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Original Article 1

Clinical and molecular characterization of patients with Gardner syndrome using whole exome sequencing

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Background
Gardner syndrome (GS) is an autosomal dominant disorder caused by mutations in the adenomatous polyposis coli *(APC)* gene, a tumor suppressor, located on chromosome 5q21 which consists of 15 exons encoding 2843 amino acids. The adenomatous polyposis coli *(APC)* protein plays a role in regulating cell growth by ensuring appropriate timing of cell cycle. The clinical presentation of Gardner syndrome involves mainly gastrointestinal polyps, soft tissue tumors, and multiple osteomas. Dental manifestations include retained deciduous teeth, impacted teeth, hypercementosis, odontomas, dentigerous cysts, supernumerary teeth, and fused or long roots.

Objectives
This study aims to investigate the clinical, oro-dental, and genetic analysis of Gardner syndrome in two unrelated families from Egypt.

Patients and methods
This study included five Gardner syndrome patients from two unrelated Egyptian families . Whole exome sequencing (WES) was performed to investigate the genetic aetiology in two patients, one from each family. Mutation analysis of the identified *APC* gene variants will be extended to the siblings and their mothers. This analysis will be performed using PCR amplification followed by Sanger sequencing of the amplified fragments.

Results
Clinical examination revealed varied dental anomalies among patients. Specifically, one patient presented with mandibular osteomas. Supernumerary teeth were observed in three patients, while another patient exhibited retained deciduous teeth and multiple impacted teeth. Whole-exome sequencing identified two previously reported variants in the *APC* gene. A pathogenic (NM_000038.6):c.4666dupA variant was identified in a male patient from family 1. Additionally, a benign intronic (NM_000038.6):c.423-4delA variant was detected in a female patient from family 2. Segregation analysis confirmed the presence of both variants in a heterozygous state within affected siblings and their mothers in both respective families.

Conclusion
This study represents the first molecular analysis of the *APC* gene in Gardner syndrome patients in Egypt. The findings expand the spectrum of reported variants associated with Gardner syndrome, though further functional studies are required to confirm the deleterious nature of the identified variants.

Keywords: Adenomatous polyposis coli gene, APC gene, Gardner syndrome, Gastrointestinal polyps, supernumerary teeth.

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Introduction

Gardner syndrome (GS) is an autosomal dominant disorder resulting from mutations in the *APC* gene, and is recognized as a phenotypic variant of familial adenomatous polyposis (FAP). Clinically, GS is characterized by gastrointestinal polyps, soft tissue tumors, and multiple osteomas [1].

Dental manifestations, which typically precede the development of gastrointestinal polyps, include retained deciduous teeth, impacted teeth, hypercementosis, odontomas, dentigerous cysts, supernumerary teeth, and fused or long roots.

Gardner syndrome (GS) exhibits a prevalence ranging from 1:7000 to 1:30000 with no reported specific ethnic or sex predilection. Inherited with nearly complete penetrance and variable expressivity, GS presents with diverse phenotypic manifestations [2]. Given the malignant transformation potential of gastrointestinal polyps, early diagnosis and treatment are crucial for patient survival. Consequently, the identification of oro-dental features can serve as an important early diagnostic marker for the syndrome [3].

Gardner Syndrome (GS), a variant of familial adenomatous polyposis (FAP), is an autosomal dominant disorder caused by mutations in the adenomatous polyposis coli (*APC*) gene, located on chromosome 5q22.2 [4,5]. GS affects approximately 10-50% of individuals with FAP, with a prevalence ranging from 1 in 8,000 to 1 in 1,400 [4]. The estimated incidence in the general population is 1 in 14,025 live births [4]. While inherited as an autosomal dominant trait, approximately 20% of GS cases arise from de novo mutations [4]. The *APC* gene functions as a tumor suppressor, encoding a multi-domain protein critical for regulating cell growth and ensuring proper cell cycle progression [5]. Consequently, *APC* gene mutations lead to uncontrolled cell growth [5].

