European Journal of Endocrinology, 2025, **193**, K5–K10
https://doi.org/10.1093/ejendo/lvaf152
Advance access publication 29 July 2025
Brief Report

Uniparental disomy leads to a novel cause of *MC2R*-related familial glucocorticoid deficiency type 1

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Abstract

Familial glucocorticoid deficiency type 1 (FGD1) is a rare autosomal recessive disease caused by pathogenic variants in the *MC2R* gene. This case report presents the first documented instance of FGD1 caused by a homozygous 1.421-kb deletion affecting the non-coding promoter region of *MC2R*. The patient, a 9-year-old girl, presented with severe cortisol insufficiency and hyperpigmentation starting at birth. Genetic testing initially missed the deletion, as standard whole-exome sequencing in 2016 did not include a copy number variation analysis. However, a whole-genome sequencing analysis in 2024 identified the deletion. The variant was inherited through paternal uniparental disomy (UPD), a rare genetic mechanism that caused the homozygous state. This case underscores the value of utilizing current genetic testing approaches, especially in cases where clinical features strongly suggest a genetic etiology despite inconclusive initial genetic testing results. Additionally, it highlights the need to consider non-coding regions and UPD in genetic diagnostics.

Keywords: *MC2R*, UPD 18, non-coding, exon 1, glucocorticoid deficiency, FGD1

Significance

To date, only variants in the coding exon 2 of the *MC2R* gene have been reported to cause familial glucocorticoid deficiency type 1 (FGD1). This report describes the first case of FGD1 caused by a homozygous deletion in the non-coding promoter region of the *MC2R* gene, inherited via paternal uniparental disomy (UPD), resulting in severe cortisol insufficiency and hyperpigmentation. Initial whole-exome sequencing in 2016 failed to detect the deletion, but whole-genome sequencing in 2024 revealed it. The findings emphasize the critical role of applying current genetic testing in cases with strong clinical indicators, as well as the importance of considering non-coding regions and UPD in genetic diagnostics for improved endocrine disease management.

Introduction

Familial glucocorticoid deficiency type 1 (FGD1; OMIM #202200) is a rare autosomal recessive disease caused by pathogenic variants in the *MC2R* gene, encoding the adrenocorticotropic hormone (ACTH) receptor. Consequently, this condition leads to ACTH resistance, resulting in adrenocortical failure characterized by low plasma cortisol levels despite elevated plasma ACTH concentrations. Familial glucocorticoid deficiency type 1 often manifests within the first days or weeks of life, with life-threatening symptoms of cortisol insufficiency, including hypoglycemia, convulsions, and prolonged jaundice, as well as marked hyperpigmentation. A later, childhood onset has also been observed, with additional symptoms including hypothyroidism, tall stature, and recurrent infections.[1,2] Additional mineralocorticoid insufficiency is exceedingly rare; however, transient salt wasting or dilutional hyponatremia occurs in some cases, occasionally resulting in misdiagnosis of adrenal hypoplasia.[2-4]

The *MC2R* gene is located on the short arm of chromosome 18 and comprises two exons. The first exon is non-coding and lies within the 5-prime untranslated region (5′ UTR) of the gene, while exon 2 encodes the full coding sequence of the receptor.[5] Although exon 1 is non-coding, it forms part of the gene's promoter region, also containing the transcription start site.[5] To the best of our knowledge, all pathogenic *MC2R* variants reported to date in the literature and genetic variant databases such as HGMD, Decipher, and ClinVar are located within the coding exon 2.

This report details an FGD1 case with disease onset in early infancy and a novel homozygous 1.421-kb deletion affecting the *MC2R* promoter region, encompassing non-coding exon 1. The case highlights the importance of considering non-coding regions in the genetic diagnostic process when FGD1 is clinically suspected. Furthermore, it illustrates how uniparental disomy (UPD) can lead to disease manifestation in a recessive disorder, even when only one parent is a carrier of the variant.

