Received: 17 April 2021 | Revised: 12 July 2021 | Accepted: 16 August 2021

DOI: 10.1002/ajmg.a.62496

AMERICAN JOURNAL OF medical genetics PART A WILEY

CLINICAL REPORT

Manifestation of epilepsy in a patient with *EED*-related overgrowth (Cohen–Gibson syndrome)

Katalin L. M. L. Hetzelt[1] | Martin Winterholler[2] | Frank Kerling[2] | Christophe Rauch[2] | Arif B. Ekici[1] | Andreas Winterpacht[1] | Georgia Vasileiou[1] | Steffen Uebe[1] | Christian T. Thiel[1] | Cornelia Kraus[1] | André Reis[1] | Christiane Zweier[1,3]

[1]Institute of Human Genetics, Universitätsklinikum Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg FAU, Erlangen, Germany

[2]Department of Neurology, Epilepsy and Movement Disorders Center, Sana-Krankenhaus Rummelsberg, Schwarzenbruck/Nuremberg, Germany

[3]Department of Human Genetics, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

Correspondence
André Reis, Institute of Human Genetics, Universitätsklinikum Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Schwabachanlage 10, 91054 Erlangen, Germany.
Email: andre.reis@uk-erlangen.de

Abstract

Cohen–Gibson syndrome is a rare genetic disorder, characterized by fetal or early childhood overgrowth and mild to severe intellectual disability. It is caused by heterozygous aberrations in *EED*, which encodes an evolutionary conserved polycomb group (PcG) protein that forms the polycomb repressive complex-2 (PRC2) together with EZH2, SUZ12, and RBBP7/4. In total, 11 affected individuals with heterozygous pathogenic variants in *EED* were reported, so far. All variants affect a few key residues within the EED WD40 repeat domain. By trio exome sequencing, we identified the heterozygous missense variant c.581A > G, p.(Asn194Ser) in exon 6 of the *EED*-gene in an individual with moderate intellectual disability, overgrowth, and epilepsy. The same pathogenic variant was detected in 2 of the 11 previously reported cases. Epilepsy, however, was only diagnosed in one other individual with Cohen–Gibson syndrome before. Our findings further confirm that the WD40 repeat domain represents a mutational hotspot; they also expand the clinical spectrum of Cohen–Gibson syndrome and highlight the clinical variability even in individuals with the same pathogenic variant. Furthermore, they indicate a possible association between Cohen–Gibson syndrome and epilepsy.

KEYWORDS
EED, epilepsy, overgrowth, PRC2

1 | INTRODUCTION

EED encodes an evolutionary conserved polycomb group (PcG) protein. Together with EZH2, SUZ12, and RBBP7/4, this protein forms the polycomb repressive complex-2 (PRC2) (Ciferri et al., 2012; Imagawa et al., 2017; Margueron & Reinberg, 2011). PRC2 is a conserved multiprotein chromatin complex important for maintaining transcriptional gene repression and plays a crucial role in the development and eukaryotic cellular identity, stem cell maintenance, and tissue homeostasis (Glancy et al., 2020; Sauvageau & Sauvageau, 2010). Its trimeric core consisting of SUZ12, EED, and EZH1/2 is sufficient, together with RBBP4/7, to catalyze monomethylation, dimethylation, and trimethylation of histone H3 at lysine residue 27 (H3K27me1/2/3) (Glancy et al., 2020; Imagawa et al., 2017). EED

contains seven-bladed β-propeller WD40 domains (Montgomery et al., 2007), disruption of which resulted in impaired interaction between EED and EZH2 (Denisenko et al., 1998; Spellicy et al., 2019).