Gardner syndrome (GS) is characterized by adenomatous colorectal polyps accompanied by various extracolonic manifestations, including desmoid tumors, osteomas, and dental abnormalities [6]. Desmoid tumors, specifically, may present in the soft tissue of the head and neck, maxillary sinus, nasopharynx, and oral cavity [6]. Multiple osteomas are observed in 50–90% of GS patients, predominantly affecting the craniofacial bones, with the mandible being the most common site [6]. Dental disorders affect over 30% of GS patients, with frequently reported dental abnormalities including congenitally missing teeth, impacted teeth, supernumerary teeth, root abnormalities, hypercementosis, dentigerous cysts, and complex and compound odontomas [4]. Additionally, oral manifestations can include osteomas and osteomyelitis [5]. The typical onset of GS is in the twenties, although cases have been reported across a wide age range, from 2 months to 70 years [4].

A delayed diagnosis of Gardner syndrome (GS) can lead to the malignant transformation of colorectal polyps and the progression of jawbone lesions, potentially resulting in facial asymmetry, discomfort, and an elevated cancer risk [5]. Given that early diagnosis and treatment are critical for patient outcomes, identifying oro-dental features can serve as an important early marker of the syndrome [3].

This study aimed to characterize the clinical, oro-dental, and genetic features of Gardner Syndrome (GS) in two unrelated Egyptian families. Our findings identified two previously reported *APC* gene variants, which segregated in both families. These results highlighted the importance of early diagnosis and treatment for Gardner syndrome patients in the Egyptian population.

Patients and methods

The study included five patients suspected to Gardner syndrome from two unrelated Egyptian families. Patients were recruited from the outpatient clinic of the oro-dental Genetics Department at the National Research Centre (NRC). The study was approved by the medical ethical committee of the National Research Centre, Cairo, Egypt (Approval number 044101223). A written informed consent was obtained from the patients and their included family members.

Clinical assessment

Patients' medical records were evaluated and a detailed medical history of the family members was obtained. A detailed pedigree was constructed for both families. The clinical, oro-dental, and radiographic examinations were performed at the time of presentation. The clinical examination revealed, one patient with osteomas in the mandible, three patients with supernumerary teeth, and the other one with retained deciduous teeth and multiple impacted teeth. The five patients were suspected to clinically diagnosis with Gardner syndrome.

Molecular analysis

Whole exome sequencing

A total of 3 ml of whole blood was collected from all patients and their available family members. Genomic DNA was extracted from peripheral blood samples of all participants using the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany). The quality and quantity of DNA samples of patients were assessed using flourometric Denovix Qubit™ dsDNA BR Assay Kit (ThermoFisher, Waltham, MA, USA). DNA samples were sequenced by using the Twist Human Core Exome Plus kit (Twist Bioscience, San Francisco, CA, USA) and Illumina NovaSeq 6000 system (Illumina, San Diego, CA, USA) according to the manufacturer's protocol. Libraries were prepared in paired end mode

(2×100 bp) for an output of 6 GB per sample, and an average coverage of 50×. Sequencing reads were demultiplexed using Illumina Genes 2022, 13, 1056 4 of 24 bcl2fastq (2.20), and adapter sequences were trimmed using Skewer (version 0.2.2) [7]. The quality of the generated FASTQ files was analyzed with FastQC software (version 0.11.5; Illumina, San Diego, CA, USA). The variant Annotation and Filtration PhenoDB tool was used to annotate Vcf files using ANNOVAR [8]. Variants were filtered based on the depth of coverage and minor allele frequencies (MAF) (less than 1% MAF) in large population databases, including dbSNP (9), 1000 Genomes Project [10], and the Genome Aggregation Database (gnomAD v2.1.1) [11].