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Received: December 19, 2024. **Revised:** March 4, 2025. **Editorial Decision:** July 21, 2025

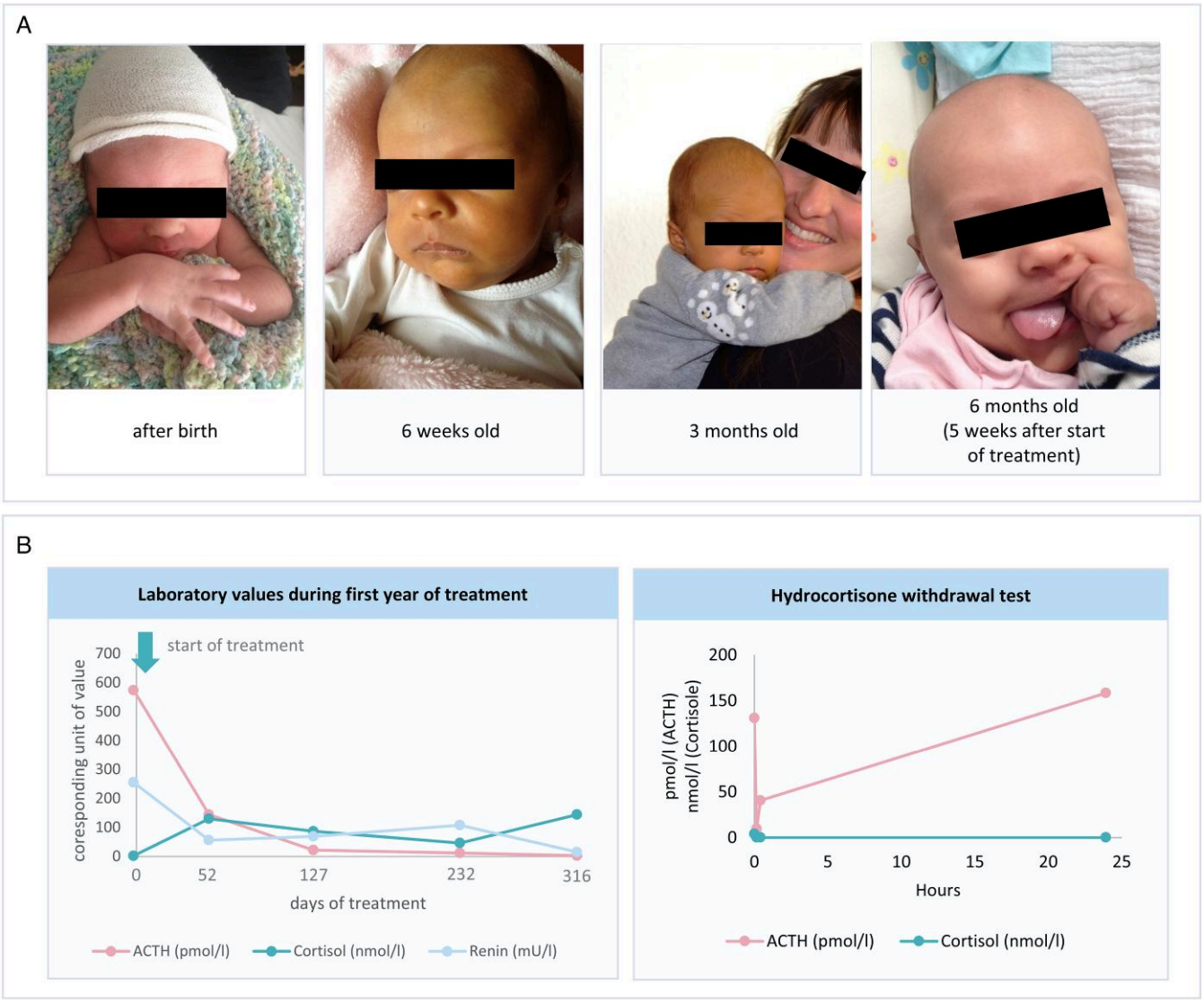

Figure 1. (A) Skin tone during the first months of age. Hyperpigmentation resolved quickly after start of hydrocortisone treatment. (B) Cortisol, ACTH, and renin values of the patient. Left panel: values during the first year of treatment, starting at first presentation, when the diagnosis was made at 5 months of age. Right panel: values of cortisone withdrawal test at age 8 years, showing no endogenous cortisol response.

