Cerebro-oculo-facio-skeletal syndrome caused by the homozygous pathogenic variant Gly47Arg in ERCC2

Janine Reunert | Alijda van den Heuvel | Stephan Rust | Thorsten Marquardt

Universitätsklinikum Münster, Klinik für Kinder und Jugendmedizin, Münster, Germany

Correspondence
Thorsten Marquardt, Klinik für Kinder und Jugendmedizin, Albert-Schweitzer-Campus 1, Gebäude A13, 48149 Münster, Germany. Email: marquat@uni-muenster.de

Abstract
DNA damage repair is a pivotal mechanism in life. The nucleotide excision repair pathway protects the cells against DNA damage and involves XPD, an ATP dependent helicase that is part of the multisubunit protein complex TFIIH. XPD is encoded by the excision repair cross-complementation group 2 gene (ERCC2). Only three patients with cerebro-oculo-facio-skeletal syndrome (COFS), caused by mutations in ERCC2, have been published so far. This report describes a boy with the homozygous amino acid change p.Gly47Arg in XPD. He presented with profound microcephaly, psychomotor retardation, failure to thrive, cutaneous photosensitivity, a bilateral hearing deficit and optic atrophy, thrombocytopenia, and recurrent episodes of pneumonia. We report the first homozygous occurrence of the pathogenic variant Gly47Arg in the ERCC2 gene. Occurring homozygous, this variant was associated with COFS syndrome, leading to early death of the patient at the age of 21 months.

KEYWORDS
COFS, DNA damage repair, ERCC2, XPD

1 | INTRODUCTION

In order to preserve DNA fidelity, eukaryotic cells have developed various DNA repair pathways. The nucleotide excision repair (NER) pathway removes bulky adducts starting with a damage recognition step followed by opening of the double stranded DNA and adduct removal, requiring the interaction of specialized protein complexes (Spivak, 2015).

TFIIH is a multisubunit protein complex that is involved in NER as well as in regular transcription (Compe & Egly, 2012; Oksenych & Coin, 2010). The TFIIH complex consists of a core-complex including the proteins XPB, p62, p52, p44, p34, trichothiodystrophy (TTD)-A and XPD, and the CAK module comprised of CDK7, cyclin H, and MAT1; core complex and CAK module are thought to be linked by the XPD protein (Oksenych & Coin, 2010).

Excision repair cross-complementation group 2 gene (ERCC2), the coding gene for XPD, is located on chromosome 19q13.3, has 23 exons and produces a protein of 761 amino acids with a molecular weight of 86.9 kDa. Variants in ERCC2 can lead to different autosomal recessive DNA repair disorders including xeroderma pigmentosum (XP), TTD, Cockayne syndrome (CS), and a severe form of CS known as cerebro-oculo-facio-skeletal syndrome (COFS). The clinical spectrum ranges from mild to severe including early death (Faghri, Tamura, Kraemer, & DiGiovanna, 2008; Fassihi et al., 2016; Suzumura & Arisaka, 2010; Wilson et al., 2016).

We report on a patient with the homozygous Gly47Arg amino acid change in the ERCC2 gene (XPD), leading to COFS syndrome and early death at the age of 21 months. He is the first published homozygous Gly47Arg patient and the fourth patient diagnosed with COFS syndrome due to variants in the XPD gene.

2 | MATERIALS AND METHODS

EDTA blood samples were obtained from the patient and his parents after informed consent. Exome sequencing as trio analysis of the DNA...
of the patient and his parents was performed as described previously (Park et al., 2019). Synonymous variants and variants in the UTR region were excluded. All variants with a minor allele frequency of >2% were also excluded and remaining variants were first compared with an in-house database of >100 exomes and pathogenicity was afterward rated using the prediction tool MutationTaster (Schwarz, Cooper, Schuelke, & Seelow, 2014). Only variants that occurred less than five times in our in-house database and were predicted to be “disease causing” by MutationTaster, were considered further. Variants in the candidate list were analyzed and interpreted using

