Hum Genet (2010) 128:3–26
DOI 10.1007/s00439-010-0827-2

REVIEW ARTICLE

Copy number variants at Williams–Beuren syndrome 7q11.23 region

Giuseppe Merla · Nicola Brunetti-Pierri · Lucia Micale · Carmela Fusco

Received: 23 February 2010 / Accepted: 13 April 2010 / Published online: 1 May 2010

Abstract Copy number variants (CNVs) of the Williams–Beuren syndrome (WBS) 7q11.23 region are responsible for neurodevelopmental disorders with multi-system involvement and variable expressivity. Typical features of WBS microdeletion comprise a recognizable pattern of facial dysmorphisms, supravalvular aortic stenosis, connective tissue abnormalities, hypercalcemia, and a distinctive neurobehavioral phenotype. Conversely, the phenotype of patients carrying the 7q11.23 reciprocal duplications includes less distinctive facial dysmorphisms and prominent speech delay. The common deletion/duplication ranges in size from 1.5 to 1.8 Mb and encompasses approximately 28 genes. This region is flanked by low copy repeats (LCRs) with greater than ~97% identity, which can mediate non-allelic homologous recombination resulting from misalignment of LCRs during meiosis. A clear genotype–phenotype correlation has been established in WBS only for the elastin gene, which is responsible for the vascular and connective tissue abnormalities. The molecular substrates underlying the other clinical features of 7q11.23 CNVs, including the neurocognitive phenotypes, are still debated. Recent studies suggest that besides the role of the genes in the deleted/duplicated interval, multiple factors such as regulatory sequences, epigenetic mechanisms, parental origin of the CNV, and nucleotide variations in the non-deleted/duplicated allele may be important in determining the variable expressivity of 7q11.23 CNV phenotypes. Here, we review the clinical and molecular findings and the recent insights on genomic disorders associated with CNVs involving the 7q11.23 region.

G. Merla (✉) · L. Micale · C. Fusco
Laboratory of Medical Genetics, IRCCS Casa Sollievo Della Sofferenza Hospital, San Giovanni Rotondo, Italy
e-mail: g.merla@operapadrepio.it

N. Brunetti-Pierri
Telethon Institute of Genetics and Medicine, Via P. Castellino 111, Naples, Italy

N. Brunetti-Pierri
Department of Pediatrics, Federico II University of Naples, Naples, Italy

N. Brunetti-Pierri
Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA

Introduction

Duplications and deletions, collectively known as copy number variants (CNVs), are the most prevalent types of structural variations in the human genome (Iafrate et al. 2004; Redon et al. 2006; Sebat et al. 2004). Analysis of the reference sequence shows that ~5% of the human genome contains CNVs (Bailey et al. 2002; McCarroll et al. 2008). While affecting functions such as inflammatory response, immunity, and cell proliferation may play a key role in human genome evolution, genomic duplications and deletions are also an important cause of human diseases (Lupski 1998) and disease susceptibility (Stankiewicz and Lupski 2002; Wain et al. 2009). Several studies found that CNVs make a substantial contribution to the genetic mechanisms underlying human diseases and provide greater insight into the etiology of phenotypes that result from complex genetic patterns of inheritance such as neurodevelopmental diseases, autism spectrum disorders, bipolar disorders, and schizophrenia (Beckmann et al. 2007). CNVs result in the alteration of a variable number of genes causing changes in gene dosages, which ultimately may lead to disease predisposition or specific clinical phenotypes. Moreover, as

emerged more recently, the disruption of regulatory regions within the CNVs can also result into altered dosage and function of genes outside the deleted or duplicated intervals (Henrichsen et al. 2009a; Henrichsen et al. 2009b; Merla et al. 2006).

