Incidental finding of APC deletion in a child: double trouble or double chance? – a case report

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Abstract

Background: 22q11.2 deletion syndrome is one of the most common genomic disorders, characterized by the variable presence of facial dysmorphisms, congenital cardiac defects, velopharyngeal insufficiency/cleft palate, thymic hypoplasia/aplasia, immunodeficiency, parathyroid hypoplasia, developmental delay, learning disabilities, psychiatric disorders, renal, ocular, and skeletal malformations, hearing loss and laryngeal abnormalities. Chromosomal microarray (CMA) hybridization is one of the most performed diagnostic tests but as a genome-wide analysis, it can point out relevant incidental copy number variations.

Case presentation: We report the case of a 2-year-old boy that came to our attention for mild psychomotor delay, poor growth, and minor facial anomalies. Considering a diagnosis of 22q11.2 deletion syndrome, we performed CMA that not only confirmed our diagnosis, but also pointed out an additional de novo 5q21.3q22.2 microdeletion, encompassing APC gene. As a result of the genetic testing we enrolled the patient in a tailored surveillance protocol that enabled the early detection of a hepatoblastoma. The child underwent surgical and chemotherapeutic treatments with complete cancer eradication.

Conclusions: The concurrent finding of an expected result and an additional deletion of APC gene represents an example of a relevant issue about the health and ethical management of secondary findings revealed by genome-wide tests. Furthermore, this report highlights the need to develop dedicated surveillance guidelines for children with APC-related polyposis and raise the question whether to suspect and screen for APC-related conditions in cases of sporadic hepatoblastomas.

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Background

Nowadays, chromosomal microarray (CMA) represents the first-tier genetic test for patients presenting with intellectual disability (ID) and/or multiple congenital anomalies of unknown origins, detecting DNA copy-number variants (CNVs), i.e. microduplications or microdeletions [1].

Among the pathogenic CNVs, 22q11.2 deletion syndrome (22q11.2DS) (OMIM #192430) is one of the most common microdeletion disorders: its incidence is relatively high and it is estimated in 1:4000 newborns, possibly underestimated due to clinical mis/under-recognition. The main clinical findings include facial dysmorphisms, congenital cardiac defects, velopharyngeal insufficiency with or without cleft palate, thymic hypoplasia/aplasia, immunodeficiency and/or autoimmune disorders, parathyroid hypoplasia, developmental delay...
(commonly borderline intellectual function), learning disabilities, psychiatric disorders, renal, ocular, and skeletal malformations, hearing loss and laryngeal abnormalities [2]. The most common heterozygous microdeletion, leading to DiGeorge/Velocardiofacial syndromes, encompasses ∼3 Mb, while 8–10% of individuals show a ∼1.5 Mb nested deletion, resulting in similar but overall milder phenotype [3]. In 90% of cases the deletion occurs sporadically, resulting from a de novo heterozygous deletion, while in the remaining 10% of individuals it is inherited, in an autosomal dominant pattern, from a parent occasionally showing mild features of the condition [2].

22q11.2DS can be diagnosed using FISH Test (Fluorescence In Situ Hybridization) with specific probes mapping the region, or with whole-genome methodologies, such as CMA. The first one can be beneficial on a strong clinical suspect but it could misdiagnose patients with atypical nested deletions [2]. CMA might be more straightforward for patients with subtle clinical presentation and/or for less experienced health professionals; however, as a genome wide analysis, it can unveil incidental microdeletions/microduplications, possibly relevant for the patient, that have to be properly communicated and managed.

Here we present a child with clinical suspect of 22q11.2DS and whose diagnostic process led to an incidental genetic finding with important consequences on the clinical management and outcome.

Case presentation
The male proband is the second child to non-consanguineous healthy parents of South-American ancestry. The family history is not contributive. Pregnancy was uneventful and the baby was born at term with a weight of 2600 g (10th centile), length of 48 cm (25th centile), occipitofrontal circumference (OFC) of 32 cm (10th centile), Apgar score of 9/10. An umbilical hernia was evident. His growth was normal until 6 months old, when he showed a progressive slowdown. His parents reported frequent infections of upper respiratory tract, treated with antibiotic therapy.

