Received: 23 November 2022 | Accepted: 18 April 2023

DOI: 10.1002/ajmg.a.63223

AMERICAN JOURNAL OF medical genetics PART A WILEY

CASE REPORT

De novo *RANBP2* variant in a fetal demise case with cerebral intraparenchymal hemorrhage

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Abstract

Fetal intracranial hemorrhage (ICH) may result from a wide array of causes, either associated with maternal or fetal risk factors. In the last decade, monogenic causes of susceptibility to fetal ICH have been described, in particular in association with *COL4A1* and *COL4A2* genes. A peculiar form of ICH is acute necrotizing encephalitis (ANE), which is characterized by a rapid-onset severe encephalopathy following an abnormal inflammatory response to an otherwise banal infection. It usually affects healthy children and it is thought to be multifactorial, with a genetic predisposition. *RANBP2* gene has been extensively associated with ANE susceptibility. We hereby present a unique case of a 42-year-old secundigravida with intrauterine fetal demise at 35 weeks of gestation. Trio-based whole-exome sequencing performed on both parents and fetal DNA showed a de novo likely pathogenic variant in the *RANBP2* gene on 2q13. At the fetal autopsy, subtentorial hematoma and cerebral intraparenchymal hemorrhage were present. We speculate that this might be a new phenotypic presentation of *RANBP2*-associated disease. However, more similar fetal cases need to be reported in order to reinforce this hypothesis.

KEYWORDS
acute necrotizing encephalopathy, fetal intracranial hemorrhage, intrauterine demise, prenatal diagnosis, RANBP2

1 | INTRODUCTION

Fetal intracranial hemorrhage (ICH) may result from different causes, either associated with maternal risk factors (i.e., maternal hypertension, preeclampsia and eclampsia, maternal alloimmune antiplatelet antibodies, coagulation disorders, placental dysfunction, seizures, severe trauma, drug use) or fetal risk factors (i.e., severe fetal anemia, congenital infections, congenital coagulopathy, congenital tumors, twin–twin transfusion syndrome, demise of a cotwin, and fetomaternal hemorrhage) (Ghi et al., 2003; Sherer et al., 1998; Sileo et al., 2022). However, in up to 50%–75% of cases, no identifiable cause is identified (Hausman-Kedem, Malinger, et al., 2021). Monogenic causes of ICH have been recently described, in particular in association with *COL4A1* and *COL4A2* pathogenic variants (Hausman-Kedem, Ben-Sira, et al., 2021; Hausman-Kedem, Malinger, et al., 2021; Lichtenbelt et al., 2012). The phenotype associated with

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alterations in these genes is very variable, ranging from prenatal hemorrhage to postnatal brain small vessels disease or even pediatric hereditary angiopathy with nephropathy, aneurysms, and muscle cramps (HANAC syndrome) (Zagaglia et al., 2018).