Variant segregation

Sanger sequencing was used to confirm that filtered variants segregated consistently among parents and available family members according to the predicted mode of inheritance. We designed primers targeting exons 5 and 13 in the *APC* gene that harbor the filtered variants of interest using the Primer3 tool. "Primer pair sequences are available upon request". Primers' quality was checked using NetPrimer software, and the predicted PCR product specificity was examined against the reference database by NCBI nucleotide blast software. A typical PCR reaction of 2 µl cDNA or 100 ng genomic DNA, 25 pmol of each primer, 0.2 mmol/l dNTPs, 1.0 mmol/l MgCl2, 1x ammonium sulphate reaction buffer, and 0.5µl (2.5 units) DNA polymerase "Fermentas, EU, Thermo Scientific" was set. The PCR cycling conditions were initial denaturation at 95 °C for 8 min, and 35 cycles of denaturation at 95 °C for 1 min, annealing for 1 min at 58 – 64 °C, extension for 1 min at 72 °C, and an additional extension for 10 min at 72 °C. The PCR products from both cDNA and genomic DNA were purified using the "QIA quick PCR purification kit" (Qiagen, Hilden, Germany), then sequenced in both directions using the "Big Dye Termination Kit" (Applied Biosystems, Foster City, California, USA), and analyzed on the "ABI Prism 310 Genetic Analyzer" (Applied Biosystems), in accordance with the instructions of the manufacturer. Identified variants were assigned following ACMG guidelines against the "NM_000038.6" reference sequence [12].

Database and *In-Silico* analyses

Querying the identified variants by browsing through several databases, including the "LOVD (Leiden Open Variation Database)" [12], "Human Gene variant Database (HGMD)" ("HGMD® home page," 2023) [13] and "NCBI dbSNP (database of single nucleotide polymorphisms, ClinVar)" [14]. Identified variants frequency was compared against the reported general population frequencies on "1000 genomes" ("IGSR | samples," 2023) [15], the gnomAD ("GLA | gnomAD," 2023) databases [16], and Varsome database [17].

Results

Clinical phenotype

This study included five patients affected with Gardner syndrome from two unrelated Egyptian non-consanguineous families .

Family #1

This family has two affected subjects: a male proband (P2) and his mother (P1). The proband, aged 14 years, presented to the clinic with a hard swelling on the left side of his mandible. A 3D CT scan revealed multiple osteomas located on the mandible, zygomatic arch, and the medial wall of the orbit. The panoramic radiograph revealed a mixed odontoma located on the left side of the mandible and an additional osteoma was found on the medial wall of the right orbit (Fig. 1).

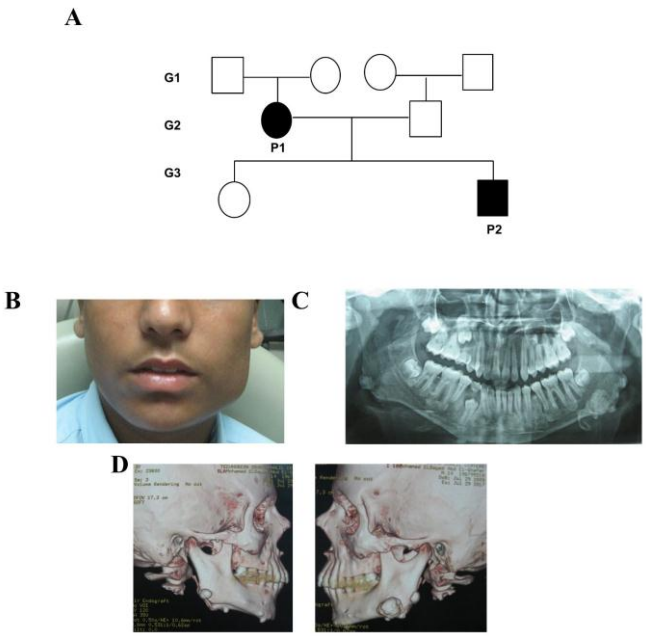

Fig. 1 (A) Three-generation pedigree of family 1 showed two affected members mother (P1) and affected son (P2) (B) Clinical presentation of the affected son (P2) showed a swelling on the left side of the mandible. (C) Panoramic radiograph showed multiple osteomas on the posterior border of the left ramus, the inferior border of the mandible, and the left and right angles of the mandible. (D) 3D Cone beam CT showing the multiple bony osteomas on the mandible. An additional osteoma is found on the medial wall of the right orbit.

Family #2

This family has three affected members: two females, aged 17 (P5) and 23 (P4), and their mother (P3), who is 48 years old. Both siblings and their mother were diagnosed with supernumerary teeth. Additionally, a family history of colon cancer has been reported within this family (Fig. 2).

