Brief Communication

Genetic characterization of growth hormone 1 gene in patients with isolated growth hormone deficiency

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ABSTRACT

Introduction: Growth hormone (GH) secretion and release is a complex and highly regulated process. Any alteration disturbing synthesis, secretion or biological action of GH, results into growth hormone deficiency (GHD). GHD is of two types-isolated growth hormone deficiency (IGHD) and combined pituitary hormone deficiency (CPHD), of which IGHD is more common. The genes implicated in its etiology are growth hormone 1(*GH1*) and receptor of growth hormone-releasing hormone (*GHRHR*). Mutations within the coding region and/or either entire or partial deletions of the *GH1*gene lead to IGHD. In addition,*GH1* possesses upstream regulatory elements and a promoter with binding sites for various transcription factors, which control its expression. **Aim:** The study was planned with an aim to identify entire *GH1* locus deletion, mutations in the *GH1* coding region and sequence variations (polymorphisms) in the promoter region of the gene in patients with IGHD. **Materials and Methods:** Thirty patients clinically diagnosed with IGHD and 30 healthy individuals who formed the controls were enrolled for the study. Genomic DNA was isolated from peripheral blood sample and processed for amplification of the desired regions followed by direct sequencing and/or restriction endonuclease digestion. **Results:** Out of the 30 IGHD patients screened, 20% of the cases showed consanguinity and 16% had a positive family history. Seven percentage of the patients showed homozygous deletion of the *GH1*gene while rest of them had heterozygous deletion. Screening of the coding region of *GH1* showed sequence variations in exon 1 in 20% of the patients whereas the promoter region showed the presence of polymorphisms–rs2005171 in 20%, rs2005172 in 15% and rs11568828 in 18% of the cases. The haplotype comprising rs2005171 and rs2005172 was observed in four patients. **Conclusion:** The present study is an attempt to characterize the *GH1* locus in IGHD patients. To the best of our knowledge this is the first study of its kind where entire *GH1*locus, upstream regulatory elements and promoter region have been studied. Such an analysis would provide valuable information on the etiology of IGHD.

Key words: GH1 gene, Isolated growth hormone deficiency, Genetics

Introduction

Growth hormone (GH) secretion and release is a complex and highly regulated process. Any alteration disturbing synthesis, secretion or biological action of GH, results in growth hormone deficiency (GHD) which is of two types-isolated growth hormone deficiency (IGHD) and combined pituitary hormone deficiency (CPHD).IGHD is more common and the genes implicated in its etiology are growth hormone 1 (*GH1*) and receptor of growth hormone-releasing hormone (*GHRHR*).IGHD can be inherited as autosomal recessive (IGHD IA and IB), autosomal dominant (IGHD II) and X-linked (IGHD III) form.[1]

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The *GH1* gene (OMIM# 139250) is located on chromosome 17q22-q24 and has 5 exons.[2] It encodes for GH,which promotes and controls various physiologic processes. *GH1*is a part of a cluster of five related genes of about 66.5 kb in length. Mutations within the coding region and/or either entire or partial deletions of the *GH1*gene lead

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to IGHD. In addition, *GH1* possesses upstream regulatory elements and a promoter with binding sites for various transcription factors, which control its expression. The promoter region of *GH1* is highly polymorphic with at least 15 well-described single nucleotide polymorphisms (SNPs). Presence of SNPs may alter the expression of the gene by hampering with the normal transcription process leading to increased or decreased levels and resulting in GHD.

The present study was planned with an aim to identify entire *GH1* locus deletion, mutations in the *GH1* coding region and sequence variations in the promoter region of the gene in patients with IGHD.

Materials and Methods

Thirty clinically diagnosed IGHD patients were recruited from the Pediatric and Adolescence Endocrine Clinic (PAEC), Department of Endocrinology and Metabolism, All India Institute of Medical Sciences. Thirty healthy individuals formed the control group.The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Ethics Committee. Detailed family history and pedigree information along with 5 ml of peripheral blood was collected from the patients and controls after taking informed consent. Genomic DNA was isolated and processed for amplification of the whole *GH1* gene followed by nested PCR for all the coding and the promoterregions. The amplified products were subjected to direct sequencingand/or restriction endonuclease digestion to screen for the nucleotide changeswhich included mutations, SNPs and whole or partial gene deletion respectively.Nucleotide sequences obtained were compared with the published complementary DNA (cDNA) sequences of *GH1* (GenBank accession number ENSG00000204414).

Results

A total of 30 IGHD patients in comparison to 30 normal controls were screened. Twenty percentage of the cases showed consanguinity and 16% had a positive family history. Seven percentages of the patients showed homozygous deletion while rest of them had heterozygous deletion of the *GH1*gene. Screening of the coding region of *GH1* showed sequence variations in exon 1 in 20% of the patients whereas screening of the regulatory and promoter region showed the presence of SNPs;rs2005171 in 20%, rs2005172 in 15% and rs11568828 in 18% of the cases. The SNP haplotype comprising rs2005171 and rs2005172 was observed in fourpatients.

Discussion

The present study reports on molecular characterization of (a) the *GH1* locus deletion, (b) mutations in the *GH1* coding region and (c) sequence variations in the promoter region of the gene in patients with IGHD.

GH expression and secretion are highly regulated.Deviation in its regulation results in heterogeneity comprisingof different isoforms (22-kDa, 20-kDa, etc.), incomplete or modified protein due to mutations and varied levels of expression due to polymorphisms in the promoter region.

Results of our pilot study indicate the existence of a different genotype profile in our patient population showing heterozygous 6.7 kb *GH1* cluster deletion in a maximum number of the cases in comparison to other studies.[3] Pathogenic *GH1* mutations were identified ina small number of patients. Reported genetic variations in the upstream *GH1* regulatory and promoter regionswere also identified in them.

The regulation of *GH1* gene expression has been characterized in detail with pituitary specific cis/transelements in the *GH1* proximal promoter giving rise to at least 40 different haplotypic combinations in different studies ranging from 17 in the Asians to about 40 in the Europeans. Genetic expression studies by Horan *et al.* (2003)[4] showed upto 12 fold increase in the gene expression level depending upon different promoter haplotypes. The promoter haplotype observed in the present study is in accordance with those reported earlier.

Thus, the genotype of an individual depends upon the presence or absence of the entire *GH1* locus along with mutations and/or variations in the coding as well as the promoter region that decides the final isoform of the GH produced, which ultimately governs the phenotype.

Conclusion

The present study is an attempt to characterize the *GH1* locus in IGHD patients. To the best of our knowledge this is the first study of its kind where the entire locus, its upstream elements and promoter region have been studied extensively. Such an analysis on a larger data set would provide valuable information on the etiology of IGHD in our patients.

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