Chromosomal rearrangements below the limit of detection of conventional karyotyping contribute significantly to the cause of mental retardation and congenital malformations (Zhang et al. 2009). Interstitial deletions of 7q11.23 cause Williams–Beuren syndrome (WBS; OMIM 194050), one of the best characterized genomic disorders affecting 1/7,500–1/10,000 live births (Stromme et al. 2002). As with many other genomic disorders, the common recurrent 1.55-Mb microdeletion occurs by non-allelic homologous recombination (NAHR) (Stankiewicz and Lupski 2002) between LCRs (Urban et al. 1996) flanking the deleted region (Bayes et al. 2003; Hillier et al. 2003) (Fig. 1). Because NAHR can generate both microdeletions and microduplications, it was suspected that reciprocal microduplication of microdeletion syndromes should also occur (Lupski 1998). With the advent of diagnostic array comparative genomic hybridization (aCGH), this prediction was verified with the identification of patients with 7q11.23 duplications (OMIM 609757).

Given the frequency of patients with de novo microdeletions of the WBS critical region, it is surprising that microduplication of WBS region was first reported only recently (Somerville et al. 2005). This is likely due to a convergence of factors. First, the phenotypes seen in patients with 7q11.23 microduplications are quite unlike those seen with the common WBS microdeletion, and fluorescent in situ hybridization (FISH) analysis of metaphase cells is unlikely to clearly detect the microduplication (Shaffer et al. 1997). Clinicians were unlikely to order interphase FISH for WBS in patients who were not clinically suspected to have WBS. In fact, the first patient reported to harbor a microduplication of chromosome 7q11.23 was initially evaluated for velocardiofacial syndrome (VCFS) by real-time quantitative PCR (qPCR) that instead fortuitously revealed duplication of markers within the WBS region (Somerville et al. 2005). Second, although the recombination reciprocal of the WBS microdeletion was postulated to occur (Lupski 1998), it would have been difficult to predict the phenotype associated with the microduplication based on what was

