

Keywords Consanguinity, Exome, Intellectual disability, Polymicrogyria

Introduction

Polymicrogyria (PMG) is a heterogeneous disorder characterized by abundant small gyri and abnormal lamination of the cortex [1], representing nearly 20% of all cortical malformations [2]. Several forms of PMG are recognized based on their topographic patterns. These encompass perisylvian polymicrogyria, which represents the most prevalent pattern, along with generalized polymicrogyria, polymicrogyria accompanied by periventricular grey matter heterotopia, frontal polymicrogyria, parasagittal parieto-occipital polymicrogyria, among others [3]. Furthermore, these types are categorized into subtypes based on imaging findings [3].

Bilateral frontoparietal polymicrogyria (BFPP) is a symmetrical bilateral polymicrogyria with decreasing anterior to posterior gradient of severity, random white matter changes, cerebellar and brainstem hypoplasia, that are detected by MRI [4]. In 2004, variants in the *ADGRG1* (Adhesion G protein coupled receptor G1) gene were linked to this disease [5]. *ADGRG1* (MIM* 004110), located on chromosome 16q21, encodes an orphan G protein coupled receptor with a N-terminus, a proteolytic site, and seven transmembrane α helix C-terminal domains [6]. It is preferentially expressed in

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neuronal progenitor cells of the cerebral ventricles and subventricular zones during neurogenesis [5].

BFPP, inherited in an autosomal recessive manner [7, 8], is characterized by motor developmental delay, cognitive impairment, seizures, ataxia and dysconjugate gaze [9].

Here, we report a novel *ADGRG1* pathogenic variant in a large consanguineous Syrian family, including five members affected with BFPP. A review of the literature is discussed and the importance of genetic counseling, especially in families with limited access to appropriate care, is highlighted.

Patients and methods

Patients

The patients are cousins from a multiply consanguineous Syrian family (Fig. 1). They presented to The Human Genetics Department in November 2022; and they have been thoroughly investigated by us for the past 10 months. Each of the family members underwent a work-up including a thorough clinical evaluation. and routine blood tests (complete blood count, serum electrolytes, blood glucose levels, cholesterol, thyroid, liver and renal function tests, and phosphatase alkaline levels). Extensive genetic testing was further done. Magnetic Resonance Imaging (MRI) was carried out following the institution's standard clinical protocols, which typically involved acquiring axial, coronal, and sagittal Spin Echo T1 HF, Spin Echo T1, FSE T2, Fast FLAIR T2.

Isolation of genomic DNA

Consent forms were collected from all family members. DNA was extracted from Leucocytes by standard salt-precipitation methods.

Whole exome sequencing

Whole exome sequencing (WES) was carried out on two affected individuals (**V6** and **V7**) at 3billion Inc. Illumina NovaSeq 6000 system (San Diego, CA, USA) was used for sequencing as 150bp paired-end reads. Alignment to the GRCh37 human reference genome was done using BWA-MEM2, and samtools v1.15 was used for bam file sorting and marking duplicates [10, 11]. Recalibration and variant calling for single nucleotide variants (SNVs) and small insertion/deletion variants (indels) were performed using GATK v4.2 [12]. Structural variants (SVs) were called using CoNIFER 0.2.2v, and 3bCNV, an internally developed tool [13]. Variants were annotated, filtered, and classified using EVIDENCE v3.2 which incorporates Ensembl Variant Effect Predictor (VEP) for annotation and the American College of Medical Genetics and Genomics (ACMG) guideline for classification [14]. The filtered and classified variants were manually reviewed by medical