During a hospitalization for a gastroenteritis at the age of 19 months, he underwent a neurological examination that showed a delayed psychomotor development (he could say only one word and he did not walk alone), hypotonia, excessive sleepiness and poor socialization. Magnetic resonance imaging (MRI) of the brain and brainstem revealed minor dysmorphic aspect of ventricular system, asymmetrical and slightly verticalized hippocampi and slightly reduced anterior-posterior diameter of pons. Cardiac and endocrinological evaluation were normal. Routine blood tests showed a microcytic anemia caused by iron deficiency, mild hypoalbuminemia and hypocalcemia. When the child was 21 months old, during a second hospital recovery for herpetic stomatitis, an otorhinolaryngologist evaluation was performed for nocturnal snoring and tonsillectomy was suggested.

For the mild psychomotor delay, poor growth and brain anomalies he was referred to the genetic consultant. On his first genetic evaluation, his weight was 9.5 kg (<3rd percentile) and his head circumference was 46 cm (<3rd percentile). Minor facial anomalies suggestive of 22q11.2DS were observed, including bitemporal constriction, low-set ears, sparse eyebrows, short palpebral fissures, bilateral epicanthic folds, depressed nasal bridge, tubular nose and mild hypoplastic alae nasi (Fig. 1).

Because of the medical history and the facial appearance, a CMA analysis was performed on the patient and his parents. The CMA analysis was performed using a 60-mer oligonucleotide probes technology (SurePrint G3 Human CGH 8x60K, Agilent Technologies, Santa Clara, CA, USA) on DNA extracted from peripheral blood. Labeling, purification and hybridization of DNA samples were carried out according to manufacturer’s protocol (Agilent Oligonucleotide Array-Based CGH for Genomic DNA Analysis, version 7.5). Raw data were generated using Agilent Feature Extraction and analyzed by CytoGenomics 4.0.3.12 using ADM-2 algorithm (Agilent Technologies, Santa Clara, CA). To improve the accuracy of the results the Diploid Peak Centralization algorithm was applied.
The aberration filter was set to detect a minimum number of 3 consecutive probes/region and the minimum absolute average Log Ratio (MAALR) was $\pm 0.25$. A second analysis was run with a MAALR of $\pm 0.15$ and with a minimum number of 3 probes/region to detect low level mosaicism.

Copy number variations weren’t reported if they coincided with published DNA variants listed in the Database of Genomic Variants (http://projects.tcag.ca/variation/). Genomic coordinates are in accord to the 37 build (March 2009) of the Human Genome Reference consortium (GRch37/hg19).

The analysis detected four rearrangements (Table 1): the small sizes of the two microduplications, their genic content and the parental origins were suggestive for a likely benign role. One de novo rearrangement was a typical 22q11.21 microdeletion associated to the 22q11.2 deletion syndrome (Fig. 2a). Furthermore, a de novo 5q21.3q22.2 microdeletion was identified: this 3.6 Mb deletion involves 12 OMIM genes, including APC, delineating a condition of APC-associated polyposis (Fig. 2b).

As a result of the genetic test the proband was enrolled for a tailored follow-up. At the first evaluation, an abnormally high alpha-fetoprotein (aFP) level was detected (266.4 μg/L, normal range < 7 μg/L) and the abdomen ultrasound showed a solid mass of 4 × 3 cm in the left lobe of the liver, with well-defined edges, ovular and bilobate shape (Fig. 3). For a more accurate evaluation of the lesion, a magnetic resonance (MRI) of the abdomen was performed and it confirmed the presence of a liver mass, in II-III-IV segment. It appeared irregularly hyperintense in T2-weighted images and hypointense in T1, with multinodular structure and a delimiting pseudocapsule, hypointense in both T2 and T1 sequences. The endovenous paramagnetic contrast agent showed an irregular enhancement that increased in venous phase, with persisting hyperdense strie in the late-phase. This lesion, according to the irregular pattern of enhancement, structure and vessel relation, was compatible with a diagnosis of hepatoblastoma (HB).

The patient then was referred to the Pediatric Oncology Unit of Istituto Nazionale dei Tumori. Clinical evaluation, radiological assessment (abdominal ultrasound) and serum alpha-fetoprotein dosage; besides, he was referred to specialists of inherited gastrointestinal cancer syndromes for the appropriate FAP surveillance. He also continued the genetic follow-up with hematologic tests, eye examination and thyroid ultrasound. At the latest evaluation, thyroid functional parameters were altered: he was referred to the endocrinologist for appropriate diagnostic framework and treatment.