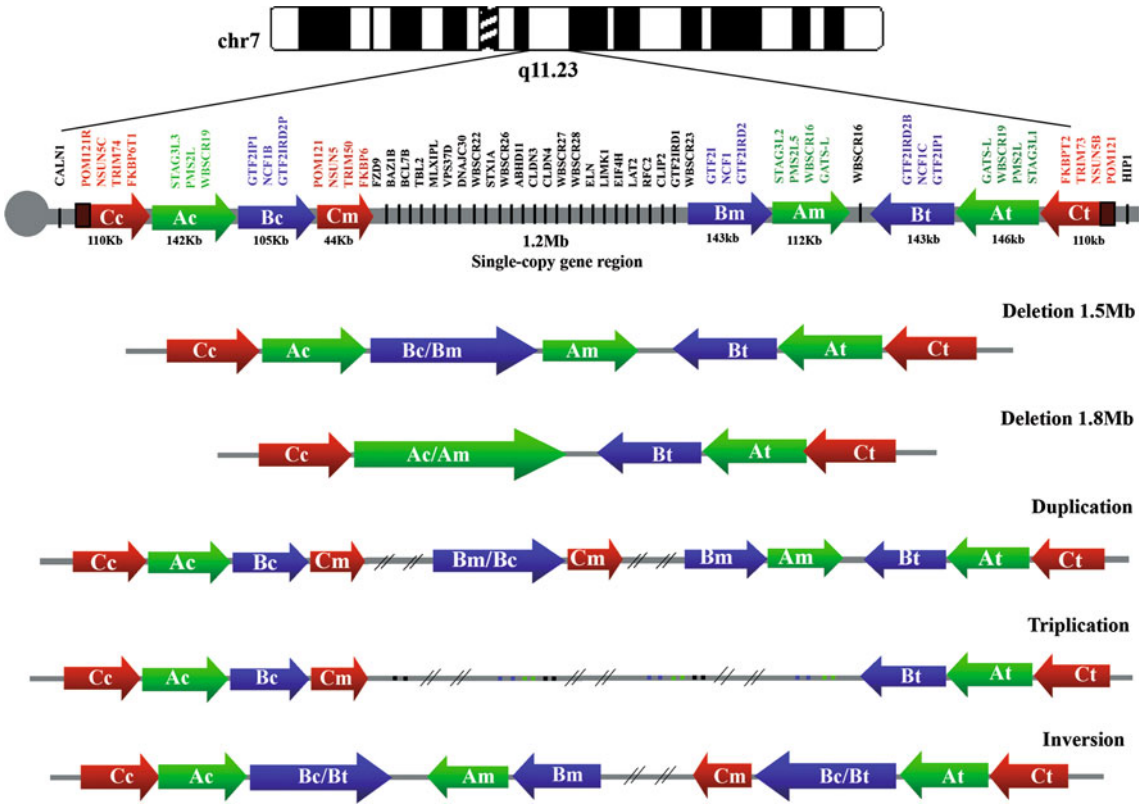

Fig. 1 Schematic representation of 7q11.23 genomic rearrangements (not drawn to scale). The centromeric (c), middle (m), and telomeric (t) LCRs are shown as *colored arrows* with their relative orientation to each other. Please note that multicopy genes within the blocks are represented only once. In the middle, the common deletions of 1.5 and 1.8 Mb are depicted; breakpoints within the centromeric and the medial copy of LCR block B and within the centromeric and the medial copy of LCR block A are shown. Schematic representation of the 7q11.23 deletion, duplication, triplication, and inversion are shown. In the triplication case, the location of the breakpoints is shown with *black dots* representing the blocks Am, Bt and the region between *FZD9* and *BAZ1B* genes, respectively

known about the contributions of genes in this region to the WBS phenotype.

7q11.23 deletion syndrome: clinical findings

The first pictures of patients with WBS were likely reported in 1956 by Dr. Schlesinger in a paper describing the association of unusual facies and infantile hypercalcemia (Schlesinger et al. 1956). Dr. Williams was the first to recognize WBS as a distinct clinical entity in 1961 (Williams et al. 1961) and shortly thereafter, Dr. Beuren reported four more WBS patients (Beuren et al. 1962). Since then the WBS phenotype has been extensively studied and affected individuals typically have a distinctive facies, cardiovascular abnormalities, connective tissue anomalies, infantile hypercalcemia, and a characteristic neurocognitive and behavioral phenotype (Pober 2010).

Facial characteristics

The distinctive WBS facial findings include broad forehead, periorbital fullness, epicanthal folds, flat nasal bridge, a short upturned nose, long philtrum, and wide mouth with full lips, full cheeks, and small jaw. In blue- and green-eyed individuals, a stellate or lacy pattern of the irides is usually present (Greenberg and Lewis 1988). Patients with WBS also exhibit malocclusion, hypoplastic enamel, a high prevalence of dental caries, small and slender roots, pulp stones, excessive interdental spacing, oligodontia, microdontia, and aberrant tooth shape (Axelsson et al. 2003; Pober 2010).

Growth and endocrine problems

Irritability which could be related to central nervous system immaturity, to pain from esophagitis, or to hypercalcemia is common in WBS infants along with feeding difficulties and vomiting due to gastroesophageal reflux, and failure to thrive. By the end of the first year, the irritability and vomiting usually diminish or resolve. Even though there is improvement of growth in mid-childhood, the linear growth of most WBS patients is reduced compared to siblings or healthy, age-matched controls (Partsch et al. 1999). Puberty typically occurs early and is associated with abbreviated pubertal growth spurt in both genders (Pankau et al. 1992; Partsch et al. 1999). Central precocious puberty has been reported in about 15% of WBS girls (Amenta et al. 2005; Ferrero et al. 2007; Partsch et al. 2002). Growth should be carefully monitored as failure to thrive may result from hypothyroidism or celiac disease, which have both increased prevalence in WBS. Therefore, systematic screening for these conditions and the use of disease-specific growth charts is recommended (Giannotti et al. 2001; Hill et al. 2005; Pittschieler et al. 1993; Partsch et al. 1999; Santer et al. 1996).

Although it was recognized early as a feature of WBS (Black and Carter 1963), transient hypercalcemia is documented only in a minority (6–15%) of patients (American Academy of Pediatrics Committee on Genetics 2001; Amenta et al. 2005; Ferrero et al. 2007).

