

Osteopathia striata with cranial sclerosis, Wilms' tumor and the *WTX* gene

Elisa Cattaneo, Sara Ciceri, Natascia Liberati, Paolo Radice, Luigi Tarani, Angelo Selicorni, Daniela Perotti

Elisa Cattaneo, Angelo Selicorni, UOS, Pediatric Genetic Unit, Pediatric Department, MBBM Foundation, S Gerardo Hospital, 20900 Monza, Italy

Sara Ciceri, Paolo Radice, Daniela Perotti, Molecular Bases of Genetic Risk and Genetic Testing Unit, Department of Preventive and Predictive Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, 20133 Milano, Italy

Natascia Liberati, Luigi Tarani, Department of Pediatrics, Policlinico Umberto I, Sapienza University, 00186 Roma, Italy

Author contributions: Cattaneo E, Ciceri S and Liberati N contributed equally to this work, they wrote the draft of the manuscript, developing the themes and the structure; Radice P, Tarani L, Selicorni A and Perotti D contributed equally to this work, they edited, wrote some sections and advised on the content.

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Correspondence to: Daniela Perotti, PhD, Molecular Bases of Genetic Risk and Genetic Testing Unit, Department of Preventive and Predictive Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Venezian, 1, 20133 Milano, Italy. daniela.perotti@istitutotumori.mi.it

Telephone: +39-02-23902644 Fax: +39-02-23903073

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patients and the involvement of *WTX* anomalies in OSCS and in WT.

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Core tip: Osteopathia striata with cranial sclerosis (OSCS), a condition often benign in females and severe and lethal in males, has a clinically heterogeneous presentation. Germline anomalies affecting the *WTX* gene, mapped to chromosome X, are causative of OSCS. Despite *WTX* mutations in Wilms' tumor (WT) that closely mirror those identified in OSCS patients, individuals with OSCS do not develop WT. This is in contrast with other syndromic conditions, in which germline mutations or epimutations, also found as somatic events in sporadic WTs, predispose to WT development.

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Abstract

Osteopathia striata with cranial sclerosis (OSCS, OMIM#300373) is an X-linked dominant sclerosing bone dysplasia that shows a distinct phenotype in females and males. In 2009, Zandra Jenkins *et al* found that germline mutations in the *FAM123B/WTX/AMER1* gene, mapped to chromosome Xq11.2, cause both the familial and sporadic forms of OSCS. Intriguingly, the *WTX* gene was already known as a putative tumor suppressor gene, since in 2007 Rivera *et al* had reported inactivating *WTX* mutations in Wilms' tumor (WT), the most frequent renal tumor of childhood. Here we review the heterogeneous clinical presentation of OSCS

OSTEOPATHIA STRIATA WITH CRANIAL SCLEROSIS

The X-linked inheritance pattern of osteopathia striata with cranial sclerosis (OSCS, OMIM#300373), previously predicted on clinical grounds, found confirmation when germline mutations involving the *WTX* gene, mapped to chromosome Xq11.2, were identified as the cause of OSCS^[1]. All mutations either deleted the whole gene or resulted in the premature termination of translation^[1].

The *FAM123B/WTX/AMER1* gene encodes a 1135-amino acid protein with multiple protein-protein

interaction domains and N-terminal phosphatidylinositol 4,5-bisphosphate binding domains mediating its localization to the plasma membrane^[1-3]. The *WTX* protein has been demonstrated to regulate the stability of β -catenin^[2], a key effector of the WNT/ β -catenin signaling pathway (reviewed in Clevers and Nusse 2012^[4]). The critical importance of this pathway during embryogenesis is clearly demonstrated by the pleiotropic clinical presentation of OPCS patients. The *WTX* gene has two splice forms, *WTXs1* full length and *WTXs2*, a shorter form encoding a 858-amino acid protein that lacks residues 50-326 and does not localize to the plasma membrane^[1,5]. Only *WTXs1* is considered to be important in regulating the WNT signaling in the context of the development since disease-causing *WTX* mutations that do not affect the integrity of *WTXs2* have been reported^[1,6-8].

Females affected with OPCS present a great variability of the phenotype and, while previous studies^[9-11] suggested, at least in some cases, a nonrandom X-inactivation^[9-11] that could explain this phenomenon^[6], Jenkins *et al*^[11] demonstrated that in 19 *WTX* mutation-bearing heterozygous females X-inactivation ratios were not skewed.

Among the features that constitute the OPCS female phenotype, sclerosis of bone (especially the increased thickness and density mostly of the cranial base) and the fine, uniform, linear striations of the tubular bones are considered the hallmarks of the disease.

Cranial sclerosis is the most typical and early feature, being present since birth. It appears before the longitudinal striae that become evident in the first years of life. Fan-like striations of the iliac bones are present in more than 50% of cases. It is worth mentioning that longitudinal striations at the metaphyses and diaphyses of the tubular bones are seen only in females and in males that are mosaic for a *WTX* mutation^[6,7,9,12].