**Discussion and conclusions**

The array-CGH analysis confirmed the clinical suspect of 22q11.2DS and led to an incidental finding of a cancer predisposition syndrome due to the deletion of the APC gene.

| Chromosome region | Copy number variation | Size | Breakpoints* | OMIM disease-causing genes involved | Inheritance | Role |
|-------------------|-----------------------|------|--------------|-------------------------------------|-------------|------|
| 2q34              | Duplication           | 432 kb | 210,021,463–210,453,149 | / | Father | Likely benign |
| 5q21.3q22.2       | Deletion              | 3.6 Mb | 108,730,323–112,313,546 | SLC25A4, WDR36, APC | De novo | Pathogenic |
| 7q21.12           | Duplication           | 307 kb | 87,811,283–88,118,091 | ADAM22 | Mother | Likely benign |
| 22q11.21          | Deletion              | 2.5 Mb | 18,919,942–21,440,514 | PRODH, SLC25A1, CDC45L, GP1BB, TBX1, TXNRD2, COMT, TANG2, RTN4R, SCARF2, PIK3A, HEP2 | De novo | Pathogenic |

*The breakpoints are reported according to the 37 build (March 2009) of the Human Genome Reference consortium (GRch37/hg19)*
Germline haploinsufficiency of the APC gene cause familial adenomatous polyposis (FAP), a highly penetrant condition characterized by development of various rectal and colonic adenomas and early-onset colorectal cancer [4]. The majority of disease-causing alterations of the APC gene are loss-of-function single nucleotide variants [5]; large cytogenetic deletions, containing APC gene, have been rarely reported and it is estimated that they account for 2–3% of patients [6, 7]. The APC gene germline mutations and deletions are not only involved in colorectal tumorigenesis, but also in other various premalignant and malignant lesions: duodenal, jejunal and gastric polyps, papillary thyroid carcinomas, desmoid tumors and embryonal tumors, such as hepatoblastoma (HB) and medulloblastoma. Whole APC gene deletions seem to cause mainly classical-FAP phenotype, with thousands of adenomatous colonic polyps and high frequency of extraintestinal FAP related manifestations such as upper gastrointestinal polyps, congenital hypertrophy of the retinal pigment epithelium (CHRPE) and desmoid tumors [6, 8, 9].

The 22q11.2 microdeletion identified in our proband could explain the clinical features of delayed psychomotor development, hypotonia, poor socialization, frequent episodes of infectious diseases, abnormal findings at electroencephalogram and encephalic MRI, hypocalcemia and hypothyroidism and characteristic facial dysmorphisms. Although 22q11.2DS has not been clearly associated with an increased risk of malignancy, few cases of pediatric cancers have been reported among these patients [10–12]: in particular Scattone et al. [10] and McDonald-McGinn et al. [12] described respectively one and two patients with 22q11.2DS and hepatoblastoma. The distinctive immunodeficiency, predisposing to higher rate of infectious diseases also from carcinogenic viruses and to impaired tumor surveillance, together with the heterozygous deletions of some specific genes involved in detoxification of carcinogenic substances (such as catechol-O-methyltransferase gene) are possible concurrent causes in the complex process of carcinogenesis [11].
In this scenario, 22q11.2DS might have contributed to the HB development along with APC deletion that remain the prevalent predisposing factor for our patient. In fact, the increased risk of developing HB in patients carrying a constitutional mutation or deletion of APC is estimated to be really low, ranging from 0.3 to 1.6% [13], but it is approximately 750–7500 times higher the prevalence of general population (0.0001%) [14]. The median age at diagnosis of HB in FAP children is similar to that of sporadic ones, predominantly between 6 months and 3 years of age [15]. Since the prognosis of HB is strictly dependent on early detection and, consequently, on the complete resection, screening test in patients with germline haploinsufficiency of APC is mandatory. Beyond increasing survival, it could allow less-intensive therapy and less organ toxicity. To date, there is not a standard agreement regarding time and method of surveillance. Given the estimated risk, similar to other genetic predisposing conditions (such as Beckwith-Wiedemann syndrome), several studies suggest αFP level monitoring in conjunction with hepatic ultrasound at least every 3 months [16], until 7 years of age [13–17].