A prevalence of 2–40% of hypothyroidism, which is more frequently subclinical, has been described (American Academy of Pediatrics Committee on Genetics 2001; Amenta et al. 2005; Cambiaso et al. 2007; Cherniske et al. 2004; Ferrero et al. 2007; Stagi et al. 2005). Reduced volume and morphological abnormalities of the thyroid gland such as hypoplasia, hemiagenesis, and ectopia have been reported (Cambiaso et al. 2007; Stagi et al. 2005). Another common endocrine abnormality, especially in WBS adults, is diabetes mellitus or impaired glucose tolerance (Cherniske et al. 2004).

Cardiovascular abnormalities and connective tissue involvement

The connective tissue abnormalities include a hoarse/deep voice, hernias, bladder/bowel diverticulae, soft/lax skin, joint laxity or limitation, and cardiovascular anomalies. The spectrum, natural history, and pathological findings of cardiovascular and connective tissue lesions in WBS patients are similar to those seen in patients with elastin (*ELN*) gene mutations (Metcalfe et al. 2000). Although with a wide range of prevalence reflecting age-dependent onset of symptoms, variable study methods, and different methods of ascertainment, cardiovascular defects are present in high proportion of WBS cases (~50–80%) and account for most of WBS morbidity and mortality. The most common anomalies are supravalvular aortic stenosis (SVAS), pulmonary artery stenosis, and coarctation or aortic arch hypoplasia (Amenta et al. 2005; Del Pasqua et al. 2009; Eronen et al. 2002; Ferrero et al. 2007). Significant and symptomatic obstruction may develop in any artery in WBS individuals and lifelong monitoring of the cardiovascular system is recommended (Ino et al. 1988; Wren et al. 1990). For instance, artery stenoses have resulted in myocardium infarction, stroke, and sudden death (Bird et al. 1996; Wessel et al. 2004). Although not frequently detected by routine imaging studies, renal artery stenosis or diffuse aortic narrowing resulting in hypertension may be present in WBS individuals (Bouchireb et al. 2010; Pankau et al. 1996; Rose et al. 2001). Structural intra-cardiac malformations such as ventricular septal defects (Del Pasqua et al. 2009; Jones and Smith 1975), tetralogy of Fallot (Del Pasqua et al. 2009; Pernot et al. 1984), and atrioventricular canal have also been reported (Eronen et al. 2002; Nakamoto et al. 2003),

but they are very uncommon and are found in <5% of patients.

Other frequent connective tissue abnormalities are gastrointestinal, urogenital, skin, and musculoskeletal problems. Besides the feeding problems and the gastroesophageal reflux occurring in infancy, gastrointestinal problems in WBS include colon diverticulosis, inguinal and umbilical hernias, rectal prolapse, constipation, and chronic abdominal pain (Partsch et al. 2005). These findings, along with anxiety and other psychiatric disorders (such as depression, obsessive–compulsive symptoms, and phobias) and hypertension, are common among elderly (>30-year-old) WBS patients (Cherniske et al. 2004).

Urinary tract abnormalities include renal structural defects and bladder diverticulae (Amenta et al. 2005; Pankau et al. 1996; Pober et al. 1993; Sforzini et al. 2002). In addition, WBS patients are at risk of developing nephrocalcinosis secondary to the hypercalcemia. Musculoskeletal problems may include joint involvement, radioulnar synostosis, kyphosis, lordosis, and scoliosis (Morris and Carey 1990; Pankau et al. 1993). Hyperextensibility of the joints is common in young children, while joint contractures are more common in older individuals (Kaplan et al. 1989; Morris et al. 1990). The joint and postural abnormalities in combination with the cerebellar dysfunction often lead to a stiff, awkward gait, especially in adults (Morris et al. 1990). The skin is very soft with fine creases, and premature sagging and prematurely gray hairs are common findings in early adulthood.

There are few reports on bone mass status in WBS. Osteopenia or osteoporosis in at least one site has been reported in a small cohort of WBS adults investigated by dual energy X-ray absorptiometry (Cherniske et al. 2004). However, it is unclear whether reduced bone mass in WBS is secondary to abnormalities of calcium metabolism, gastrointestinal problems (i.e. celiac disease), or simply a consequence of decreased physical activity, which is commonly observed in adults with mental disabilities.