Case presentation

The patient is a 9-year-old girl, born to non-consanguineous parents of European descent at 38-week gestation after an uneventful pregnancy (birth weight 2780 g [18th percentile], birth length 50 cm [43th percentile]). She first presented with recurrent hypoglycemic episodes starting from 12 h after birth. After glucose infusion and transition to oral maltodextrin supplementation, no further episodes of hypoglycemia were recorded after the third day of life. Pronounced jaundice with elevated bilirubin serum levels was observed, although liver enzyme elevations were mild and liver sonography was unremarkable. However, despite spontaneously decreasing bilirubin levels, the baby's intensely dark skin tone persisted, and the mother reported that, because of this dark skin color, she was repeatedly asked by both health professionals and friends about the ethnicity of the child's father. Years later, the parents still recall this as a cause of significant additional distress on top of their concerns about their child's health at the time.

Differential diagnosis of hyperpigmentation was mentioned but not further investigated. In the course of preparation for a liver biopsy, an elevated thyroid-stimulating hormone (TSH) level was found in the patient, leading to referral to pediatric endocrinology.

Diagnostic assessment and treatment

On presentation, the skin of the 5-month-old girl clinically appeared hyperpigmented rather than jaundiced (Figure 1A) and blood tests revealed highly elevated ACTH and renin levels in the complete absence of cortisol, as well as all adrenal and ovarian steroids (Dehydroepiandrosterone sulfate [DHEAS], androstenedione, 17-Hydroxyprogesterone [17-OHP], estradiol). Electrolytes were normal; aldosterone levels were low. Anti-adrenal antibodies were negative. Liver enzyme and bilirubin levels were still elevated (Table 1). Diagnostics ruled out Wilson's disease and viral hepatitis. An abdominal ultrasound revealed normal internal female sex organs as well as apparently normal adrenal glands.

In light of the adrenal insufficiency, treatment with hydrocortisone was initiated. Additionally, despite normal electrolyte

Table 1. Laboratory values of patient compared between and during treatment.

	Before treatment		4 months into treatment			
Laboratory values	Result		Result		Unit	Normal range
Adrenal cortex						
Cortisol	0.6	–	162.7	–	nmol/L	*
ACTH	574		22	+	pmol/L	1.04-10.8
Renin	255.2	+	69.3	+	mU/L	2.8-39.9
Aldosterone	149	–	<83	–	pmol/L	*
Sex hormones						
Androstenedione	<0.11		<0.11		nmol/L	
17-Hydroxyprogesterone	<0.10	–	<0.10		nmol/L	0.7-8.4
Thyroid gland						
Free triiodothyronine	6.82		–		pmol/L	2.91-8.85
Thyrotropin (TSH)	8.37		–		mU/L	0.61-10.7
Free thyroxine	13.84		–		pmol/L	12.3-23.5
Liver						
Alanine aminotransferase	1.42	+	0.61		µkat/L	0.07-0.82
Aspartate aminotransferase	3.63	+	1.14		µkat/L	0.24-1.29
Total bilirubin	28.8	+	4.9		µmol/L	<17.1
Bilirubin, indirect	21.1	+	<15.4		µmol/L	<15.4
Electrolytes						
Potassium	5.46		5.17		mmol/L	3.7-5.7
Sodium	138.6		138.6		mmol/L	135-145

