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PREDICTION BY IN SILICO ANALYSIS OF THE OUTCOME OF MISSENSE MUTATION IN THE HUMAN IGF2 GENE

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Abstract: Gestational hypertensive syndromes(SHG),Gestational hypertension (HG) and chronic arterial hypertension (CAH) are among the major causes of maternal and fetal death and may be related to the polymorphism of the human IGF2 gene.Method: On the platformensemble, OtranscribedIGF2-205was identified in UNIPROT by the codeP01344.Of the 150 missense variants deposited in the databank, 11 were selected for in silico analysis, using theSIFT algorithms, Polyphen2 andMetaLR. Results:Youalgorithmsused to predict the effects of missense variants on the proteins encoded by the IGF2 gene in humans, showed agreement in the prediction of molecular consequences, and can be considered reliable tools for the characterization of new mutations foundin thisgene.The protein encoded by the IGF2 gene has an evolutionarily conserved sequence, suggesting that the gene is sensitive to mutations and, therefore, the identified site is probably related to the etiology of the disease.s pathologies.Conclusion:Based on these results, we can conclude that the morphofunctional alterations of proteins resulting from mutations in the IGF2 gene may be associated with harmful processes and changes in the structural stability of the protein, hindering its action in the physiological process. Understanding these alterations can help in the search for genetic markers, contributing to clarifying the prognosis, diagnosis, prevention and treatment of human diseases related to gestational hypertensive syndromes, gestational hypertension, chronic arterial hypertension, among others.

Keywords: Genetic polymorphism,IGF2, Variants, Bioinformatics, Missense.

INTRODUCTION

Abioinformatics is a science that offers different tools and computational technologies used to analyze data.and predict the molecular consequences of amino acid substitution based on protein structure, providing important information for identifying possible mutations that cause human genetic diseases.Gestational hypertensive syndromes (SHG), gestational hypertension (HG) and chronic arterial hypertension (CAH) are among the major causes of maternal and fetal death (WHO, 2011)and may be related to the polymorphism of the human IGF2 gene. The IGF2 gene (insulin-like growth factor 2), is located in the chromosomal region 11p15.5 and undergoes genomic imprinting,epigenetic phenomenon that occurs during gametogenesis.This gene has 4 exons distributed along 5580 bp of genomic DNA.The IGF2 geneencodes insulin-like growth factor II (IGFII or insulin-like growth factor II) with 180 amino acids that play an important role in embryonic development, controlling both the placental supply and the genetic demand for maternal nutrients for the mammalian fetus (CONSTANCIA et al, 2002).Insulin-like growth factor 2 is one of three protein hormones that share structural similarity with insulin.A missense mutation or "Missense" is a point mutation type of substitution of a base in the DNA (gene) that can cause an amino acid change within the coding region of the protein that can be deleterious to its function in the organism. Based on the importance of the IGF2 gene for embryonic development, it is important to analyze the missense mutations that directly affect the protein due to the change of amino acid, which can negatively impact the appearance of several diseases.

GOALS

This study aims to evaluate the impacts of missense mutations of the human IGF2 gene using three different in silico prediction software (SIFT, PolyPhen-2 and MetaLR) that bring information based on the evolutionary conservation of amino acids, identification of positions known as essential for protein composition, sequence homology, protein folding and information from a mutation database, in order to predict the molecular consequence of 11 different missense mutations in this gene.

METHODOLOGY

SELECTION OF VARIANTS

The Ensembl database (http://www.ensembl.org/), which evaluates the change of amino acids and their positions; and UniProt (https://www.uniprot.org/), which verifies protein sequences and functional information, were used as the main tools to select the variants analyzed in this work. the transcriptIGF2-205, at Ensemble,was identified in UniProtby code **P01344.** In this transcript, 150 missense variants deposited in the databank are described, of which 11 were selected for this analysis.