Neurological problems

Neurological problems include coordination difficulties (for example, trouble walking down a staircase), hyperreflexia, cerebellar dysfunction such as ataxia and dysmetria (Chapman et al. 1996; Cherniske et al. 2004), strabismus (esotropia) (Kapp et al. 1995; Winter et al. 1996), nystagmus, hypersensitivity to sound, and sensorineural hearing loss (Marler et al. 2005). The hypotonia noted in young children typically improves in childhood (Chapman et al. 1996). Seizures are relatively rare affecting <10% of individuals with WBS (Amenta et al. 2005), and there are few reports of children with infantile spasms and hypsarrhythmia, usually associated with larger 7q11.23-q21.2 deletions involving the *MAGI2* gene (Mizugishi et al. 1998; Morimoto et al. 2003; Trauner et al. 1989; Tsao and Westman 1997).

Brain malformations are relatively infrequent and are not consistent in the WBS population. Type I Chiari malformation (Ferrero et al. 2007; Mercuri et al. 1997; Pober and Filiano 1995) and corpus callosum shape changes (Schmitt et al. 2001; Tomaiuolo et al. 2002) are the recurrent reported defects. Using brain magnetic resonance imaging (MRI), reduction of the overall brain size and of the fronto-parietal brain region, which is known to be involved in the visual guidance of the movement, have been reported (Eckert et al. 2005; Jernigan and Bellugi 1990; Jernigan et al. 1993; Wang et al. 1992).

Cognitive and behavioral profiles

The WBS individuals have a unique cognitive and personality profile with areas of relative strength and weakness (Francke 1999; Morris et al. 1988). The cognitive profile generally consists of mild–moderate mental retardation with intelligence quotients (IQs) in the high 50s to low 70s. However, IQ scores alone do not convey the distinctive profile of cognitive skills of WBS individuals, which is characterized by a severe visuospatial construction deficit contrasting with a relative strength in verbal short-term memory and language. Early reports drew attention to the "*cocktail party*" pattern of speech emphasizing strong verbal abilities but lack of depth in understanding. This aspect of the syndrome has been often exaggerated by secondary sources, and the initial view that individuals with WBS had normal language abilities despite mild–severe mental retardation (Bellugi et al. 1990) was due to choice of Down syndrome as comparison group. These results were not confirmed when WBS verbal performances were evaluated on standardized assessments of language which clearly indicated that their language is below age expectations (Mervis 2006).

Impairment in visuospatial construction is a hallmark of the WBS neurocognitive profile, and is characterized by poor performance on tests of block design or pattern construction (Mervis et al. 2000). WBS individuals may focus on the particular, while failing to appreciate the global aspects (Tassabehji 2003). Moreover, WBS individuals exhibit impaired capacity to reorient in the environment (Lakusta et al. 2010).

From a behavioral standpoint, striking features of individuals with WBS are their high sociability and empathy for others, leading them to engage in social interaction even with strangers (Klein-Tasman and Mervis 2003; Mervis and Klein-Tasman 2000). They also appear to have impaired detection of social threat (Santos et al. 2010). Although the excessive drive to socialize is an hallmark of

WBS, and individuals with WBS appear to be particularly drawn to faces (Gagliardi et al. 2003b; Wang et al. 1995), their socialization is often "*shallow*" with conversations focusing on their own interests rather than engaging in a more typical give-and-take exchange (Einfeld et al. 1997). Intriguingly, their remarkable hypersociability is associated with general and anticipatory anxieties, phobia related to non-social objects, and depression (Dykens 2003; Klein-Tasman and Mervis 2003; Leyfer et al. 2006; Stinton et al. 2010).

Even though autism or autism spectrum disorders have been described in association with WBS only in a small number of patients (Gillberg and Rasmussen 1994; Herguner and Mukaddes 2006; Levitin et al. 2005; Leyfer et al. 2006), the occurrence of these disorders may not be coincidental. Attention deficit hyperactivity disorder (ADHD), predominantly inattentive type or combined type, is particularly common (>50%) in children and adolescents with WBS (Leyfer et al. 2006). Many children with WBS have difficulties in initiating and maintaining sleep, which could exacerbate ADHD symptoms (Einfeld et al. 1997; Sarimski 1996).