Laboratory values of the patient, values taken before the diagnosis was made and after 4 months of treatment.
+ and – indicate values deviating from the reference range (+ elevated, – decreased). Values show normalization of ACTH and renin, as well as liver markers.
*No normal range given by the local laboratory for this age.

levels, fludrocortisone was started due to high renin and low aldosterone levels as a precautionary measure to prevent a salt-wasting crisis. Subsequently, ACTH levels quickly normalized, liver enzymes and bilirubin decreased, and hyperpigmentation also rapidly improved (Figure 1B and Table 1). Therefore, the liver biopsy was canceled, and hydrocortisone substitution was titrated between 8 and 14 mg/m² body surface per day throughout the following years. Currently, fludrocortisone is given in a dose of 0.025 mg per day and the family is instructed to give a stress dose of hydrocortisone in times of fever or physical stress. An ACTH stimulation test confirmed primary adrenal insufficiency at the age of 3 years. A hydrocortisone withdrawal trial at 8 years revealed still no intrinsic cortisol production, along with elevated ACTH levels (Figure 1B). Currently, there is no hyperpigmentation, and no salt wasting has occurred. The patient is thriving well, with good physical health, good school performance, and no increased susceptibility to infections. Puberty has not yet started at the age of 9 years.

Based on the clinical presentation and laboratory findings, the patient was suspected to have an underlying genetic cause for her glucocorticoid deficiency, and ACTH resistance was considered. Consequently, she underwent trio whole-exome sequencing (WES) at 11 months of age in 2016. Analysis of the trio-WES data did not include a copy number variation (CNV) analysis. Consequently, as a complement to the trio-WES, multiplex ligation-dependent probe amplification (MLPA) was performed, covering exon 2 of *MC2R* to identify possible CNVs in the coding exon of the gene. This was negative.

In 2024, a trio whole-genome sequencing (WGS) analysis that included a CNV analysis was undertaken and enabled the identification of a homozygous 1.421-kb deletion (seq[GRCh38] 18p11.21 (13914685 × 2,13914686_13916107 × 0,13916108 × 2)) affecting the non-coding *MC2R* promoter region (Figure 2A). This deletion encompassed the non-coding exon 1, explaining why it was not detected by the 2016 MLPA analysis. The deletion was absent from gnomAD v4 and genetic variant databases (ClinVar, HGMD, and Decipher). Intriguingly, only the patient's father was a heterozygous carrier of the deletion. Use of an in-house tool, altAFplotter,[6] revealed that 90.7% of the patient's chromosome 18 was covered by regions of homozygosity, suggesting that a paternal UPD (Figure 2B) was the probable underlying cause of the homozygous deletion in the patient. An additional microsatellite analysis on chromosome 18 confirmed the paternal UPD. Given that the homozygous occurrence of the deletion was caused by a UPD, we considered it a *de novo* event. This, together with the fact that the deletion affected the 5′ UTR of a gene in which loss-of-function variants have been reported as pathogenic, allowed us to classify the deletion as likely pathogenic according to the guidelines of the American College of Medical Genetics[7] and the Association for Clinical Genomic Science (https://www.acgs.uk.com/media/12533/uk-practice-guidelines-for-variant-classification-v12-2024.pdf, accessed: 12/11/2024).

Whole-genome sequencing identified no additional pathogenic variants in known disease-causing genes that may have contributed to the patient's symptoms, especially not in genes affecting aldosterone synthesis (*CYP11B2*, *SF-1*, *CDKN1C*) or key steroidogenesis-related genes (eg, *STAR*, *CYP11A1*, *HSD3B2*, *CYP21*).

