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CASE REPORT

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Pharmacogenotyping disproves genetic cause of drug-related problems in family history: a case report

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Abstract

Background In clinical practice, family medication history is not routinely assessed as part of a patient's family health history (FHH). The information is self-reported and can depend on the individual's subjective perception. To illustrate how pharmacogenetic (PGx) testing results could be used to validate self-reported family medication history on drug-related problems (DRP), as well as to inform medication-related decisions, we herein present a case involving ten members of the same family.

Case Presentation Prior to a planned surgery, a preemptive PGx panel test was performed for a nine-year-old girl due to self-reported family medication history. The PGx panel test was also performed for her three siblings, parents, and grandparents. The focus was directed to the paternal grandmother, as she reported DRP from the hypnotic agent propofol, and to the maternal grandmother, as she described DRP after the administration of codeine and tramadol. A commercial PGx panel test of 100 variations in 30 different genes was conducted and analyzed focusing on genetic variants in cytochrome P450 enzyme 2B6 (*CYP2B6*), and *CYP2D6* as they are involved in the biotransformation of propofol and the bioactivation of codeine and tramadol, respectively. The girl was identified as (1) CYP2B6 intermediate metabolizer (IM) with reduced enzyme activity and (2) CYP2D6 poor metabolizer (PM) with no enzyme activity. Regarding the planned surgery, it was recommended (1) to carefully titrate propofol dosage with increased monitoring of potential DRP and (2) to avoid opioids whose activation is mediated by CYP2D6 (e.g. codeine and tramadol). Further PGx testing revealed (1) the paternal grandmother as CYP2B6 normal metabolizer (NM) and (2) the maternal grandmother as CYP2D6 NM.

Conclusion The original trigger for PGx testing was the self-reported, conspicuous family medication history of DRP reported by the grandmothers. However, the girl's genotype predicted phenotypes of *CYP2B6* IM and *CYP2D6* PM, differed from the grandmothers'. With this exemplary case, we propose that hereditary concerns based on self-reported information on DRP should be verified by a PGx panel test, when the respective drug exhibits a PGx association. Also, the girl's PGx testing results provided important medication recommendations, which were considered perioperatively by the anesthetist suggesting to use PGx testing results preemptively to inform medication-related decisions.

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Keywords Family medication history, Pharmacogenetics, Anesthetics, Analgesics, Opioids, CYP2D6, CYP2B6

Background

The assessment of a patient's family health history (FHH) can comprise different components depending on the purpose of collection and is an integral element of clinical practice. A differentiation can be made between family medical history and family medication history. Up to now, FHH predominately comprises the collection of medical information for health-risk evaluations and prediction of familial-related diseases (e.g. hereditary cancer susceptibility) [1–4]. The assessment of family medication history is, however underutilized, although one should not strictly distinguish between medical history and medication history, as these interdepend [5, 6]. Genes and therefore inherited information can determine both, disease risk and changes in drug metabolism [7–9]. Accordingly, the information on drug-related problems (DRP) in the family, i.e. therapy failure (TF) or adverse drug reaction (ADR), could support therapy decisions by physicians and pharmacists [10].

In anesthesiology, FHH is of great importance comprising both family medical and medication history. In the preoperative assessment and patient preparation, FHH is collected in a standardized way to assess the risk of malignant hyperthermia, bleeding tendency, and DRP. The overall objective is to ensure safe and effective perioperative anesthesia and analgesia [11–14]. Though, family medication history has one major constraint, since it is mostly self-reported and cannot be validated. Especially if the information is communicated orally by third parties (e.g. family members without written records), incorrect or incomplete information might result [15–18]. This potential information bias represents a challenge in clinical practice, as it is not evident if and how to consider self-reported information in therapy decisions [19]. Moreover, there are no guidelines on how to consider family medication history in pharmacotherapy so far.