Individuals with WBS demonstrate hypersensitivity to high frequency sounds (Levitin 2005), strong attraction to sounds and music (Levitin et al. 2004), use of vocal prosody and a relative strength in auditory rote memory (Udwin and Yule 1991; Wang and Jernigan 1994).

7q11.23 duplication syndrome: clinical findings

The phenotype of reciprocal WBS duplications has emerged only recently, and the full clinical spectrum likely still needs to be delineated. Nevertheless, it is clear that the presentation of 7q11.23 duplications is milder and facial features are different and less distinctive than those of WBS (Table 1). This situation is mirrored in other genomic disorders where milder pathological consequences tend to arise with gene duplications compared with the reciprocal deletions, as shown by duplications versus deletions of 22q11.2 (Ensenauer et al. 2003) and duplications versus deletions of 1q21.1 (Brunetti-Pierri et al. 2008). Given the less distinctive features of reciprocal WBS duplications, it is likely that this syndrome remains often undiagnosed. The most intriguing and distinctive feature of 7q11.23 duplications is the speech involvement further suggesting that specific gene(s) in the region are sensitive to dosage changes and can affect human speech and language. Recently, the identification of the first case of triplication of the WBS region in a patient with severe speech delay further supports this hypothesis (Beunders et al.

Table 1 Comparison of clinical features of 7q11.23 CNVs

Finding	7q11.23 deletion	7q11.23 duplication
Facial characteristics	Broad forehead	Broad forehead
	Low nasal root	High, broad nose
	Long philtrum	Short philtrum
	Full lips	Thin lips
Growth and endocrine problems	Growth retardation	Normal growth[a]
	Hypercalcemia	Normocalcemia
Cardiovascular abnormalities	SVAS	Congenital heart defects
	Hypertension	
Connective tissue abnormalities	Joint laxity	Joint laxity
Neurological problems	Hypotonia	Hypotonia
		Seizures
	Brain MRI abnormalities (non-specific)	Brain MRI abnormalities (non-specific)
Cognitive abnormalities	Developmental delay	Developmental delay
	Mental retardation	Mental retardation[b]
	Relative strength in expressive language	Speech and language delay
	Deficit of visuospatial skills	Visuospatial skills spared[c]
Behavioral problems	Excessively social	Deficits of social interaction/aggressive behavior
	Autism spectrum behaviors	Autism spectrum behaviors
	ADHD	ADHD

[a] Few patients with growth retardation have been reported

[b] Transmitting parents with normal cognition have been reported

[c] Poor visuospatial skills reported in two patients with 7q11.23 duplication (Depienne et al. 2007; Torniero et al. 2007)

2010). Another striking finding of 7q11.23 duplications is the increased prevalence of autism, which has also been noted in other duplication syndromes (Brunetti-Pierri et al. 2008; Glessner et al. 2009; Potocki et al. 2007).

Facial characteristics

All reported patients have dysmorphic features, although these findings are mild and non-specific. Therefore, a distinctive facial pattern has been difficult to recognize (Van der Aa et al. 2009). Recurrent dysmorphic craniofacial features include a broad forehead, high broad nose, neatly placed straight eyebrows, and a thin upper lip.

Growth and endocrine problems

Growth appears to be normal in the majority of the cases, and only few cases with short stature have been reported (Merritt and Lindor 2008; Somerville et al. 2005; Van der Aa et al. 2009). The head circumference varies between 50th and 97th centile in most patients with overt macrocephaly in few cases (Berg et al. 2007; Torniero et al. 2007; Van der Aa et al. 2009).

Cardiovascular abnormalities and connective tissue involvement

Cardiovascular abnormalities are not frequently reported in patients with WBS region duplication (Berg et al. 2007; Depienne et al. 2007; Kirchhoff et al. 2007; Merritt and Lindor 2008; Torniero et al. 2007). The reported abnormalities are atrial and ventricular septum defects (Kriek et al. 2006; Van der Aa et al. 2009), subvalvular pulmonal stenosis (Kriek et al. 2006), SVAS (Orellana et al. 2008), and patent ductus arteriosus (Van der Aa et al. 2009). Interestingly, one patient with congenital heart defect carried a small 0.3–0.4 Mb microduplication encompassing a single gene, *FKBP6* (Kriek et al. 2006).