Discussion

This report presents the first documented case of FGD1 caused by a likely pathogenic variant in the non-coding region of the *MC2R* gene, thereby expanding the spectrum of genetic alterations leading to FGD1. Given that *MC2R* is only expressed in the adrenal gland and not in accessible tissues such as the skin or blood, we were not able to perform a gene expression analysis to determine the possible effect of the variant. This is a limitation of our study; however, as the deletion affects the *MC2R* promoter region and eliminates the transcription start site, its functional impact can be inferred based on the

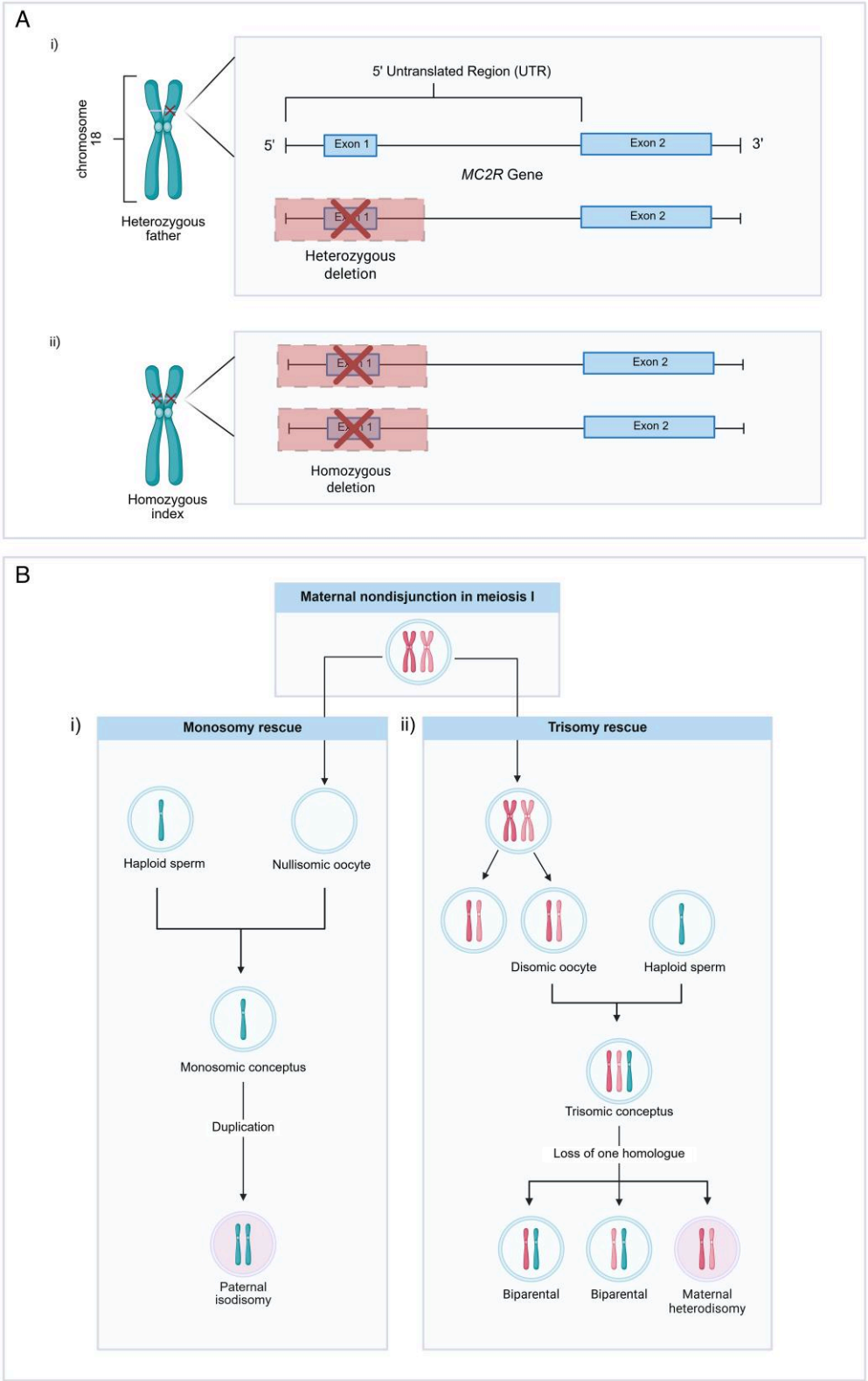

Figure 2. (A) Schematic representation of the *MC2R* gene and the identified deletion. (i) The heterozygous deletion (indicated by the red box) in the unaffected father, encompassing non-coding exon 1 within the 5′ untranslated region of the *MC2R* gene on the short arm of chromosome 18. (ii) The paternally inherited deletion, occurring homozygous in the index case due to uniparental disomy. (B) Common mechanisms of UPD. (i) Monosomy rescue mechanism: maternal nondisjunction in meiosis I leads to a nullisomic oocyte. Fertilization with a normal sperm forms a monosomic conceptus. Duplication of the single chromosome results in paternal isodisomy. (ii) Trisomy rescue mechanism: maternal nondisjunction in meiosis I results in the production of a disomic oocyte. Subsequent fertilization with a normal (haploid) sperm leads to the creation of a trisomic conceptus. In approximately one-third of cases, trisomy rescue may occur randomly, resulting in UPD, with both retained chromosome copies originating from the same parent. This is known as heterodisomy. Figure created in BioRender.com.

well-established role of promoter sequences in gene regulation. Pathogenic variants, including deletions, affecting promoter regions of other genes have been shown to significantly reduce or abolish gene expression,[8,9] supporting the link between this deletion, a possible complete loss, or severe reduction in *MC2R* gene expression and our patient's observed clinical phenotype.

Compared with previously reported coding sequence variants, this promoter deletion provides new insight into the mechanisms by which *MC2R* disruption leads to adrenal insufficiency. Clinically, this case is typical for patients with FDG1, including hyperpigmentation, hypoglycemic episodes, and jaundice with elevation of liver parameters, with an additional disturbance of the renin–angiotensin system and complete lack of sex steroids, which is not seen in all patients, but in some.