Verification of a self-reported suspicion of a DRP could involve a pharmacogenetic (PGx) test. PGx is an area of personalized medicine that aims to tailor drug therapy to individual patients. PGx testing can target inherited genetic variations associated with alterations in the pharmacokinetic (PK) and pharmacodynamic (PD) behavior of certain drugs [20]. Hitherto, the effects of genetic variability on the PK and the PD of drugs for several indications have been reported [21].

The most important enzyme system for phase I metabolism is the cytochrome P450 (CYP) superfamily. Genetic polymorphisms in genes coding for specific CYP enzymes are associated with changes in drug disposition and even therapy outcomes (ADR/TF).[22] As an illustration, for several drugs, the highly polymorphic cytochrome P450 enzyme 2D6 (*CYP2D6*) is of great therapeutic relevance. CYP2D6 bioactivates certain opioids like tramadol and codeine catalyzing the formation of their analgesically active metabolites (O-desmethyltramadol and morphine), which exhibit an approximately 30-fold higher affinity for particular opioid receptors than the parent molecules [22]. Different alleles of *CYP2D6* translate into altered enzyme activity, that can be classified into four major phenotypes [23]. An individual with normal enzyme activity (normal function alleles) is called a normal metabolizer (NM); an increased enzyme activity (duplicated or multiduplicated normal function alleles) results in an ultrarapid metabolizer (UM); a decreased enzyme activity (normal function allele + decreased function allele or loss-of-function allele) predicts an intermediate metabolizer (IM); and low to nearly no enzyme activity (decreased function or loss-of-function alleles) is found in a poor metabolizer (PM) [24, 25]. For opioids like tramadol and codeine, the UM phenotype can lead to higher plasma concentration of the active metabolite, resulting in a rapid onset of drug effect with the risk of ADR, whereas a PM could suffer from insufficient analgesia (TF) due to limited bioactivation [26]. In general, PGx variability concerning opioids is well-documented and there are dosing guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) [27, 28].

For intravenous anesthetics, no PGx dosing recommendations exist because of limited evidence. Though, there is evidence for drug-gene-interactions influencing the metabolism of propofol, which is the most commonly used short-acting anesthetic for intravenous administration [29]. Indeed, a high interindividual variability in drug response has been observed and it is known that propofol is extensively metabolized by CYP enzymes [30, 31]. Hereby, CYP2B6 catalyzes the hydroxylation of propofol to 4-hydroxypropofol in humans and therefore significantly contributes to the detoxification of propofol [32, 33]. Thus, genetic variation affecting *CYP2B6* activity might influence the PK behavior of propofol [34]. A special focus is directed to the single nucleotide polymorphism (SNP) rs3745274 in *CYP2B6*. Multiple studies associated this SNP with a decrease in biotransformation rate and higher plasma concentrations of propofol, which could then influence clinical outcomes [35–38]. As a potential consequence ADRs (e.g. prolonged sedation, bradycardia, hypotension) might be observed.

However, not only variations in genes coding for phase I enzymes (e.g. CYP2D6, CYP2B6), but also for phase II enzymes (e.g. catechol-O-methyltransferase (COMT)),

receptors (e.g. opioid receptor μ1 (OPRM1)) or transporters (e.g. ATP binding cassette subfamily B member 1 (ABCB1)) were reported in single studies to alter drug response and may therefore be considered in a PGx panel test approach [39, 40].

Taken together, a PGx panel test could be used to validate DRP in family histories to further inform and support clinical decision-making. To illustrate how PGx testing results are interpreted in the context of a self-reported family medication history and are adopted in an interprofessional healthcare setting, we present an exemplary case series.

Family case series presentation

A PGx panel test was conducted for three generations of a family, including a nine-year-old girl and her first-degree relatives (three siblings, and parents) and second-degree relatives (maternal and paternal grandparents). All participants or parents as legal representatives for their children gave written informed consent for PGx testing and health data retrieval. The adults were additionally part of an observational case series study approved by the local ethics committee (ClinicalTrials.gov identifier: NCT04154553).

