Personalized surveillance in giant congenital melanocytic nevus, including the role of AI, histopathology and MC1R genotyping: A case report

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Abstract. Giant congenital melanocytic nevi (GCMN) are rare pigmented skin lesions present at birth that carry an increased risk of malignant melanoma and neurocutaneous melanosis. Early diagnosis and long-term follow-up care are essential for high-risk patients. The combination of modern imaging techniques with genetic testing can enable a more comprehensive risk assessment. The present case describes a 55-year-old woman with a bathing-trunk-type GCMN and >30 additional nevi. The patient was monitored using total body mapping combined with artificial intelligence (AI)-assisted dermoscopy (MoleAnalyzer Pro; FotoFinder Systems GmbH). Due to suspicious features, several lesions were surgically excised. Histopathology revealed a rare plexiform melanocytic schwannoma with low proliferative activity, showing immunopositivity for S100 protein and SOX10, with focal expression of Melan-A (MART-1). Germline testing by next-generation sequencing identified two high-risk melanocortin 1 receptor (MC1R) variants, p.Arg151Cys and p.Arg160Trp, in compound heterozygous state, both associated with melanoma susceptibility. No pathogenic variants were detected in NRAS or BRAF. The present case highlighted the integrative value of AI-assisted dermoscopy, histopathology, and genetic profiling in the surveillance of patients with GCMN. Compound heterozygosity for MC1R high-risk alleles may explain the extensive nevus burden and support intensified surveillance. Personalized follow-up strategies guided by advanced imaging and genomics can improve early detection and prevention of melanoma.

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Introduction

Giant congenital melanocytic nevi (GCMN) are rare pigmented skin lesions present at birth, often enlarging to 20 cm in adulthood (1,2). Their development results from an abnormal migration and proliferation of neural crest-derived melanoblasts, which may involve not only the skin but also deeper structures such as leptomeninges (1). Individuals with GCMN face a higher lifetime risk of malignant melanoma and neurocutaneous melanosis (1,2). Modern surveillance combines clinical examination with total body mapping and artificial intelligence (AI)-assisted dermoscopy. These technologies allow sensitive detection of morphological changes and objective comparison over time, thus facilitating early recognition of malignant transformation (3,4). Alongside imaging, genetic predisposition strongly influences melanoma risk. The melanocortin 1 receptor (MC1R) gene is central in regulating pigmentation, and its high-risk variants are well documented as low- to moderate-penetrance melanoma susceptibility alleles. Identifying such variants may explain individual nevus burden and guide tailored follow-up. The aim of the present case report was to present a patient with a bathing-trunk-type GCMN who underwent integrative follow-up with AI-enhanced dermoscopy, histopathology, and germline genetic analysis. The case illustrates how combining clinical and molecular tools supports personalized surveillance in high-risk patients (5,6).

Case report

Patient. A 55-year-old woman was referred for dermatologic evaluation due to a bathing-trunk type GCMN and multiple additional nevi distributed over the trunk and extremities. The present study was approved (approval no.755/19.12.2023) by the Ethics Commission of the Medical University-Pleven, (Pleven Bulgaria). Written informed consent for participation

and publication was obtained from the patient in the present study.

Dermatological evaluation. Cutaneous examination was performed with total body mapping using an AI-assisted dermoscopy system (MoleAnalyzer Pro version 3.5.6.0; FotoFinder Systems GmbH). The software applies convolutional neural networks trained on large annotated image datasets to identify and score melanocytic lesions according to asymmetry, border, color, and structure. Sequential imaging allows objective detection of new or evolving lesions.