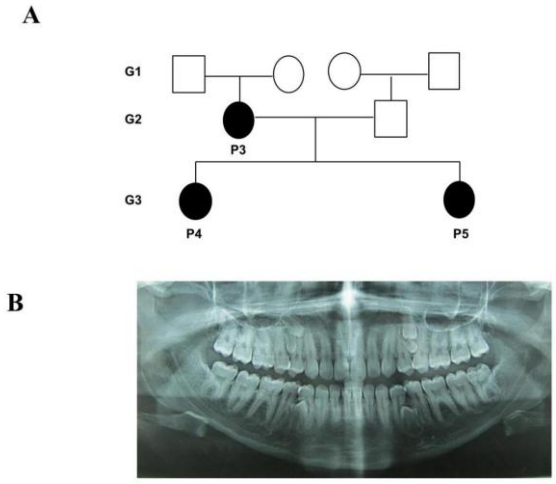

Fig. 2 (A) Three-generation pedigree of family 2. (B) Panoramic radiograph showed multiple impacted supernumerary teeth.

Molecular Analysis

The analysis of the WES data revealed the presence of two previously reported variants in the *APC* gene; the pathogenic frameshift variant c.4666dupA (p.Thr1556fsX3) was identified in exon 16 and the benign intronic variant c.423-4delA was detected in splice region of intron 4.

Sanger sequencing confirmed the presence of both variants in a heterozygous status. Familial co-segregation analysis has shown that the variant c.4666dupA is present in the two examined subjects of family 1, the proband (P2) and affected mother (P1), in the heterozygous status. The variant c.423-4delA was co-segregated with the phenotype and detected in all three examined subjects of family 2, the proband (P4), the affected sister (P5), and their affected mother (P3), in a heterozygous status (Fig. 3). The variant details are summarized in Table 1.

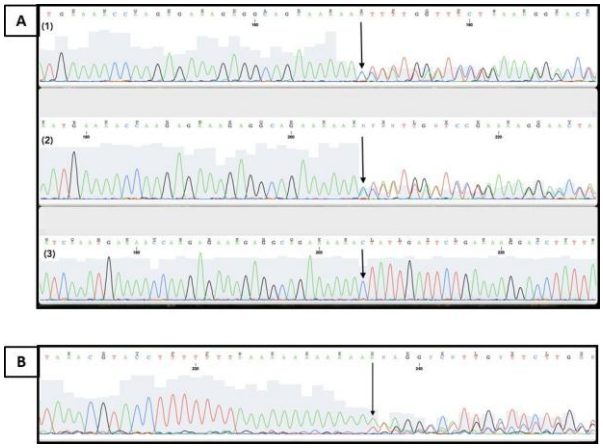

Fig. 3 DNA sequencing chromatogram of the two families. (A1) The proband (P2) of family 1 showing a heterozygous c.4666dupA variant (Reference sequence: A_6CT and alternative sequence: A_7CT). **(A2)** Mother (P1) of family 1 showing a heterozygous c.4666dupA variant. **(A3)** The normal sibling sister of family 1 showing normal c.4666 sequence. **(B)** Family 2 showing a heterozygous c.423-4delA variant in the two probands (P4) and (P5) and their mother (P3) (Reference sequence: ATAGGTC and alternative sequence: -TAGGTC).

Table 1: The genotypes of variants in the *APC* gene in Gardner patients in this study

Variant /Location	Family	Type	dbSNP	ClinVar	Clinical Significance
NM_000038.6: c.4666dupA p.T1556Nfs*3 **Exon 16**	1	Frameshift	rs587783031	VCV000428112.25 Variation ID: 428112	Pathogenic
NM_000038.6: c.423-4delA Splice region of **Intron 4**	2	Intronic del	rs730881230	VCV000181781.69 Variation ID: 181781	Benign

Discussion

Gardner syndrome (GS) is an autosomal dominant disorder caused by mutations in the APC gene, which is associated with colon cancer and Familial Adenomatous Polyposis (FAP) [1]. Approximately 50% of *APC* gene mutations developed Gardner syndrome, characterized by oral manifestations such as osteomas, impacted teeth, and supernumerary teeth [4].

In the current study, the c.4666dupA variant was associated with osteomas located on the mandible, zygomatic arch, and medial wall of the orbit. A case study of a 2-year-old boy with a de novo c.4666dupA mutation presented with an aggressive phenotype, including a soft tissue mass of the forehead, multiple desmoid tumors, and subdermal lesions. This early onset and severe presentation highlighted the deleterious nature of this specific variant [18].