Acute necrotizing encephalopathy (ANE) is mostly known as a pediatric disease. It affects previously healthy children and is characterized by fever and rapidly-progressing neurologic symptoms, such as seizures and coma, occurring within days after an infectious illness. Rates of neurological sequelae are elevated, leading to the death of the patient in up to 30% of cases (Morishima et al., 2002). The triggering infectious agents are mostly respiratory viruses, but cases following bacterial infections have been reported, particularly with *Mycoplasma pneumoniae* (Mizuguchi et al., 2021). It is still unclear how the infection leads to the neurologic sequelae: in contrast with classic viral or bacterial encephalopathies, in ANE there is no pathological evidence of infection or inflammatory cell infiltration (Mizuguchi et al., 2007). In children with ANE, brain magnetic resonance imaging (MRI) shows multiple symmetrical lesions affecting the thalami (Mizuguchi et al., 2021). Other areas involved are upper brainstem, periventricular white matter, internal capsule, putamen, upper brainstem tegmentum, and cerebellum (Wu et al., 2015). Treatment of this condition is based on supportive therapy, steroids, and immunoglobulins (Mizuguchi et al., 2021; Okumura et al., 2009). It is hypothesized that a genetic predisposition causes an exaggerated response to the infectious insult, involving metabolic and mitochondrial derangements and deregulated immunological response, with the induction of an uncontrolled cytokine storm (Neilson, 2010). Interestingly, the microbial agent seems to make no difference in disease severity (Lindahl & Bryceson, 2021), suggesting that genetic factors influence the course of the disease more than the infectious trigger. Although its incidence is unknown, ANE is likely a rare condition (Wu et al., 2015). The first gene discovered in association with ANE was *RANBP2*, while *CPT2* variants have been more recently associated (Kobayashi et al., 2019). RANBP2 protein has several different roles within the cell, and it has been hypothesized that ANE could be a consequence of altered nuclear signaling causing a cytokine storm, in combination with altered metabolism and/or mitochondrial function (Levine et al., 2020). *RANBP2* missense pathogenic variants have been described in multiple families so far (Neilson et al., 2009; Singh et al., 2015). RAN Binding Protein 2 (RANBP2) is a nuclear pore protein expressed ubiquitously, characterized by a broad range of intracellular functions. The inheritance of *RANBP2*-associated ANE is autosomal dominant with incomplete penetrance and variable expressivity (Gika et al., 2010), making the risk of development of ANE 40% in a subject carrying the pathogenic variant (Neilson et al., 2003). To our knowledge, no cases of fetal ICH in association with a *RANBP2* variant have been reported in the literature. We hereby present a case of fetal demise which may be linked to a *RANBP2* likely pathogenic variant and hypothesize a new *RANBP2* phenotypic association with prenatal onset.

2 | CASE PRESENTATION

A 42-year-old woman, gravida 2 para 1, pregnant at 35 weeks and 1 day of gestational age without significant comorbidities, presented to our attention in active labor with no evidence of fetal heartbeat. The pregnancy was uneventful and she did not report fever, abdominal pain, nor vaginal discharge. The patient had a healthy girl from a previous pregnancy with a different partner; there was no consanguinity with the present partner and family history was negative for genetic diseases, congenital malformations, or infant sudden deaths. In the current pregnancy, the Non-Invasive Prenatal Testing resulted in low risk, and ultrasound scans were normal. The patient was admitted for the abortive labor. After delivery, Gram positive, Gram negative bacteria, and Mycoplasmataceae infections at the fetal oropharynx and at maternal and fetal sides of placenta were excluded. The bacterial research was completed with the vaginal and endocervical swabs collected from the patient at the time of admission, which were all negative with the exception of the endocervical swab, which resulted positive for *Mycoplasma hominis* with high bacterial load (10,000 UFC/mL) and resistance to macrolides and tetracyclines. The mother was negative for SARS-COV19, HIV, HBV, HCV, Parvovirus B19, and Enterovirus. She was immune to *Cytomegalovirus*, *Rubella*, and *Toxoplasma gondii* as per preconceptional serologies. No postmortem imaging of the fetus was performed.

Samples of placenta, umbilical cord, fetal skin, and bones were sent for genetic testing. Conventional karyotyping on fetal skin biopsy was infeasible due to poor specimen quality. Chromosomal microarray showed no pathological microdeletions or duplications.

The analysis of the placenta demonstrated features of both fetal and maternal vascular malperfusion. Placenta weight was on the third centile for gestational age and 70% of its volume was occupied by thrombo-hematomas and organized infarctions. Obliterative fetal vasculopathy and aspects of hemorrhagic endovasculitis were observed, indicating ante-mortem fetal vascular malperfusion. At the level of the membranes, mild acute chorionitis was present (stage I, grade I) (Khong et al., 2016). The post-mortem examination described a female fetus with normal morphological features. The biometry was overall low for the gestational age, with a fetal weight, measured right after delivery, at the first centile (Nicolaides et al., 2018). Notably, at the brain level, a voluminous hematoma subtentorial in the posterior cranial fossa and a cerebral intraparenchymal hemorrhage were found. The state of poor conservation of the brain tissue did not allow a correct evaluation of the topography of the lesions. No alterations in the remaining fetal organs were observed. Based on the post-mortem findings, Trio whole-exome sequencing (WES) was carried out, leading to the identification of a de novo heterozygous variant, c.2387 C>T, p.Ser796Phe, in *RANBP2* gene. The variant was classified as likely pathogenic according to ACMG criteria (PM2, PP3, and PS2 criteria of pathogenicity) (Richards et al., 2015). Post-hoc comprehensive viral analysis was performed on the sample and was negative for multiple pathogens.