PGx panel test was conducted with a buccal swab sample by the commercial provider Stratipharm® by humatrix AG (Pfungstadt, Germany). Polymerase chain reaction (PCR) is applied using Life Technologies QuantStudio 12k flex (Thermo Fisher, MA, USA) with the respective optimized and commercially available chemistry. The panel test includes 100 polymorphisms in 30 genes and an assessment of CYP2D6 Copy Number Variations (CNV) using probes in exon 9 and intron 6, respectively.

Pharmacogenotyping of the girl

The case started with a preemptive PGx panel test for the girl. She suffered from a painful cartilaginous exostosis extending from the medial distal femoral metaphysis and therefore had to undergo elective surgery for removal. In advance of the surgery, her mother contacted the pharmacy for a preemptive PGx panel test, because she was concerned due to their family medication history. In the past, the paternal grandmother underwent hip arthroplasty under anesthesia with propofol and reported postoperative ADR including prolonged sedation and a decrease of vital parameters, especially hypotension. Additionally, the maternal grandmother self-reported TF after intake of codeine and tramadol in the context of surgeries due to breast cancer.

At the time of PGx testing, the girl did not have other diseases or co-medication. Therefore, the focus of preemptive PGx testing was directed to the determination of genetic variation in *CYP2B6* and *CYP2D6*. Also, *ABCB1*, *COMT*, and *OPRM1* were considered, as they are reported to potentially impact the response to anesthetics and analgesics [28, 41, 42].

Interpretation of the genotype predicted the girl's phenotype as CYP2D6 PM (homozygous *4 allele carrier). For CYP2B6, the girl's phenotype was predicted as IM (*2/*6 or *2/*7 allele carrier) as she was heterozygote for the SNP rs3745274, which resides on star allele 6, as well as *7 allele, however, both are attributed with decreased function [43, 44]. In addition, the girl exhibited a heterozygosity for rs1128503 in *ABCB1.* For rs4680 and rs1799971 in the *COMT* and *OPRM1*, respectively no variation was detected. The selected PGx results are summarized in Table 1.

Pharmacogenotyping of the family

The girl exhibited relevant genetic variation, which suited to the self-reported medication history and the suspected drug-gene-interaction (DGI) of the grandmothers (paternal grandmother: propofol and *CYP2B6*; maternal grandmother: codeine/ tramadol and *CYP2D6*). Therefore, the same PGx panel test was conducted reactively for the grandmothers. The test identified the paternal grandmother as CYP2B6 NM (homozygous *1 allele carrier) and the maternal grandmother as CYP2D6 NM (homozygous *1 allele carrier). For the reconstruction of the inheritance of the girl's genetic variations, PGx panel test was then also conducted for further family members.

Table 1 Selected results of girl's pharmacogenotyping

Gene	Variant	Genotype	Diplotype	Predicted phenotype
ABCB1	rs1128503 c.1236 T > C	T/C	NA	substance specific function
COMT	rs4680 c.472 G > A	G/G	NA	substance specific function
CYP2B6	rs8192709 c.64 C > T	C/T	*2/	decreased function (IM)
	rs3745274 c.516 G > T	G/T	*6 or *7	
CYP2D6	rs1065852 c.100 C > T	T/T	*4/	no function (PM)
	rs3892097 c.506-1 G > A	A/A	*4	
OPRM1	rs1799971 c.118 A > G	A/A	NA	substance specific function

Abbreviation: IM: Intermediate metabolizer; NA: Not applicable; PM: Poor metabolizer. Note: For the assessment of the respective predicted phenotype, it is necessary to know that no genetic variation was detected in *CYP2B6* rs28399499 (functional star alleles *18) and *CYP2D6* rs35742686, rs5030655, rs5030867, rs5030865, rs5030656, rs201377835, rs28371706, rs59421388, rs28371725 (functional star alleles *3, *5, *6, *7, *8, *9, *10, *14, *17, *29, *41, *114). CNV in exon 9 and intron 6 were also tested