FIGURE 1 The patient at the age of 10 and 14 months. He presented with bilateral enophthalmia with nystagmus, unilateral cataract, micrognathia, microcephaly, a prominent nasal bridge, and large ear pinna with deep set ears. Flexure contractures of knees, hips, toes and elbows are evident and his hands were fisted. (a) Development of head circumference, length and weight showing a progressive microcephaly and height and weight partially more than 3 SDs below mean (b)
cumference 32 cm (Z-score = −1.25), length 50 cm (Z-score = +0.06) and occipitofrontal circumference 32 cm (Z-score = −1.94) (see Figure 1b). Besides his microcephaly, a limitation of abduction of the hips and cryptorchidism were noted and he failed the neonatal otocoustic emissions screening. Brain-stem-evoked-response audiometry confirmed bilateral sensorineural hearing loss. In the following weeks, severe failure to thrive, nystagmus, axial muscular hypotonia with increased muscle tone, and flexion pattern in the limbs and light sensitivity of the skin were noted. At 2 months of age, the boy was hospitalized due to feeding difficulties and failure to thrive. A few months later, a cytomegalovirus (CMV) infection was diagnosed with elevation of serum transaminases (AST 122 U/L [<80], ALT 144 U/L [<65]) and he was referred to our hospital.

At the age of 6 months, he presented with microcephaly (see Figure 1), muscle hypotonia, profound failure to thrive, and significantly delayed psychomotor development; reddened dry and scaly skin in sun-exposed areas and a horizontal nystagmus were noted. All his life, he never learned to roll or sit independently. In extensive blood examinations, a hypereosinophilia was noted and confirmed in several independent blood samples. Metabolic screening for congenital disorders of glycosylation and organic acids was normal. No arguments for hematological (thrombocyte count normal), oncologic or immunologic diseases were found. CMV-PCR on neonatal dry blood spot was negative, ultrasound showed no signs suspicious of congenital CMV infection either. MRI showed brain atrophy, a well formed but thin corpus callosum and megacisterna magna; myelination and migration seemed age appropriate. Ultrasound of the abdomen showed no organ enlargement or lesions. Ophthalmologic evaluation found bilateral optic atrophy and posterior polar cataract of the right eye. CMV infection was excluded as explanation for his clinical syndrome and genetic investigations were initiated.

At the age of 10-month, application of a percutaneous endoscopic gastrostomy tube was necessary due to persistent feeding problems with vomiting. Eosinophilia improved and body weight increased (see Figure 1b), although bilious vomiting persisted. Recurrent episodes of pneumonia required frequent hospitalization including intubation and ventilation once.

Figure 1a shows the boy at the age of 10 and 14 months. He had bilateral enophthalmia with nystagmus, unilateral cataract, micrognathia, microcephaly, a prominent nasal bridge and large ear pinna with deep set ears. Flexure contractures of knees, hips, toes and elbows are evident and his hands were fisted. His skin appeared to be dry, scaly, and photosensitive. The parents recall skin reddening and irritations in sun-exposed areas since birth with blister forming. Besides mild facial freckling, no abnormal skin pigmentation was noted at that time.

From the age of 14 months, a persistent and at times severe thrombocytopenia (min. 11,000/μl [206–445 k/μl] see Figure 2) was diagnosed with two relevant bleeding episodes. Platelet transfusions showed no lasting improvement. Differential diagnosis raised suspicion of an inefficient megakaryopoiesis, but at the same time, multiple solid lesions in liver, spleen and kidney were found. These lesions were never fully explained. Tumor markers were not elevated and viral screening was negative. As they were very stable and no growth was noticed over time, an infectious or tumorous origin is unlikely. As he needed a bilateral orchietomy (for cryptorchidism) at the age of 16 months, a liver biopsy was done at the same time to better define these lesions. Pathology of the liver sample showed a mild steatohepatitis with a beginning fibrosis and an increased number of heterolysosomes.

At 18 months of age, predominant clinical symptoms were microcephaly, severe psychomotor developmental retardation (developmental age 8 weeks), failure to thrive, increased muscle tone with contractures of hips and knees, visual and hearing impairment, photosensitivity and numerous and increasing skin pigmentation spots, an incomplete set of primary teeth, thrombocytopenia and recurrent pneumonia. He died at the age of 21 months due to another pneumonia with respiratory failure.