Germline pathogenic variant detection. After informed consent, peripheral blood was collected in EDTA tubes. DNA extraction was performed with the MagCore® Genomic DNA Whole Blood Kit (cat. no. MGB400-04; RBC Bioscience Corp.). Genomic DNA integrity was assessed using an Agilent 2200 TapeStation system with Genomic DNA ScreenTape (Agilent Technologies, Inc.), following the manufacturer's instructions. Concentration and purity were evaluated using the Qubit 4 Fluorometer and NanoDrop One spectrophotometer (both from Thermo Fisher Scientific, Inc.). Genetic analysis was performed with massive parallel next-generation sequencing (NGS). Library preparation was carried out using the TruSight One Expanded Panel (6699 genes; Illumina, Inc.), followed by paired-end sequencing (2x150 bp) on the Illumina NextSeq 550 High Output Kit v2.5 (300 cycles; cat. no. 20024907; Illumina Inc.). Bioinformatic processing included alignment to hg19 and generation of gVCF files. The mean sequencing depth across all targeted regions was 256. Coverage analysis demonstrated that ≥99% of target regions were covered at ≥20x. Variants were filtered using custom thresholds: Minimum depth ≥20x, variant allele frequency (VAF) ≥0.20, exclusion of synonymous variants, and prioritization of nonsynonymous, splicing, and frameshift changes. Variant annotation used ClinVar, dbSNP, and Ensembl databases. Classification followed the ACMG five-tier framework (7).

Histopathology. Excised lesions were fixed in 10% neutral buffered formalin (Sigma-Aldrich; Merck KGaA) for 12-24 h at room temperature, paraffin-embedded, and sectioned at 3-4 μm. Sections were stained with hematoxylin and eosin following standard histopathological procedures. Hematoxylin staining was performed at room temperature for 4-6 min, followed by eosin staining at room temperature for 1-2 min. Hematoxylin (Mayer's hematoxylin; Merck KGaA) and eosin (Eosin Y; Merck KGaA) were used according to the manufacturer's protocols. Formalin-fixed, paraffin-embedded tissue sections (4 μm) were deparaffinized in xylene, rehydrated through a descending ethanol series, and subjected to heat-induced antigen retrieval in citrate buffer (pH 6.0) at 95-98˚C for 20 min. Endogenous peroxidase activity was quenched using 3% hydrogen peroxide for 10 min, followed by blocking with 5% normal goat serum (Vector Laboratories, Inc.) for 20 min at room temperature. Primary antibodies were applied under the following conditions: S100 (1:400; overnight at 4˚C; cat. no. IR504; Dako; Agilent Technologies, Inc.); SOX10 (1:200; overnight at 4˚C; cat. no. A-1028, Cell Marque/Merck KGaA); Melan-A (1:100; 1 h at room temperature; code no. M7196; Dako; Agilent Technologies, Inc.) Sections were incubated with the EnVision+ System HRP secondary antibody (cat. no. K4001; Dako; Agilent Technologies, Inc.) for 30 min at room temperature, and chromogenic detection was performed using DAB+ (code no. K3468; Dako; Agilent Technologies, Inc.). Slides were counterstained with Mayer's hematoxylin (Merck KGaA) at room temperature (20-25˚C) for 1-2 min, dehydrated through graded alcohols, cleared in xylene, and mounted. Immunoreactivity was evaluated using a bright-field microscope (Olympus BX43; Olympus Corporation) at a magnification of x100-x400.

Clinical presentation and histopathological findings. The female patient presented with a large bathing-trunk-type GCMN, accompanied by over 30 satellite nevi (0.5-7 cm) across the trunk and limbs. Neurological examinations, performed due to prior seizure episodes, revealed no structural abnormalities. In 2023 (at the age of 54 years), three pigmented tumors (total diameter 28 cm) in the lumbar region were surgically excised. Histology revealed a multinodular plexiform melanocytic schwannoma composed of spindle-shaped melanocytes, extending into subcutaneous tissue, with low mitotic activity. Immunohistochemistry showed diffuse S100 and SOX10 positivity, focal Melan A expression, and a low Ki-67 index. These markers supported schwannoma with melanocytic differentiation rather than malignant melanoma.