Pathogenic variants, which lead to an exchange of amino acids in EED were implicated in Cohen–Gibson syndrome (COGIS, OMIM# 617561). So far, eight individuals with *de novo* pathogenic variants and three further cases with one parent missing for segregation analysis were reported (Cohen et al., 2015; Cohen & Gibson, 2016; Cooney et al., 2017; Griffiths et al., 2019; Imagawa et al., 2017; Smigiel et al., 2018; Spellicy et al., 2019; Tatton-Brown et al., 2017). All presented with fetal or early childhood overgrowth and with mild to severe intellectual disability. Other frequent clinical features included cardiac (mitral valve regurgitation, persistent ductus arteriosus, atrial septal defect, ventricular septal defect, murmur), skeletal (scoliosis, cervical spinal canal stenosis, camptodactyly), ophthalmological (myopia, strabismus, cataract, chorioretinitis), genitourinary (cryptorchidism, nephromegaly, duplex kidney), and dermatological abnormalities (abnormal pigmentation, nevi, capillary hemangioma or thin and fragile skin). Other findings in a few affected individuals, respectively, were endocrine anomalies (hyperinsulinemia and hypoglycemia), hernias, bifid uvula, Hirschsprung's disease, constipation or diarrhea, dysplastic enamel, tracheomalacia, bruxism, lipodystrophy, Willebrand disease, and hearing loss. While cerebral magnetic resonance imaging (MRIs) were reported to be normal in the majority of affected individuals, for example, abnormal corpus callosum and septum pellucidum cysts were reported in a few (Cohen et al., 2015; Cohen & Gibson, 2016; Cooney et al., 2017; Griffiths et al., 2019; Imagawa et al., 2017; Smigiel et al., 2018; Spellicy et al., 2019; Tatton-Brown et al., 2017).

Of note, also EZH2 and SUZ12 are implicated in overgrowth syndromes. Variants in *EZH2* are associated with Weaver syndrome (WVS, OMIM# 277590) and variants in *SUZ12* with Imagawa–Matsumoto syndrome (IMMAS, OMIM# 618786). Although the affected proteins belong to the same polycomb repressive complex, the associated disorders show some differences in clinical presentation. While overgrowth is common in all COGIS, WVS, and IMMAS, intellectual disability is more frequent in individuals with COGIS (Spellicy et al., 2019) or WVS than in individuals with IMMAS (Cyrus et al., 2019; Imagawa et al., 2018). Epilepsy and seizures were reported mainly in individuals with WVS (Gibson et al., 2012; Kamien et al., 2018) and only in a single patient with IMMAS (Imagawa et al., 2018) or COGIS, respectively (Cohen et al., 2015). While many overgrowth syndromes are associated with an increased risk for tumors (Kamien et al., 2018), this seems to be low for WVS (Tatton-Brown & Rahman, 1993) and so far not evident for IMMAS (Cyrus et al., 2019) or COGIS (Griffiths et al., 2019; Imagawa et al., 2018).

We now report on an adult individual with Cohen–Gibson syndrome harboring the heterozygous, recurrent missense variant c.581A > G, p.(Asn194Ser) in exon 6 of *EED* and presenting with epilepsy as an additional clinical feature. Our findings confirm the WD40 repeat domain as a mutational hotspot and suggest that also seizures might be a clinical aspect of Cohen–Gibson syndrome.

2 | CLINICAL REPORT

The reported male individual is the only child of non-consanguineous healthy parents of European origin. Pregnancy was uneventful. He was born by cesarean section due to umbilical cord wrapping in gestational week 38 with normal growth parameters (weight 3840 g (+1.22 *SD*); length 53 cm (+0.83 *SD*); head circumference 36 cm (+0.79 *SD*)). While motor development was unremarkable with walking at age of 14 months, severely delayed speech development was noted. He was only able to speak short sentences at age 6–7 years. Through speech therapy, he caught up well on his speech and language skills and is now able to speak full sentences. Moderate intellectual disability was diagnosed (no formal test available). He attended a school for children with special needs and now lives and works in a sheltered environment. At age of 5 years, absence epilepsy was diagnosed, which responded well to treatment with ethosuximide with subsequent occurrence of occasional seizures, only. At age of 13 years, focal, secondary generalized seizure with tonic–clonic convulsions, salivation, and loss of consciousness occurred. Because of secondary generalization, anticonvulsive treatment was changed to valproate. At age of 15 years, a grand-mal episode with three seizures in a row occurred. Subsequent EEG showed isolated right, pseudofocal, partly bifrontal spikes compatible with generalized epilepsy. Reduced Factor VIII and von-Willebrand-factor were noted in routine testing and considered as potential side effects. Thus, treatment was successively tapered and substituted by lamotrigine. Subsequently, the patient remained seizure-free. Behavioral abnormalities such as aggressive episodes toward his family were reported during adolescence, co-occurring with antiepileptic treatment change from ethosuximide to valproate. Due to suspicion of a schizoaffective disorder, the patient was temporarily treated with olanzapine and promethazine, which, however, were discontinued due to dizziness. Social behavior as a young adult and after moving into a sheltered accommodation was adequate. MRI was unremarkable apart from a possible microadenoma in the posterior lobe of the pituitary gland. An echocardiographic examination showed a discreet mitral valve prolapse. At latest physical examination at age 21 years, his height was 2.02 m (+3.12 *SD*), weight was 80 kg (body mass index 20), and he was macrocephalic with a head circumference of 61 cm (+2.64 *SD*). Multiple nevi all over the body and molluscae contagiosae on both hands were noted. He had myopia. Subtle facial dysmorphism included a triangularly shaped face, large and low set ears, hypertelorism, a prominent philtrum, a horizontal chin crease, and retrognathia. Furthermore, scoliosis, long fingers, large feet, and a funnel chest were noted. Behavior and language appeared adequate.

Due to the combination of tall stature, cardiac and skeletal anomalies, Marfan syndrome (MFS, MIM# 154700) was initially suspected, and testing of *FBN1* was initiated. This, however, did not detect any pathogenic variant. Conventional karyotyping and chromosomal microarray analysis did not show pathogenic aberrations, either, apart from a maternally inherited 4.5 kb heterozygous deletion in 3q27.1 (chr3:182755006–182759538). This deletion is harboring the *MCCC1*-Gen (NM_001293273:e8-10del). Autosomal recessive

variants in *MCCC1* are associated with 3-methylcrotonyl-CoA carboxylase 1 deficiency (MCC1D, MIM# 210200). However, there was no single nucleotide variant on the other *MCCC1*-allele detectable by exome sequencing. Trio exome sequencing on a HiSeq 2500 platform (Illumina) after enrichment with TWIST Human Core Exome Enrichment Technology (TWIST Bioscience) revealed a de novo heterozygous missense variant (c.581A > G, p.(Asn194Ser)) in exon 6 of *EED* (NM_003797.3). This variant has been reported in two other individuals before (Griffiths et al., 2019; Spellicy et al., 2019) (Table 1). Since seizures do not appear to be a consistently reported clinical feature in Cohen–Gibson syndrome, we specifically searched for additional variants in epilepsy-associated genes in the exome data. This revealed only a heterozygous variant c.11397G > C, (p.(Gln3799His)) of unknown significance in *ADGRV1* (NM_032119). To date, a variant in this gene was only detected in a single family with febrile seizures (OMIM# 604352). The identified variant in *ADGRV1* in our patient was furthermore inherited from the healthy father, thus likely being a polymorphism.

Written informed consent and consent to publish mutational and clinical details were obtained from the mother as legal guardian.

3 | DISCUSSION

The reported individual carrying the p.(Asn194Ser) variant in *EED* showed typical clinical aspects of Cohen–Gibson syndrome such as overgrowth, moderate intellectual disability, speech delay, cardiac abnormalities (mitral valve prolapse), and facial dysmorphism (Figure 1). Additionally, he presented with epilepsy, which is not a typical or frequent aspect of Cohen–Gibson syndrome. So far, seizures were only reported in two individuals with pathogenic variants in *EED* (Cohen et al., 2015; Griffiths et al., 2019). Confirmed epilepsy with irregular wave pattern in the EEG, manifesting at age 4.5 years was diagnosed in one individual with the p.(Arg302Ser) variant in *EED* (Cohen et al., 2015). EEG abnormalities were responsive to phenytoin and primidone (Cohen et al., 2015). Another individual, carrying the same p.(Asn194Ser) variant as the herewith reported individual, developed seizures at age of 8 years (Griffiths et al., 2019), which, however, were later attributed to hyperinsulinemic hypoglycemia (Griffiths et al., 2019).

Downregulation of H3K27me3 plays an essential role in neurogenesis and development of the brain (Akizu et al., 2010) as well as in seizure susceptibility by regulating the expression pattern of febrile seizure-related genes *DPP4* (OMIM#102720) and *IL6* (OMIM#147620) (Wang et al., 2017). Also, H3K27me3 was progressively downregulated during epileptogenesis in rat hippocampus (Zybura-Broda et al., 2016).

A role in epileptogenesis of the EED interactor and H3K27me3 methylation co-regulator EZH2 is already evident by the occurrence of seizures in individuals with Weaver syndrome (Gibson et al., 2012; Kamien et al., 2018) and functionally by its ability to regulate differentially expressed genes across multiple rodent models of acquired epilepsy (Khan et al., 2019). Therefore, *EED* variants might also contribute to epileptogenesis, resulting in the occurrence of seizures as an infrequent aspect of Cohen–Gibson syndrome. Better future estimates on frequency and penetrance of epilepsy within Cohen–Gibson syndrome might be possible based on larger numbers of affected individuals.

The identified missense variant p.(Asn194Ser) in the WD40 repeat 3 is located in the H3K27me3 binding pocket of the EED protein (Spellicy et al., 2019). All pathogenic variants in *EED* identified so far are located in a mutational hotspot altering amino acids in or near the WD40 repeats 3 to 5 (Cyrus, Burkardt, et al., 2019; Griffiths et al., 2019; Spellicy et al., 2019). A reduced PRC2 methyltransferase activity was demonstrated in a lymphoblastoid cell line derived from an individual with the p.(Arg236Thr) mutation in *EED* (Imagawa et al., 2017) and for several other *EED* variants (Lee et al., 2018). It was speculated that variants in mutational hotspots specifically impair the interaction between EED and the EZH2-SRM domain and thus result in reduced PRC2 function (Spellicy et al., 2019). Such a residue-specific consequence is supported by the observation of recurrent

TABLE 1 Clinical variability within three individuals with the recurrent p.(Asn194Ser) *EED*-variant

	Current report	Griffiths et al. (2019)	Spellicy et al. (2019)
	EED: c.581A > G, p.(Asn194Ser)		
Generalized overgrowth	+	+	+
Intellectual disability	"Moderate"	"Mild"	IQ 44
Scoliosis	+	−	+
Dermatological abnormalities	+	−	+
Genitourinary abnormalities	−	+	+
Cardiac abnormalities	+	−	+
Ocular abnormalities	+	−	+
Abnormal MRI findings	+	−	−
Joint hypermobility	+	−	−
Hearing loss	−	−	−
Epilepsy	+	−	−
Hypoglycemia/hyperinsulinemia	−	+	−