Other skeletal defects reported in the literature, although quite rare, are thoracic (pectus excavatum, broad flat ribs) and vertebral anomalies (2%), digital flexion contractures, phalangeal duplication, syndactyly, short or absent fibula and club feet (3%)^[12]. Coronal craniostenosis has been described in one patient only^[9].

Facial dysmorphisms are rather frequent and sometimes the only pathological feature in addition to the sclerosis of the skull and the longitudinal striation of the long bones. Macrocephaly is documented in almost half of patients, followed by frontal and occipital bossing, prominent forehead, maxillary hypoplasia, mandible overgrowth with protuberance of the jaw and dental malocclusion. Female patients can also manifest ocular hypertelorism, downslanting palpebral fissures, broad and depressed nasal bridge, narrow high arched palate and low set dysplastic ears^[13-22]. Dental anomalies have been reported in 30% of patients^[20]. Regarding the neurological manifestations, intellectual disability has been described in a small percentage of patients, mainly associated with central nervous system defects (ventricular dilatation, abnormal gyration, corpus callosum hypoplasia or agenesis, hydrocephalus), as well as developmental and

speech delay.

Conductive hearing loss can be considered a distinctive symptom of the disease, occurring in almost 50% of patients. In the remaining half, hearing loss is sensorineural or of mixed type^[6,7,12,20,23]. Deafness is the result of bone sclerosis of mastoid cells, narrowing of the middle ear cavity, the mastoid antrum and the Eustachian canal, and of impaired mobility of the ossicles. High resolution computed tomography of the temporal bone has shown the presence in different patients of bilateral thickening and bone sclerosis of the skull base and mastoid cells, and the abnormal ossicular fixation to the bone surface of the middle ear cavity^[23]. Sensorineural hearing loss could instead be due to the nerve encroachment.

Other cranial nerve deficiencies (oculomotor and hypoglossal, abducens and maxillary nerves) due to the narrowing of the nerve canals and foramina by the sclerosing process are reported. Unilateral peripheral facial palsy and congenital facial palsy were described in 4 patients^[20,24]. The optic nerve may also be involved due to the narrowing of the optic foramina. Nerve palsy might be due to the sclerosing bone process^[25] but it is also hypothesized that disruption of the nerve supporting vessels may lead to secondary cranial nerve deficiencies^[20]. Lumbar spinal stenosis, defined as narrowing of the lumbar spinal canal, nerve root canal or intervertebral foramina, has been described in one patient only and could be thought of as a neurological complication of the disease^[26].

As already mentioned, OPCS manifests only with the hallmarks of the syndrome (cranial sclerosis and longitudinal striations of the long bones) accompanied by minor facial dysmorphisms or in association with internal organ anomalies, growth and mental retardation.

In female patients, the most frequently affected organs are the heart, with congenital defects including ventricular septal defects, patent ductus arteriosus, pulmonary atresia and valve stenosis, the lungs and the respiratory system in general, and the gastrointestinal and urogenital systems. The respiratory system may be affected in many patients. In particular, laryngotracheomalacia, nasal obstruction and recurrent bronchitis are reported in 13.5% of patients^[12,20]. Cleft palate (Pierre Robin's triad) and bifid uvula can also be observed. Gastrointestinal anomalies, including omphalocele, intestinal malrotation and Hirschsprung's disease have been reported in 12% of patients^[9,27,28]. Anal stenosis has been described in two girls only^[29,30].

OPCS in males is more severe than in females because it follows an X-linked dominant pattern of inheritance that determines hemizygoty of the mutation and, consequently, a wide spectrum of severe clinical manifestations, such as abortion, stillbirth and post-natal lethality. Despite this, cases with long survival are also described, allowing a clinical distinction in severe and mild forms in males. The male severe phenotype exhibits macrocephaly, facial dysmorphisms (frontal bossing, hypertelorism, low set ears, broad depressed nasal bridge and micrognathia) and bony sclerosis (more marked than in females), with

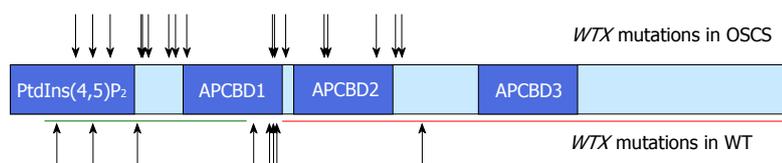


Figure 1 *WTX* mutations in osteopathia striata with cranial sclerosis and Wilms' tumor. The full length *WTX* protein possesses two phosphatidylinositol(4,5)-bisphosphate [PtdIns(4,5)P₂] binding domains, three adenomatous polyposis coli binding domains (APCBD) and a β -catenin binding region (red line)^[2,3]. The smaller *WTX* isoform lacks amino acids 50-326 (green line)^[1,5]. Functionally relevant mutations include whole gene deletions and truncating mutations. Arrows indicate the position of mutations introducing a stop codon or causing a frameshift of the reading frame and a premature stop codon^[1,6-8,12,24,38,39,44,46,47].