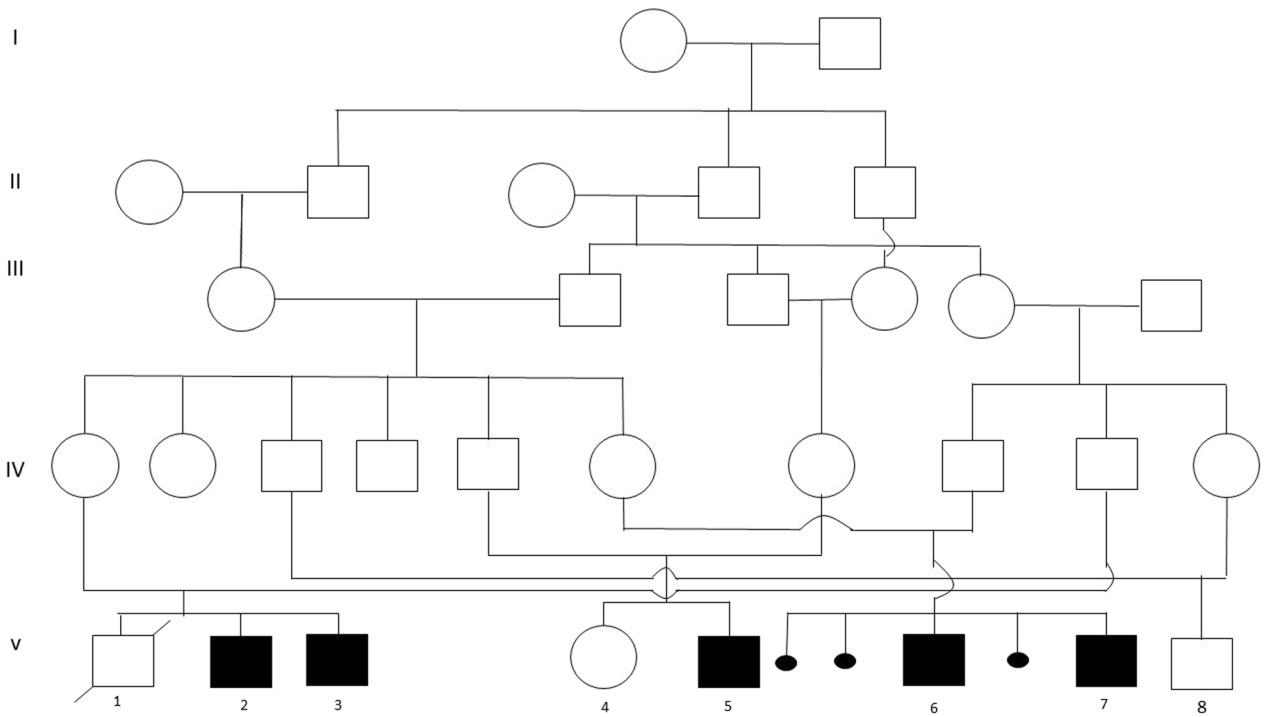

Fig. 1 Pedigree of the family

geneticists and physicians. The most likely variants that can explain the patient's phenotype were selected for reporting.

Sanger sequencing

The selected variant was studied in the patients V2 and V5 by Sanger sequencing. Genomic and cDNA sequences of *ADGRG1* were obtained from UCSC Genomic Browser (NM_201525.4). Primers used for PCR amplification were designed using Primer3 software (http://frodo.wi.mit.edu) to amplify the region surrounding the mutation detected by exome sequencing. PCR products were purified by exonuclease I/Shrimp Alkaline Phosphatase treatment (ExoSAP-IT; Fisher Scientific SAS, Illkirch, France) according to the manufacturer's instructions and both strands were sequenced using the Big Dye® Terminator v1.1 Cycle Sequencing Kit (Applied Biosystems). Sequence reactions were purified on Sephadex G50 (Amersham Pharmacia Biotech, Foster City, CA) and capillary electrophoresis was performed on Genetic Analyser 3100 (Applied Biosystems). Electropherograms were analyzed on the Sequence Analysis Software version 5.2 (Applied Biosystems) and aligned with the wild-type *SAMD9* gene sequence using ChromasPro version 1.22 (Technelysium, Queensland, Australia).