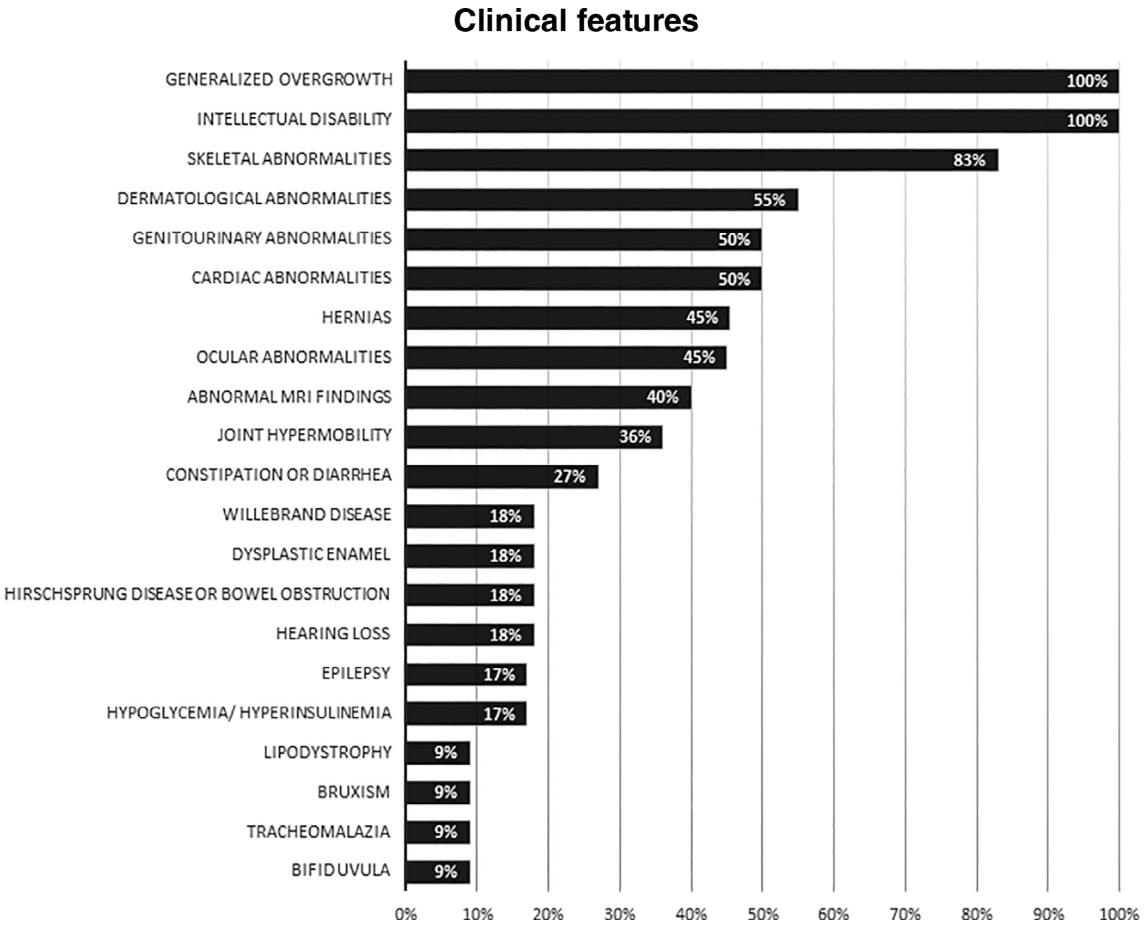

FIGURE 1 Clinical features in 12 individuals with pathogenic variants in EED reported so far (including this report) (Cohen et al., 2015; Cohen & Gibson, 2016; Cooney et al., 2017; Griffiths et al., 2019; Imagawa et al., 2017; Smigiel et al., 2018; Spellicy et al., 2019; Tatton-Brown et al., 2017)

pathogenic missense variants at only four amino acids (Cohen et al., 2015; Cohen & Gibson, 2016; Cooney et al., 2017; Griffiths et al., 2019; Imagawa et al., 2017; Smigiel et al., 2018; Spellicy et al., 2019; Tatton-Brown et al., 2017) and by the fact that despite a high pLI score of 1 (o/e = 0.04 [0.01–0.19]) in gnomAD (Karczewski et al., 2020), indicating intolerance to haploinsufficiency, no pathogenic truncating variants in *EED* or pathogenic deletions of *EED* have been reported, so far. The Decipher database (Firth et al., 2009) contains two deletions with a size of 202.31 or 366.74 kb containing *EED* and 4 or 6 neighboring genes. Both deletions are of unclear significance, one of them being even maternally inherited.

The deleterious effect of the recurrent missense variants seems to be homogeneous. No apparent genotype–phenotype correlation could be delineated (Spellicy et al., 2019), and even between the three individuals with the identical p.(Asn194Ser) variant a high clinical variability was observed (Griffiths et al., 2019; Spellicy et al., 2019).

This report raises the number of described individuals with Cohen–Gibson syndrome to 12, with 5 being adults, (Cohen et al., 2015; Cohen & Gibson, 2016; Cooney et al., 2017; Griffiths et al., 2019; Imagawa et al., 2017; Smigiel et al., 2018; Spellicy et al., 2019; Tatton-Brown et al., 2017). As the total number is still very small, further studies and larger cohorts of individuals with *EED* variants will be required to define the clinical spectrum and clinical variability.