[3] The possible complete absence of *MC2R* expression in this patient underscores the broader endocrine consequences of a nonfunctional ACTH receptor, particularly in mineralocorticoid regulation and sex steroid deficiency—features that are not universally observed in all FGD1 patients. As discussed by Lin et al.,[3] ACTH receptors in the zona glomerulosa play a facilitative role in mineralocorticoid synthesis, and the possible complete absence of ACTH receptor expression in this patient may have contributed to the pronounced effect, particularly given that this mechanism is more significant in cases of relative adrenal hypoplasia, such as in young children or critically ill patients—both of which apply here. Alternative explanations for hypoaldosteronism, such as secondary adrenal failure, genetic variants affecting aldosterone synthesis, or congenital adrenal hypoplasia, are unlikely in this patient and can largely be ruled out based on the available clinical and genetic findings.

From a communication perspective, this case highlights the need for medical professionals to take parental concerns seriously to avoid unnecessary distress. The mother faced repeated, unfounded questions about paternity based on the baby's skin color, which not only added emotional strain but also delayed the patient's diagnosis, as pathological hyperpigmentation was dismissed. The dismissal of parental concerns by healthcare professionals is not unique to our case and future research quantifying these emotional impacts through comprehensive surveys could help healthcare professionals better understand and address the psychological toll on families.

The involvement of UPD in this case introduces an additional layer of complexity. Uniparental disomy occurs when both copies of a chromosome are inherited from one parent, potentially leading to the expression of recessive disorders.[10] In this instance, the UPD caused the paternally inherited heterozygous variant to manifest as a homozygous deletion in the child. While UPD is a relatively rare genetic mechanism (prevalence between 0.05% and 0.2% in a genetic diagnostic setting[11,12]), it should be considered during genetic diagnosis and analysis, especially in cases like ours where the patient has a recessive disorder and only one parent is a carrier of the pathogenic variant. Although not standard in all diagnostic laboratories, UPDs can be readily identified with the help of open-source tools, such as the altAFplotter[6] (freely available at https://altafplotter.uni-leipzig.de/), that use WES, panel, or WGS data (.vcf-files) as input. As such, we have integrated UPD detection into our laboratory's next-generation sequencing diagnostic workflow and encourage other laboratories to do the same.