Although joint laxity is a non-specific finding, which may be due to multiple causes, its presence in several cases may suggest that increased elastin dosage could play a role. Whether other connective tissue abnormalities are also features of 7q11.23 duplications has not been determined yet.

Other medical problems

Various congenital anomalies have been reported in one or few cases, including hydrocephalus, congenital glaucoma, strabismus, astigmatism, choanal atresia, clefting, facial asymmetry, congenital diaphragmatic hernia, severe vesicoureteral reflux, cryptorchidism, cutis marmorata, and neutropenia. It is unclear whether these abnormalities are present coincidently or they are indeed part of the phenotype of 7q11.23 duplication syndrome.

Neurologic problems

Hypotonia and epilepsy are the most commonly reported neurologic problems in the duplication of WBS region (Van der Aa et al. 2009). Epilepsy has been reported in ~20% of duplication patients, and therefore, its prevalence appears to be higher than WBS (Van der Aa et al. 2009). Brain MRI has been frequently abnormal, but no consistent brain abnormalities have been found (Torniero et al. 2007; Van der Aa et al. 2009).

Cognitive and behavioral profiles

Most patients are developmentally delayed. However, formal IQ-testing revealed normal intelligence in few patients and in some transmitting parents (Van der Aa et al. 2009). Language delay is seen in almost all patients, either expressive or receptive language or both. The significant language impairment with sparing of visuospatial cognitive skills in most patients with 7q11.23 duplication syndrome is in direct contrast to the typical cognitive profile of WBS patients, in whom verbal skills are a relative strength and visuospatial skills are severely impaired (Mervis and Klein-Tasman 2000). Some of the transmitting parents showed language delay (Torniero et al. 2008). Interestingly, some of them had a history of motor and language delay or learning difficulties, which eventually resolved (Merritt and Lindor 2008; Van der Aa et al. 2009). In adult life, these parents are usually employed and functioning well, and in one case neither speech nor cognitive impairment was evidenced (Berg et al. 2007). It remains to be determined whether patients outgrow some of their cognitive problems or whether the phenotype of these adult patients represents the mild end of the phenotypic spectrum. Some children with 7q11.23 duplication syndrome have developed nonverbal gestures as a means of communicating and compensating for their significant speech delays although they differed in the degree to which they were fluent in using these signs and gestures (Berg et al. 2007). These features share some similarity to developmental verbal dyspraxia (OMIM 602081), a disorder of speech production and language processing that has been associated with mutations in the *FOXP2* gene located on 7q31 (Lai et al. 2001).

Deficits of social interaction have also been noted in 7q11.23 duplication patients. Formal diagnosis of autism or autistic spectrum features such as poor eye contact, poor social interaction, limited facial expressions, repetitive behaviors, repetitive play, repetitive speech, sensory integration problems, or withdrawal have been reported. Additional problems such as ADHD, self-injury, anxiety,

and aggression have also been described (Berg et al. 2007; Depienne et al. 2007; Van der Aa et al. 2009).

Diagnosis and genetic counseling

Since 1993 when the genetic cause of WBS was discovered (Ewart et al. 1993), the WBS is diagnosed by FISH on metaphase chromosomes (Fig. 2a) using the elastin gene as probe and/or microsatellite/single nucleotide polymorphism (SNP) genotyping. FISH remains the most widely used method to confirm the clinical diagnosis. However, FISH is labor-intensive, time-consuming, and it does not allow the detection of the exact size of the deletion, whereas microsatellite/SNP genotyping depends on their relative informativeness and availability of parental DNA to ascertain the deletion. Thus, these techniques cannot be informative for cases harboring atypical deletions, which are helpful to dissect genotype–phenotype correlations (see below). Moreover, although FISH can reliably detect genomic deletions, the difficulty of obtaining accurate interphase FISH interpretation for duplications (Shaffer et al. 1997) makes interphase FISH highly problematic for the diagnosis of 7q11.23 duplication syndrome. Conversely, the DNA dosage-based methods to detect small segmental aneuploidies are robust, easy to interpret, and simple to set up. For these reasons, techniques such as qPCR, multiplex ligation-dependent probe amplification (MLPA), and aCGH are rapidly emerging as confirmatory or first-line testing (Fig. 2b–d).