This and previous reports also bring into question whether to suspect and screen for APC-related conditions in cases of sporadic hepatoblastomas. HB accounts for about 1% of all pediatric tumors and represents the most common liver cancer in childhood: if our case had not been tested before, his HB would be classified as “sporadic” one, as he had no suggestive family history or other manifestations of FAP. Aberrant activation of Wnt-signaling pathway occurs in the vast majority of HBs through somatic mutations at beta-catenin gene (CTNNB1, OMIM *116806), particularly point mutations or in-frame deletions involving exon 3 [16–18]; APC protein is a key negative regulator of Wnt-signaling pathway. The reported rate of germline APC mutations in apparently sporadic HBs is highly variable: Sumazin et al. [18] found approximately 1.1% of sporadic HBs with an APC germline mutation, while Aretz et al. [15] and Young et al. [19] reported an incidence of 10–20%, therefore suggesting routine APC testing of all patients with HB. Since somatic CTNNB1 and germline APC mutations have been shown to occur in a mutually exclusive manner in hepatoblastomas and in all tumor types studied so far [18–20], the identification of a somatic activating CTNNB1 mutation in an HB patient directly reduces the risk of carrying a germline APC mutation [20]. Based on these data, a two-step approach would be preferable: testing for somatic mutations of CTNNB1, trough immunochemistry and/or genetic analyses on tumor blocks, should be performed firstly; then all CTNNB1-negative patient should undergo screening for germline APC mutation/deletion with a combination of sequencing methods and MLPA (multiplex ligation-dependent probe amplification). This must be a first-tier analysis instead in cases with extra-liver FAP manifestations or a suggestive family history.

Like APC, many other genes and correlated syndromes have a well-known increased risk to cancer in pediatric age; at least 8–10% of them reveal a germline mutation in cancer predisposition genes known at this days, with APC as the second most frequent mutated gene in this type of patients [21]. Detailed guidelines for genetic analyses in apparently sporadic childhood cancers are
missing: testing all pediatric cancer patient for germline cancer predisposition genes could be a waste in resources and most importantly could lead to a notable number of unknown significant variants with the consequent massive family impact that these type of “uncertain diagnoses” bring with them. Instead, as the first step, somatic tumor screening can not only provide information about distinct molecular risk subtype and help clinical management, but it can also aid in distinguishing sporadic tumors from those related to a genetic predisposition syndrome.

Our case is a perfect example of genetic “double diagnosis” made with a genomic testing like CMA: if we would confirm the clinical suspect of 22q11.2DS using FISH technique, we would miss the APC deletion with important repercussion on the patient’s care. Nowdays, genome-wide tests, such as CMA and whole exome sequencing (WES), have not only considerably increased the diagnostic yield but the rate of unexpected and uncertain findings as well. Talking about CMA, an incidental finding could be defined as unexpected CNVs not directly related to the patient’s clinical indication that has however some medical implications, conferring susceptibility to cancer, neurodegenerative adult-onset pathologies or revealing a carrier status. These incidental findings are also relevant for the repercussions on other family members, often leading to critical testing in healthy-appearing individuals and raising emblematic ethical dilemmas such as testing siblings in childhood [22]. While, for exome and genome sequencing, whether and which incidental variants must be reported is an ongoing discussion topic [23], the contribution of CNVs is under-explored especially considering that it is currently used as the first diagnostic tool. Some large studies have investigated the proportion of incidental CNVs and their genetic counselling implications [24–27]. In particular, based on a literature meta-analysis by Talukdar et al., the incidence of CNVs involving cancer susceptibility genes (CSGs) in individuals that underwent CMA is 0.6% [17]. According this UK consensus group, microdeletions encompassing APC are categorised as “recognised deletion/duplication syndrome involving a cancer susceptibility gene with a demonstrable elevated lifetime risk of cancer evident from the literature, for which surveillance is recommended”, for which laboratory report is mandatory [17]. In the Italian setting, specific recommendations for this topic are lacking; however we strongly believe that, in pre-test counselling, the medical geneticist must inform, with an appropriate consent form, the patient or his parents about the possible incidental findings and they can freely decide whether to know. However if the patient’s willpower of not knowing is more acceptable for adult-onset diseases with no therapy or preventive care, finding an incidental CNVs that could lead to therapeutic/prevention measures, especially for children, open a strong ethical problem for clinicians [27]. For our case, not reporting the APC deletions would have been morally difficult and worrying for the patient’s health; and this made us realise how much international guidelines for incidental CNVs report are needed.