Dermatological status. Cutaneous examination revealed extensive pigmentary changes involving the face, trunk, and both upper and lower extremities. The findings included a symmetrically distributed bathing-trunk-type GCMN, accompanied by multiple satellite nevi ranging from 0.5 to 7 cm in diameter. In the sacral region, a linear, cross-shaped atrophic scar was noted, consistent with the site of prior surgical excision. The scar was surrounded by numerous dark brown to black colored macules. (Fig. 1A-C) The dermatological examination with a Total body mapping and AI dermoscopy device (MoleAnalyzer Pro) did not identify melanoma-like evolution. Histopathological analysis of the excised multinodular, plexiform, non-encapsulated lesion demonstrated a proliferation of oval and spindle-shaped cells extending from the epidermis through the dermis and into the deep subcutaneous adipose tissue, as visualized with hematoxylin and eosin staining (Fig. 2). Immunohistochemistry showed diffuse S100 and SOX10 positivity, focal Melan A expression, and a low Ki-67 index (Fig. 3A-D). These markers supported schwannoma with melanocytic differentiation rather than malignant melanoma. NGS analysis identified two pathogenic MC1R variants: c.451C>T (p.Arg151Cys) and c.478C>T (p.Arg160Trp), both in compound heterozygous state (Fig. 4). No pathogenic variants were detected in NRAS or BRAF. No additional high-risk variants were identified across the panel.

Discussion

GCMN represent rare developmental anomalies of melanoblast migration and proliferation, with a reported melanoma risk of ~5% over a lifetime (8,9). Early recognition of malignant transformation is essential. These developmental abnormalities are frequently linked to somatic mutations in genes such as NRAS (particularly Q61 variants) and BRAF

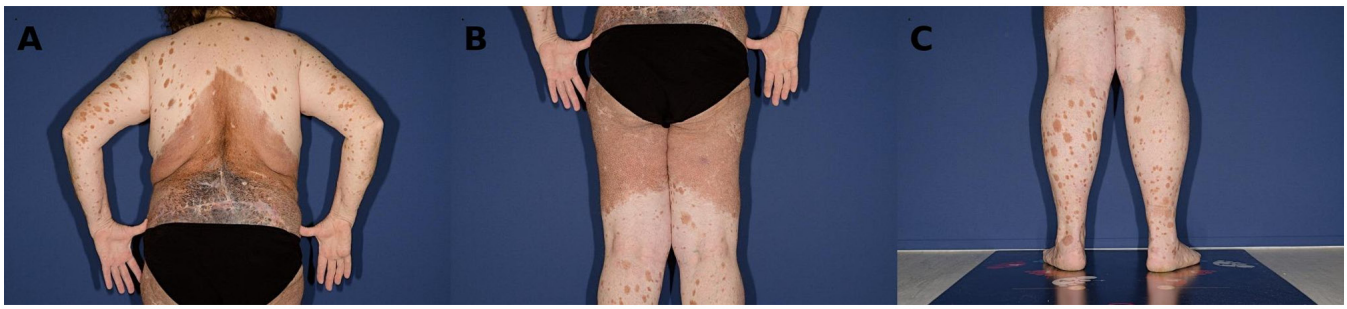

Figure 1. Cutaneous findings in the patient with extensive congenital melanocytic nevi. (A) Multiple pigmented nevi involving the upper and lower back. Of note the central hyperpigmented plaque with thickened skin and irregular borders. (B) Extension of the pigmented lesion over the gluteal region and posterior thighs. Lichenification and verrucous appearance are present. (C) Distribution of satellite nevi over the lower legs, showing sharply demarcated pigmented macules and plaques.

