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Review article

Antenatal diagnosis of cardio-facio-cutaneous syndrome: Prenatal characteristics and contribution of fetal facial dysmorphic signs in utero. About a case and review of literature

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ABSTRACT

Antenatal diagnosis of cardio-facio-cutaneous syndrome: prenatal characteristics and contribution of fetal facial dysmorphic signs in utero. This paper is a case study and review of literature.

"RASopathies" is the term coined for a group of genetic diseases that share modulation inside the MAPKinase pathway. Mutations inside the coding sequence of any of these genes may be responsible for the upregulation of the RAS pathway, leading on the clinical level to Type 1 Neurofibromatosis (NF1), Noonan syndrome (NS), Costello syndrome (CS), Multiple Lentigines, Loose Anagen Hair syndrome, Cardio-Facio-Cutaneous syndrome (CFCS), and, more recently, Legius syndrome. While the postnatal presentation of this group is well-known, prenatal findings are less well recognized. The presence of a RASopathy during the prenatal period can be suspected on account of non-specific abnormalities: polyhydramnios, cystic hygroma or high nuchal translucency, macrosomia with proportionate short long bones, macrocephaly, renal, lymphatic, or cardiac defects. The current case report underlines the characteristic dysmorphic facial features on 3D-ultrasound (hypertelorism, down-slanting palpebral fissures, a long and marked philtrum, and low-set posteriorly rotated ears) that allow for a "RASopathy" to be postulated. After detecting a copy number variation (CNV) absence on a CGH array, we performed a RASopathy gene panel analysis, which identified a so-far unreported heterozygous de novo mutation in the *BRAF* gene (namely NM_004333.4 : c.1396 G > C ; p.Gly466Arg). Genetic counseling has, therefore, focused on the diagnosis of a RASopathy and predictable phenotype of CFCS, a distinct entity characterized by an increased risk of intellectual disability and early-onset feeding problems. We suggest that a more detailed prenatal facial evaluation should be performed in fetuses presenting high nuchal thickness, heart defects, or unusual findings, along with the absence of a CNV on a CGH array. Due to the dysmorphic facial features, targeted RASopathy genes are presumed to likely to be responsible for NS, CFCS, and CS.

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Introduction

RASopathy is the generic term used for a family of genetic diseases caused by a dysregulation of the RAS/MAKP (mitogen-activated protein kinase) signaling pathway. This pathway, which is well-known for its role in oncogenesis and tumor proliferation, has been involved in cell growth and differentiation, as well as apoptosis and senescence. Identified constitutional mutations pertaining to one of the genes encoding phosphatase or protein within the pathway are responsible for the gain-of-function effect leading to increased pathway activity. An illustration of this pathway is shown in Fig. 1. This RAS-MEK-ERK pathway represents a protein signaling pathway chain that responds to mitogenic binding to a cell surface receptor. This chain of protein communication occurs through the sequential phosphorylation of proteins, finally affecting the transcription of nuclear DNA leading to different cell changes. Abnormalities of several factors along the pathway are likely to be responsible for distinct conditions (Fig. 2). Therefore, RASopathy family includes: Type 1 neurofibromatosis (NF1), Noonan syndrome (NS) and its variants (CBL syndrome, loose anagen hair syndrome, and Noonan-multiple lentigines syndrome, previously referred to as LEOPARD syndrome), Costello syndrome (CS), cardio-facio-cutaneous syndrome (CFCS), and linear sebaceous nevus syndrome [1]. NS is caused by mutations responsible for a gain of function in phosphatase for *PTPN11*, *SOS1*, *RAF1*, *KRAS*, *NRAS*, *SHOC2*, *CBL*, or *RIT1* genes encoding proteins. CS is caused by activation mutations in *HRAS*, and CFCS by activating mutations in *BRAF*, *KRAS*, *MEK1*, or *MEK2* [2,3]. As a group, RASopathies display an estimated prevalence ranging between 1/700 and 1/1250 live births [4].

CFCS is a rare autosomal dominant multiple congenital malformation condition (OMIM 115150), whose global prevalence is not precisely known. Its prevalence in Japan has been estimated at one case per 810,000 individuals [5]. Postnatal CFCS, first described in 1986 [6,7], is mainly characterized by facial dysmorphism, dermatologic abnormalities, congenital cardiac defects, and growth retardation. Facial dysmorphic features include relative macrocephaly with a large forehead, bi-temporal narrowing, increased facial width and depth, a rather coarse face, and thin curly hair. Sparse or absent hair and eyebrows, as well as eyebrows with hyperkeratosis, are very common in CFCS. Ocular features comprise ptosis, hypertelorism, down slanting palpebral fissures, and epicanthic folds. The nose is often short with a broad root, bulbous tip, and anteverted nostrils. The philtrum is deep. The ears are low-set and posteriorly rotated [8,9]. With age, the face tends to become coarser. The dermatological manifestations are cardinal in CFCS, yet their severity and ectodermal involvement may vary. The most common cardiac abnormality is pulmonary valve stenosis, present in approximately 45% of cases. Septal defects and hypertrophic cardiomyopathy are the main congenital heart defects [8]. Intellectual disability, universally described, is of a moderate-to-severe type. Hypotonia and speech delay are the most characteristic traits [8,10]. The risk of neoplasia, such as acute lymphoblastic leukemia and lymphomas, is only marginally increased, unlike other RASopathies, with no precise long-term surveillance required [11].

Despite distinctive features, in case of CFCS, differential diagnosis must be elaborated with two other RASopathies, namely NS and CS. More precisely, in a prenatal setting, CFCS signs may be absent, thus not enabling accurate diagnosis, whereas postnatal prognosis on intellectual disability and cancer risk outcomes may differ [12]. In the absence of established clinical diagnostic criteria, it is, indeed, difficult to differentiate CFCS from a severe NS form. Precise genotype identification/definition may ensure better prognosis. While the prenatal characteristics of NS and CS have been extensively described in the literature, we have retrieved only six manuscripts focused on CFCS via PubMed search [11, 13–17]. Moreover, there is no report available dealing with the potential contribution of the prenatal dysmorphic feature assessment concerning any of the syndromes. Advances made in medical imaging, in particular the development of 3D ultrasound, render it possible now to compare the postnatal dysmorphological assessment in comparison to that of the antenatal period. The present report has, thus, been aimed to: 1) present a clinical CFCS case,