3 | DISCUSSION

The pregnancy of our fetus had been uneventful until the mother presented with unexplained abortive labor at 35 + 1 weeks of gestational

age. Pathological examination of the placenta identified features of fetal and maternal vascular malperfusion. The female fetus had normal morphology and no major internal organs abnormalities and it had a lower than expected biometry for gestational age. The only major fetal abnormality identified was a subtentorial hematoma in the posterior cranial fossa together with cerebral intraparenchymal hemorrhage. The vascular phenotype was likely the cause of the demise, but no environmental cause that could justify it was found. In particular, no infectious agent was isolated apart from *M. hominis* on the endocervical swab; however, this pathogen tends to be very common in the general population and is only rarely linked to preterm birth and midtrimester abortions in colonized women (Donders et al., 2017).

Standard microarray analysis did not identify any remarkable microdeletion or microduplication alteration, while WES allowed to detect a de novo variant in the *RANBP2* gene. We therefore hypothesized that this genetic finding might have had a role in the fetal presentation with a new mechanism of pathogenicity compared to what has been previously described for the gene. Our idea is that *RANBP2* alterations might confer susceptibility to ICH in the prenatal period, differently from the ANE described in pediatric and adult patients and possibly in the absence of an identifiable infectious trigger. This would parallel the variable prenatal and postnatal phenotype described in association to pathogenic variants in *COL4A1* and *COL4A2* genes. Indeed, both genes have been reported to cause prenatal susceptibility to hemorrhage, while also being associated to a variable phenotypic spectrum in pre and postnatal life, ranging from porencephaly and periventricular leukoencephalopathy to ophthalmological alterations and extracerebral findings such as renal cysts and elevated creatinine kinase (Meuwissen et al., 2015). *COL4A1* and *COL4A2*-associated phenotypes present not only with variable expressivity, but also with reduced penetrance, as it is the case of ANE for *RANBP2* gene. We speculate that this might also be true for a possible RANBP2-associated susceptibility to fetal hemorrhage. More similar cases would however need to be described in order to have concrete reference to draw conclusions on, and also for establishing whether the fetal hemorrhage was, in our case, concurrent with or a consequence of the placental malperfusion. Additionally, the role of an infectious trigger in the prenatal setting needs to be further investigated.

At the time being, it is not clear how pathogenic variants in *RANBP2* can, in presence of an infection, cause ANE. To date, 11 ANE-associated variants have been found in *RANBP2*, with Thr585Met being the most common one (Alawadhi et al., 2018; Bashiri et al., 2020; Hu et al., 2022) (see Figure 1). All the variants reported in literature are missense, it must however be stressed that only three variants have been repeatedly been found in different families with ANE, and are therefore well-associated with disease, notably Thr585Met, Thr653Ile, and Ile656Val (Neilson, 2014).The variant detected in our fetus has never been described in literature and it is not located in any specific domain or repeat region of the RANBP2 protein (Figure 1). Our variant is considered likely pathogenic based on PM2, PP3, and PS2 criteria of pathogenicity from ACMG guidelines; functional studies are however needed in order to demonstrate the effect of the variant on the protein, especially in association with a new prenatal phenotype.

Overall, it would be important to consider ANE as an etiological factor of fetal morbidity and mortality when suggesting findings are encountered at the brain level in the prenatal setting or during an autopsy. Due to decreasing costs of Next Generation Sequencing technology, WES and whole genome sequencing (WGS) are increasingly used in the clinical setting (Clark et al., 2018). In centers where either WES or WGS are available, it would be advisable and cost-effective to include RANBP2 within gene panels for cases of fetal demise, since there would be no associated increase in costs and