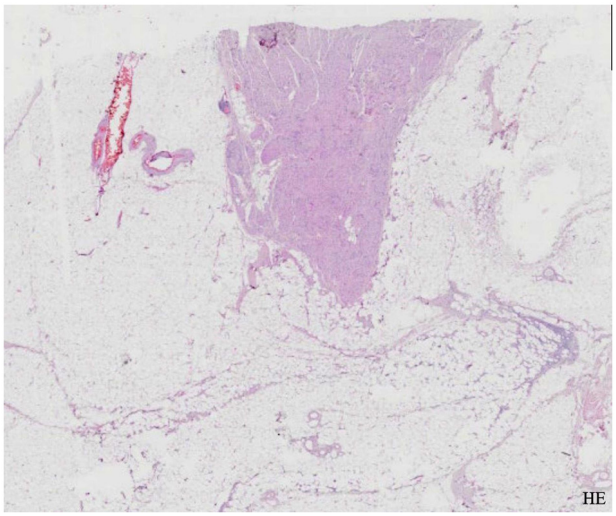

Figure 2. Histopathological evaluation of a pigmented skin lesion (hematoxylin and eosin staining; x200 magnification). Moderately cellular lesion located in the dermis, composed of spindle-shaped melanocytes with bland nuclear features. There is no significant mitotic activity or atypia.

(notably V600 mutations), as well as dysregulation of pathways involving hepatocyte growth factor/scatter factor (10).

Various classification systems exist for CMN, with the most widely accepted being that of Kopf *et al* (11), which categorizes lesions by maximum diameter: Small (<1.5 cm), medium (1.5-19.9 cm), and large or giant CMN (>20 cm) . The overall incidence of CMN in neonates ranges from 0.2 to 2.1%, with a slight female predominance reported (male-to-female ratios between 1:1.17 and 1:1.4) (12). Data from the Giant Congenital Melanocytic Nevus Registry at the Federal University of Minas Gerais, based on patient records between 1999 and 2011, estimated the lifetime risk of melanoma in individuals with GCMN to be ~5% (13). Anatomical distribution patterns showed a predominance on the trunk (68.4%), followed by the head and neck (17.5%), and the extremities (14.1%) (13).

Total body mapping involves systematic photographic documentation of the entire skin surface, followed by digital dermoscopic analysis of selected melanocytic lesions. This approach facilitates longitudinal comparison, enabling the detection of subtle morphological changes or the emergence of new lesions over time (14). In the present case, total body mapping combined with AI-enhanced dermoscopy was employed, offering a sensitive and objective method for surveillance. Regular imaging at 6 to 12-month intervals is especially beneficial in individuals with GCMN, where early recognition of malignant transformation is critical.

Surgical management remains a topic of ongoing discussion. A systematic review by Krengel *et al* (12), analyzing 49 reported cases of CMN-associated melanoma, found that in 67% of patients the malignant transformation occurred within the congenital lesion itself . Based on such findings, prophylactic surgical excision is sometimes advocated, particularly in large or atypical nevi. While the impact of surgery on melanoma risk reduction remains inconclusive, the procedure often yields aesthetic and functional improvements, which are important considerations for both patients and families when deciding on treatment.

The histological diagnosis of plexiform melanocytic schwannoma required careful differentiation from melanoma. Positive staining for S100 and SOX10 confirmed Schwann cell origin, while focal Melan A expression reflected melanocytic differentiation. Similar immunoprofiles have been reported in rare schwannoma variants (15). Although an association between MC1R and schwannomas was not established, the findings of the present study raise the question whether pigmentation genes may modulate tumor phenotype, a hypothesis warranting further investigation. Ranson *et al* (16) described a case involving a 66-year-old man with a tumor sharing similar histological and immunophenotypic characteristics, including co-expression of S100, SOX10, and HMB45, consistent with the findings in the present case.

Pigmentation traits such as red hair, fair skin, freckling, and poor tanning capacity have long been recognized as genetically driven risk factors for both melanoma and non-melanocytic skin cancers particularly when combined with environmental exposure to ultraviolet radiation (17). MC1R, a G protein-coupled receptor expressed in cutaneous melanocytes located in the basal epidermal layer, plays a central role in regulating pigment production (18,19). Genetic variation within the MC1R gene contributes substantially to interindividual differences in skin phototype and pigmentation phenotype.