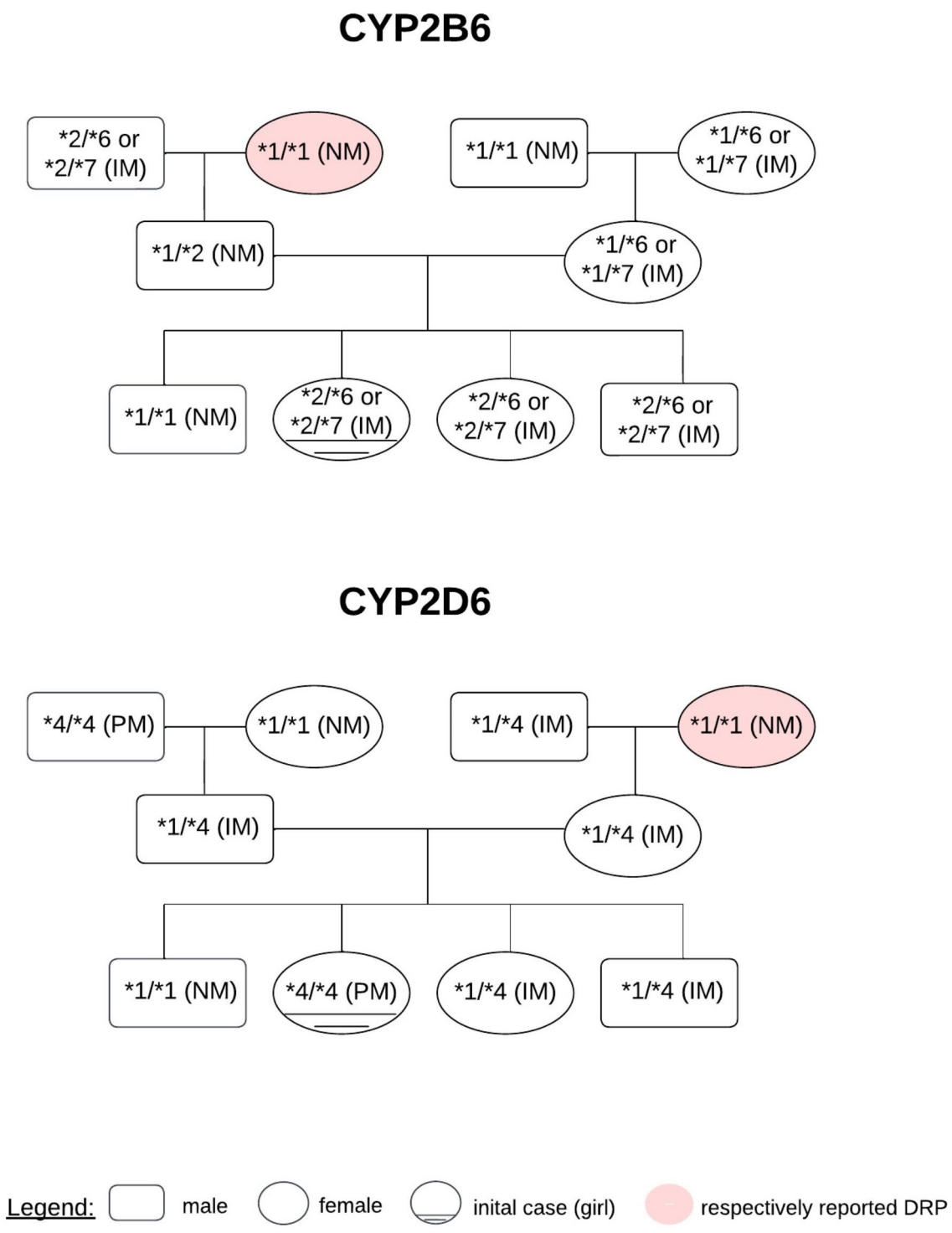

Fig. 1 (See legend on next page.)

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Fig. 1 Family's pedigree of the inheritance of *CYP2B6* and *CYP2D6*.**Note**: For *CYP2B6*, the girl's father was identified as heterozygous *2 allele carrier (NM), inherited from the paternal grandfather. The girl's mother was identified as heterozygous *6 or *7 allele carriers (IM), which originated from the maternal grandmother. The firstborn sibling got both normal function alleles from his parents resulting in a homozygous *1 allele carrier (NM). The other two siblings were identified as *2/*6 or *2/*7 allele carriers (IM). For *CYP2D6*, the girl's parents were identified as heterozygous *4 allele carriers (IM) with the loss-of-function alleles originating from both grandfathers. Again, the firstborn sibling was identified as a homozygous *1 allele carrier (NM). The other siblings got one loss-of-function allele and one normal function allele resulting in heterozygous *4 allele carriers (IM), similar to the parents. **Abbreviations**: DRP: Drug-related problem; IM: Intermediate metabolizer; NM: Normal metabolizer; PM: Poor metabolizer

The family's pedigrees of the inheritance of *CYP2B6* and *CYP2D6* are illustrated in Fig. 1.

Further selected PGx results of the family regarding genes potentially contributing to the metabolism of selected analgesics and opioids (*ABCB1*, *COMT*, *CYP2C8*, *CYP2C9*, *CYP2C19*, *CYP3A4*, *CYP3A5*, *NAT-2*, *OPRM1*) are summarized in Additional File 1.

Discussion

Interpretation of the girl's PGx results in regard to the surgery

The decisive factor for the girl's preemptive PGx test was the family medication history concerning DRP with propofol, codeine, and tramadol. Propofol is the most commonly used hypnotic agent for anesthesia, and the opioids codeine and tramadol are frequently used for perioperative pain management in adults and children over 12 years [45–47]. Moreover, all substances exhibit a PGx association (www.pharmgkb.org). For codeine and tramadol, there are even existing dosing recommendations based on genetic variation in *CYP2D6* [27, 28]. Thus, the involved pharmacist supported the mother's request to conduct a preemptive PGx test for the girl provided recommendations for safe and effective perioperative medication.

The girl's heterozygous variation in *CYP2B6* polymorphism rs3745274 is expected to lead to higher plasma concentrations of propofol due to a decreased biotransformation [35–37]. Thus, ADRs (e.g. prolonged sedation, hypotension) could possibly result. Moreover, a heterozygous variation in the *ABCB1* polymorphism rs1128503 was detected. *ABCB1* encodes the transmembrane p-glycoprotein (p-gp), which serves as an efflux transporter for numerous xenobiotics, including drugs (e.g. propofol) [48]. SNPs in *ABCB1* might therefore contribute to an interindividual drug response [49]. There is a study suggesting that children who are homozygote carriers of *ABCB1* polymorphism rs1128503 show an increased response to propofol and remifentanil [41]. However, this refers to a single study and has therefore a low level of evidence [50]. Also, it is unclear whether it is of relevance for children exhibiting heterozygosity for rs1128503.

In general, there are no clinical guidelines on how to consider genetic variations for intravenously administered anesthesia. In addition to *ABCB1*, also the study associations between propofol and *CYP2B6* are still limited (PharmGKB: Level 3) [50]. PharmGKB categorizes variant-drug combinations into levels of evidence ranging from 1 A (high evidence) to 4 (unsupported), with the CYP2B6-propofol combination on level 3 representing a low evidence which is based on single studies. At this point it is also important to mention, that propofol is the first-line anesthetic for intravenous administration in children and adults and has a high safety profile [51, 52]. Thus, we did not recommend switching to another anesthetic but rather using propofol with an increased awareness of potential ADRs and tight monitoring of dosage escalation.