Clinical presentation

The family investigated in this study included 5 affected members (Fig. 1) born after normal vaginal deliveries without any exposure to pre- or perinatal environmental toxins. Psychomotor developmental delay was evident in all the patients in the first few months of life Indeed, limited social interaction, minimal verbal abilities without forming coherent words, inability to achieve toilet training and independent eating were observed in almost all cases. Individual V5 was the only sibling able to socially interact with his surroundings and to say a few words at the age of 4. Siblings V6 and V7 both suffered from oromotor dyspraxia. Patients V3, V5, V7 were not able to walk, and patients V2 and V6 started walking at 4 and 5 years of age, respectively. No dysmorphic features were noted in any of the patients. Microcephaly was noted in cases V6 and V7 (Table 1).

Neurological examination revealed prominent ataxia, pyramidal signs, increased deep tendon reflexes and spasticity for V6 and V7; whereas, mild ataxia was only detected in patient V2. Moreover, individuals V5, V6 and V7 showed tone abnormalities. As for the oculomotor findings, strabismus was present in all individuals;

Table 1 Clinical features of the patients

Patient/clinical features	V2	V3	V5	V6	V7
Gender	Male	Male	Male	Male	Male
Age at examination	5 years	1 year and 7 months	4 years 7 months	5 years and 8 months	3 years and a half
Head circumference	Normal	Normal	Normal	< 3rd percentile	< 3rd percentile
Dysmorphic features	Absent	Absent	Absent	Absent	Absent
Cognitive impairment	Severe	Severe	Severe	Severe	Severe
Motor delay	Severe	Severe	Severe	Severe	Severe
Age of appearance of motor delay	4 months	3 months	3 months	5 months	5 months
Age at walking	4 years	Does not walk	Does not walk	5 years	Does not walk
Tone abnormalities	Normal	Normal	Hypotonia	Hypotonia mainly in Lower limbs and hypertonia	Hypotonia mainly in Lower limbs and hypertonia
Pyramidal signs	N/A	N/A	N/A	Increased deep tendon reflexes, spasticity	Increased deep tendon reflexes, spasticity
Cerebellar signs	Mild ataxia	Absent	Absent	Prominent ataxia	Prominent ataxia
Oculomotor findings	Strabismus	Strabismus	Strabismus	Strabismus, Nystagmus	Strabismus, Nystagmus
Oromotor dyspraxia	Absent	Absent	Absent	Present	Present
Seizures	Absent	Absent	Present	Present	Present
Age at onset			2 years	At birth	At birth
Type of seizure			N/A	Grand Mal	Grand Mal
Type of Medication			Sodium Valproate	Topiramate, Sodium Valproate	Topiramate, Sodium Valproate
Refractory to medication			Yes, 6–7 episodes/day	Yes, 1 crisis/2–3 days	Yes
Age it became refractory			3 years	N/A	N/A

and nystagmus was also detected in patients V6 and V7. Three patients (V5, V6 and V7) suffered from seizure episodes that were noted as early as the first couple of months for patients V6 and V7, or at age of 2 for patient V5. These were not resolved by medications and were still manifesting every 2 or 3 days in the mentioned cases (Table 1).

Imaging findings

A brain MRI performed for V2 at 1 year of age showed subcortical hyperintense signals with bilateral frontal–parietal and occipital topography, in addition to hyperintense zones in the periventricular and frontal horns areas. This was initially thought to be resulting from an infection with Herpes Simplex or Cytomegalovirus (CMV). Another brain MRI performed in this patient at age of 3 did not show any abnormality.

On the other hand, an MRI performed on the patient V5 at the age of 4 years showed the presence of a thick cortex of both cerebral hemispheres with sparse cortical sulci; multiple small hyperintense signal areas in the periventricular and deep white matter of both cerebral hemispheres. The lateral and third ventricles were mildly dilated, with normal fourth ventricles. The basal cisterns in both supra and infratentorial regions were prominent. These findings were first interpreted as being consistent with pachygyria–agyria complex (lissencephaly) (Fig. 2a).

MRI done on patient V6 at 1 year of age showed hyperintense signals in the periventricular and subcortical areas, accompanied by cerebral atrophy and secondary dilatation of the ventricular system. This was interpreted as lissencephaly (Fig. 2b).