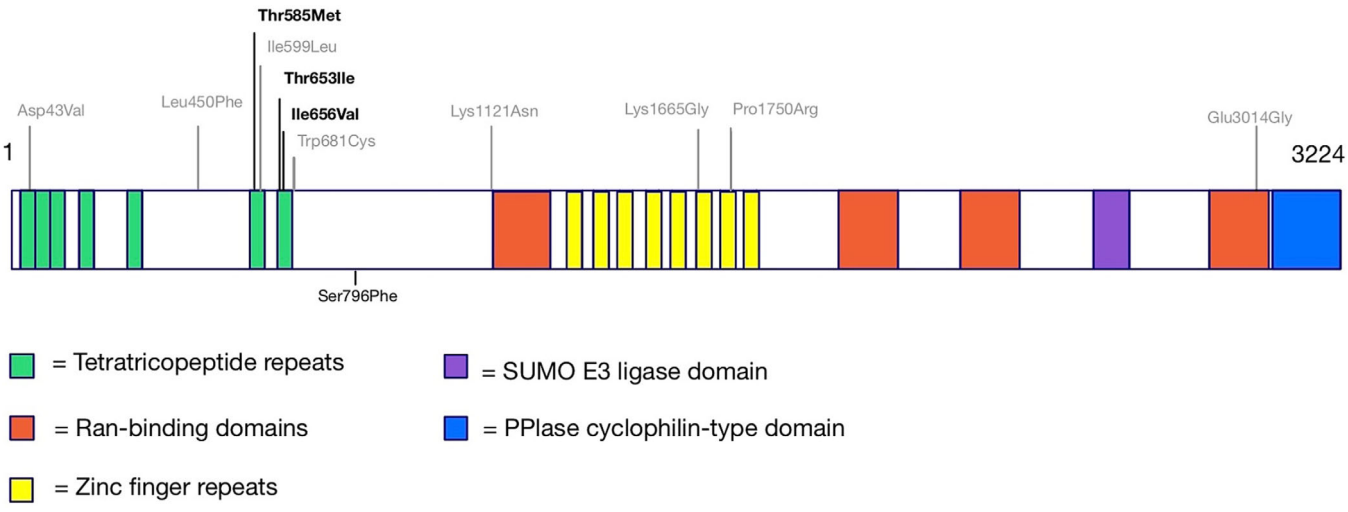

FIGURE 1 RANBP2 protein structure and location of the variants currently reported in the literature. There are only three variants that have been consistently found in different families in association with ANE (highlighted in bold); all the other previously published variants, in light gray, have only been reported in single cases and further validation of their pathogenicity is needed. The variant described for our patient is reported in black in the lower part of the protein. ANE, acute necrotizing encephalitis.

valuable data for future reference might be produced, allowing to identify other cases of fetal demise in which altered RANBP2 function might have played a role.

WES is still not routinely performed in cases of fetal demise due to lack of familiar interest and/or high costs, and it is therefore likely that many diagnoses and opportunities to better understand human development are lost on the way (Scheimberg, 2013; Stanley et al., 2020). Once NGS sequencing is performed, it is however cost-effective to include new genes in silico panels for a specific presentation, as no further experiment is needed to obtain the data. We would therefore recommend to include *RANBP2* in panels performed in cases of fetal demise with unknown etiology. This would help more cases to be uncovered in the future and to establish a clearer genotype–phenotype correlation for *RANBP2* pathogenic variants in the prenatal setting. It would furthermore be interesting to investigate whether cases of unexplained fetal demise are present in extended families in which a diagnosis of genetic ANE has been established in the past, as this might be a detail not spontaneously reported by family members and must be explicitly asked for.

4 | CONCLUSIONS

This could be the first reported case of fetal intracerebral hemorrhage associated with a novel missense variant in *RANBP2*. This is however an isolated finding that will need validation in further cases. We therefore invite laboratories to include this gene in NGS panels performed for fetal pathology and report whether other significant variants in the gene emerge. Furthermore, we encourage clinicians following families with established diagnosis of familial ANE to investigate whether cases of unknown fetal demise are present, in order to try and understand whether susceptibility to intracerebral hemorrhage might be included in the RANBP2-associated spectrum.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Meroni, A., Kalantari, S., Arossa, A., Spinillo, A., Melito, C., Scatigno, A. L., Cesari, S., Giorgio, E., Furione, M., Homfray, T., & Sirchia, F. (2023). De novo *RANBP2* variant in a fetal demise case with cerebral intraparenchymal hemorrhage. *American Journal of Medical Genetics Part A*, 1–5. https://doi.org/10.1002/ajmg.a.63223