no metaphyseal striations, while other features are less frequent. The latter include genitourinary malformations (18%), bilateral absence of fibula (65%), cardiac defects (patent ductus arteriosus, atrial and ventricular septal defects, left ventricular non-compaction, tricuspid insufficiency and vascular ring) (31%), omphalocele and cleft of lips and palate (50%), ventriculomegaly and duplicated phalanges (30%)^[8,31]. Prominent lumbar lordosis, joint luxation, camptodactyly and flexion contractures are also present with a lower incidence. Gastrointestinal anomalies such as omphalocele, duodenal web, malrotation of the gut, inguinal hernia and Hirschsprung's disease have also been reported^[9,10,21,27,32].

In the severe form, the prognosis is related to the severity of visceral malformations and a short survival is often present.

The mild phenotype is qualitatively different from the severe one, being characterized by the presence of mild neurodevelopmental delay (50% of patients), which might be attributable to the relative longevity of these patients and progressive neuromuscular disease, histologically similar to nemaline myopathy^[8], and by the absence of some anomalies such as fibular aplasia, duplicated phalanges, syndactyly^[1,8], and gastrointestinal^[9,10,21,27,32], cardiac^[9,21,27,31,33,34] and genitourinary malformations^[1,8,21,35,36].

Characteristic features of the mild form are short stature, facial dysmorphisms and macrocephaly with cranial sclerosis, frontal bossing, hearing loss, high arched and cleft palate (75%), bifid uvula (25%), and extensive bony sclerosis with absent metaphyseal striations^[8]. Milder bony sclerosis has been detected in males with mosaic mutation of *WTX*^[37]. Striations of the long bones have also been observed in molecularly confirmed or suspected mosaics for *WTX* mutations^[8,24,26,34,37,38].

A possible genotype-phenotype correlation between the position of the *WTX* mutation and survival in males had been initially proposed^[1] but further studies showed that this correlation is not absolute^[6,7].

WILMS' TUMOR

Intriguingly, *WTX* has been also identified as a putative tumor suppressor gene in Wilms' tumor (WT). Since this gene, as already mentioned, resides on the X chromosome, it has been speculated that its anti-oncogenic activity can be inactivated by a single "hit" both in hemizygous males and in heterozygous females if the mutation affects the only functional allele on the active X chromosome^[39].

WT, the most common renal tumor of childhood, is an embryonal malignancy of the kidney that is thought to arise from metanephric mesenchyme. Histologically, it resembles fetal kidney, with varying proportions of blastemal, epithelial and stromal elements^[40]. Approximately 40% of WTs occur in association with nephrogenic rests (NRs), embryonal remnants in the kidney which are known precursor lesions for WT^[41]. The genetics of WT is heterogeneous and the *WT1* gene at 11p13 and the *WT2* locus at 11p15.5 have been associated with WT pathogenesis (reviewed in Huff^[42] 2011, Royer-Pokora^[43] 2013). Further genes involved in WT development include, in addition to *WTX*, *CTNNB1* and *TP53*^[42,43]. *WTX* anomalies have been described in approximately 20% of WTs^[39,44-47]. While *WTX* deletions and truncating mutations are somatically acquired, missense mutations of unknown functional relevance can be present in the germline (reviewed in Huff^[42] 2011).

OSC'S, WT AND *WTX* MUTATIONS: IS THERE AN ASSOCIATION?

Whole gene deletions represent the majority of *WTX* mutations in WTs, whereas truncating mutations are more common in OSCS (reviewed in Huff^[42] 2011). However, the spectrum of *WTX* truncating mutations in OSCS patients and in WTs is very similar^[1,42] (Figure 1).

Different syndromic conditions associated with susceptibility to WT, such as the WAGR, the Denys-Drash and the Beckwith-Wiedemann syndromes, are due to germline mutations or epimutations affecting genes/loci also found involved in somatic events in sporadic WTs (reviewed in Scott *et al.*^[48] 2006). In contrast, individuals with OSCS do not seem to have any predisposition to develop either WT or other malignancies^[1,22,35], although in a few of these patients the presence of bilateral multifocal NRs has been reported^[8,35]. However, it has to be noted that NRs are found in approximately 1% of infant autopsies and that most of them do not form WT but spontaneously undergo regression or involution^[40]. Thus, the detection of NRs in OSCS patients does not allow establishing a link with WT. Consistently, the *WTX*-knockout mice, despite exhibiting somatic overgrowth and malformation of several organs including kidney, do not appear to be tumor prone^[49]. The lack of association between OSCS and WT could be explained assuming that *WTX* is mainly involved in WT progression rather than

in its early phase. This possibility is supported by a study detecting various levels of *WTX* mutation in different microdissected areas of the same tumor^[46].

Overall, current evidence suggests a possible involvement of the *WTX* gene in kidney development but is not consistent with its role in *WT* predisposition.

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