IN SILICO ANALYSIS AND PREDICTION

SIFT: It is a tool that predicts the possible effects that missense variants may have on protein function based on sequence homology and physicochemical similarities between amino acidssubstituted (Ng, PC & Henikoff S. (2003). Its scores can vary between 0 (deleterious) and 1 (tolerated). PolyPhen-2: Software capable of predicting the effects of missense variants on proteins, based on physical and comparative properties. Their scores can range from 0 to 1 (benign, possibly harmful, and probably harmful) (Adzhubei, et al., 2010). **MetaLR:** It is a tool capable of predicting the pathogenicity of single nucleotide variants (SNPs) using an ensemble method based on logistic regression.

RESULT AND DISCUSSION

The results obtained after the analysis (Table 1) were that the mutations p.G2V, p.G2E, p.S20W, p.R27C, p.G34D, p.R62L were harmful in MetaLR, probably harmful in PolyPhen and predicted as deleterious in SIFT. While the variants p.S20L p.R27S, p. R27H, p.A56T, p.L133F and p.L133V were predicted as tolerable, benign and tolerable in SIFT, PolyPhen and MetaLR respectively. However, the variant located at position 27 (R/L) in the protein (p.R27L), was predicted to be deleterious in SIFT, probably harmful and tolerable in PolyPhen and MetaLR respectively. Mutations p.L10V and p.L10P were shown to be benign for PolyPhen and in SIFT, p.L10V is predicted to be tolerable. In MetalR, p.L10V and p.L10P are shown to be deleterious and harmful, respectively. The p.R127L and p.R127H variants were predicted to be deleterious, the variantrs 1858937182,(p.G34D) (Table 1) is shown to be deleterious in SIFT, probably harmful in PolyPhen and harmful in MetaLR. this variant*of IGF2*in paternal allele fheyevidenced and suggested as another resource for the diagnosis of Silver-Russell Syndrome (SRS), proposing the inclusion in the panel of specific genes designed for routine diagnosis of SRS(Liu, Deguo, et al. 2017). DeChiara et al. (1991) showthat only the paternal allele of the gene is functional, while the maternal one is silenced in the organism, revealing a paternally methylated imprinting. The protein has an evolutionarily conserved sequence (Liu, Deguo, et al. 2017), this indicates that the gene is sensitive to mutation and, therefore, the location identified is probably the etiology of

Missense Variants ID	Wasteamino acid	codons	SIFT	PolyPhen	MetaLR
rs781634507	p.G2V (Gly / Val)	GGA, GTA	0.0	0.896	0.782
	p.G2E (Gly/ Glu)	GGA, GAA	Deleterious	Probably Harmful	harmful
rs1361412373	p.L10V (Read / Val)	CTG, GTG	0.07 tolerated	0.433 Benign	0.722 Deleterious
rs984257990	p.L10P (Read / Pro)	CTG, CCG	0.04 Deleterious	0.046 Benign	0.706 harmful
rs142012621	p.S20L (Be /Leu)	TCG, TTG	0.56 tolerated	0.001 Benign	0.305 tolerated
rs142012621	p.S20W (Ser /Trp)	TCG, TGG	0.04 deleterious	0.68 Probably Harmful	0.613 harmful
rs1230176657	p.R27 C (Arg / Cys)	CGC, TGC	0.03 deleterious	0.628 Probably Harmful	0.658 harmful
rs1230176657	P. R27S (Arg / Ser)	CGC, AGC	0.29 tolerable	0.015 Benign	0.411 Tolerable
rs1356855570	P. R27H (Arg / His)	CGC, CAC	0.06 Deleterious	0,007 Benign	0.415 Tolerable
rs1191719522	p.R27L (Arg / Leu)	CGC, CTC	0.0 Deleterious	0,999 probably harmful	0,353 Tolerable
rs1858937182	p.G34D (Gly /Asp)	GGC, GAC	0 Deleterious	1 Probably Harmful	0.971 harmful
rs1212009594	p.A56T (Wing /Thr)	GCA, ACA	1 Tolerable	0.147 Benign	0.207 Tolerable
rs768105151	p.R62L (Arg / Leu)	CGC, CTC	0.03 deleterious	0.864 Probably Harmful	0.768 Harmful
rs768105151	p.R62H (Arg /His)	CGC, CAC	0.07 tolerable	0.967 Probably Harmful	0.832 harmful
rs1191719522	p.R127L (Arg / Leu)	CGC, CTC	0 Deleterious	0.999 Probably Harmful	0.353 Tolerable
rs1191719522	p.R127H (Arg / His)	CGC, CAC	0 Deleterious	1 Probably Harmful	0.355 Tolerable
rs530101369	p.L133F (Leu/Phe)	CTC, TTC	0.15 Tolerable	0.055 Benign	0.072 Tolerable
rs530101369	p.L133V (Read / Val)	CTC, GTC	0.15 Tolerable	0.441 Benign	0.099 Tolerable

