SHBG (sex hormone-binding globulin)

Nicoletta Fortunati, Maria Graziella Catalano

Lab Endocrinologia Oncologica, Dip Oncologia, AOU San Giovanni Battista & Dip Fisiopatologia Clinica, Universita di Torino, Via Genova 3, 10126 Torino, Italy (NF, MGC)

Published in Atlas Database: November 2010

DOI: 10.4267/2042/45983

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.
© 2011 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Identity

Other names: ABP; MGC126834; MGC138391; SBP; TEBG
HGNC (Hugo): SHBG
Location: 17p13.1

Note
This gene encodes a steroid binding protein that was first described as a plasma protein secreted by the liver; lately, it was recognized to be produced also by testis germ cells; the protein is now thought to participate in the regulation of steroid responses at cell level. The encoded protein in biological fluids is a dimer formed from identical or nearly identical monomers; in each monomer one steroid binding pocket has been recognized. SHBG binds androgen and estradiol with different affinity. Alternate promoters and several spliced transcripts were reported.

DNA/RNA

Description
The human SHBG gene is located on the short arm of chromosome 17 (17pter-p12) and consists of eight exons.

Schematic representation of SHBG gene. Exons are represented by the blue boxes.

Transcription
Two major SHBG transcripts are known, each originating from a different promoter. The variant 1, which has also been referred to as SHBG-L, encodes the longest protein (isoform 1), while the variant 2 uses an alternate in-frame splice site in the 3' coding region compared to variant 1. These two transcripts differ in their 5' sequence and in the absence of exon 7 in the latter one.

Protein

Note
402 amino acids; 43779 Da each subunit: homodimer.

Description
SHBG is a homodimer; each monomer is constituted of 402 aa, molecular weight 43.7 kDa. The protein consists of a signal peptide (1-29 aa) and 2 laminin G-like domains (domain 1: 45-217 aa; domain 2: 224-390 aa). Each SHBG monomer has an O-linked oligosaccharide at Thr(36) and up to two N-linked oligosaccharides at Asn(380) and Asn(396).
Localisation

SHBG is secreted by liver into the bloodstream and it is synthesized by testis germ cells; it also recognizes a specific binding site located on membranes of sex steroid target cells (e.g. breast, prostate).

Function

SHBG binds and carries sex steroids, regulating their biological active fraction; it also regulates sex steroid effects in target cells by direct action.

Homology

Protein S, Gas6, laminin, agrin.

Mutations

Note
CCG-CTG; Pro-Leu156; reported in hyperandrogenism.
GAC-AAC; Asp-Asn327; reported in estrogen-dependent breast cancer.
(TAAAA)$_n$ promoter, n=6-11; n>8; reported in: polycystic ovary syndrome; CAD in postmenopausal women; reduced bone mineral density in men; metabolic syndrome.

Implicated in

Breast cancer

Note
Human serum sex hormone-binding globulin (SHBG) regulates the bioavailable fraction of circulating estradiol that is known to be a critical factor in breast cancer. In a case-controlled study within the European Prospective Investigation into Cancer and Nutrition (EPIC), SHBG levels in postmenopausal women who developed breast cancer were confirmed to be significantly lower compared with controls, while no significant difference was observed in premenopausal women.

SHBG has a direct effect in breast cancer cells; it interacts with membranes of these cells, initiates subsequently a specific intracellular pathway leading to cross-talk with the estradiol-activated pathway, finally inhibiting several effects of estradiol in breast cancer cells, e.g. cell proliferation.

The Asp327Asn polymorphism of SHBG gene is related to breast cancer risk. Cui et al. observed a significant association of the Asp327Asn polymorphism with reduced breast cancer risk and Becchis et al. reported a significantly higher frequency of the polymorphism in postmenopausal patients with ER-positive breast cancer than in ER-negative; more recently Costantino and co-workers suggested a protective role of this polymorphism since mutated SHBG is more effective than wild type protein in inhibiting estradiol-induced cell proliferation and apoptosis, and this is due to the fact that D327N SHBG binds to MCF-7 cells to a greater extent than does wild type protein.

Prostate cancer

Note
Patients with prostate cancer showed lower SHBG levels than benign prostate hypertrophy patients and controls.

Alternative splicing of SHBG gene is more pronounced in LNCaP and MCF-7 cancer cell lines; at least six independent transcripts each, resulting from alternative splicing of exons 4, 5, 6, and/or 7 were described.

SHBG might be a significant multivariate predictor of lymph node invasion in patients with prostate cancer.

The use of preoperative serum SHBG could help to identify patients at risk of lymph node invasion.

Type 2 diabetes mellitus

Note
Epidemiological studies consistently show that circulating SHBG levels are lower in type 2 diabetes patients than in non-diabetic individuals.

Low circulating levels of SHBG are a strong predictor of the risk of type 2 diabetes in women and men.

Carriers of a variant allele of the SHBG single-nucleotide polymorphism (SNP) rs6259 and carriers of
a rs6257 variant were associated with a risk of type 2 diabetes following their associated sex hormone-binding globulin levels.

**Insulin resistance and polycystic ovary syndrome (PCOS)**

**Note**

SHBG concentrations are inversely associated with insulin resistance, and in turn, with the risk of type 2 diabetes. Women with polycystic ovary syndrome (PCOS) present low SHBG levels that are negatively correlated with body mass index and waist to hip ratio, and are, furthermore, associated with insulin resistance.

**Breakpoints**

**Note**

An X;17 translocation breakpoint was characterized in a 5-year-old female with hypomelanosis of Ito (HI) who exhibits characteristic hypopigmented lesions, psychomotor retardation, and choroid plexus papilloma. A chromosome-17-specific DNA fragment was isolated and used to identify cosmid clones crossing the translocation from chromosome 17p13. Exon trapping identified two known genes from chromosome 17: FMR1L2 (the fragile X mental retardation syndrome like protein 2) and SHBG (human sex hormone-binding globulin). Mapping the FMR1L2 and SHBG genes showed that neither gene was disrupted by the translocation.

**References**


Porto CS, Musto NA, Bardin CW, Gunsalus GL. Binding of an extracellular steroidal binding globulin to membranes and soluble receptors from human breast cancer cells (MCF-7 cells). Endocrinology. 1992 May;130(5):2931-6


Xita N, Tsatsoulis A, Chatzikiaklidou A, Georgiou I. Association of the (TAAA)n repeat polymorphism in the sex hormone-binding globulin (SHBG) gene with polycystic ovary syndrome and relation to SHBG serum levels. J Clin Endocrinol Metab. 2003 Dec;88(12):5976-80


This article should be referenced as such: