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Low-level complex mosaic with multiple cell lines affecting the 18q21.31q21.32 region in a patient with de novo 18q terminal deletion

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ABSTRACT

We describe a 5-year-old girl who was diagnosed at birth with 18q de novo homogeneous deletion at G-banding karyotype. Her clinical condition, characterized by hypotonia, psychomotor retardation, short stature, deafness secondary to bilateral atresia of the external auditory canals, was in agreement with the 18q deletion syndrome though presence of coloboma of a single eye only suggested a mosaic condition as an unusual sign. By combining multiple technologies including array-CGH, FISH, and WGS, we found that the terminal deletion 18q21.32q23 (21 Mb) was in segmental mosaicism of the proximal region 18q21.31q21.32 (2.7 Mb), which showed a variable number of copies: one, two, or three, in 7, 41 and 55% of the cells respectively. Breakpoint junction analysis demonstrated the presence of an inv-dup del (18q) with a disomic segment of 4.7 kb between the inverted and non-inverted copies of the duplicated region 18q21.31q21.32. From these results, we propose that all three types of abnormal chr18 (the inv-dup del and the two 18q terminal deletions of different sizes) arisen from breaks in a dicentric mirror chromosome 18q, either in more than one embryo cell or from subsequent breaking-fusion-bridge cycles. The duplication region was with identical polymorphisms as in all non-recurrent inv-dup del rearrangements though, in contrast with most of them, the 18q abnormality was of maternal origin. Taking into account that distal 18q deletions are not rarely associated with inv-dup del(18q) cell lines, and that the non-disjunction of chromosome 18 takes place especially at maternal meiosis II rather than meiosis I, multiple rescue events starting from trisomic zygotes could be considered alternative to the postmitotic ones. From the clinical point of view, our case, as well as those of del(18q) in mosaic with the dic(18q), shows that the final phenotype is the sum of the different cell lines that acted on embryonic development with signs typical of both the 18q deletion syndrome and trisomy 18. Asymmetrical malformations, such as coloboma of the iris only in the right eye, confirm the underlying mosaicism regardless of whether it is still detectable in the blood.

1. Background

Partial deletions of the long arm of chromosome 18, including terminal and interstitial monosomy, occur in 1/40.000 live births (Cody et al., 2015), while partial 18q duplications account approximately 2% of all chromosome 18 trisomies (0.3/1000 live birth) with the majority of them resulting in unbalanced translocation either de novo or from a parent with balanced translocation (Tucker et al., 2007). A few cases of distal 18q deletion have been reported in mosaic with a cell line containing a pseudoisodicentric or mirror dicentric chromosome 18 (Morrissette et al., 2005; Rittinger et al., 2015). In none of these cases the 18q rearrangements were defined at the molecular level although the roughly different breakpoints suggested nonrecurrent events. Here, we describe a 5-year-old female with psychomotor delay and numerous

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malformations who was diagnosed at birth with 18q de novo homogeneous deletion. Cytogenomics investigations in blood DNA, such as array-CGH, whole-genome sequencing (WGS), and FISH, allowed to reveal a mosaic with three cell lines, two with 18q deletions of different sizes and the third line with an inv-dup of (18q). The origin of the mosaic, its effect on the phenotype, and the likelihood that other homogeneous terminal deletions are similar cryptic mosaics are discussed.

2. Case presentation

Written informed consent was received from the family, and this study was conducted in accordance with the Declaration of Helsinki and approved by the ethical review boards at Scientific Institute, IRCCS Eugenio Medea, Bosisio Parini (Approval number: Prot. N. 07/19 – CE).

A 5-year-old girl came to our attention after a homogeneous de novo terminal deletion of chromosome 18q21.3 was detected by conventional karyotype analysis when she was 1 year old. At the time of conception, her parents were 33 years old. At the age of 4 months, atrial septal defect was surgically corrected and bilateral aural atresia of external auditory canal, in addition to right iris coloboma were diagnosed.

At 5 years of age, her weight was 14 kg (3rd centile), height 99 cm (10th centile), and head circumference 47 cm (<3rd centile). She showed several dysmorphic features (Fig. 1A) including horizontal nistagmus, right exophoria, slightly high-set and posteriorly rotated ears, ogival and partial cleft of soft palate, bifida uvula and rhinolalia. Diffuse hypotonia and joint ligamentous laxity were observed. She was able to crawl and stand with support showing still very precarious balance of trunk and limbs. Insulin-like growth factor-1 level was 40 ng/mL (normal range: 33.5–171.8 ng/mL). Griffiths scale scores revealed moderate intellectual disability (IQ: < 50, mental age equivalent to 10 months), and very poor language limited to a few words. She experienced sensorineural hearing impairment sustained by hearing aids. Ophthalmological evaluation revealed bilateral nystagmus and large chorioretinal coloboma without macula, involving the right iris. 3T magnetic resonance imaging showed no brain abnormalities while confirming ocular coloboma and bilateral auricular atresia of the external auditory canal with normal inner ear morphology. The electroencephalography recording showed irregular background activity during wakefulness and widespread bilateral fronto-central epileptic abnormalities during sleep.

Patient's karyotype was 46,XX,del(18) (q21.3)dn in the 50 metaphases analyzed. Array-CGH analysis confirmed the presence of a distal 18q deletion of ~21 Mb at 18q21.32q23, from 59,198,608 to 80,252,149 (hg38), with the average log2 ratio of – 0,97, concordant with the presence of the deletion in 100% of lymphocyte, as detected by karyotype analysis. However, this investigation also highlighted a ~2.7 Mb chromosomal region, from 56,327,483 to 59,094,086 (hg38), having average log2 ratio +0.279, suggestive of a mosaic duplication (Fig. 1B). The final interpretation of the rearrangement accordingly with the ISCN 2020, was 46,XX,del(18) (q21.3)dn. arr[GRCh38]18q21.31q21.32 (56,327,483–59,094,083)x3[0.27],18q21.32q23(59,198,608-80,252,149)x1 (DECIPHER, ID: 480213). These results were indicative of the mosaicism for two cell lines sharing the same terminal 18q: a minor one with a dup-del (18q) detected by the array-CGH in 30% of the cells and a second one with a simple 18q deletion as detected by the analysis of the karyotype. However, confirmatory FISH analysis uncovered a third cell line that had escaped both the karyotype and array-CGH. Indeed, RP11-153B11 (AQ388001 in 18q21.31, labeled green), positioned within the copy number gain, produced: three signals in 52% of the nuclei indicating dup del (18q), two signals in 41% indicating a cell line in which the 18q deletion was distal to this probe and a single signal in 7% indicating a cell line in which the deletion was larger

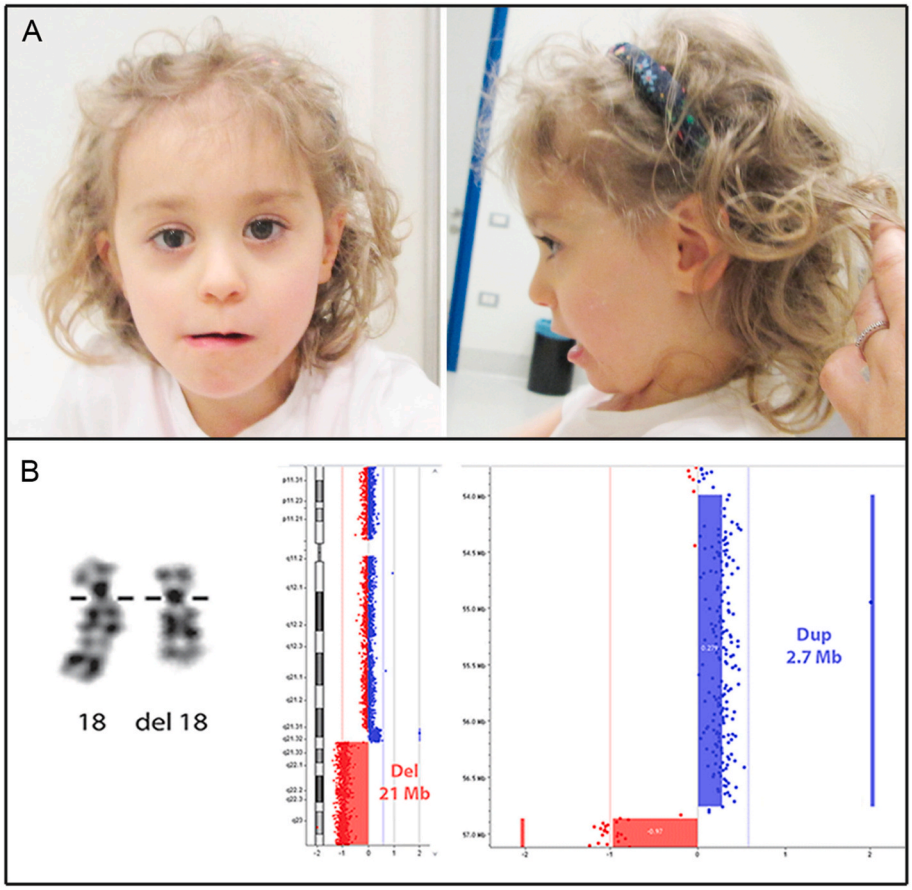

Fig. 1. Patient's clinical and cytogenetic findings:
A. Front and lateral view of the patient at the age of 5 years. Note bilateral epicanthus, high nasal root, long philtrum, downturned corners of the mouth with thin lips and coloboma of the right iris,
B. (left) cut-out of normal chromosome 18 aligned with its homologue deleted 18q in G-banding; (middle) array-CGH profile of chromosome 18 showing a terminal deletion of 21 Mb shaded in red at 18q21.32q23 and duplication at 18q21.31q21.32 shaded in blue; (right) enlargement of duplicated portion of 2.7 Mb (chr22: 56327483_59094083bps hg38), having an average log2 ratio of +0.279. . (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

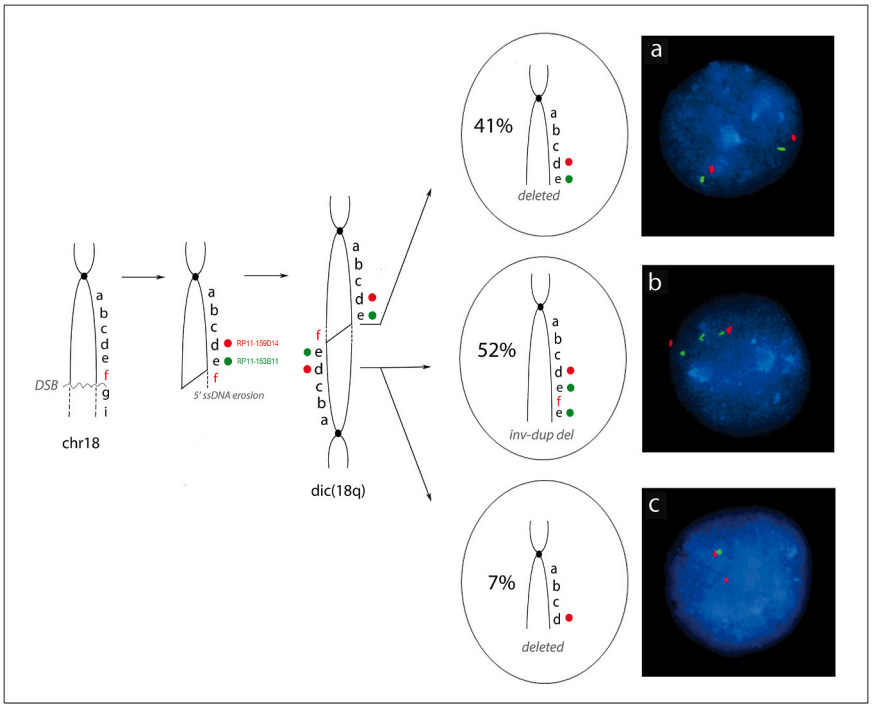

Fig. 2. Formation of the dicentric mirror and its successive breakages leading to three lineages of cells

A double-stranded break of chr18 followed by helix erosion and fold-back rejoining results in mirror-dicentric chromosome [dic (18q)] containing two identical 18pter- > q18q32.2 portion, interrupted by the single copy region "f "of 4.7 kb. The three types of abnormal chr18 we detected in proband's blood derive by the breakages of a dic(18q) either in different embryo cells or from successive breakage-fusion-bridge cycles. The percentage of each clone (a, b, and c) has been estimated according to FISH results in interphase nuclei using two 18q probes [RP11-159D14, AQ373473.1, chr18:52273619–52438253, (in red) and RP11-153B11, AQ388001.1,chr18:56999975–57159676, (in green) and in agreement with the log2 ratio in array-CGH findings. In "a" the two pairs of signals locate the deletion proximal to the last 21 Mb of 18q while in "c" only one green signal is visible indicating that the 18q deletion is larger, at about 24 Mb from 18q telomere. In "b" the series of red-green-green signals confirms the duplication and, together with three-color FISH (Fig. S1), shows that it is inverted. All genomic data are in agreement with GRCh38/hg18. . (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

(Fig. 2a–c). Three-color FISH analysis demonstrated the inverted orientation of the duplicated 18q21.31q21.32 segment (Fig. S1). Pan-telomeric sequences were present on both the normal and the 18q deleted chromosome in 100% of metaphases cells (Fig. S2).

Thus, the final interpretation was a mosaic with three cell lines:

- the first was present in 41% cells and consisted of a 21 Mb deletion at 18q32.2-qter (Fig. 2a).
- the second was present in 52% of cells and consisted of an inv-dup del(18q) with a deletion of 21 Mb and a proximal duplication of 2.7 Mb (Fig. 2b)
- the third was present in 7% of cells and consisted of a deletion of 23.7 Mb at 18q21.31-qter (56,327,483–80,252,149, hg38) (Fig. 2c)

SNP-array and paired-end WGS investigation (see below) did not show homozygosity in any portion of 18q, indicating that no copy neutral loss of heterozygosity (CN-LOH) was present in the rearranged

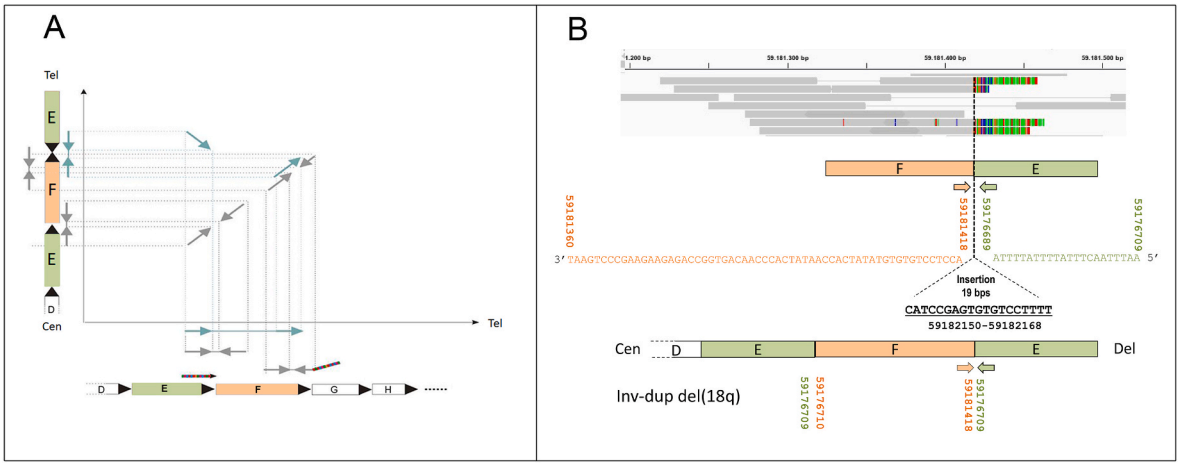

Fig. 3. Final interpretation of the inv-dup del 18q after WGS data analysis

A. Schematic representation of the inverted duplication showing the reads mapping at the reference genome (x-axis) and their corresponding counterparts in the patient's genome (y-axis). The gray arrows represent the normally oriented paired-end reads while the green arrows represent the discordant reads. Reads with multi-colored soft-clipped portion along the reference genome map across the breakpoint of the inverted duplication. The 4.7 kb genomic segment "F" represents the disomic region between the duplicated segment "E". For graphical clarity, the figure is not in scale.

B. (Top) Read alignments surrounding the inv-dup del breakpoint at chromosome 18q IGV browser screenshot of the breakpoint region: a cluster of reads having a multi-colored soft-clipped portion at their ends is shown.

(Middle) schematic representation of the insertion of 19bp into the junction of the inverted fragment "E" and "F". Also shown are the sequences of the disomic (orange), inverted duplication (green) and 19 bp (black) insertion fragments as derived from a representative soft clipped read. (Bottom) The final model of the inv-dup of (18q) as determined by the chromosome microarray, FISH and WGS, showing the inverted copy segment "E" with the interposed disomic region "F" of 4.7 kb. . (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

portion and thus confirming the interpretation. Since the 18q deletion was not of paternal origin (Table S1), the mother's DNA was studied by WGS, and no genomic rearrangement predisposing to chromosome 18 abnormality in the proband was identified. Manual inspection at the breakpoint junction of the duplicated region 18q21.31q21.32 showed discordant read-pairs mapping in the same orientation (Fig. 3A), thus confirming the inverted orientation of the duplicated segment. Furthermore, the discordant read pairs spaced ~4.7 kb from each other, indicating the presence in the inv-dup del cell line of a disomic segment between the inverted and non-inverted copies of the duplication, which was not detected by array-CGH. Split read analysis allowed us to capture the exact localization of the disomy-inversion breakpoint and to map the proximal and the distal ends of the copy-number-neutral segment at nt 59181418 and nt 59176709, respectively (Fig. 3B). Sequence analysis of the breakpoint also revealed a 19-bp insertion between the disomic and the inverted duplicated fragments. Interestingly, the insertion showed high homology (18/19 nt) with a sequence mapping ~ 700 bp telomeric to the disomic segment in an inverted orientation in respect to the reference genome (Fig. 3B). Finally, we did not identify any specific signature at the distal breakpoints that may have suggested a telomere capture or telomere healing mechanism for stabilization of the terminal chromosomal deletions.

3. Discussion

We describe the case of a 5-year-old girl whose parents requested a second opinion after the first diagnosis of 18q deletion she had at birth. Her clinical condition, characterized by hypotonia, delayed motor milestones, poor coordination, wide-based gait, short stature, deafness secondary to bilateral aural atresia of external auditory canals, was in agreement with the diagnosis made by the conventional G-banding karyotype of chromosome 18q deletion syndrome (OMIM# 601808, Cody et al., 2015), with coloboma of the right eye only as unusual sign.

Combining multiple technologies including array-CGH and FISH, followed by WGS analysis, we detected in her lymphocytes two de novo terminal deletions of different size and an inv-dup del(18q). This complex mosaic, undetected by G-banding karyotype, suggested the occurrence of either a pre-a post-zygotic mirror dicentric chromosome which ignited a breakage-fusion-bridge cycle resulting in the inv-dup del chromosome (Figs. 2 and 3, S1) in 52% of the cells (Fig. 2b), and in two types of terminally deleted chromosome 18q, one of 21 Mb and the other of 23.9 Mb in 41 and 7% of cells respectively (Fig. 2a, c). Notably, cases of inv-dup del with complex mosaics showing different products of the original mirror dicentric chromosome, such as deletions or even unbalanced translocations, have been reported (Pramparo et al., 2004; Voet et al., 2011; Bonaglia et al., 2018). Disentangling of breakpoints and genotyping of trios revealed that meiotic non-allelic homologous recombination (NAHR) was associated with the formation of recurrent inv-dup del rearrangements as the inv-dup del (8p). Instead, in non-recurrent ones or in their original mirror dicentric chromosomes, a replication-based mechanism that repaired an initial double strand break followed by 3′-5′ exonuclease erosion of a single strand and its template switch was suggested (Hermetz et al., 2014; Kato et al., 2020). The absence of segmental duplications flanking the single copy region between the inverted and non-inverted duplicated segments, as we have shown in our case (Fig. 3B), well fits this mechanism. Furthermore, the non-recurrent inv-dup dels, unlike the recurring inv-dup dels (8p), are largely of paternal origin (Zuffardi et al., 2022) and, regardless of parental origin, have identical polymorphisms with respect to the duplication region (Kato et al., 2020). The observation that in inv-dup del(18q)/del(18q) mosaics the haplotype analysis consistently revealed the maternal origin of the rearrangement with identical polymorphisms (Rittinger et al., 2015) as in our case, suggests a possible connection with chromosome 18 nondisjunction which mainly occurs at maternal meiosis II instead of meiosis I as with all other chromosomes (Hassold and Hunt, 2001). If this correlation is not accidental, we should assume that the inv-dup del(18q) derives from the partial rescue of a free trisomy 18 generated by the nondisjunction of meiosis II in an asynaptic meiosis.