ACKNOWLEDGMENT

We thank the family for participation in this study. Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Katalin L. M. L. Hetzelt: Writing—original draft. **Martin Winterholler**: Collected clinical data. **Frank Kerling**: Collected clinical data. **Christophe Rauch**: Collected clinical data. **Arif B. Ekici**: Formal analysis. **Andreas Winterpacht**: Collected molecular data. **Georgia Vasileiou**: Writing. **Steffen Uebe**: Formal analysis. **Christian T. Thiel**: Formal analysis. **Cornelia Kraus**: Formal analysis. **André Reis**: Writing—original draft. **Christiane Zweier**: Writing—original draft.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Katalin L. M. L. Hetzelt https://orcid.org/0000-0002-1888-1366
Arif B. Ekici https://orcid.org/0000-0001-6099-7066
Georgia Vasileiou https://orcid.org/0000-0002-1993-1134
Christian T. Thiel https://orcid.org/0000-0003-3817-7277
André Reis https://orcid.org/0000-0002-6301-6363
Christiane Zweier https://orcid.org/0000-0001-8002-2020

REFERENCES

Akizu, N., Estarás, C., Guerrero, L., Martí, E., & Martínez-Balbás, M. A. (2010). H3K27me3 regulates BMP activity in developing spinal cord. *Development*, *137*(17), 2915–2925. https://doi.org/10.1242/dev.049395

Ciferri, C., Lander, G. C., Maiolica, A., Herzog, F., Aebersold, R., & Nogales, E. (2012). Molecular architecture of human polycomb repressive complex 2. *eLife*, *1*, e00005. https://doi.org/10.7554/eLife.00005

Cohen, A. S., & Gibson, W. T. (2016). EED-associated overgrowth in a second male patient. *Journal of Human Genetics*, *61*(9), 831–834. https://doi.org/10.1038/jhg.2016.51

Cohen, A. S., Tuysuz, B., Shen, Y., Bhalla, S. K., Jones, S. J., & Gibson, W. T. (2015). A novel mutation in EED associated with overgrowth. *Journal of Human Genetics*, *60*(6), 339–342. https://doi.org/10.1038/jhg.2015.26

Cooney, E., Bi, W., Schlesinger, A. E., Vinson, S., & Potocki, L. (2017). Novel EED mutation in patient with Weaver syndrome. *American Journal of Medical Genetics. Part A*, *173*(2), 541–545. https://doi.org/10.1002/ajmg.a.38055

Cyrus, S., Burkardt, D., Weaver, D. D., & Gibson, W. T. (2019). PRC2-complex related dysfunction in overgrowth syndromes: A review of EZH2, EED, and SUZ12 and their syndromic phenotypes. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*, *181*(4), 519–531. https://doi.org/10.1002/ajmg.c.31754

Cyrus, S. S., Cohen, A. S. A., Agbahovbe, R., Avela, K., Yeung, K. S., Chung, B. H. Y., Luk, H.-M., Tkachenko, N., Choufani, S., Weksberg, R., Lopez-Rangel, E., C.A.U.S.E.S. Study, Brown, K., Saenz, M. S., Svihovec, S., McCandless, S. E., Bird, L. M., Garcia, A. G., Gambello, M. J., … Gibson, W. T. (2019). Rare SUZ12 variants commonly cause an overgrowth phenotype. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*, *181*(4), 532–547. https://doi.org/10.1002/ajmg.c.31748

Denisenko, O., Shnyreva, M., Suzuki, H., & Bomsztyk, K. (1998). Point mutations in the WD40 domain of EED block its interaction with Ezh2. *Molecular and Cellular Biology*, *18*(10), 5634–5642. https://doi.org/10.1128/mcb.18.10.5634

Firth, H. V., Richards, S. M., Bevan, A. P., Clayton, S., Corpas, M., Rajan, D., Van Vooren, S., Moreau, Y., Pettett, R. M., & Carter, N. P. (2009). DECIPHER: Database of chromosomal imbalance and phenotype in humans using Ensembl resources. *The American Journal of Human Genetics*, *84*(4), 524–533. https://doi.org/10.1016/j.ajhg.2009.03.010

