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RESEARCH REPORT

Reanalysis of a novel variant in the *IGF1R* gene in a family with variable prenatal and postnatal growth retardation and dysmorphic features: benefits and feasibility of IUSM–URDC (Undiagnosed Rare Disease Clinic) program

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Abstract *IGF1R*-related disorders are associated with intrauterine growth restriction (IUGR), postnatal growth failure, short stature, microcephaly, developmental delay, and dysmorphic facial features. We report a patient who presented to medical genetics at 7 mo of age with a history of IUGR, poor feeding, mild developmental delays, microcephaly, and dysmorphic facial features. Whole-exome sequencing revealed a novel c.1464T > G p.(Cys488Trp) variant in the *IGF1R* gene, initially classified as a variation of uncertain significance (VUS). We enrolled the patient in the URDC (Undiagnosed Rare Disease Clinic) and performed additional studies including deep phenotyping and familial segregation analysis, which demonstrated that the patient's *IGF1R* VUS was present in phenotypically similar family members. Furthermore, biochemical testing revealed an elevated serum IGF-1 level consistent with abnormal IGF-1 receptor function. Workup resulted in the patient's variant being upgraded from a VUS to likely pathogenic. Our report expands the variant and phenotypic spectrum of *IGF1R*-related disorders and illustrates benefits and feasibility of reassessing a VUS beyond the initial molecular diagnosis by deep phenotyping, 3D modeling, additional biochemical testing, and familial segregation studies through the URDC, a multidisciplinary clinical program whose major goal is to end the diagnostic odyssey in patients with rare diseases.

[Supplemental material is available for this article.]

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Ontology terms: downslanted palpebral fissures; high forehead; long philtrum; low hanging columella; microcephaly; mild global developmental delay; moderate intrauterine growth retardation; moderate postnatal growth retardation; tented upper lip vermilion

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INTRODUCTION

Pathogenic variants in the *type 1 insulin-like growth factor receptor (IGF1R)* gene are rare and the prevalence of *IGF1R*-related disorders is unknown (Giabicani et al. 2020). IGF1R is a cell-surface tyrosine kinase receptor broadly expressed across both fetal and postnatal tissues

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and plays an important role in normal somatic growth and development (Walenkamp et al. 2013). IGF1R is activated by the binding of secreted growth factor ligand insulin-like growth factor-1 (IGF-1) and, with lower-affinity insulin-like growth factor-2 (IGF-2) and insulin. Activation of IGF1R results in a variety of cellular responses including cell proliferation and represents the principal pathway responsible for somatic growth (LeRoith et al. 1995; Kawashima et al. 2012). IGF1R is structurally related to the insulin receptor (INSR) and epidermal growth factor receptor (EGFR) and consists of an α2/β2 heterotetramer (Garrett et al. 1998). The α-subunit contains the IGF-binding site, whereas the β-subunit possesses the intrinsic tyrosine kinase activity (Adams et al. 2000; De Meyts and Whittaker 2002).

Pathogenic variants in *IGF1R* lead to a change in IGF-1 receptor functioning, either by affecting ligand binding and internalization or reducing cell-surface IGF1R levels. Overall, this leads to IGF-1 resistance and elevated circulating levels of IGF-1 in the bloodstream of most patients with *IGF1R*-related disorders (Klammt et al. 2011; Giabicani et al. 2020). Previous reports of *IGF1R* pathogenic variants described variable phenotypes, but often included microcephaly, intrauterine growth restriction (IUGR), and failure to thrive (Solomon-Zemler et al. 2017).

Although IGF1R deficiency in recessive form has been so far observed in a few families, most prior case reports indicate that *IGF1R* pathogenic variants often follow a pattern of autosomal dominant inheritance (Abuzzahab et al. 2003; Prontera et al. 2015; Yang et al. 2018; Giabicani et al. 2020; Shapiro et al. 2020). In addition to heterozygous variants affecting receptor activity or stability, structural chromosomal aberrations involving *IGF1R* have been reported including 15q26.1-qter deletion, unbalanced translocations, and ring chromosomes (Klammt et al. 2011). Depending on the size of the rearrangement of the 15q26 region and the genes involved, clinical manifestations ranged from *IGF1R*-related disorders to more complex phenotype involving cardiac and limb abnormalities (Klammt et al. 2011).