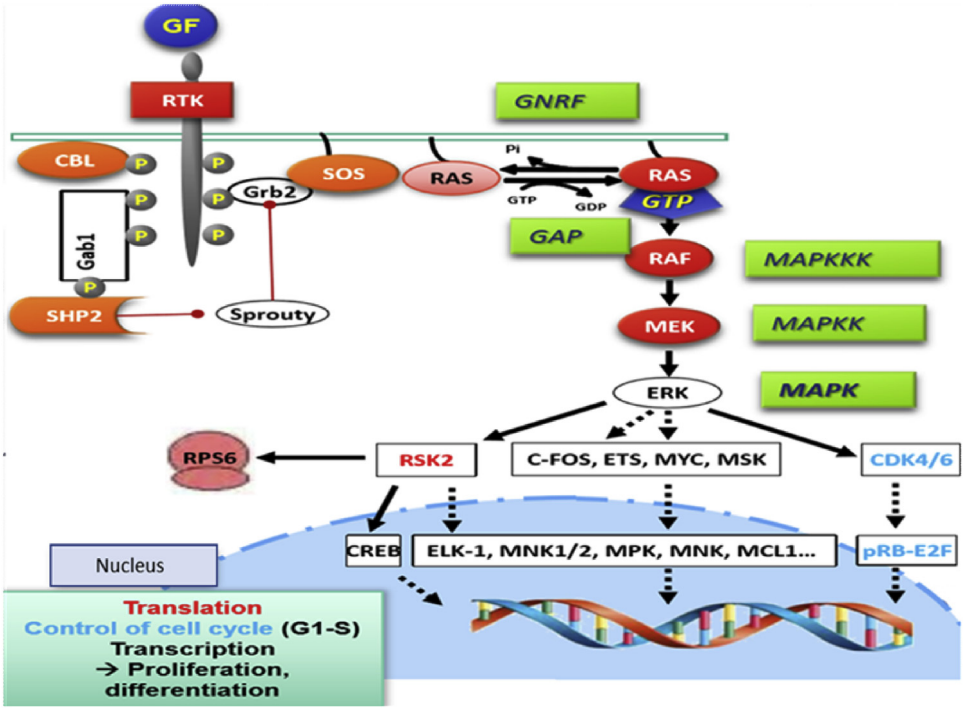

Fig. 1. Illustration of RAS/MAPK pathway. (Reproduced with permission of Professor A. Verloes, Robert Debre Hospital, Paris, France).

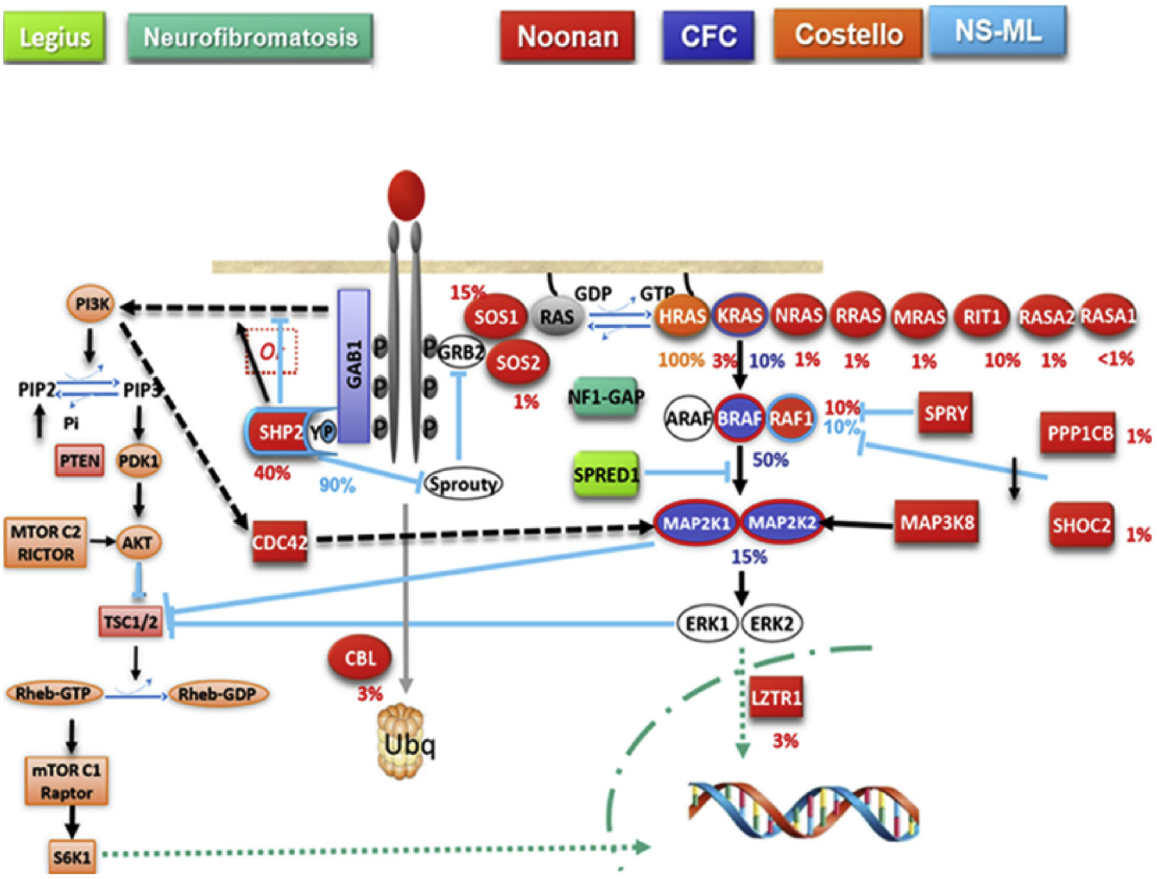

Fig. 2. Illustration of abnormalities along the RAS/MAKP pathway that may lead to different « RASopathies ». (Reproduced and modified with permission of Professor A. Verloes, Robert Debre Hospital, Paris, France).