In conclusion, this report presents a 22q11.2DS child with an additional deletion in APC discovered with CMA. Involving a cancer predisposing condition, this incidental finding let us disclose it to the family, leading to an early diagnosis of hepatoblastoma and to its complete eradication. This case highlights some emerging health management and ethical issues about current genome-wide tests and incidental findings, even more notable being these analyses available also for non-genetic healthcare professionals. In this scenario, a tight collaboration among the different healthcare professionals involved in clinical management appears essential.

Abbreviations
22q11.2DS: 22q11.2 deletion syndrome; aFP: Alpha-fetoprotein; hCG: Beta human chorionic gonadotropine hormone; CMA: Chromosomal microarray; CNVs: Copy-number variants; CSGs: Cancer susceptibility genes; FAP: Familial adenomatous polyposis; FISH: Fluorescence In Situ Hybridization; HPF: High power fields; HB: Hepatoblastoma; ID: Intellectual disability; MAAoR: Minimum absolute average Log Ratio; MRI: Magnetic resonance imaging; OFC: Occipitofrontal circumference; WES: Whole exome sequencing

Acknowledgements
This work has been generated within the European Reference Network on Rare Congenital Malformations and Rare Intellectual Disability (ERN-ITHACA).

Authors’ contributions
DM evaluated the patient, coordinated the diagnostic and follow-up process, and took care of the conception and design of the study. ER collected the information and drafted the initial manuscript. BR and DM critically reviewed and revised the manuscript. RS and SG provided the patient’s neoplastic treatment and helped to draft the manuscript. AC performed abdomen ultrasound. PGM critically revised the manuscript and supervised patient management. All authors read and approved the final manuscript.

Funding
No funding.

Availability of data and materials
Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Ethics approval and consent to participate
Parental informed consent for publication was obtained.

Consent for publication
Written informed consent was obtained from the patient’s legal guardians for publication of this case report and any accompanying images.

Competing interests
The authors declare that they have no competing interests.

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References

1. Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR, Carter NP, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. Am J Hum Genet. 2010;86:749–64.

2. McDonald-McGinn DM, Emanuel BS, Zackai EH, et al. 22q11.2 deletion syndrome. 1999 Sep 23 [updated 2020 Feb 27]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews®. Seattle: University of Washington, Seattle; 1993-2020.

3. Bumsrose RD. 22q11.21 deletion syndromes: a review of proximal, central, and distal deletions and their associated features. Cytogenet Genome Res. 2015;146(2):89–99.

4. Kerr SE, Thomas CB, Thibodeau SN, Ferber MJ, Halling KC. APC germline mutations in individuals being evaluated for familial adenomatous polyposis: a review of the mayo clinic experience with 1591 consecutive tests. J Mol Diagn. 2013;15:31–43.

5. Hirschman BA, Pollock BH, Tomlinson GE. The spectrum of APC mutations in children with hepatoblastoma from familial adenomatous polyposis kindreds. J Pediatr. 2005;147:263–6.

6. Aretz S, Thienie D, Uhlhaas S, Thoelen R, van Cutsem E, Vermeesch JR, et al. Structural aberrations with secondary implications (SASIs): consensus recommendations for reporting of cancer susceptibility genes identified during analysis of copy number variants (CNVs). J Med Genet. 2019;56:e26991.

7. Michl G, Tejpar S, Thoelen R, van Cutsem E, Vermeesch JR, Fryns J-P, et al. Novel strategies for comprehensive mutation screening of the APC gene. Neoplasia. 2017;19(4):338–43.

8. Quadri M, Vetro A, Gismondi V, Marabelli M, Bertario L, et al. APC rearrangements in familial adenomatous polyposis: heterogeneity of deletion lengths and breakpoint sequences underlies similar phenotypes. Familial Cancer. 2015;14:441–9.