MC1R variants are typically categorized into two groups: Low-penetrance alleles (denoted as ‘r’) and high-penetrance alleles (‘R’) in relation to their association with red hair color and melanoma risk (20,21). Common ‘r’ alleles

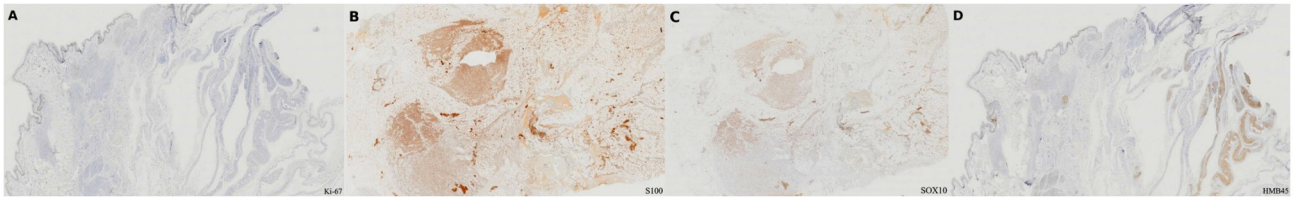

Figure 3. Immunohistochemical profile of the lesion. (A) Ki-67 showed very low proliferative index. (B) Diffuse nuclear and cytoplasmic positivity for S100 in the melanocytic population. (C) Nuclear expression of SOX10 in the neoplastic cells. (D) Focal positivity for HMB-45 predominantly in the superficial dermis.