Gibson, W. T., Hood, R. L., Zhan, S. H., Bulman, D. E., Fejes, A. P., Moore, R., Mungall, A. J., Eydoux, P., Babul-Hirji, R., An, J., Marra, M. A., FORGE Canada Consortium, Chitayat, D., Boycott, K. M., Weaver, D. D., & Jones, S. J. (2012). Mutations in EZH2 cause Weaver syndrome. *American Journal of Human Genetics*, *90*(1), 110–118. https://doi.org/10.1016/j.ajhg.2011.11.018

Glancy, E., Ciferri, C., & Bracken, A. P. (2020). Structural basis for PRC2 engagement with chromatin. *Current Opinion in Structural Biology*, *67*, 135–144. https://doi.org/10.1016/j.sbi.2020.10.017

Griffiths, S., Loveday, C., Zachariou, A., Behan, L. A., Chandler, K., Cole, T., D'Arrigo, S., Dieckmann, A., Foster, A., Gibney, J., Hunter, M., Milani, D., Pantaleoni, C., Roche, E., Sherlock, M., Springer, A., White, S. M., Childhood Overgrowth Collaboration, & Tatton-Brown, K. (2019). EED and EZH2 constitutive variants: A study to expand the Cohen-Gibson syndrome phenotype and contrast it with Weaver syndrome. *American Journal of Medical Genetics. Part A*, *179*(4), 588–594. https://doi.org/10.1002/ajmg.a.61066

Imagawa, E., Albuquerque, E. V. A., Isidor, B., Mitsuhashi, S., Mizuguchi, T., Miyatake, S., Takata, A., Miyake, N., Boguszewski, M. C. S., Boguszewski, C. L., Lerario, A. M., Funari, M. A., Jorge, A. A. L., & Matsumoto, N. (2018). Novel SUZ12 mutations in Weaver-like syndrome. *Clinical Genetics*, *94*(5), 461–466. https://doi.org/10.1111/cge.13415

Imagawa, E., Higashimoto, K., Sakai, Y., Numakura, C., Okamoto, N., Matsunaga, S., Ryo, A., Sato, Y., Sanefuji, M., Ihara, K., Takada, Y., Nishimura, G., Saitsu, H., Mizuguchi, T., Miyatake, S., Nakashima, M., Miyake, N., Soejima, H., & Matsumoto, N. (2017). Mutations in genes encoding polycomb repressive complex 2 subunits cause Weaver syndrome. *Human Mutation*, *38*(6), 637–648. https://doi.org/10.1002/humu.23200

Kamien, B., Ronan, A., Poke, G., Sinnerbrink, I., Baynam, G., Ward, M., Gibson, W. T., Dudding-Byth, T., & Scott, R. J. (2018). A clinical review of generalized overgrowth syndromes in the era of massively parallel sequencing. *Molecular Syndromology*, *9*(2), 70–82. https://doi.org/10.1159/000484532

Karczewski, K. J., Francioli, L. C., Tiao, G., Cummings, B. B., Alföldi, J., Wang, Q., Collins, R. L., Laricchia, K. M., Ganna, A., Birnbaum, D. P., Gauthier, L. D., Brand, H., Solomonson, M., Watts, N. A., Rhodes, D., Singer-Berk, M., England, E. M., Seaby, E. G., Kosmicki, J. A., … MacArthur, D. G. (2020). The mutational constraint spectrum quantified from variation in 141,456 humans. *Nature*, *581*(7809), 434–443. https://doi.org/10.1038/s41586-020-2308-7

Khan, N., Schoenike, B., Basu, T., Grabenstatter, H., Rodriguez, G., Sindic, C., Johnson, M., Wallace, E., Maganti, R., Dingledine, R., & Roopra, A. (2019). A systems approach identifies enhancer of Zeste homolog 2 (EZH2) as a protective factor in epilepsy. *PLoS One*, *14*(12), e0226733. https://doi.org/10.1371/journal.pone.0226733

Lee, C. H., Yu, J. R., Kumar, S., Jin, Y., LeRoy, G., Bhanu, N., Kaneko, S., Garcia, B. A., Hamilton, A. D., & Reinberg, D. (2018). Allosteric activation dictates PRC2 activity independent of its recruitment to chromatin. *Molecular Cell*, *70*(3), 422–434.e6. https://doi.org/10.1016/j.molcel.2018.03.020