9. Michl G, Tejpar S, Thoelen R, van Cutsem E, Vermeesch JR, FYns J-P, et al. Large deletions of the APC gene in 15% of mutation-negative patients with classical polyposis (FAP): a Belgian study. Hum Mutat. 2005;25(2):125–34.

10. Scattone A, Caruso G, Mazzullo A, Piscitelli D, Gentile M, Bonadonna L, et al. Neoplastic disease and deletion 22q11.2: a multicentric study and report of two cases. Pediatr Pathol Mol Med. 2003;22:323–6.

11. Stevens T, van den Akker M. Risk of malignancy in 22q11.2 deletion syndrome. Clin Cancer Res. 2017;65:e27103.

12. McDonald-McGinn DM, Emanuel BS, Zackai EH, et al. 22q11.2 deletion syndromes: a review of proximal, central, and distal deletions and their associated features. Cytogenet Genome Res. 2015;146(2):89–99.

13. Krawczuk-Rybak M, Jakubiuk-Tomaszuk A, Skiba E, Plavski A. Hepatoblastoma as a result of APC gene mutation. J Pediatr Gastroenterol Nutr. 2012;55:334–6.

14. Aretz S, Koch A, Uhlhaas S, Friedl W, Propping P, Von Schweinitz D, et al. Should children at risk for familial adenomatous polyposis be screened for hepatoblastoma and children with apparently sporadic hepatoblastoma be screened for APC germline mutations? Pediatr Blood Cancer. 2006;47:811–9.

15. Trobaugh-Lotario AD, López-Terrada D, Li P, Feusner JH. Hepatoblastoma in patients with molecularly proven familial adenomatous polyposis: clinical characteristics and rationale for surveillance screening. Pediatr Blood Cancer. 2018;65:e27103.

16. Talukdar S, Hawkes L, Hanson H, Kulkarni A, Brady AF, McMullan DJ, et al. Structural aberrations with secondary implications (SASIs): consensus recommendations for reporting of cancer susceptibility genes identified during analysis of copy number variants (CNVs). J Med Genet. 2019;56:718–26.

17. Sumazin P, Chen Y, Treviño LR, Sarabia SF, Hampton OA, Patel K, et al. Genomic analysis of hepatoblastoma identifies distinct molecular and prognostic subgroups. Hepatology. 2017;65(1):104–21.

18. Yang A, Sisson R, Gupta A, Tiao G, Geller JI. Germline APC mutations in hepatoblastoma. Pediatr Blood Cancer. 2018;65:e26892.

19. Dubbink HJ, Hollink HJM, Avenca Valente C, et al. A novel tissue-based β-catenin gene and immunohistochemical analysis to exclude familial adenomatous polyposis among children with hepatoblastoma tumors. Pediatr Blood Cancer. 2018;65:e26991.

20. Zhang J, Walsh MF, Wu G, Edmonson MN, Gruber TA, East j, et al. Germline mutations in predisposition genes in pediatric Cancer. N Engl J Med. 2015;373:2336–46.

21. Brodeur GM, Nichols KE, Pion SE, Schiffman JD, Malkin D. Pediatric Cancer predisposition and surveillance: an overview, and a tribute to Alfred Knudson Jr. Clin Cancer Res. 2017;23:e1–5.

22. Green RC, Berg JS, Grody WW, Kalia SS, Martin CL, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genet Med. 2013;15(7):565–74.

23. Pichert G, Mohammed SN, Ahn JW, Ogilvie CM, Izzat L. Unexpected findings in cancer predisposition genes detected by array comparative genomic hybridization: what are the issues? J Med Genet. 2011;48(8):535–9.

24. Boone PM, Soens ZT, Campbell WM, Stankiewicz P, Cheung SW, Patel A, et al. Incidental copy-number variants identified by routine genome testing in a clinical population. Genet Med. 2013;15(1):45–54.

25. Hann M, Mikhail FM, Hollenbeck D, Farmer M, Robin NH. Incidental detection of cancer predisposition gene copy number variations by array comparative genomic hybridization. J Pediatr. 2014;165(5):1057–9 e1–4.

26. Lefebvre M, Sanlaville D, Marke N, Thauvin-Robinet C, Gautier E, Chehadé SE, et al. Genetic counselling difficulties and ethical implications of incidental findings from array-CGH: a 7-year national survey. Clin Genet. 2016;90(5):630–5.

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