The MRI of V7 performed at 4 years of age revealed an intraventricular cyst bulging into the lateral ventricles' posterior body. It was located inferior to the fornices which were displaced superiorly. There was no solid component, no calcifications, and the content followed CSF on all sequences. The occipital and temporal horns were prominent on the left, suggesting an impairment of the CSF flow caused by the cysts.

Genetic analysis

Whole exome sequencing was performed on patients V6 and V7. DNA was sequenced at 3billion using 3B-EXOME proband. A homozygous missense variation in the *ADGRG1* gene (NM_201525.4: c.308T > C; p.Leu103Pro) was detected in both (Fig. 3). This variant was not observed in the gnomAD v2.1.1 dataset. Segregation analysis confirmed the presence of this variant in V6, and V7. In silico prediction tools suggest a damaging effect of the variant on the gene product (REVEL: 0.32; 3Cnet: 0.90).

Discussion

Here, we describe five individuals with apparent brain malformations, intellectual disability, motor difficulties and seizures. Patients are descendants of a large Syrian family exhibiting many interrelated marriages. Whole

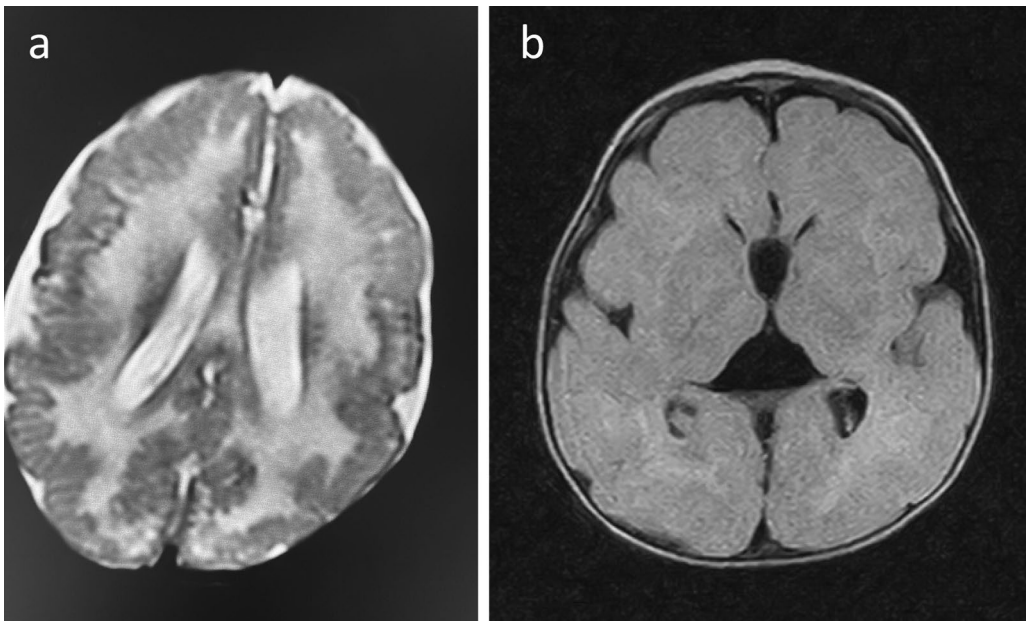

Fig. 2 **a** Axial T2 brain MRI of patient V5 displaying diffuse high signal intensity on T2 in the white matter alongside posterior polymicrogyria and pachygyria. **b** Axial FLAIR brain MRI of patient V6 revealing pachygyria and lissencephaly