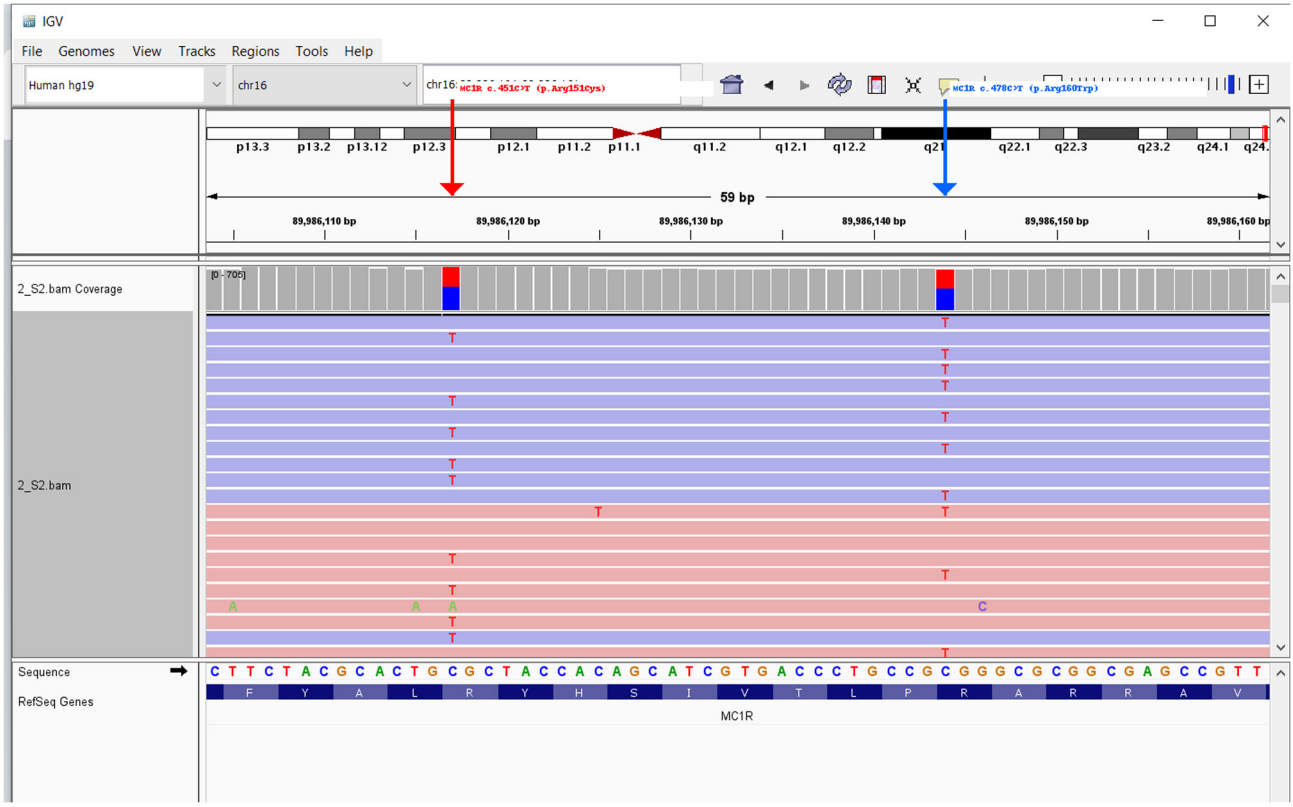

Figure 4. Genomic visualization of MC1R variant using Integrative Genomics Viewer. Snapshot of next-generation sequencing data aligned to the human genome (hg19), showing a heterozygous variant in the MC1R gene. The base substitution is visualized as a T peak in both forward and reverse reads. MC1R, melanocortin 1 receptor.

include Val60Leu, Val92Met, and Arg163Gln, while 'R' alleles, such as Asp84Glu, Arg142His, Arg151Cys, Ile155Thr, Arg160Trp, and Asp294His, are more strongly associated with phenotypic traits and increased susceptibility to skin malignancies (20).

In the current case, genetic analysis identified two high-risk MC1R alleles (Arg151Cys and Arg160Trp), both categorized as 'R' variants. Compound heterozygosity for R alleles is linked to fair phototype, high nevus count, and increased melanoma susceptibility. Both variants have been shown to exert dominant-negative effects by impairing MC1R receptor trafficking and downstream cAMP signaling (22). This genotype aligns with findings by van der Poel *et al* (23), who demonstrated a positive association between the 'R/R' genotype and increased total nevus count. Consistently, the patient in the present case had >30 nevi and a large back-located GCMN. Further supporting this association, a more recent study involving 175 healthy carriers of MC1R variants reported that individuals with 'R' alleles tend to develop larger nevi, particularly on the back and upper limbs. Moreover, their nevi often displayed dermoscopic features such as visible vascular structures, globules, and pigmented spots (24). These features were also observed in the present case, reinforcing the phenotypic impact of the compound 'R' genotype on nevus morphology and distribution. The limitations of the present case report include its basis in a single patient, the absence of functional validation or familial segregation studies, and the analysis of only germline DNA; somatic alterations in lesional tissue remain unknown. Despite these limitations, the case illustrated the integrative value of combining clinical imaging and genomic data. In conclusion the present case emphasized that personalized surveillance of patients with GCMN benefits from integration of AI-assisted dermoscopy, histopathology, and germline genetics. The compound heterozygous MC1R variants may explain the nevus burden of the patient and justified intensified follow-up. AI technology allowed precise, noninvasive monitoring, while

histology ruled out melanoma and guided management. An integrative, multidisciplinary approach should be considered standard for high-risk GCMN patients, as it enhances early detection and supports informed clinical decisions.

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Availability of data and materials

The data generated in the present study may be found in ClinVar under accession numbers SUB15686128 and SUB15686145.

Authors' contributions

PV recruited the patients. IY, PV, ZK and SP collected clinical and biological data. ZK performed the molecular analysis. PV and IY were responsible for diagnosis and treatment of the patient. ZK analyzed the data. PV, ZK, SP and IY were involved in the writing and revision of the manuscript. SP and IY reviewed and revised the manuscript. All authors read and approved the final manuscript. ZK and PV confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was approved (approval no.755/19.12.2023) by the Ethics Commission of the Medical University-Pleven, (Pleven Bulgaria). Written informed consent for participation was obtained from the patient.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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