Animal experiments have shown that only heterozygous mutations are viable, which is consistent with most case reports of heterozygous *IGF1R* pathogenic variants in humans (Solomon-Zemler et al. 2017). Moreover, patients with compound heterozygous or homozygous variants in *IGF1R* display a more severe phenotype, which often includes severe global delay and intellectual disability (Yang et al. 2018).

Here, we report on a now 2-yr-old female with poor growth, microcephaly, and dysmorphic facial features found to have a variant of uncertain significance (VUS) in the *IGF1R* gene. The patient was enrolled in the Undiagnosed Rare Disease Clinic (URDC), a multidisciplinary program established in 2020 at Indiana University School of Medicine (IUSM). Following additional studies, including variant segregation, deep phenotyping, biochemical analyses, and in silico analyses, the variant was upgraded to likely pathogenic.

RESULTS

Clinical Presentation

The patient initially presented to medical genetics at 7 mo of age with delayed growth and development and dysmorphic facial features (Fig. 1B). She had a history of IUGR, low birth weight (1.98 kg; −2.72 SD), poor feeding, mild developmental delays, microcephaly, and two prior hospital admissions for failure to thrive and had been placed in foster care for concerns of underfeeding (Fig. 1D; Supplemental Material). On physical exam she was found to have downslanting palpebral fissures, a high forehead, hanging columella, a tented upper lip, and a long philtrum. At that time, no specific syndrome was recognized.

Chromosomal microarray analysis yielded no abnormalities. The patient was reevaluated at 14 mo old because of continued poor weight gain at which time whole-exome sequencing (WES) was obtained. While WES analysis was pending, she was evaluated by pediatric