Accordingly, the anesthetist decided to administer alfentanil (15 µg/kg) and propofol (3 mg/kg) for the induction of her anesthesia. Since no variation in *OPRM1* (rs1799971) was detected, no altered response to Alfentanil was expected. In a single study, the exhibited heterozygosity in *ABCB1* (rs1128503) was associated with an increased likelihood of ADR, as well as TF to sevoflurane [53]. Still, anesthesia maintenance was managed with nitrous oxide and sevoflurane. Normally, the anesthetist would have preferred total intravenous anesthesia (TIVA) with propofol and remifentanil for maintenance of anesthesia in this age group, but decided to further limit propofol administration, because of the known CYP2B6 IM status. At the end of the girl's surgery, propofol was once again administered (0.7 mg/kg) to ensure asleep extubation. According to the physician's anesthesia protocol, the awakening behavior was adequate. About one hour after the end of the surgery, the girl was already drinking. Vital parameters were perioperatively within normal range and did not indicate any exceptional alterations in drug response.

In addition, the girl was identified as *CYP2D6* homozygous *4 allele carrier (PM) with low to no enzyme activity at all, which is an important information for perioperative pain management. Codeine and tramadol are both bioactivated by CYP2D6. For CYP2D6 PM, it is expected that the bioactivation is strongly decreased and pain relief is limited [54, 55]. For this phenotype, the CPIC, as well as the DPWG guideline, recommend avoiding codeine and tramadol and switching to another opioid or a non-opioid analgesic, which is not metabolized by CYP2D6 [27, 28, 56]. Again, this information was considered perioperatively. In detail, it was decided to administer nalbuphine as the main opioid during surgery. After the surgery, analgesia was managed with paracetamol and ibuprofen, which were not affected by any of the known

PGx variability according to her testing results (for ibuprofen: CYP2C8 and CYP2C9 NM, see Additional File 1).

Validation of self-reported family medication history

Since genetic variations can be inherited and the girl's genetic profile suited to the observed DRP of the grandmothers, we presumed similar PGx results for them. However, the respective PGx profile did not match our expectations. The paternal grandmother was identified as CYP2B6 NM. Consequently, it was not possible to confirm the suspected DGI between propofol and *CYP2B6*. Also, the maternal grandmother was identified as CYP2D6 NM, so again we could not confirm the suspected DGI between *CYP2D6* and codeine/tramadol. Here, it is important to note that the self-reported DRP of the grandmothers might not be incorrect information, it was just not possible to associate the DRP with one of the tested genetic variations of the used panel test. There are other possible genetic markers, that were not part of the selected panel test (e.g. *UGT1A9*, *SLC22A1*), which is a limitation. Single variants of these genetic markers have been associated with a risk of propofol and tramadol toxicities, however, only based on limited evidence (PharmGKB: Level 3). The used panel test follows a targeted approach, since the selected gene variants are based on current recommendations and guidelines. This is also important as in Switzerland it is not allowed to provide excess information from PGx tests, e.g. disease risks, which are more likely to be detected using a less targeted approach like next generation sequencing (NGS).

Besides genetics, it is known, that several other factors can influence drug response, e.g. demographics, comorbidities, organ function, and drug-drug-interaction (DDI) [57, 58]. Likewise, self-reported information can be affected by various factors, e.g. unawareness, bad recall, psychological factors, and subjective perception of health-related events [59–65].

After PGx testing of further family members, it was possible to reconstruct the inheritance of the girl's genetic variations. For *CYP2D6*, both of her loss-of-function alleles (*4/*4) originated from the paternal and maternal grandfather (see Fig. 1). For *CYP2B6*, the *2 haplotype was inherited by the paternal grandfather, and the *6 or *7 haplotype by the maternal grandmother (see Fig. 1).

As summarized in Additional File 1, it was also possible to detect further genetic variations in the family (e.g. CYP2C9 PM status of the paternal grandfather, CYP2C19 IM status of all children), which should be considered for future pharmacotherapies. It should also be mentioned that both grandfathers already had surgical interventions with applied anesthetics and analgesics and did not report any DRP. Here, we want to emphasize that women experience in general more ADR than men [66, 67]. Additionally, pain perception also differs with gender [68, 69].