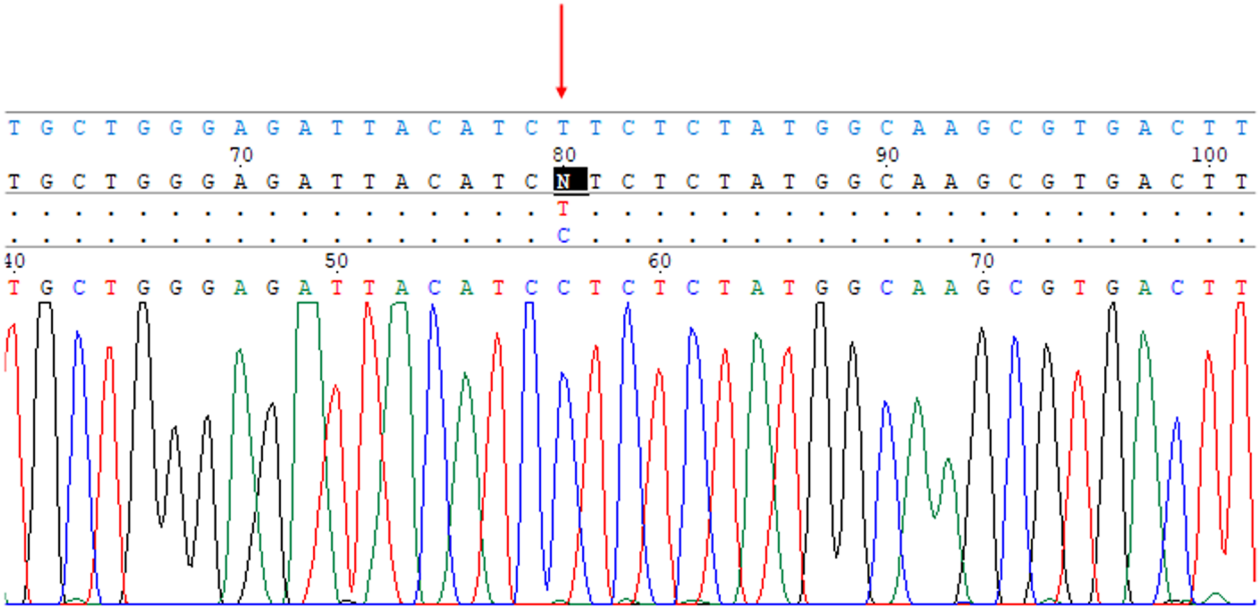

Fig. 3 Electropherogram showing the pathogenic variant identified at homozygous state in patient V6

exome sequencing carried out on two of the affected members, revealed a novel pathogenic variant in *ADGRG* ; and sanger sequencing confirmed its segregation with the disease in the family; thus, supporting the diagnosis of BFPP.

To date, *ADGRG1* pathogenic variants have been reported in a total of 92 patients [8, 15–19]. All reported cases show homogeneity in the following clinical features: intellectual disability, motor difficulties, epilepsy, cerebellar manifestations, and oculomotor abnormalities [20]. Table 2 illustrates the frequency of occurrence of the clinical characteristics related to BFPP, in the previously reported cases [8, 15–19]. The herein described cases mostly mirrored these findings. Similarly, to most of the reported cases (79.2%), cognitive impairment is severe to profound in the family herein studied. On clinical examination, ataxia, reflecting positive cerebellar signs, is noted in three of the five patients included. This finding is also observed in 88.9% of the previously reported cases with BFFP. As for the pyramidal signs which are noted in 75% of the reported cases, they were seen in two members of this family. Seizures were present in three of our patients (V5, V6, V7), which is consistent with the reported findings where 90.4% of the cases had seizures. On the other hand, unlike the present report where seizures were refractory to treatment in all the three patients, they are usually were refractory to medication in 54.7% of the reported cases. Furthermore, oculomotor findings were found in all the patients herein reported, entirely aligning with the previously reported cases. Likewise, as in several studies reporting abnormal tone [1, 15–17, 20–22], hypotonia was found in patients V5, V6 and V7; and hypertonia in V6 and V7. On the other hand, motor impairment is more severe in this family compared to reported patients with BFPP. In fact, while most of the BFPP cases mentioned in literature (70%) were able to walk at a median age of 3.5 years old [15], only two out of five of our patients (V2 and V6) managed to walk at 4 and 5 years, respectively. Besides, among our cases, three individuals exhibited strabismus, and two presented with both strabismus and nystagmus; the latter co-occurrence was only noted in 23.9% of cases. Oromotor dyspraxia, a rare feature of the disease [6, 23], was also observed in two of our patients. Last but not least, while dysmorphic features were noted in multiple cases in the literature [1, 5, 15, 21, 22, 24–26], our patients did not present any.