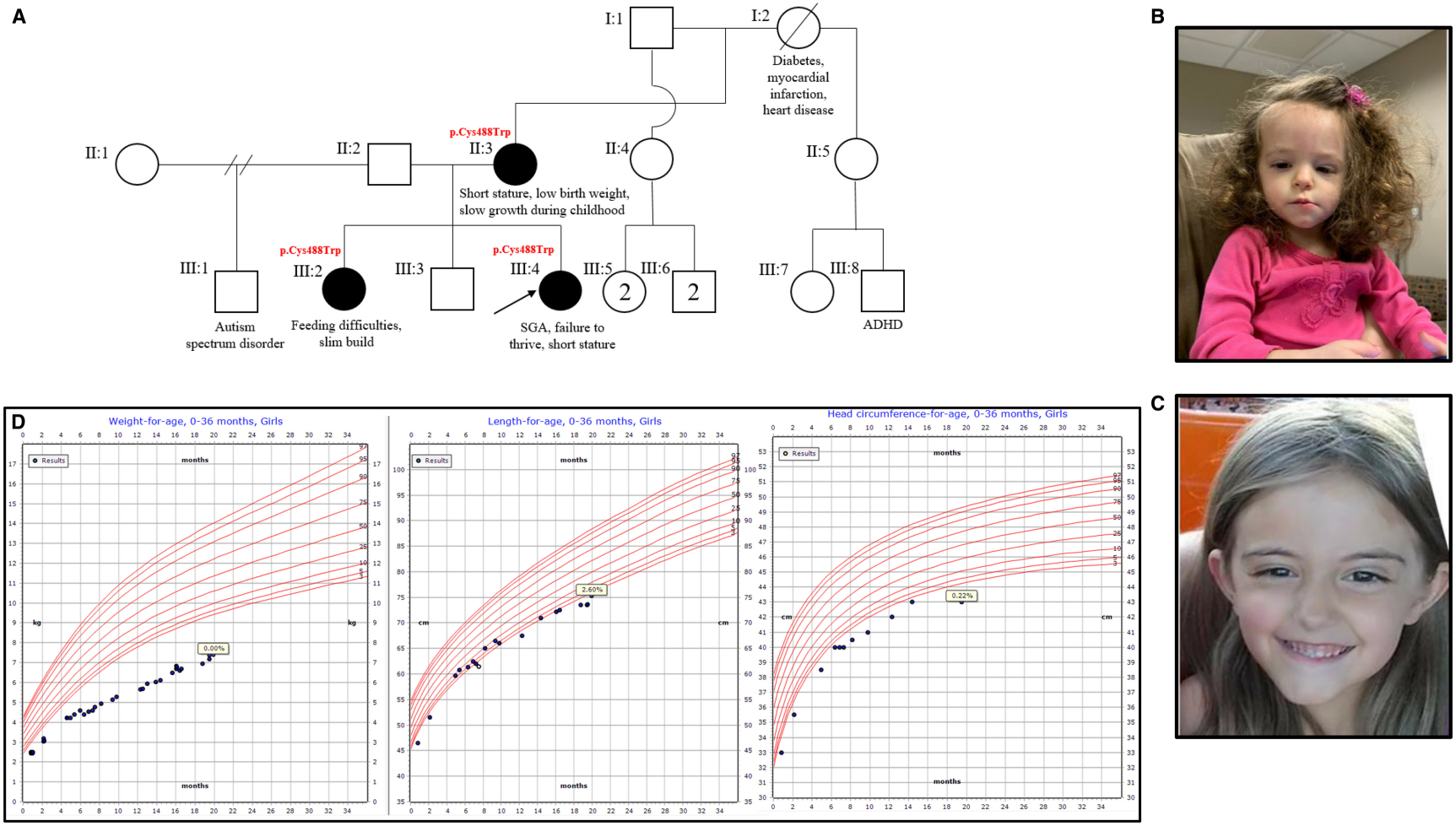

Figure 1. Patient characteristics. (*A*) Pedigree of the proband and her family. The genotype obtained by Sanger sequencing or next-generation sequencing (NGS) is indicated next to the symbol. (III:2) Affected sister, (III:4) proband, (III:3) unaffected brother, and (II:3) affected mother. Similar facial features including triangular face, downslanting palpebral fissures, a high forehead, hanging columella, small facial features for face, a tented upper lip, long philtrum, and microcephaly are observed in both the proband (*B*) and the affected sister (*C*). (*D*) Growth curves of the proband.

Table 1. Variant table

Gene	Chromosome	HGVS DNA reference	HGVS protein reference	Predicted effect	In silico predictions	Genotype	ClinVar ID	Parent of origin
IGF1R (NM_000875.5)	15:99454545	c.1464T > G	p.(Cys488Trp)	Substitution	PolyPhen-2: damaging; SIFT: damaging; MutationTaster: disease-causing; LRT: damaging; DANN: 0.994; REVEL: 0.833	Heterozygous	SCV002061317	Maternal

endocrinology who raised concern for Russell–Silver syndrome (RSS), although linear growth (Fig. 1) along with her history of microcephaly, were reassuring, especially considering that patients with RSS usually present with relative macrocephaly at birth (Wakeling et al. 2017). Initial trio-based WES analysis at GeneDx (Gaithersburg, MD) revealed a c.1464T > G p.(Cys488Trp) heterozygous, maternally inherited variant in the *IGF1R* gene (NM_000875.5), classified as a VUS (Table 1). Based on the available information, variant interpretation was performed according to American College of Medical Genetics and Genomics (ACMG) guidelines (Richards et al. 2015) with the initial lines of evidence being (1) absent from gnomAD population database (PM2), (2) predicted to be deleterious by multiple in silico bioinformatic predicting tools (PP3), and (3) highly specific phenotype (PP4).

Variant Reassessment and Reclassification

The patient and her family were referred to the URDC for further evaluation, which included deep phenotyping and familial segregation analysis of the variant c.1464T > G p.(Cys488Trp) in *IGF1R*. Additional phenotyping information and a more detailed family history revealed that the biological mother had a history of short stature, low birth weight, slow growth during infancy and childhood, and a similar facial appearance to the patient. Additionally, the patient's 6-yr-old sister was found to have a similar history of feeding difficulties, slim build, and a similar facial appearance to the patient and their mother (Fig. 1C). The patient's 4-yr-old brother had a normal birth weight and no feeding or growth concerns. Familial segregation analysis revealed the patient's phenotypically similar mother and sister tested positive for the variant on WES and Sanger sequencing, respectively, whereas the patient's brother did not (Sanger sequencing was performed by GeneDX, data not shown) (Fig. 1A). Because most patients with *IGF1R*-related disorders have been reported to have above average or drastically elevated IGF-1 levels (Kansra et al. 2012; Walenkamp et al. 2019; Giabicani et al. 2020;), we pursued further testing, which revealed an elevated serum IGF-1 level of 341 ng/mL (normal: 9–146 ng/mL) in the patient, consistent with the *IGF1R*-related disorders diagnosis.