Certain limitations should be acknowledged in this case, particularly concerning the initial genetic testing methods employed. The MLPA kit used only covered the coding exon 2 of *MC2R*, while the deletion occurred in the non-coding promoter region. Moreover, CNV analysis was not included in our standard WES pipeline available in 2016, though it is now a routine part of WES analyses. Had current WES analysis pipelines and enrichment kits been available at the time of testing, the deletion would have been identified more readily, although pinpointing its exact size and breakpoints would still have required WGS or targeted long-read sequencing.

Given recent advancements in genetic testing, patients with suspected FGD1 and previous negative results should consider re-analysis of their existing WES data or pursue new WES or WGS testing that covers exon 1 of *MC2R* and includes a CNV analysis. WGS, or targeted long-read sequencing of *MC2R*, may be particularly useful in cases where only one pathogenic variant was identified in exon 2, as older techniques may have missed potential variants in the non-coding region. This could uncover previously undetected genetic variants that are critical for a more accurate diagnosis. In settings where WGS or long-read sequencing is not available to identify a second *MC2R* variant, we suggest doing a simple targeted qPCR of exon 1 to at least rule out a deletion similar to the one reported here.

Overall, we recommend WES with CNV analysis as the first-line diagnostic tool over targeted panels, which may initially be cheaper but may not cover all clinically relevant genes, especially in cases where the clinical diagnosis is unclear but in which an underlying genetic cause is suspected. In terms of accessibility, WES is now widely available in many clinical genetics centers and laboratories, making it a practical choice for most healthcare settings. Targeted gene panels may only be more useful and cost-effective as a first-line diagnostic approach when a patient's clinical picture is clear and highly specific for a certain gene/set of genes and when these panels include coding and non-coding regions of the genes of interest. Importantly, the herein-reported deletion would have also been identified using our current in-house WES analysis, highlighting the utility of up-to-date WES as a good first-line diagnostic approach.

In conclusion, this case demonstrates the value of utilizing current genetic testing approaches to identify novel genetic variants in cases with previous, negative genetic testing but clinical features strongly suggestive of a genetic etiology. Furthermore, it emphasizes the necessity of considering non-coding regions and UPD in genetic diagnostics.

Acknowledgments

The authors sincerely thank the family and the patient for providing us with information and photographs. The authors acknowledge the use of AI and AI-assisted technologies in the writing process. During the preparation of this work, the authors used ChatGPT (Open AI, San Francisco, California, USA) selectively to improve readability and language. After using this service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Funding

A.C.M.-N. and R.P. did not receive any public or commercial funding. This work was funded by the German Research Foundation (Deutsche Forschungsgemeinschaft) (project number 493646873—MD-LEICS) for E.W.

Authors' contributions

A.C.M.-N. and E.W. were involved in writing—original draft, investigation, and writing—review and editing. R.P. was involved in writing—review and editing and investigation.

Amica Müller-Nedebock (Investigation [equal], Writing—original draft [equal], Writing—review & editing [equal]), Eric Wenzel (Investigation [equal], Writing—original draft [equal], Writing—review & editing [equal]), and Roland Pfäffle (Investigation [equal], Writing—review & editing [equal]).

Conflict of interest: None declared.

Ethical approval

This research was approved by the Ethics Committee of the University of Leipzig (402/16-ek) and in accordance with the Declaration of Helsinki, the Bioethics Convention (Oviedo), and the EU Clinical Trials Directive. Written informed consent for the publication of clinical details and clinical images was obtained from the parents of the patient.

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