Interestingly, radiological findings in BFPP can mimic those observed in patients infected with Herpes Simplex or Cytomegalovirus (CMV); which may hinder the accurate diagnosis of patients presenting with this rare disease; as in patient V2 [17]. On the other hand, unlike all cases with BFPP showing radiological abnormalities, MRI performed during the first year of life of patient V3 was normal. Besides, radiological findings in patients V5 and V6 initially suggested lissencephaly [4, 27]. This further highlights the importance of genetic testing in readdressing the diagnosis of these patients, especially that radiological findings could be wrongly interpreted in underdeveloped countries with limited access to specialized centers. Genetic testing is also essential to enable the

Table 2 Review of clinical features associated with BFPP syndrome

Clinical feature	*n* (%)
Motor impairment	
Able to walk	44 (70)
Unable to walk	19 (30)
Missing	26
Cognitive impairment	
Severe	57 (79.2)
Moderate	12 (16.7)
Mild	3 (4.1)
Missing	17
Cerebellar signs	
Present	56 (88.9)
Absent	7 (11.1)
Missing	24
Pyramidal signs	
Present	53 (78)
Absent	15 (22)
Missing	21
Oculomotor findings	
Present	73 (93.6)
Strabismus	36 (53.7)
Nystagmus	15 (22.4)
Strabismus + nystagmus	16 (23.9)
Missing	17
Absent	5 (6.4)
Missing	11
Head circumference	
Normal	64 (81)
Microcephaly	10 (12.7)
Macrocephaly	5 (6.3)
Missing	10
Seizures	
Present	75 (90.4)
Age at onset in years, median (IQR)	
Refractory	41 (54.7)
Missing	23
Absent	8 (9.6)
Missing	6

patients to benefit from an appropriate counseling, and help the family make informed choices in their future pregnancies, especially in underdeveloped areas that lack awareness about genetic diseases.

Conclusion

In conclusion, this is the first case report of BFPP in a consanguineous Syrian family. Our study reports a novel pathogenic variant in *ADGRG1*, and highlights the clinical heterogeneity of BFPP that manifests with variable intrafamilial expressivity.

Reporting patients with similar rare genetic disorders remains important to raise better awareness about these conditions and contribute to a better diagnosis and follow-up of patients affected with these diseases. This is much needed, especially in underdeveloped countries in our region which lack a well-founded databases such as the Catalogue for Transmission Genetics in Arabs (CTGA) Database [28].

Acknowledgements
We express our appreciation to the family for their cooperation throughout the study.

Author contributions
DEK, MH, SS, CM, EC, SWR, JK, AM have made a substantial contribution to the concept of the case report and the interpretation of data for the article; DEK, MH, SS, AM contributed to the follow-up and clinical evaluation of the patient. DEK, MH, CM and AM drafted the article content; All authors approved the version to be published;

Funding
The authors received no financial support for the research authorship and / or publication of this article.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Approval to conduct the study was obtained from the Institutional Review Board of the Lebanese American University, Beirut, Lebanon. The IRB operates in compliance with the national regulations pertaining to research under the Lebanese Minister of Public Health's Decision No.141 dated 27/1/2016 under LAU IRB Authorization reference 2016/3708, the international guidelines for Good Clinical Practice, the US Office of Human Research Protection (45CFR46) and the Food and Drug Administration (21CFR56). LAU IRB U.S. Identifier as an international institution: FWA00014723 and IRB Registration # IRB00006954 LAUIRB#1. Parents signed an informed consent for participation and sample collection.

Consent for publication
Parents signed an informed consent for data publication.

Competing interests
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Received: 7 November 2023 Accepted: 21 February 2024
Published online: 26 April 2024

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