Most recently, the patient continues to struggle with poor appetite, insufficient weight gain, and failure to thrive. Her body mass index (BMI) *z*-score has dropped from −3.22 to −4.45 in the last year, placing her in the category of severe malnutrition, which is being managed by pediatric gastroenterology. Diagnosis, health status, and treatment planning, including potential future treatment with growth hormone, were discussed at a recent multidisciplinary patient care conference. The confirmation of the genetic diagnosis helped

to inform this discussion, and growth hormone is now a potential therapy, whereas it was not prior to the confirmation of the diagnosis.

We performed additional molecular analyses of the c.1464T > G p.(Cys488Trp) variant in *IGF1R* by using publicly available bioinformatic tools and the EMEDGENE platform (https ://www.emedgene.com). The variant results in a nonconservative amino acid substitution with large physiochemical differences. It is located in the conserved L2 domain at an amino acid position that is highly conserved from *Danio rerio* to *Homo sapiens* (Fig. 2A,E). In silico predictive tools including SIFT (damaging), Mutation Taster (disease-causing), DANN

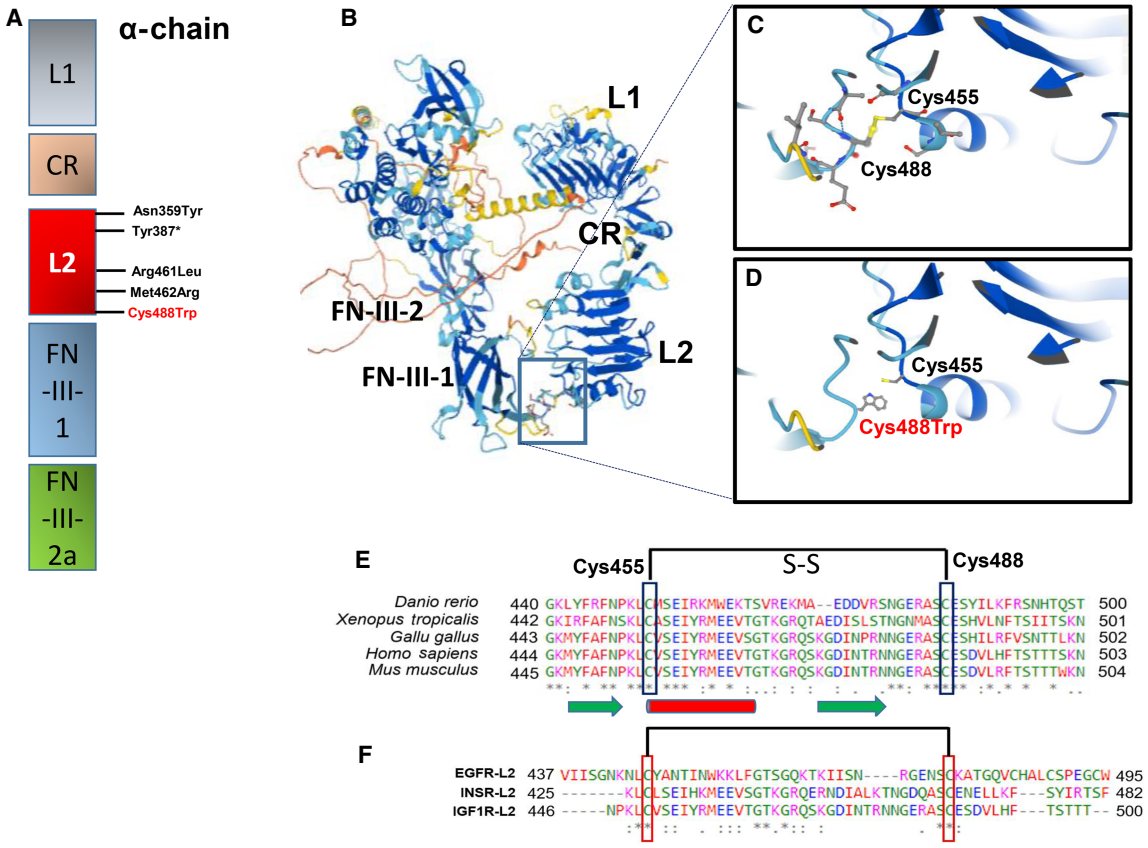

Figure 2. Alignments and molecular modeling of the impact of the Cys488Trp variant on the L2 domain. (*A*) Schematic representation of the IGF1R hemi-receptor extracellular domain: (L1, L2) leucin-rich domain, (CR) cysteine-rich domain, (FN-III-1/2) fibronectin repeats. Previously reported variant is shown on the L2 domain (black) along with the Cys488Trp (red). (*B*) 3D model of the IGF1R (PDB accession code 5U8R, modeled by AlphaFold, https://alphafold.com/). The conserved L2 region where the Cys488 interfaces the FN-III-1 is boxed. (*C*) Magnification of the disulfide bond Cys488–Cys455 in the normal configuration. (*D*) Effect of the Cys488Trp substitution in the L2 carboxy-terminal region. The replacement of the Cys488 with Trp will eliminate the highly conserved disulfide bridge and could destabilize the cap region interfacing the FN-III-1 region. (*E*) ClustalW multiple alignment analysis shows high-level evolutionary conservation of the human Cys488 and the entire carboxy-terminal region containing the critical Cys455–Cys488 disulfide bond across multiple species (boxed). (*F*) Alignment of the critical cysteine region among the growth factor receptor family (IGF1R, INSR, EGFR). The critical Cys–Cys bridges are boxed in red. The horizontal cylinder in red represents the highly conserved carboxy-terminal region corresponding to an α-helix encompassing residues 456–467 (VSEIYRMEEVTG) and the green arrows indicate the short asparagine ladder, which forms a highly conserved β-sheet (478-482 NTRNN). Previously reported affected amino acids are indicated by an asterisk (see also main text).