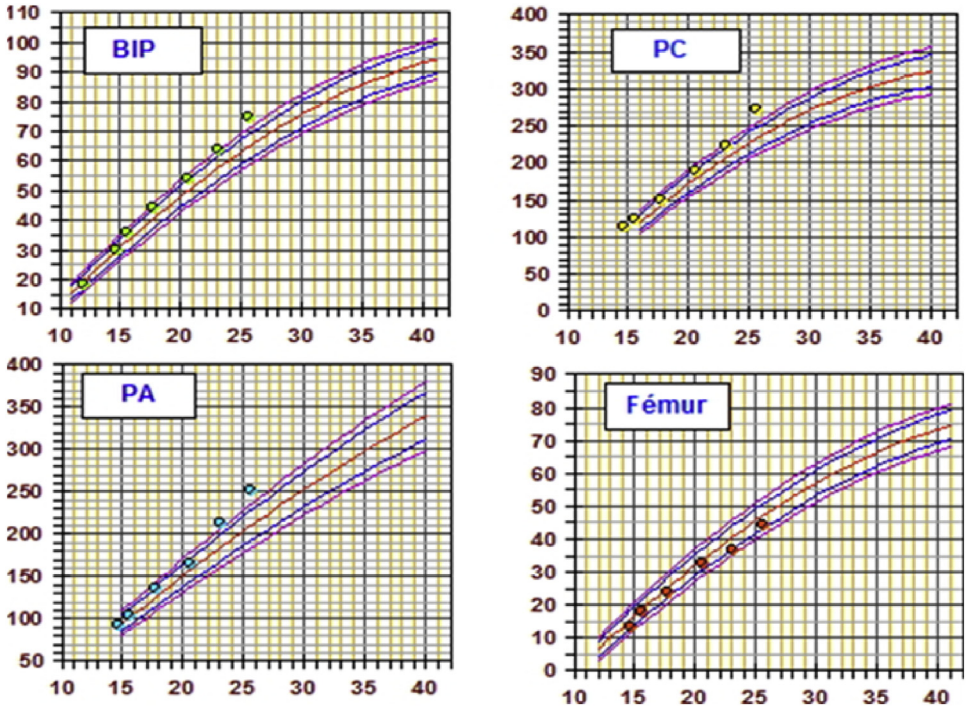

Fig. 3. Growth curves of the main fetal parameters.

with a confirmed new de novo *BRAF* gene mutation, admitted to the Fetal Medicine Unit of Saint-Luc University Hospital in Brussels; 2) review the syndrome's prenatal characteristics; 3) discuss the contribution of prenatal dysmorphological analysis in this setting.

Case report

A 33-year-old woman (G2P0) was referred to the Fetal Medicine Unit of Saint Luc University Hospital in Brussels (Belgium) due to the detection of an 8.3 mm cystic hygroma at the 11th week of gestation. The pregnancy had been obtained through in vitro fertilization (IVF) for andrological reasons, with an advanced paternal age noted (52 years at the time of IVF). A chorionic villous sampling was recommended, owing to the ultrasound anomaly. Aneuploidy was ruled out after analyzing rapid FISH probes for chromosomes 13, 18, and 21, while the molecular karyotype did not detect any copy number variant (CNV) (Microarray: Affymetrix Cytoscan – 750 K). Long-term follow-up consisted of an anatomic ultrasound at the 15th and 17th gestational weeks for early screening and morphologic evaluation. The fetus was identified with a relatively large head circumference, though below +2DS. The complete ultrasound did not allow for the gallbladder to be identified, with an hygroma persistent at 7.7 mm. Fig. 3 provides the growth curves with a progressive fetal macrosomia associated with a relatively short femur around the 10th to 15th percentile. The 20th week ultrasound revealed the following abnormalities: persistence of the cystic hygroma at 10 mm, bilateral pyelocaliceal hypotonia, and persistence of the right umbilical vein, while the gallbladder was identified, as medially located. No cardiac malformation was noted except for a possible post-valvular dilation of the pulmonary artery. This anomaly was, however, not confirmed by the fetal/pediatric cardiologist. An excess of amniotic fluid (Phelan index at 19) was observed. There was no limb edema, nor any other effusion. At the 22th week of gestation, a more detailed examination of the fetal face was carried out. From a strictly sagittal view, the fetus displayed a prefrontal edema (7 mm) and short snub nose (Fig. 4). The upper facial angle was measured at 136° (normal), while the lower facial angle was normal, without any retrognathia noted. The transversal plane through the orbits identified the presence of hypertelorism without anomalies in the eye cavities. Visualization of the 3D face (Fig. 5) confirmed the following dysmorphic signs: hypertelorism, down-slanting palpebral fissures, and a long philtrum. These features may be evocative of a RASopathy. After discussion with a clinical geneticist, it was decided to perform a genotype investigation for a more in-depth genetic counseling. Molecular investigation was conducted on a panel of 12 genes involved in the MAPkinase pathway (HaloPlex Noonan Spectrum panel v1, Agilent, MiSeq), based on fetal DNA extracts from chorionic villi. The pregnancy was reevaluated at a gestational age of 25 weeks to provide an update based on a new ultrasound evaluation and to confront the genotype findings. At this stage, a major polyhydramnios was noted (Phelan index 35). The facial dysmorphic features found are illustrated in Fig. 6. An analysis of the ears in parasagittal view enables us to objectively identify low-set posteriorly rotated ears (Fig. 7). The refined analysis of the external ear proved to be difficult at this rather early age, though suggested an increased helix thickness (Fig. 8).

Within 4 weeks, the RASopathy gene panel results were made available, with an heterozygous change c.1396 G > C in *BRAF* gene identified. This substitution predicts, at the protein level, the replacement of a glycine with an arginine at codon 466 (p.Gly466Arg). This amino acid has been shown to be highly conserved through the species. Though the in-silico data orientate towards a pathogenic effect, this substitution had not yet been

