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Cloning and developmental expression of WSTF during *Xenopus laevis* embryogenesis

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Abstract

The gene WSTF is deleted in the autosomal dominant hereditary disorder Williams–Beuren syndrome. This disorder is caused by a 1.3 megabase deletion in human chromosome 7, encompassing at least 17 genes. The WSTF protein contains a bromodomain, found predominantly in chromatin-associated proteins. Reported association of WSTF with chromatin remodeling factors and functional data support a role for WSTF during chromatin remodeling. Here, we report the cloning and developmental expression pattern of *Xenopus laevis* WSTF. *Xenopus laevis* WSTF is a protein with a predicted amino acid sequence of 1441 amino acids. Three discrete domains can be identified in the *Xenopus laevis* WSTF protein, a PHD finger, a DDT domain and a bromodomain. Alignment of *Xenopus* WSTF with the corresponding orthologues from *Homo sapiens*, *Gallus gallus*, *Mus musculus* and *Danio rerio* demonstrates an evolutionary conservation of WSTF amino acid sequence and domain organization. In situ hybridization reveals a dynamic expression profile during embryonic development. WSTF is expressed differentially in neural tissue, especially during neurulae stages in the eye, in neural crest cells and the brain.

Keywords: *Xenopus laevis*; Neural; Williams–Beuren; WSTF; Bromodomain

1. Results and discussion

1.1. WSTF—an introduction

WSTF (Williams syndrome transcription factor, = WBSCR9 or BAZ1B) was first identified during the search for genes deleted in patients with Williams–Beuren syndrome (Lu et al., 1998; Peoples et al., 1998). Williams–Beuren syndrome, an autosomal dominant hereditary disorder, is characterized by multiple symptoms including supravalvular aortic stenosis, elfin face, mental retardation, growth deficiency and infantile hypercalcemia (Francke, 1999; Morris et al., 1988; Bellugi et al., 1990). Incidence of Williams–Beuren syndrome is approximately 1:20,000 in live births. The genomic 1.3-megabase-region deleted in Williams–Beuren syndrome maps to human chromosome 7q11.23 (Ewart et al., 1993). Several candidate genes are located in this region, including the locus of the WSTF gene. It is possible to link some symptoms of Williams–Beuren to dysfunctionality of these candidate genes. The deletion of *elastin* leads to the vascular defect of supravalvular aortic stenosis (SVAS) (Ewart et al., 1993, 1994; Olson et al., 1995) and deletion of LIM-kinase 1 (*LIMK1*) is implicated in impaired visuospatial constructive cognition (Frangiskakis et al., 1996). There is evidence that WSTF could play a role in eliciting infantile hypercalcemia through interaction with the vitamin D receptor (Kitagawa et al., 2003).

Human WSTF, a large protein of 1483 amino acids is characterized by three domains, a PHD zinc finger domain, a bromodomain (Lu et al., 1998; Peoples et al., 1998) and a DDT domain (Doerks et al., 2001). Bromodomains and PHD domains are found in proteins involved in chromatin remodeling and modulation of transcription (Winston and Allis, 1999; Aasland et al., 1995). Bromodomains, 110 amino acid sequences (Winston and Allis, 1999), can be found in yeast as well as in invertebrate and vertebrate proteins (Haynes et al., 1992). An important protein family involved in chromatin remodeling are proteins with histone acetyltransferase (HAT) activity. Most proteins with HAT activity or proteins associated with HAT-proteins (Jones et al., 2000) possess a bromodomain. The demonstration that bromodomains interact specifically with acetylated lysine, a target of HAT-protein action, argues for a role of bromodomains in

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A

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MAPLLGRRPFPLVKPLSEAATGEGEEEVYMIEHSKEAFRSREEYESRLERYAERIWTCKS 60
TGSSQLTHKEAWDEEQEVAELLKEEFPVWYEKQVLEMVHHNTISLDKLVDQSWMEIMTKY 120
ADGEECDFEVGPEKYLRAKIVKVHPLEKEEQASEKKSEGSCDSPSSDKENSNKVAQDIQL 180
KEESNRLESLSSLRESDRARRSPRKLPTSLKKEEKKWVPPKFLPHKYDVKLLNEDKVISF 240
VPVDSLYRSERPPNKEILRYFIRHNALRIGTGENAPWVVEDELVKKYTLPSKFSDFLLDP 300
HKYMTLNPSSATKRKSLGSPDQKPAKKSKKSPLSPSSWSLANLKKTAVNSSSSEEEMQLM 360
IGANLNKKGSIGKKSDKKKPKNGKSQVLNGQKISAKTRSPKKGLKSPKLKQMTLLDMAKS 420
TPKVSRAQKGGSNTPRSSSKPNKYLPPAALHLISYYRDNKNREDRKSALSALISKVARML 480
SAEDRKRLPDDLQELVQKRYELLEHRKQWAVMTEEQREEYMRKKREALKARIKEKTRERK 540
QKEREERLEKQKRYEDQDLTGKSLPTFKLVDTPEGLPNALFGDVAMVIEFLSGYSDLLLP 600
DGQYPVTAVSLMEALAAEKGGFMYLNRGLVVLLQTLLQDEIAEDYGELGMKLSEIPLTLH 660
SASELVRLCLRKSDSPAGENESIEKGDEDSEGSAVYQDDEVEDEYLEKLETSEFFELTTE 720
EKLHILAALCHRILMTYSVQDHVDAKQQRSGELWKERLAILKEENDKKRAEKQKRKEQGT 780
VKPKEEVQAAKIVKKQEKINTQQDNDAEDMISAVKSRRLQAMQAKKEKEEHEKLTKERIE 840
RETEEERSRKQKASAEKAFHEGIAKAKLVLRRSPLGTDRNHNRYWLFSDEVPGLYIEKGW 900
VHDSINYRFSPESKQDSEQDAEESEDANSSIGCPDDSTQREEKHAETTVPKQGQNLWFLC 960
DTQKELDELLDSLHPQGFRESQLKERLQNRYQDIMHSIHLARKQNLGLKTCDGQQELLNF 1020
LRSDIIEVATRLQKGGLGYLDDTTEFEAKVRTFENLKDFGECIVFLQAAVIKKFLQGFMA 1080
PKQKKRKHQSEEAAAKAEEQDEEKKMAEEAKVASAVEKWKVAIRDAQTFSRMHVLLGMLD 1140
ACIKWDMSSENARCKVCRKKGEDDKLILCDECNKAFHLFCLRPVLFNIPDGEWLCPACQP 1200
ATARRSSRGRNYAEDSTQDEDEEEEEESEEEEEESDEEEEEQEMMGQRLRSRKAAKGK 1260
PGRPTRRGRPPKNNTHSRVSRQRYVEDTEADVEEMVRQSKPTSRRQNQEFQKCEEILAKL 1320
IKYRFSWPFREPFNADEIEDYTKVVTTPMDFQTMQSKCSCGSYQTVQEFLNDLKLVFGNT 1380
ELYYEAGSSQLSCLEKTEQCARDLLGKHLPAHTYQRRHRKHQSPEPEPETANPGRGRKQK 1440
K                                                              1441
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B