Based on this exemplary family case, we propose that family medication history and associated DRP should be collected as part of patients' FHH, not only by pharmacists, but also by physicians. Self-reported family medication histories concerning DRP with PGx associated drugs could be verified by a PGx test. In this case series, the PGx test was used as a validation for the family medication history and to inform medication decisions for the girl's perioperative management. For opioids, there are already existing clinical guidelines [27, 28], which facilitate PGx-based therapy decisions for healthcare professionals (HCP). The same applies to non-steroidal anti-inflammatory drugs (NSAID e.g. ibuprofen) [70], also used for postoperative pain management. For anesthetics, the evidence concerning PGx is limited. There is a CPIC guideline that provides therapeutic recommendations for potent volatile anesthetics and succinylcholine used in patients with variations in the ryanodine receptor 1 (*RYR1*) or the calcium voltage-gated channel subunit alpha 1 S (*CACNA1S*), which might affect susceptibility for the development of life-threatening malignant hyperthermia. Besides this exception, there are no clinical PGx guidelines for anesthetic agents. However, PGx testing results regarding anesthetics can also be used as an alert that potential DRP might occur with the clinical consequence of increased awareness and tight monitoring.

Conclusion

With this family case report, we firstly want to demonstrate that information on family medication history is important to collect, still, it should be verified. Concerning the involvement of PGx associated drugs, PGx panel testing can be used to verify that information by determining the hereditable component of DRP. However, the decision to apply a PGx panel test should be done on a person-by-person evaluation and should not be precluded given the opposite scenario (i.e. negative family medication history).

Secondly, PGx panel testing results can be useful to inform medication-related decisions preemptively, again, if the respective drug is PGx associated.

To conclude, we want to encourage HCPs to integrate verified information on family medication history into patients' FHH and to combine the information complimentary with a PGx panel test where applicable and useful. Both might contribute to improve medication safety and efficacy in clinical practice.

Abbreviations

ABCB1	ATP binding cassette subfamily B member 1
CACNA1S	Calcium voltage-gated channel subunit alpha 1 S
COMT	Catechol-O-methyltransferase

CYP2A7P1	Cytochrome P450 Family 2 Subfamily A Member 7 Pseudogene1
CPIC	Clinical Pharmacogenetics Implementation Consortium
CNV	Copy Number Variation
DDI	Drug-drug-interaction
DGI	Drug-gene-interaction
DPWG	Dutch Pharmacogenetics Working Group
HCP	Healthcare professionals
NGS	Next generation sequencing
NSAID	Non-steroidal anti-inflammatory drugs
OPRM1	Opioid receptor μ1
p-gp	P-glycoprotein
PharmGKB	Pharmacogenomics knowledge database platform
RYR1	Ryanodine receptor 1
SNP	Single nucleotide polymorphism
TIVA	Total intravenous anesthesia
UGT1A9	UDP-glucuronosyltransferase 1–9
UM	Ultrarapid metabolizer
SLC22A1	Solute-like carrier family 22 member 1 gene

Supplementary Information

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Supplementary Material 1

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Author contributions
KH, HM, CS: conceptualization and study design. AB, CS: investigation and interpretation of genotyping data. AB: writing original draft preparation. KH, HM, SA, CS: critical review and editing. HM, SA, CS: supervision. All authors have read and agreed to the published version of the manuscript.

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Data availability
The genetic data presented in this study are available on request from the corresponding author. The data are not publicly available for ethical and privacy reasons.

Declarations

Ethics approval and consent to participate
All ten patients provided written informed consent to use the data for research purposes. The six adult patients were part of the observational study "Pharmacogenetic Testing of Patients with unwanted Adverse Drug Reactions or Therapy Failure", which was conducted according to the guidelines of the Declaration of Helsinki and approved by the local ethics committee of "Ethikkommission Nordwest- und Zentralschweiz" (2019 – 01452, 31.10.2019).

Consent for publication
All ten patients provided written informed consent for publishing this case report.

Competing interests
The authors declare no competing interests.

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