Margueron, R., & Reinberg, D. (2011). The Polycomb complex PRC2 and its mark in life. *Nature*, *469*(7330), 343–349. https://doi.org/10.1038/nature09784

Montgomery, N. D., Yee, D., Montgomery, S. A., & Magnuson, T. (2007). Molecular and functional mapping of EED motifs required for PRC2-dependent histone methylation. *Journal of Molecular Biology*, *374*(5), 1145–1157. https://doi.org/10.1016/j.jmb.2007.10.040

Sauvageau, M., & Sauvageau, G. (2010). Polycomb group proteins: Multi-faceted regulators of somatic stem cells and cancer. *Cell Stem Cell*, *7*(3), 299–313. https://doi.org/10.1016/j.stem.2010.08.002

Smigiel, R., Biernacka, A., Biela, M., Murcia-Pienkowski, V., Szmida, E., Gasperowicz, P., Kosinska, J., Kostrzewa, G., Koppolu, A. A., Walczak, A., Wawrzuta, D., Rydzanicz, M., Sasiadek, M., & Ploski, R. (2018). Novel de novo mutation affecting two adjacent aminoacids in the EED gene in a patient with Weaver syndrome. *Journal of Human Genetics*, *63*(4), 517–520. https://doi.org/10.1038/s10038-017-0391-x

Spellicy, C. J., Peng, Y., Olewiler, L., Cathey, S. S., Rogers, R. C., Bartholomew, D., Johnson, J., Alexov, E., Lee, J. A., Friez, M. J., & Jones, J. R. (2019). Three additional patients with EED-associated overgrowth: Potential mutation hotspots identified? *Journal of Human Genetics*, *64*(6), 561–572. https://doi.org/10.1038/s10038-019-0585-5

Tatton-Brown, K., Loveday, C., Yost, S., Clarke, M., Ramsay, E., Zachariou, A., Elliott, A., Wylie, H., Ardissone, A., Rittinger, O., Stewart, F., Temple, I. K., Cole, T., Childhood Overgrowth Collaboration, Mahamdallie, S., Seal, S., Ruark, E., & Rahman, N. (2017).

Mutations in epigenetic regulation genes are a major cause of overgrowth with intellectual disability. *American Journal of Human Genetics*, *100*(5), 725–736. https://doi.org/10.1016/j.ajhg.2017.03.010

Tatton-Brown, K., & Rahman, N. (1993). EZH2-related overgrowth. In M. P. Adam, H. H. Ardinger, R. A. Pagon, S. E. Wallace, L. J. H. Bean, K. Stephens, & A. Amemiya (Eds.), *GeneReviews*(®). University of Washington.

Wang, Z., Zhang, Y., Fang, J., Yu, F., Heng, D., Fan, Y., Xu, J., Peng, B., Liu, W., Han, S., & He, X. (2017). Decreased methylation level of H3K27me3 increases seizure susceptibility. *Molecular Neurobiology*, *54*(9), 7343–7352. https://doi.org/10.1007/s12035-016-0197-4

Zybura-Broda, K., Amborska, R., Ambrozek-Latecka, M., Wilemska, J., Bogusz, A., Bucko, J., Konopka, A., Grajkowska, W., Roszkowski, M., Marchel, A., Rysz, A., Koperski, L., Wilczynski, G. M., Kaczmarek, L., & Rylski, M. (2016). Epigenetics of epileptogenesis-evoked upregulation of matrix metalloproteinase-9 in hippocampus. *PLoS One*, *11*(8), e0159745. https://doi.org/10.1371/journal.pone.0159745

How to cite this article: Hetzelt, K. L. M. L., Winterholler, M., Kerling, F., Rauch, C., Ekici, A. B., Winterpacht, A., Vasileiou, G., Uebe, S., Thiel, C. T., Kraus, C., Reis, A., & Zweier, C. (2021). Manifestation of epilepsy in a patient with *EED*-related overgrowth (Cohen–Gibson syndrome). *American Journal of Medical Genetics Part A*, *188*A:292–297. https://doi.org/10.1002/ajmg.a.62496