In the register of chromosome 18 structural abnormalities, collecting more than 350 18q-individuals defined at CMA level, genotype-phenotype correlation allowed to classify the deleted genes as contributing to the final phenotype according to their degree of penetrance (Cody et al., 2018). Our findings suggest that part of the phenotypic variability may also be due to the presence of cryptic mosaicism leading to 18q deletions of different size and 18q duplication associated with the inv-dup del rearrangement.

A crucial question is whether and to what extent mosaic cell lines influence the final phenotype. In many cases, patients have characteristics largely overlapping those associated with most of the chromosomal imbalances (psychomotor retardation/intellectual disability, growth retardation, non-specific dysmorphic facial features). This makes it difficult to discriminate how these features are affected by the additional imbalances of other cell lines. In the case presented here, the patient's clinical condition was fairly in agreement with those of the distal 18q deletions although a malformation, ie coloboma of the iris, was present only in one eye and the other one was completely normal. Furthermore, the nearly 3 Mb duplication of the inv-dup del (18q) cell line may have played a role in the final phenotype. Indeed, the NEDD4L gene, located in the region, encodes a ubiquitin ligase that regulates several membrane proteins. Its duplication could worsen the patient's psychomotor retardation and, together with the *TSHZ1* deletion, cause cleft palate (Cellini et al., 2019; Conte et al., 2016).

4. Conclusions

Advanced genomic analyzes revealed that the distal de novo 18q deletion reported in the patient was a mosaic with deletions of different sizes and an inv-dup of the same chromosome suggesting the previous presence of a dicentric mirror chromosome. Other distal 18q deletions were reported as mosaic with a pseudodicentric 18q and, in the few investigated, the duplication region contained identical maternal alleles (Rittinger et al., 2015) as in our case. Since trisomy 18 is the only one in which nondisjunction at maternal meiosis II is prevalent over nondisjunction at meiosis I (Hassold and Hunt 2001; Chen et al., 2005), there may be a link between the two events. If so, trisomies, the most frequent chromosomal abnormalities in humans, could also be the basis of some mirror dicentric chromosomes and their derivatives, as demonstrated for other de novo structural rearrangements such as unbalanced translocations, small supernumerary chromosomal markers and insertions (Bonaglia et al., 2018; Kurtas et al., 2019; Kato et al., 2020; Zuffardi et al., 2022). From the clinical point of view, our case, as well as those of del (18q) in mosaic with psudic (18q), shows that the final phenotype is the sum of the different cell lines that have acted on embryonic development. The underlying mosaicism, detectable or not in the blood, should also be suspected in the presence of asymmetrical malformations, such as coloboma of the iris which in our patient was present in only one eye.

Ethical approval and consent to participate

This study was approved by ethical review boards at Scientific Institute, IRCCS Eugenio Medea, Bosisio Parini (Approval number: Prot. N. 07/19 – CE) and consent for participation was received from the family.

Consent for publication

Consent for publication was received from the family.

Availability of data and materials

The materials described in the manuscript, including whole genome sequencing raw data, will be freely available to any researcher wishing to use them for non-commercial purposes, without breaching participant confidentiality.

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Authors contribution

MCB: conceptualization, methodology. MCB and MF performed the experiments and together with OZ discussed the interpretation of the results. SM, RR: were responsible for the patient's clinical examination ; MCB, MF and OZ : Writing - Review & Editing ; MCB: Supervision and Acquisition of the financial support for the project leading to this publication.

Declaration of competing interest

The authors declare no conflict of interest.

Data availability

Data will be made available on request.

Acknowledgments

We are grateful to the family for participating in this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmg.2022.104596.

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