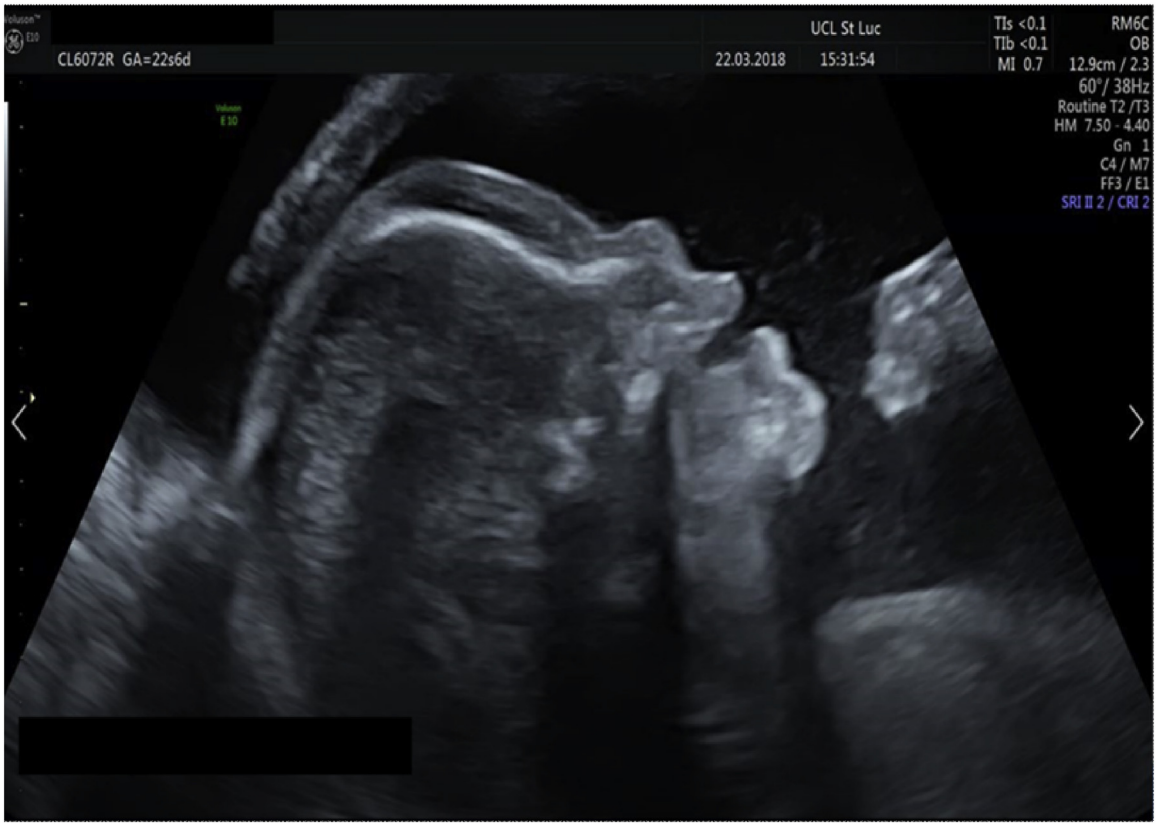

Fig. 4. Fetal profile at 22th week of gestation.

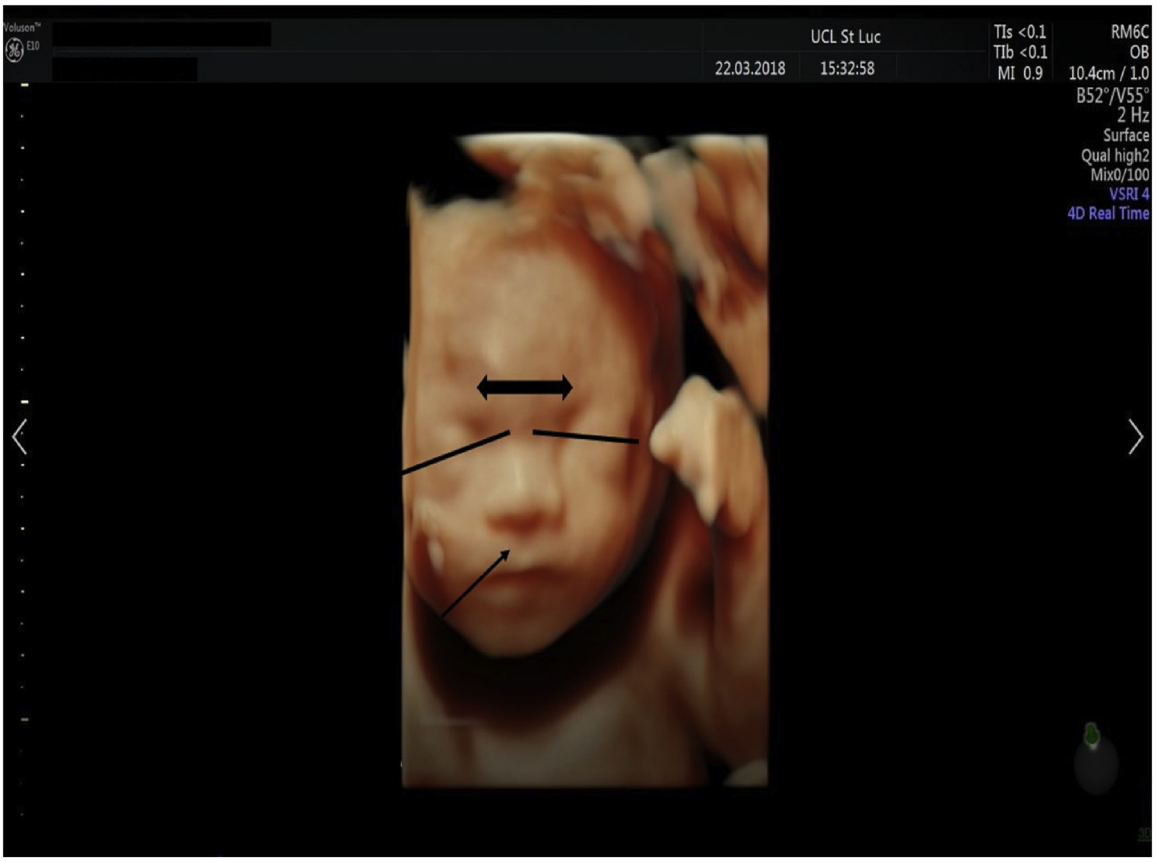

Fig. 5. 3D live fetal face appearance at 22th week of gestation: hypertelorism, down slanting palpebral fissures, long philtrum.

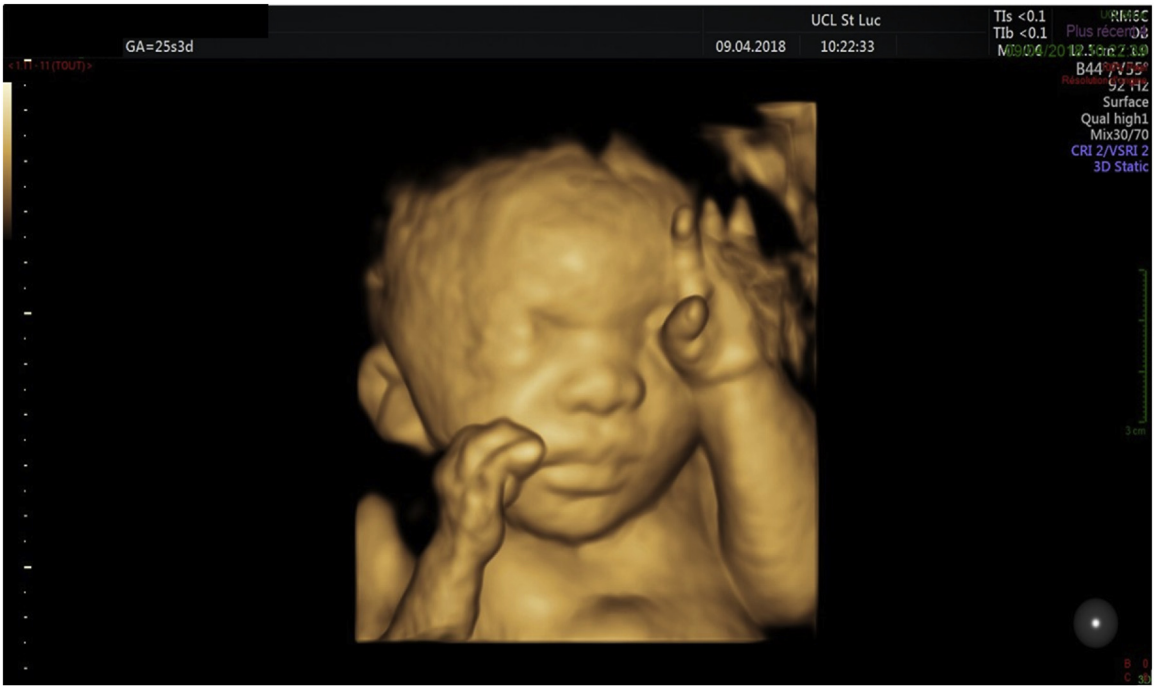

Fig. 6. 3D surfacic mode of the face at 25th week of gestation: hypertelorism, down slanting palpebral fissures, short snub nose, long and marked philtrum.