Table 1.Prediction of missense variants of the IGF2 gene harmful to the human organism, showing the substitution of amino acids.

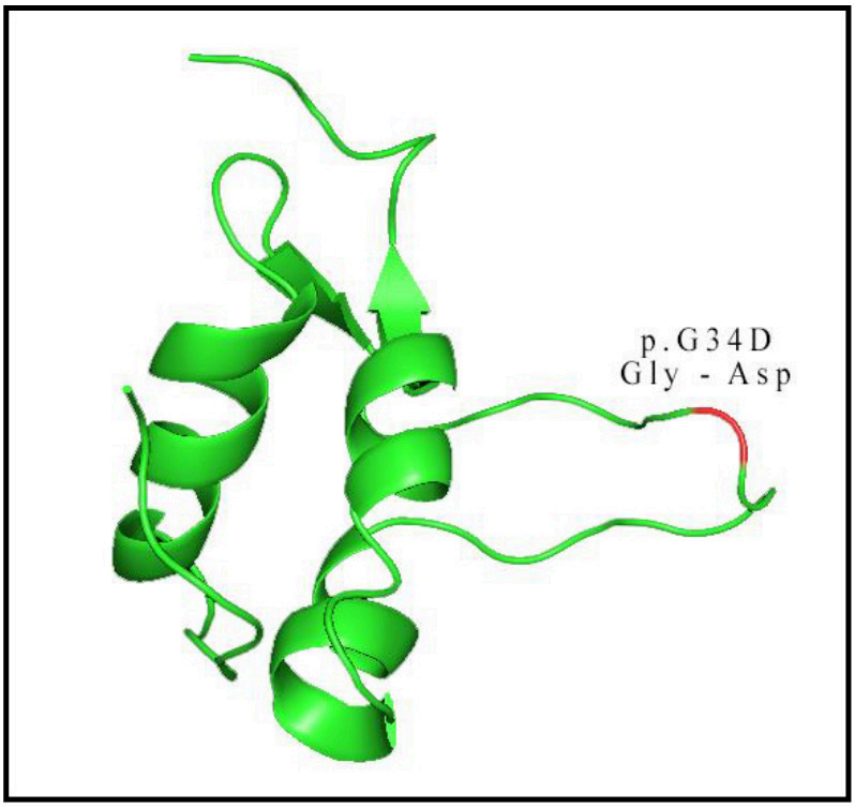

Figure 1.Schematic drawing of the protein encoded by the IGF2 gene in humans, showing the location of the variantrs1858937182in its structure.

the disease (Figure 1).As can be seen, in silico studies of the polymorphisms of the gene under analysis can help in the interpretation of gene variations, possibly associated with hypertensive syndromes during the gestational period in humans. The software used to predict the effects of missense variants on proteins encoded by IGF2 in humans showed agreement in predicting the molecular consequences and can be considered reliable tools for the characterization of new mutations found in this gene.

CONCLUSION

In silico studies of IGF2 gene polymorphisms may help in the interpretation of gene variations that may be associated with hypertensive syndromes during pregnancy in humans. What we can conclude from these results regarding the analysis of the variants of the IGF2 gene is that the morphofunctional alterations of the proteins, resulting from mutations in this gene, may be associated with harmful processes and changes in the stability and structure of the protein, making it difficult to action in the physiological process. Furthermore, the understanding of the morphofunctional alterations resulting from the IGF2 gene, can help in the search for genetic and molecular markers, contributing to the understanding of the prognosis, diagnosis, prevention and treatment for diseases in humans related to gestational hypertensive syndromes, gestational hypertension, chronic arterial hypertension, among others. others.

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