(0.994), LRT (damaging), and PolyPhen-2 (damaging) predicted a pathogenic effect to the function of the protein. Furthermore, we have used REVEL, which predicts the pathogenicity of missense changes based on a combination of scores from 13 individual tools (Ioannidis et al. 2016). The REVEL score can range from 0 to 1 and is recommended by CLINGEN consortium (https://www.clinicalgenome.org/) as a stand-alone meta-predictor for variant assessment (Kountouris et al. 2021). The c.1464T > G p.(Cys488Trp) reached a significantly high score of 0.833; in general, a score >0.75 is considered evidence of pathogenicity.

To further determine the effect of the p.Cys488Trp variant, we generated a 3D protein model of IGF1R by using available crystal structure in the AlphaFold database (Fig. 2B–D; Supplemental Fig. S1). The affected amino acid residue Cys488, located in the carboxyl terminus of the L2 domain, is highly conserved among species (Fig. 1E) and among other related growth factor receptors and forms an invariant disulfide bond with the Cys455. The same recurring Cys–Cys disulfide bond in the relatively conserved positions is also present in the L2 domains of INSR and EGFR (Fig. 1F), suggesting an essential yet not well-characterized role of this domain (Garrett et al. 1998). Although the exact role of this region has not been fully elucidated, previous studies suggested that the L2 domain could be involved in IGF1R internalization. Kawashima et al. (2012) provided experimental evidence that the variant Arg461Leu occurring in L2 and identified in a family with *IGF*-related disorder can result in inhibition of IGF-dependent cell proliferation and attenuation of IGF-1 signaling owing to decreased internalization of the IGF-1/IGF1R complex (Fig. 2A).

In summary, according to the new information and further analyses obtained after the enrollment in the URDC program, the initial assessment was revisited and the variant was eventually reclassified according to ACMG guidelines (Richards et al. 2015). Taken together, because the c.1464T > G p.(Cys488Trp) variant cosegregated perfectly with the disorder in the family (PP1), its absence from database of normal population gnomAD (PM2_moderate), its location in a highly conserved structurally invariant residue predicted to be pathogenic by multiple in silico tools (PP3), and the highly specific phenotype, corroborated by the biochemical findings (elevated IGF-1R) specifically associated with *IGF1R*-related disorders (PP4_moderate), the variant was reclassified as likely pathogenic.

DISCUSSION

In this study, we report how enrolling a previously undiagnosed patient, carrying a c.1464T > G p.(Cys488Trp) variant of uncertain clinical significance in the *IGF1R* gene, in the URDC can resolve the diagnostic uncertainty and has the potential to guide the therapy. The patient is a 2-yr-old female with history of IUGR, microcephaly, poor growth, mild developmental delays, and facial dysmorphisms. The patient's findings are consistent with the phenotype described in *IGF1R*-related disorders (Solomon-Zemler et al. 2017).