reported in general population databases, such as ExAC and GnomAD, nor had it been described in either specific database (NSEuroNet) or in the literature reports on patients exhibiting a *BRAF* gene mutation. The parents did not carry this substitution, which further confirms its *de novo* occurrence. Concerning the pathogenic interpretation, a substitution involving the same codon is described as a causal mutation (gain-of-function effect of the pathway (p.Gly466Glu) and responsible for CFCS [18]. Genetic

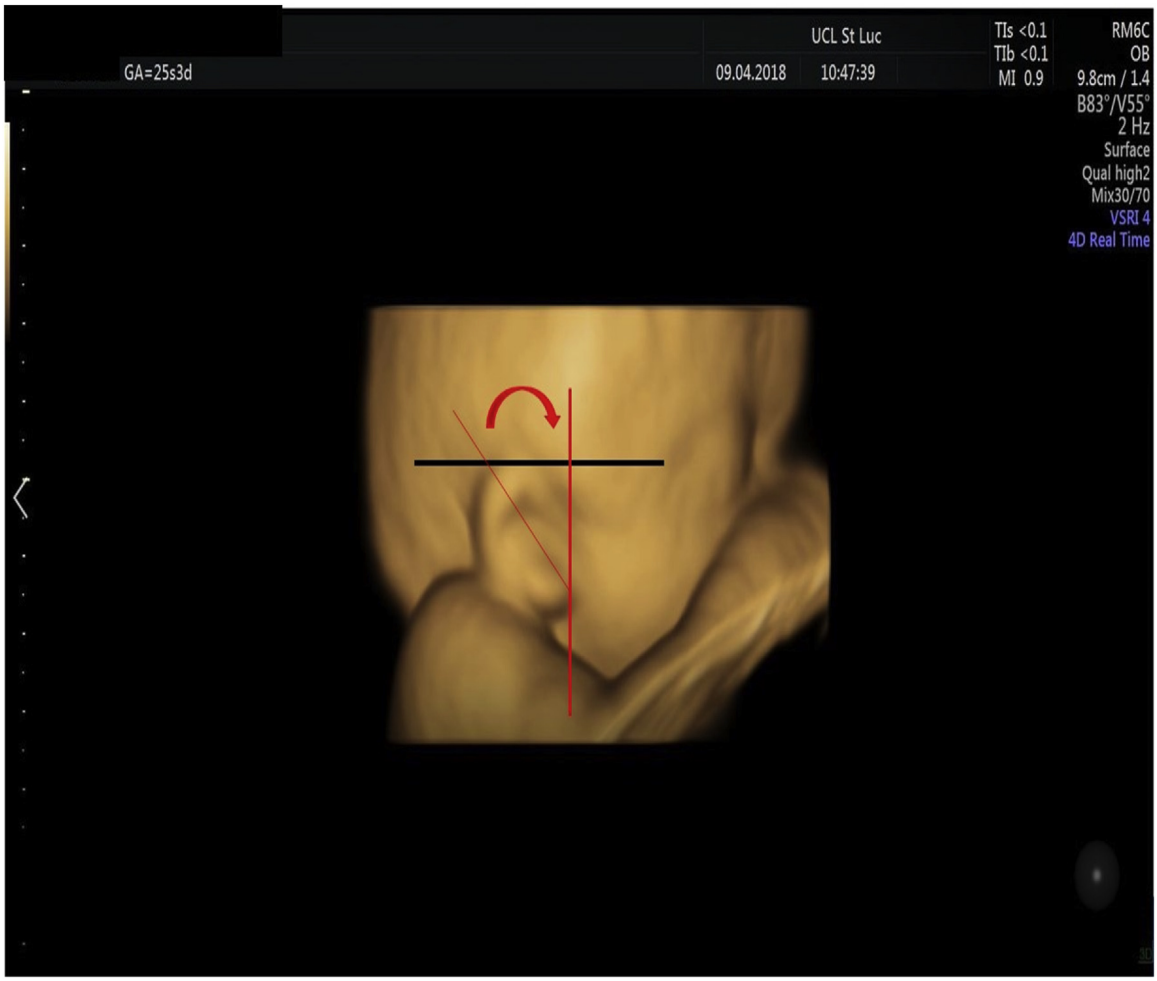

Fig. 7. Low implanted ears in posterior rotation in 3D surfacic mode.

counseling has, therefore, focused on the diagnosis of a RASopathy and the predictable CFCS phenotype, a particular entity with a much more reserved prognosis towards normal intellectual development.

Based on these findings, along with the potential compromised postnatal outcome for intellectual disability/development, the couple asked for termination of the pregnancy (TOP). The prenatal diagnosis committee validated the couple's request and TOP occurred at a gestational age of 27 weeks. The patient gave birth to a boy with the following measurements: weight 1515 g (above the 90th centile), height 38 cm (90th centile), and head circumference 29 cm (above the 90th centile) (reference curves: www.ucalgary.ca/fenton). Macroscopic analysis of the fetus confirmed the dysmorphic signs that had been prenatally identified (Figs. 9 and 10).

Due to its de novo occurrence, genetic counseling with respect to any future pregnancy of the mother is currently based on the risk of recurrence related to germinal mosaicism. This recurrence risk is estimated to be 4% and, based on current guidelines, does not require a pre-implantation diagnosis procedure or early invasive prenatal diagnosis. To rule out this low recurrence risk for any future pregnancy, access for an amniotic fluid puncture should be discussed.

Discussion

CFCS is a rare syndrome that can be diagnosed prenatally, as shown here, in our case. Indeed, careful research for typical RASopathy features and facial dysmorphism can be performed by a trained sonographer, and the anomaly can be suspected and diagnosed through a multidisciplinary collaboration between obstetricians, neonatologists, and geneticists.