DDT-domain:

```
Xenopus   NALFGDVAMVIEFLSGYSDLLLPDGQYPVTAVSLMEALAAEKGGFMYLNRGLVVLLQTLLQDEIA
Gallus    NTLFGDVAMVVEFLSCYSGLLMPDAQYPITAVSLMEALCAEKGGFLYLNRVLVILLQTLLQDEIA
Homo      NTLFGDVAMVVEFLSCYSGLLLPDAQYPITAVSLMEALSADKGGFLYLNRVLVILLQTLLQDEIA
Mus       NTLFGDVALVVEFLSCYSGLLLPDAQYPITAVSLMEALSADKGGFLYLNRVLVILLQTLLQDEIA
Danio     NTIFGDVAMVVEFLHCYSGLLMPDDQYPITSIALLEALAGEKAGFLYLNRVLVVLLQTLLQDELA
          *  ***** * ***  ** ** ** *** *   * ***   * ** **** ** ********* *
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PHD-domain:

```
Xenopus   RCKVCRKKGEDDKLILCDECNKAFHLFCLRPVLFNIPDGEWLCPACQ
Gallus    RCKVCRKKGEDDKLILCDECNKAFHLFCLRPALYEIPDGEWQCPACQ
Homo      RCKVCRKKGEDDKLILCDECNKAFHLFCLRPALYEVPDGEWQCPACQ
Mus       RCKVCRKKGEDDKLILCDECNKAFHLFCLRPALYEVPDGEWQCPACQ
Danio     RCKVCRRKGEDDKLILCDECNKAFHLFCLRPALYRIPAGEWLCPACQ
          ****** ************************ *   * *** *****
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BROMO-domain:

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Xenopus   TSRRQNQEFQKCEEILAKLIKYRFSWPFREPFNADEIEDYTKVVTTPMDFQTMQSKCSCGSYQTVQEFLN
Gallus    TARRQSLELQKCEEILSKLIKYRFSWPFREPVTTEEAEDYCEVISNPMDFQTMQSKCSCGNYRSVQEFLS
Homo      SSRRQSLELQKCEEILHKIVKYRFSWPFREPVTRDEAEDYYDVITHPMDFQTVQNKCSCGSYRSVQEFLT
Mus       ISRRQSLELQKCEDILHKLVKYRFSWPFREPVTRDEAEDYYDVIEHPMDFQTIQNKCSCGNYRSVQEFLT
Danio     PSRKKDVELQKCEEILQKIMKFRHSWPFREPVSAEEAEDYQDVITSPMDLTTMQGKFKSSEYHSASDFIE
            *    * **** ** *  * * *******    * ***  *   ***  * * *     *     *

Xenopus   DLKLVFGNTELYYEAGSSQLSCLEKTEQCARDLLGKHLP
Gallus    DMKQVFSNAERYNQNGSHVLSCLEKTEQCLIDMVHKHLP
Homo      DMKQVFTNAEVYNCRGSHVLSCMVKTEQCLVALLHKHLP
Mus       DMKQVFANAELYNCRGSHVLSCMEKTEQCLLALLQKHLP
Danio     DMKLIFSNAEEYNQPSSNVLTCMSRTEEAFVELLQKSLP
          * *  * * * *    *  * *   **        * **
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Fig. 1. Predicted amino acid sequence of Xenopus WSTF and alignment of WSTF domains. (A) The predicted WSTF amino acid sequence comprises 1441 amino acids. Domains of WSTF are highlighted in different colours, the DDT domain in red, the PHD domain in green, and the bromodomain in blue. (B) Alignment of the predicted domains of Xenopus WSTF and the corresponding domains of WSTF proteins of major model organisms. Amino acids which are conserved among all species are indicated by an asterisk.