Deep phenotyping and familial segregation analysis demonstrated that the c.1464T > G p.(Cys488Trp) variant in *IGF1R* is present in phenotypically similar first-degree relatives, the proband's mother and sister, and absent in the patient's phenotypically normal brother (Baldridge et al. 2017). This is consistent with the autosomal dominant mode of inheritance published in prior case reports.

The patient's elevated serum IGF-1 level is likely due to a dominant negative functional impact on the IGF-1 receptor, resulting in impaired negative feedback (Giabicani et al. 2020). The potential pathogenic effect of the p.Cys488Trp was further assessed using 3D structural modeling and additional literature searches. The crystal structure model showed that the p.Cys488Trp in the L2 domain of IGF1R abolishes the essential S–S bridge between the short α-helix, corresponding to residues 456–467 (VSEIYRMEEVTG) and the region formed by a small β-helix and a characteristic short asparagine ladder (478–482 NTRNN) (Fig. 1;

Supplemental Fig. S1; Garrett et al. 1998). This change in turn could destabilize the highly conserved and characteristic cap region that separates the L2 domain from the Fn-III-1 (Fig. 1E,F; Garrett et al. 1998). Of note, other variants that cluster in the same domain, p.Arg461Leu and p.Met462Arg, have been previously reported in two other studies. The p.Met462Arg is predicted to be pathogenic by in silico tools and is absent form gnomAD, but has not been fully characterized (Walenkamp et al. 2019). However, the nearby amino acid substitution p.Arg461Leu has been functionally validated and the results of the study suggested that the L2 domain might play a pivotal role in IGF-1/IGF1R assembly and internalization (Kawashima et al. 2012). Intriguingly, another study reported a de novo likely pathogenic variant affecting the L2 domain (p.Asp359Tyr) in a microcephalic patient with prenatal and postnatal growth impairment and elevated levels of IGF-1 (Juanes et al. 2015). Functional studies performed in patients' fibroblasts revealed a proliferation defect attributable, according to the authors, to a defective receptor/ligand internalization (Juanes et al. 2015).

From the therapeutic standpoint, a retrospective study identified 19 patients with mutations in the *IGF1R* gene, 12 with likely pathogenic or pathogenic mutations, who were treated with recombinant growth hormone between 2005 and 2015 in the Netherlands. Patients were treated with a mean dose of 1.1 mg/m^2/d. After 3 years of growth hormone therapy, the standard deviation score (SDS) of height gain was measured. Height gain in patients with a likely pathogenic variant in *IGF1R* was compared to height gain in a large group of Dutch children born with small gestational age (SGA) without spontaneous catch-up growth. Use of growth hormone in children who were SGA resulted in a significantly better response, as measured by height gain SDS, compared to patients with a likely pathogenic variant in *IGF1R* who were also treated with growth hormone (Walenkamp et al. 2019). Use of growth hormone to treat patients with *IGF1R*-related disorders can lead to a moderate increase in height. Overall, this study indicated that growth velocity and possibly also adult height in children carrying a heterozygous likely pathogenic variant in *IGF1R* can respond well to long-term growth hormone treatment.

In summary, we identified a novel likely pathogenic variant in the *IGF1R* gene, which expands the phenotypic and mutational spectrum of *IGF1R*-related disorders, confirmed the previously hypothesized functional importance of the L2 domain, and demonstrated that a variant-centric approach beyond the initial evidence available to the clinical laboratory could lead to variant reclassification. A URDC reanalysis protocol that combined variant segregation analysis and deep phenotypic characterization to include specific biochemical IGF-1 testing, 3D protein modeling, and other in silico studies represented a feasible approach to overcome the "VUS conundrum."

Nevertheless, future functional studies aimed at the direct assessment of the impact of Cys488Trp on the IGF1R signaling are warranted and will shed some light on this new class of rare variants affecting this still poorly characterized, albeit highly conserved, L2 domain.

Taken together, results of the deep phenotyping, familial segregation analysis, biochemical testing, and 3D/in silico modeling has resulted in the c.1464T > G p.(Cys488Trp) *IGF1R* variant being upgraded from variant of uncertain significance to a likely pathogenic variant. This may ultimately guide a specific targeted treatment with growth hormone therapy and will likely benefit the patient and other affected family members.

METHODS

Genetic Testing and Variant Interpretation

Genomic DNA was extracted from the peripheral blood of the proband and her parents. Initial trio-based WES analysis and Sanger sequencing were performed by GeneDx

(Gaithersburg, MD) (please refer to Supplemental Table S1 in Supplemental Material for sequencing coverage information). Genomic DNA from the specimen was enriched for coding regions and splice site junctions for most genes on the human genome, sequenced on an Illumina platform, and then filtered and analyzed using their custom analysis tool. Variant reanalysis was performed using EMEDGENE analytical pipeline (https://iuhealth.emedgene.com/) and manually. Sequence variants were checked with population databases gnomAD (http:// gnomad.broadinstitute.org/) and evaluated using PolyPhen-2, MutationTaster, REVEL, Mutation Taster, DANN, LRT, and SIFT. Variant pathogenicity was interpreted according to the ACMG guidelines (Richards et al. 2015). Additional 3D structural analyses were performed by using AlphaFold (https://alphafold.com/), Phyre2 (http://www.sbg.bio.ic.ac.uk/phyre2/html/page.cgi?id=index), SuSpect method (Supplemental Fig. S1), and paralog and ortholog alignment by ClustalW (https://www.genome.jp/tools-bin/clustalw).

ADDITIONAL INFORMATION

Data Deposition and Access

The *IGF1R* variant and our interpretation has been submitted to ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) and can be found under accession number SCV002061317. Permission to deposit raw sequencing data was not granted.

Ethics Statement

The research project used medical health information and specimens that had been collected as part of an ongoing research study at the Undiagnosed Rare Disease Clinic at Indiana University. Written informed consent was obtained from both parents for the collection, research use, and storage of the specimens according to the approved protocol by the Indiana University Institutional Review Board (IRB #2005902680).

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Author Contributions

F.V. and E.C. proposed the meaning and concept of the study and designed the plan for the case. P.P., K.T., C.B., A.J., B.M.H., E.C., and F.V. made contributions to data collection and analysis. P.P., C.B., A.J., B.M.H., E.C., and F.V. drafted and revised the manuscript. All of the authors read and approved the final manuscript to be published and agreed to be responsible for the accuracy of the data and details.

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Competing Interest Statement

The authors have declared no competing interest.

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REFERENCES

Abuzzahab MJ, Schneider A, Goddard A, Grigorescu F, Lautier C, Keller E, Kiess W, Klammt J, Kratzsch J, Osgood D, et al. 2003. IGF-I receptor mutations resulting in intrauterine and postnatal growth retardation. *N Engl J Med* **349:** 2211–2222. doi:10.1056/NEJMoa010107

Adams TE, Epa VC, Garrett TP, Ward CW. 2000. Structure and function of the type 1 insulin-like growth factor receptor. *Cell Mol Life Sci* **57:** 1050–1093. doi:10.1007/PL00000744

Baldridge D, Heeley J, Vineyard M, Manwaring L, Toler TL, Fassi E, Fiala E, Brown S, Goss CW, Willing M, et al. 2017. The Exome Clinic and the role of medical genetics expertise in the interpretation of exome sequencing results. *Genet Med* **19:** 1040–1048. doi:10.1038/gim.2016.224

De Meyts P, Whittaker J. 2002. Structural biology of insulin and IGF1 receptors: implications for drug design. *Nat Rev Drug Discov* **1:** 769–783. doi:10.1038/nrd917

Garrett TP, McKern NM, Lou M, Frenkel MJ, Bentley JD, Lovrecz GO, Elleman TC, Cosgrove LJ, Ward CW. 1998. Crystal structure of the first three domains of the type-1 insulin-like growth factor receptor. *Nature* **394:** 395–399. doi:10.1038/28668

Giabicani E, Willems M, Steunou V, Chantot-Bastaraud S, Thibaud N, Abi Habib W, Azzi S, Lam B, Bérard L, Bony-Trifunovic H, et al. 2020. Increasing knowledge in *IGF1R* defects: lessons from 35 new patients. *J Med Genet* **57:** 160–168. doi:10.1136/jmedgenet-2019-106328

Ioannidis NM, Rothstein JH, Pejaver V, Middha S, McDonnell SK, Baheti S, Musolf A, Li Q, Holzinger E, Karyadi D, et al. 2016. REVEL: an ensemble method for predicting the pathogenicity of rare missense variants. *Am J Hum Genet* **99:** 877–885. doi:10.1016/j.ajhg.2016.08.016