This condition has, indeed, a set of prenatal clinical features, rendering it possible to evocate abnormalities of the MAPkinase pathway. The expression of the disease can, indeed, be suspected with the early identification of increased nuchal translucency or a cystic hygroma13. Besides, prenatal lymphatic abnormalities have been reported by Myers et al. [16] to be present in 43% (72/169) of cases in a RASopathy series. These abnormalities were found in 14% (7/51) of CFCS, 53% (54/102) of NS, and 69% (11/16) of CS cases, though this high incidence in CS is not confirmed by all studies [11]. In the Templin et al study [11], two out of 16 fetuses (12.5%) with CFCS exhibited a nuchal anomaly. Other call signs described are the progressive onset of polyhydramnios with macrosomia [13,15,16]. Myers [16] found an overall polyhydramnios rate of 57% (38% (39/102) in NS, 73% (71/97) in CS, and 62% (48/78) in CFCS). Studies targeting CFCS have reported similar values between 62% (Allanson et al [15]) to 67% (Templin et al [11]) and 89% in nine patients separately described by Myers et al [16]. This amniotic fluid anomaly probably reflects the early prenatal onset of swallowing disorders that these children frequently experience during the postnatal period [13]. The rate of a frank macrosomia, defined as an abdominal circumference above the 90th centile, was also shown to vary from one study to another, though found in only 14% (8/56) of the global RASopathies series reported by Myers et al. [16]

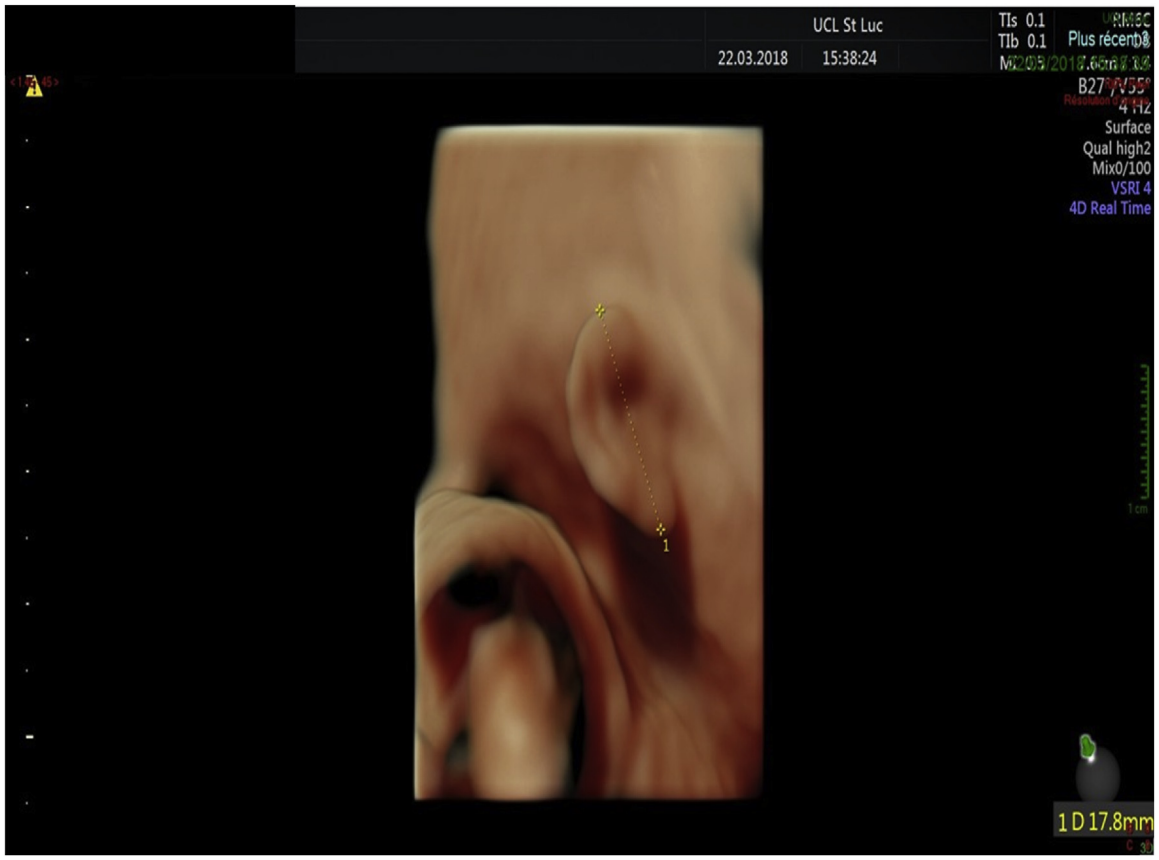

Fig. 8. Pavilion appearance of the ear in 3D live mode.