### 3.2 | Mutation analysis

The patient was found to be homozygous for the previously reported pathogenic variant c.139G > A, p.(Gly47Arg) (NC_000019.9: g.45872372C > T; GRCh37) in the ERCC2 gene (Gene ID: 2068). Additionally to MutationTaster (score 0.999999999999247), the Gly47Arg amino acid change is also predicted to be disease causing by the in silico programs Provean and Polyphen2 (Adzhubei et al., 2010; Choi & Chan, 2015); CADD score is 29.4 (Rentszch, Witten, Cooper, Shendure, & Kircher, 2019). The variant has been reported in compound heterozygosity with different defective alleles and different diseases (Cleaver, Thompson, Richardson, & States, 1999; Fujimoto et al., 2005; Horibata et al., 2015; Kondo et al., 2016; Taylor et al., 1997; Theron et al., 2005; Zhang et al., 2017). Both parents are heterozygote carriers and not affected by the disease.

The number of de novo variants was comparable to other in-house exomes. There were no de novo variants in known disease genes.

### 4 | DISCUSSION

The XPD protein belongs to a highly conserved superfamily of ATP-dependent helicases (SF2), which are built by seven helicase motifs, walker motif I, II, III, IV, V, and VI (Bienstock, Skorvaga, Mandavilli,
van Houten, 2003; Gorbalenya & Koonin, 1993). XPB and XPD have 3’ > 5’ and 5’ > 3’ translocation polarity, respectively. It has been suggested earlier that these helicases jointly open the ds-DNA helix at opposite sides of the lesion (Schaeffer et al., 1994). However, they have different roles in transcription and in the NER pathway. Whereas ATPase activity of XPB is required for DNA opening in both processes, the helicase activity is less pronounced in NER. In contrast to XPB, the helicase activity of XPD is pivotal in NER, but less active in transcription (Coin, Oksenych, & Egly, 2007; Dvir, Conaway, & Conaway, 1997; Guzder et al., 1994; Richards, Cubeddu, Roberts, Liu, & White, 2008). Helicase activity of XPD has been shown to be regulated through interaction between the C-terminal end of XPD and the TFIIH subunit p44 (Coin et al., 1998). Most known mutations in ERCC2 are located in the C-terminal region and affect p44 interaction (Coin et al., 1998; Dubaele et al., 2003). The Gly47Arg amino acid change is located in the N-terminus in motif I (AA 35–51), required for ATP binding and hydrolysis to fuel helicase activity. Gly47Arg abolishes these activities completely (Dubaele et al., 2003), however it does not destroy the TFIIH complex. The amount of TFIIH complex containing the Gly47Arg variant is reduced as well as basal transcription (Dubaele et al., 2003). In our Gly47Arg homozygous patient, we observed a phenotype that is largely overlapping with the severe phenotypes of the ERCC2-associated disease spectrum.

COFS is usually caused by mutations in the XPG and CSB gene. Only three patients with COFS syndrome caused by mutations in the ERCC2 gene have been published so far (Graham et al., 2001; Horibata et al., 2015), leading to death in early childhood. The patient described by Graham et al. carried the compound heterozygous amino acid changes Arg616Trp/Asp681Asn and died at the age of 3 1/2 years (Graham et al., 2001). COFS-05-135 (Ile619del/Arg666Trp) died at the age of 12 months due to respiratory insufficiency and COFS-Chiba1 (Gly47Arg/Ile619del) died from pneumonia at the age of 5 months (Horibata et al., 2015). Horibata et al. showed that Ile619del is functionally null and assumed that single expression of Gly47Arg or Arg666Trp was the disease defining cause (Horibata et al., 2015). These findings are in accordance with the severe phenotype of our patient who solely expresses a protein with the Gly47Arg substitution. Gly47Arg has been published in patients with a compound heterozygous genotype (Cleaver et al., 1999; Fujimoto et al., 2005; Horibata et al., 2015; Kondo et al., 2016; Taylor et al., 1997; Theron et al., 2005; Zhang et al., 2017). Of all Gly47Arg compound heterozygotes, one was assessed as XP-D, three as XP-D/CS (mild to severe) and two as COFS, including our patient (see Table 1). As most of the XPD patients carry compound heterozygous variants, a prediction of genotype-phenotype correlations is difficult.