Juanes M, Guercio G, Marino R, Berensztein E, Warman DM, Ciaccio M, Gil S, Bailez M, Rivarola MA, Belgorosky A. 2015. Three novel *IGF1R* mutations in microcephalic patients with prenatal and postnatal growth impairment. *Clin Endocrinol* **82:** 704–711. doi:10.1111/cen.12555

Kansra AR, Dolan LM, Martin LJ, Deka R, Chernausek SD. 2012. IGF receptor gene variants in normal adolescents: effect on stature. *Eur J Endocrinol* **167:** 777–781. doi:10.1530/EJE-12-0565

Kawashima Y, Higaki K, Fukushima T, Hakuno F, Nagaishi J, Hanaki K, Nanba E, Takahashi S, Kanzaki S. 2012. Novel missense mutation in the IGF-I receptor L2 domain results in intrauterine and postnatal growth retardation. *Clin Endocrinol* **77:** 246–254. doi:10.1111/j.1365-2265.2012.04357.x

Klammt J, Kiess W, Pfäffle R. 2011. *IGF1R* mutations as cause of SGA. *Best Pract Res Clin Endocrinol Metab* **25:** 191–206. doi:10.1016/j.beem.2010.09.012

Kountouris P, Stephanou C, Lederer CW, Traeger-Synodinos J, Bento C, Harteveld CL, Fylaktou E, Koopmann TT, Halim-Fikri H, Michailidou K, et al. 2021. Adapting the ACMG/AMP variant classification framework: a perspective from the ClinGen Hemoglobinopathy Variant Curation Expert Panel. *Hum Mutat* doi:10.1002/humu.24280

LeRoith D, Werner H, Beitner-Johnson D, Roberts CT. 1995. Molecular and cellular aspects of the insulin-like growth factor I receptor. *Endocr Rev* **16:** 143–163. doi:10.1210/edrv-16-2-143

Prontera P, Micale L, Verrotti A, Napolioni V, Stangoni G, Merla G. 2015. A new homozygous *IGF1R* variant defines a clinically recognizable incomplete dominant form of SHORT syndrome. *Hum Mutat* **36:** 1043–1047. doi:10.1002/humu.22853

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, et al. 2015. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* **17:** 405–424. doi:10.1038/gim.2015.30

Shapiro MR, Foster TP, Perry DJ, Rosenfeld RG, Dauber A, McNichols JA, Muir A, Hwa V, Brusko TM, Jacobsen LM. 2020. A novel mutation in insulin-like growth factor 1 receptor (c.641-2A>G) is associated with impaired growth, hypoglycemia, and modified immune phenotypes. *Horm Res Paediatr* **93:** 322–334. doi:10.1159/000510764

Solomon-Zemler R, Basel-Vanagaite L, Steier D, Yakar S, Mel E, Phillip M, Bazak L, Bercovich D, Werner H, de Vries L. 2017. A novel heterozygous IGF-1 receptor mutation associated with hypoglycemia. *Endocr Connect* **6:** 395–403. doi:10.1530/EC-17-0038

Wakeling EL, Brioude F, Lokulo-Sodipe O, O'Connell SM, Salem J, Bliek J, Canton APM, Chrzanowska KH, Davies JH, Dias RP, et al. 2017. Diagnosis and management of Silver–Russell syndrome: first international consensus statement. *Nat Rev Endocrinol* **13:** 105–124. doi:10.1038/nrendo.2016.138

Walenkamp MJ, Losekoot M, Wit JM. 2013. Molecular IGF-1 and IGF-1 receptor defects: from genetics to clinical management. *Endocr Dev* **24:** 128–137. doi:10.1159/000342841

Walenkamp MJE, Robers JML, Wit JM, Zandwijken GRJ, van Duyvenvoorde HA, Oostdijk W, Hokken-Koelega ACS, Kant SG, Losekoot M. 2019. Phenotypic features and response to GH treatment of patients with a molecular defect of the IGF-1 receptor. *J Clin Endocrinol Metab* **104:** 3157–3171. doi:10.1210/jc.2018-02065

Yang L, Xu DD, Sun CJ, Wu J, Wei HY, Liu Y, Zhang MY, Luo FH. 2018. *IGF1R* variants in patients with growth impairment: four novel variants and genotype–phenotype correlations. *J Clin Endocrinol Metab* **103:** 3939–3944. doi:10.1210/jc.2017-02782