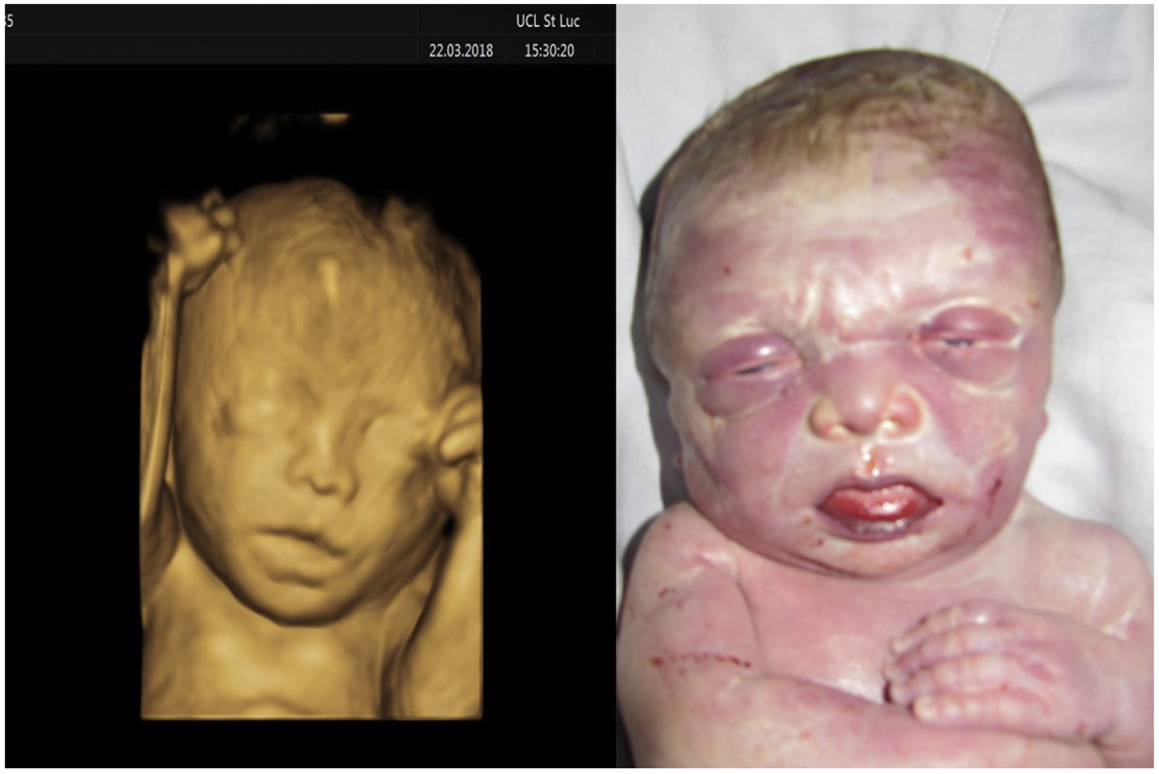

Fig. 9. Pre- and postnatal appearance of the face (front view).

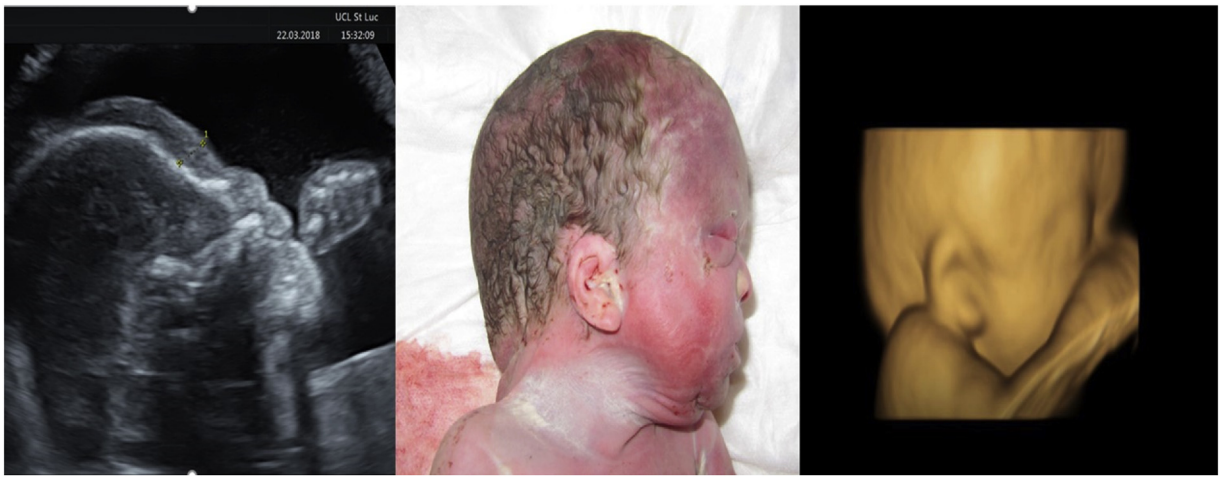

Fig. 10. Pre- and postnatal appearance of the face (lateral view).

(25% [1/4] in NS, 100% [3/3] in CS, and 8% [4/49] in CFCS). Studies conducted by Allanson et al. [15] and Templin et al. [11] focused on CFCS reported rates of 34% and 77%, respectively. Macrocephaly, defined as a cranial perimeter above the 90th centile, is also a sign associated with RASopathies and reported by Myers et al. [16] in 20% (4/20) of her case series (25% [1/4] in NS, 29% [2/7] in CS, and 11% [1/9] in CFCS). Templin et al. [11] found the anomaly in 33% of CFCS in the second trimester of pregnancy and in 72% in the third trimester. However, higher measurements of the cephalic pole and the abdomen contrast with a paradoxical shortening of the femur noted by Templin et al. [11] in 81% (13/16) of fetuses carrying CFCS. This particularity had previously been described by others in the three entities, as mentioned by the author. These traits were all present in our case report and must, therefore, evocate the possibility of a RASopathy. Other less-specific malformations may orientate the diagnosis, such as cardiac, urinary, and lymphatic anomalies, and are common to all three syndromes. In CFCS, approximately 75% of patients are likely to develop a cardiac abnormality, the most common being pulmonary valve stenosis, septal defects, and hypertrophic cardiomyopathy [8]. However, the rate of detecting prenatal cardiac abnormalities remains low due to the at times late and progressive onset of symptoms [13]. Myers et al. [16] reported only one out of 9 (11%) cases of their cohort, with prenatal heart disease diagnosis. In the Templin et al. [11] series, a case of cardiac asymmetry was described out of 16 cases, though this anomaly was not confirmed by postnatal ultrasound. In our case, dilation of the pulmonary artery exactly after the valve was similarly suspected at 22 weeks by the antenatal sonographer, without being confirmed by the fetal pediatric cardiologist at this stage of pregnancy. We cannot, of course, rule out a later evolution towards valvular stenosis. Renal abnormalities were likewise reported to occur with a higher frequency. Within the CFCS framework, they are estimated to affect between 17 and 33% [8,15] of cases, involving pyelectasis, hydronephrosis, or increased kidney volumes. This increased prevalence was confirmed in the Myers et al. [16] (14%, *i.e.*, 7/49) and Templin et al. [11] (47%, *i.e.,* 7/15) studies.

All these associated malformative signs should, therefore, draw the attention of the obstetrician towards the potential risk of a RASopathy. Nevertheless, given that these anomalies are not specific and not always simultaneously present, they do not guarantee a fully accurate diagnosis, as they can be present in many other conditions. Beckwith-Wiedmann syndrome, Simpson-Golabi-Behmel syndrome, or maternal diabetes are some examples.