A clear distinction between CS and COFS is difficult as symptoms are overlapping (Laugel et al., 2008; Natale, 2011; Suzumura & Arisaka, 2010). Also in the literature, the classification is not consistent and a few cases that were previously reported as CS, have been proposed later by others to suffer from COFS as they fulfill the diagnostic criteria (Laugel et al., 2008; Natale, 2011). Our patient was born with microcephaly, hip contractures, severe eye, and ear involvement, cryptorchidism and had feeding difficulties from the beginning. These findings together with an extremely severe psychomotor retardation and recurrent infections led to early death at the age of 21 months. Regarding his clinical appearance and severe progress, we would rather define this as COFS instead of severe CS. Recurrent episodes of pneumonia occurred in our patient and also led to death at age < 30 months in approximately 80% of COFS patients (Graham et al., 2001). Thrombocytopenia, which was persistent and clinically relevant in our patient, has been present in at least two other patients with Gly47Arg (see Table 1). These patients have been diagnosed with XP-D/CS. The frequent occurrence of thrombocytopenia suggests that it is a consequence of the ERCC2 defect.
| Patient | First allele | Second allele | Age | Diagnosis | Gender | Intrauterine growth retardation | Microcephaly | Micrognathia | Failure to thrive | Flexion contracture | Thrombocytopenia | Neoplasm of the skin | Hearing impairment | Cutaneous photosensitivity | Cryptorchidism | Abnormality of the eye | Abnormality of the nervous system | Imaging abnormality (MRI/CT) |
|---------|-------------|--------------|-----|-----------|--------|-----------------------------|-------------|-------------|----------------|----------------|--------------|------------------|----------------|----------------------|----------------|------------------|---------------------|---------------------|
| XP1NE  | Gly47Arg    | Leu461Val + del 716–730 | Deceased at 43 years due to sepsis | XP-D, XP-D/CS | Female | + Birth weight 2,325 g | + | ns | + | ns | + | + | + | + | ns | + | Mild growth retardation |
| XP1JI  | Gly47Arg    | Ile619del    | Deceased at 28 months due to severe liver dysfunction | XP-D/CS | Male | – | + | + | – | – | ns | – | – | ns | + | + | + | + | + | + |
| COFS-Chiba1 | Gly47Arg | Arg616Gly | Deceased <1 year due to pneumonia | COFS | Male | – | + | + | – | – | ns | – | – | ns | + | + | + | + | + | + | + |
| Patient in Kondo et al. (2016) | Gly47Arg | Ile595Ser | Deceased at 23 months due to renal failure | XP-D/CS | Male | – | + | + | – | – | ns | – | – | ns | + | + | + | + | + | + | + | + |
| Patient 4 in Zhang et al. (2017) | Gly47Arg | – | Deceased at 10 years due to respiratory failure | XP-D | Male | – | + | + | – | – | ns | – | – | ns | + | + | + | + | + | + | + | + |
| Patient in this study | Gly47Arg | – | Deceased at 21 months due to respiratory failure | COFS | Male | – | + | + | – | – | ns | – | – | ns | + | + | + | + | + | + | + | + | + | + |

**TABLE 1** Overview of known patients carrying the pathogenic variant NP_000391.1:p.Gly47Arg in ERCC2 (Gene ID: 2068)
It should be noted, that the involvement of XPD in DNA repair of UV-induced lesions does primarily explain the XP-phenotype, that is, photosensitivity, and as such of course is mainly restricted to light exposed areas of the body. Therefore, we suggest that other phenotypes in CS, TTD, and COFS are likely due to effects on the whole TFIIH complex in transcription. It has been shown that a reduced basal transcription due to TFIIH-defects is associated with TTD (Dubaele et al., 2003). The TFIIH may also affect transcription of specific groups of genes by interaction with further transcription factors. For example, it has been shown, that ERCC2-mutations may prevent TFIIH-dependent transactivation by nuclear receptors (Keriel, Stary, Sarasin, Rochette-Egly, & Egly, 2002). With the XPD-Gly47Arg-variant up to now, it has been explicitly shown for one artificial template that transcription to mRNA was reduced to 37% of wild type (Dubaele et al., 2003). It may be expected, that there is some range of differential expression that finally may contribute to the observed CS and COFS phenotypes. Unfortunately, our patient died suddenly and no cells for such expression analyses were left. Future XPD/CS/COFS cases should be analyzed for transcriptome changes to get more insight into the pathophysiology of CS/COFS.

In conclusion, we report on the first patient with the homozygous pathogenic variant Gly47Arg in the ERCC2 gene. In compound heterozygous status, this variant is thought to cause XP, XP-D/CS, and COFS syndrome dependent on the variant located on the second allele. Occurring homozygous, this pathogenic variant leads to severe COFS syndrome and early death.

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CONFLICT OF INTEREST
The authors declare that they have no conflict of interest.

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

ORCID
Thorsten Marquardt https://orcid.org/0000-0002-9982-2981

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