The c.4666dupA variant was also reported in a typical Familial Adenomatous Polyposis (FAP) patient in the study conducted by Aceto et al. in 2005 [19]. Another case study described a 44-year-old Tunisian Gardner syndrome patient with a heterozygous pathogenic frameshift variant, c.4652-4655delAGAA, in *APC* exon 16, who presented with sebaceous cysts, frontal and maxillomandibular osteomas, and colorectal polyposis [20]. The c.4666dupA variant is adjacent to the c.4666, resulting in a premature stop codon, leading to a truncated protein [20]. Several studies indicate that pathogenic variants in the C-terminal region of the *APC* gene are associated with classical FAP and may increase the risk of developing desmoid tumors [21–24] and dental abnormalities [25,26]. These features are consistent with the broader phenotype of Gardner syndrome [27].

The pathogenic c.4666dupA variant, identified in *APC* exon 16, is a duplication of A at codon 4666, causing a translational frameshift with a predicted alternate stop codon (p.T1556Nfs*3). The pathogenic T1556Nfs*3 variant causes a shift in the reading frame starting at amino acid 1556, leading to

premature truncation of the 2843 amino acid APC protein and a subsequent loss of function .

The c.4666dupA variant was classified as pathogenic according to the ACMG guidelines and ClinVar database [28]. This frameshift variant introduces a premature translation stop signal in the APC gene (p.T1556Nfs*3), which is predicted to disrupt the C-terminal portion of the APC protein and consequently disrupt gene function. This constitutes very strong evidence of pathogenicity (PVS1). The previously reported pathogenic truncation variant p. Tyr2645Lysfs*14 that located downstream of our variant p.T1556Nfs*3, suggesting the critical role of this APC protein region in causing the disease [29].

The c.423-4delA variant is located within a repetitive AT-rich region (T7A13) of intron 3 in the *APC* gene (nucleotide -32 to -4). This region was among the first intronic sequence variants identified in FAP patients. In 1992, Miyoshi et al., initially reported a deletion in the A13 tract of this region (c.423-4delA variant) as a pathogenic splice variant [30]. However, two decades later, Palmirotta et al. demonstrated the limitation of Sanger sequencing in accurately resolving this repetitive AT-rich region, which led to the misinterpretation of the splice acceptor site as a frameshift variant. Furthermore, their study confirmed the benign nature of the c.423-4delA variant through RNA assays and computational analysis, revealing no effect of this variant on splicing or protein function [31].

The intronic *APC* gene variant c.423-4delA, characterized by an adenine deletion at position -4 of intron 4, met three criteria codes for benign variant classification, which are the BA1, BS3 Supporting, and BP4 [32]. The BA1 criteria describe a high allele frequency in populations (GnomAD Popmax Filtering Allele frequency ≥0.1%). The BS3_Supporting criteria describe no mRNA aberration results of the RNA assay, indicating that this variant does not affect protein function. The BP4 criteria describe the presence of ≥ 2 *in silico* splicing predictors (MaxEntScan, SpliceAI, and VarSeak) suggesting no impact on splicing, indicating no impact on the gene or its product [32].

The 423-4delA variant has been classified as benign/likely benign of germline origin in individuals with hereditary cancer-predisposing syndrome and colorectal cancer. Given that Gardner syndrome (GS) is an autosomal dominant disorder with variable expressivity, the presence of benign 423-4delA variant in Family 2 may correlate with less severe clinical symptoms and milder dental manifestations.

Early diagnosis of GS is critical due to the significantly increased risk of colorectal cancer in affected patients. Dental anomalies, such as impacted teeth and odontomas, often precede the development of intestinal polyposis, making them crucial early indicators that can prompt genetic analysis.

Conclusions

Genetic analysis of *APC* gene is essential for assessing the risk of developing colorectal cancer and other complications associated with Gardner syndrome. The identification of specific *APC* gene variants can help predict the severity of the disease and guide personalized management strategies. Furthermore, it can identify asymptomatic family members who carry the *APC* gene variant, allowing for early intervention and prevention of colorectal cancer.

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