As underlined by the current case report, a detailed analysis of the facial morphology (from the second trimester of pregnancy onwards) can bring, in certain situations, more evocative elements for the diagnosis. The systematic approach of dysmorphological examination, such as the one conducted for the newborn or the child, must be applicable to any prenatal ultrasound anatomic evaluation involving the three classic incidences of the two-dimensional echography, namely the sagittal, transverse, and frontal views. With the development of 3D-ultrasound, a finer analysis of facial and ear features is likely to be accessible shortly. Altogether, we recommend discreet evaluation of the following parameter set: the forehead, eyes, palpebral fissures, nose, philtrum, mouth, lips, tongue, palate, chin, and ears [19]. In our case report, the description of the face definitively provided the clue to initiate molecular investigation targeted at a RASopathy: hypertelorism, palpebral fissures oriented downwards and outwards, short snub nose, long and marked philtrum, and low-implanted ears in posterior rotation. However, the limitations of this prenatal examination must be kept in mind. First, the conditions of the examination can render the analysis difficult. Maternal obesity, fetal position with anterior column, oligohydramnios, anterior placenta, or the very end of pregnancy are circumstances that do not always enable the acquisition of quality images. Second, the morphology of the face does evolve during pregnancy and in postnatal life. In the first trimester of pregnancy, the face's lower and middle areas are more advanced than the upper area, while the ear is in a very low position. It may be preferable to restrict this dysmorphological examination to fetuses of the well-established second trimester or the beginning of the third trimester. Third, the age of the dysmorphic feature onset in genetic syndromes proves to be quite variable, namely sometimes early, sometimes late, or even post-birth. Several diagnostic features will not always be present, while some parameters may be difficult to interpret, being not sufficiently distinct or precise, or even un-evaluable. The analysis of eyelashes, eyebrows, or hair is currently still inaccessible for most sonographers. Dysmorphology is a real medical specialty requiring experience, with a very good knowledge of the normal face and its variability. It is, therefore, essential that the prenatal approach to dysmorphism be provided in a multidisciplinary setting, combining a sonographer experienced in investigating the normal face and a trained dysmorphology geneticist. Nevertheless, it is likewise crucial that obstetricians as reference sonographers develop expertise in dysmorphology and fetal syndromology [20]. This diagnostic approach is only possible if strict recommendations are respected. It should be part

of other pregnancy information, such as family surveys, fetal biometrics, psychomotor development of relatives, paraclinical examination results, and sometimes the clinical examination of both parents. If the analysis of the face is routinely performed to look for malformations, such as facial clefts or ocular abnormalities, the dysmorphic examination cannot be carried out in all pregnancies, owing to the risk of generating numerous false positives. It should rather come to complete the morphologic examination of the fetus presenting with major or minor malformative signs (isolated or associated malformations, polyhydramnios, fetal growth disorders), generally after ruling out the presence of any CNV on SNP-array.

The presence of a RASopathy during the prenatal period can be suspected, as we have seen, based on various non-specific abnormalities: polyhydramnios, macrosomia with short long bones, macrocephaly, renal or lymphatic, and cardiac abnormalities [11,16]. The detection of facial dysmorphic signs certainly allows for diagnostic rates to be increased. Nevertheless, based on antenatal ultrasound, establishing the differential diagnosis between NS, CS, or CFCS remains difficult. The characteristic features, along with their frequencies, of the three entities have been well summarized in the Myers A et al. publication [16]. Finally, the formal diagnosis must always be based on the molecular analysis, using pathogenic mutations based on a panel of RASopathies genes, including *PTPN11*, *SOS1*, *RAF1*, *BRAF*, *KRAS*, *MEK1*, *MEK2*, *HRAS*, *NRAS*, *SHOC2*, *CBL*, and *RIT1*. In our case, we used the Belgian reference genetic center at the KUL, Leuven, in charge of the RASopathy gene panel sequencing. Diagnostic confirmation was obtained within 4 weeks. The turnaround time is usually obtained within 15 working days when interpretation proves to be straightforward (wild-type or class 4 and 5 substitutions). In our case, the prescription for the RASopathy gene panel was performed later, at the 22nd gestational week, when a secondary call sign was recorded. Indeed, the presence of one isolated feature like cystic hygroma in the first trimester without any CNV on molecular karyotype was not considered to be distinctive enough for a gene panel analysis to be carried out from the outset. Bakker et al. [21], Croonen et al. [22], and Mucciolo et al. [23] recommended prenatal sequencing for the RAS gene panel in pregnancies with increased nuchal translucency or cystic hygroma to be performed in the presence of at least one of the following additional features: polyhydramnios, hydrops fetalis, renal anomalies, distended jugular sacs, hydrothorax, cardiac anomalies, ascites, or specific facial abnormalities. To date, one retrospective cohort study conducted by Hakami et al. [24] supported RASopathy molecular screening to be performed when one single criterion was recorded because the mutation detection rate reached 67%. Stuurman et al. [25] recently reviewed a 6-year prenatal RASopathy testing conducted in the Netherlands. Only 40 pathogenic variants were detected over 424 fetal samples (9.4%) based on different ultrasound findings. The authors recommended a RASopathy prescription when fetuses were identified with isolated nuchal translucency $\geq$5.5 mm. These last two studies raised the issue concerning the high prevalence of nuchal translucency or single call sign, and the figures these authors reported seemed to be well above the RASopathy prevalence rates. One additional comment relies on the use of public health resources while extending molecular or complementary investigations. In Belgium, pregnancy termination may be validated at any gestational age, provided it is supported by a medical indication of poor prognosis. Healthcare systems operate inside an annual closed budget (the cost for an NGS multiple genes panel attains 1350 euros for index patients, with an additional 300 euros needed for de novo confirmation/absence to both parents). In this context, it is paramount to evaluate the effectiveness and diagnostic strategy on consistent and validated recommendations, along with a cost/benefit approach.

Another interesting point arising from our case report is that we have highlighted a new pathogenic mutation in the *BRAF* gene (mutation c.1396 G > C; p.Gly466Arg) submitted to the NSE database. The discussion of the pathogenic nature of this so-far unreported substitution was completed by the description of our clinical case. It is only based on this molecular analysis that the formal CFCS diagnosis could be made and genetic counseling be offered. Since the present substitution had not yet been reported, additional time was taken to guarantee appropriate variant classification (Class 4 – likely pathogenic). The phenotype of patients with a *BRAF* gene mutation encompasses typical RASopathy features, being more prone to develop moderate-to-severe intellectual deficits, feeding difficulties, and a failure-to-thrive [15].

In conclusion, as underlined in this report, our work based on a careful search for ultrasound features has enabled the diagnosis of a rare condition with a precise prognosis. This effective management has been the result of a multidisciplinary collaboration between dysmorphology obstetrician sonographer, neonatologist, and geneticist. The prenatal CFCS presentation is often characterized by polyhydramnios associated with macrosomia/relative macrocephaly, paradoxical shortening of the femur, and mainly cardiac, renal, and lymphatic abnormalities. These fetuses may already exhibit characteristic facial dysmorphic features, such as a triangular face, large front with bitemporal narrowing, relative macrocephaly and down-slanting palpebral fissures. When present, these abnormal signs suggestive of a RASopathy should orientate the diagnostic approach towards a molecular strategy targeting the panel of genes within the MAP kinase pathway.

Declaration of competing interest

The author(s) declared no conflict of interest with respect to the research, authorship, and publication of this article.

Data availability statement

The data that support the study findings can be made available by the corresponding author upon reasonable request.

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