The qPCR allows estimation of the relative quantity of an analyzed locus by designing multiple assays within and outside the segmental aneuploidy. This method allows precise mapping of the size of deletion or duplication (Fig. 2b). Furthermore, qPCR allows the processing of several DNA samples within the same run (Howald et al. 2006; Schubert and Laccone 2006).

The MLPA is also an efficient and reliable assay for dosage screening of multiple genomic loci in a single reaction and is based on the use of synthetic probe sets containing sequences derived from the genes within the deleted/duplicated region (Hannes et al. 2009; Sellner and Taylor 2004) (Fig. 2c).

In addition, microarray-based CGH using either bacterial artificial chromosomes (BACs) or oligonucleotides as probes are very sensitive at detecting copy number alterations of increasingly smaller regions (Edelmann et al. 2007) (Fig. 2d).

In contrast to the rarity of parental transmission in the WBS (Morris et al. 1993; Ounap et al. 1998; Pankau et al. 2001; Sadler et al. 1993), and again similar to other duplication syndromes (Brunetti-Pierri et al. 2008; Ou et al. 2008), there is a high frequency of parental transmission in 7q11.23 duplication patients. Clearly, an important consideration in genetic counseling for the 7q11.23 duplication syndrome is the potential for reduced penetrance and variable expressivity, which has also been reported for well-characterized syndromes, such as 22q11.2 microdeletion, where phenotypically mild deletion carriers have escaped clinical recognition until they had children with more severe manifestation (Wilson et al. 1992). Findings such as these and the recently described 16p13.11, 15q13.3, and 1q21.1 microdeletion syndromes (Brunetti-Pierri et al. 2008; Hannes et al. 2009; Sharp et al. 2008) raise difficult questions in the context of genetic counseling for newly diagnosed cases and particularly for prenatal diagnosis.

Mechanisms of rearrangements at 7q11.23

As the molecular mechanisms causing the 7q11.23 rearrangements have been extensively described in some recent reviews (Schubert 2009; Zhang et al. 2009), they will be only briefly presented herein.

Large and complex segmental duplications flanking the commonly deleted interval act as substrates for NAHR that mediates duplications, deletions, and inversions (Lupski 2009). Human chromosome 7 contains several segmental duplications, with an 8.2% overall content and a predominant enrichment of intrachromosomal duplications (7% of the sequence) (Antonell et al. 2005; Hillier et al. 2003). The genomic architecture of the 7q11.23 region is complex with a single-copy interval flanked by three blocks (A, B, and C) of >320 kb in size. The commonly deleted region results in meiotic NAHR involving LCRs (Bayes et al. 2003) (Fig. 1). The three blocks are organized in complexes located on the centromeric (cen), medial (mid), and telomeric (tel) segment of the WBS locus (Fig. 1). The medial and centromeric LCR blocks have transcription direction in the opposite orientation to the telomeric LCR complex (Karmiloff-Smith et al. 2003) (Fig. 1). The single-copy gene region is located between the blocks C-mid and B-mid and spans a region of ~1.2 Mb.

A 1.5-Mb commonly deleted interval, which is present in >95% of individuals with clinically diagnosed WBS, is caused by an unequal meiotic recombination between B-cen and B-mid; ~3–5% of typical WBS patients display a deletion of ~1.8 Mb, between the A-cen and A-mid (Fig. 1), and 2–3% of WBS patients carry atypical deletions (Schubert 2009).

The higher sequence homology between blocks B-cen and B-mid (99.6%) compared to the sequences of blocks A-cen and A-mid (98.2%), and the shorter size of blocks B-cen and B-mid compared to the size of block A-cen and A-mid promote rearrangements involving predominantly blocks B-cen and B-mid (Fig. 1).

The deletions in the WBS region arise as a consequence of interchromosomal or interchromatid and intrachromatid misalignment resulting in unequal crossing over between

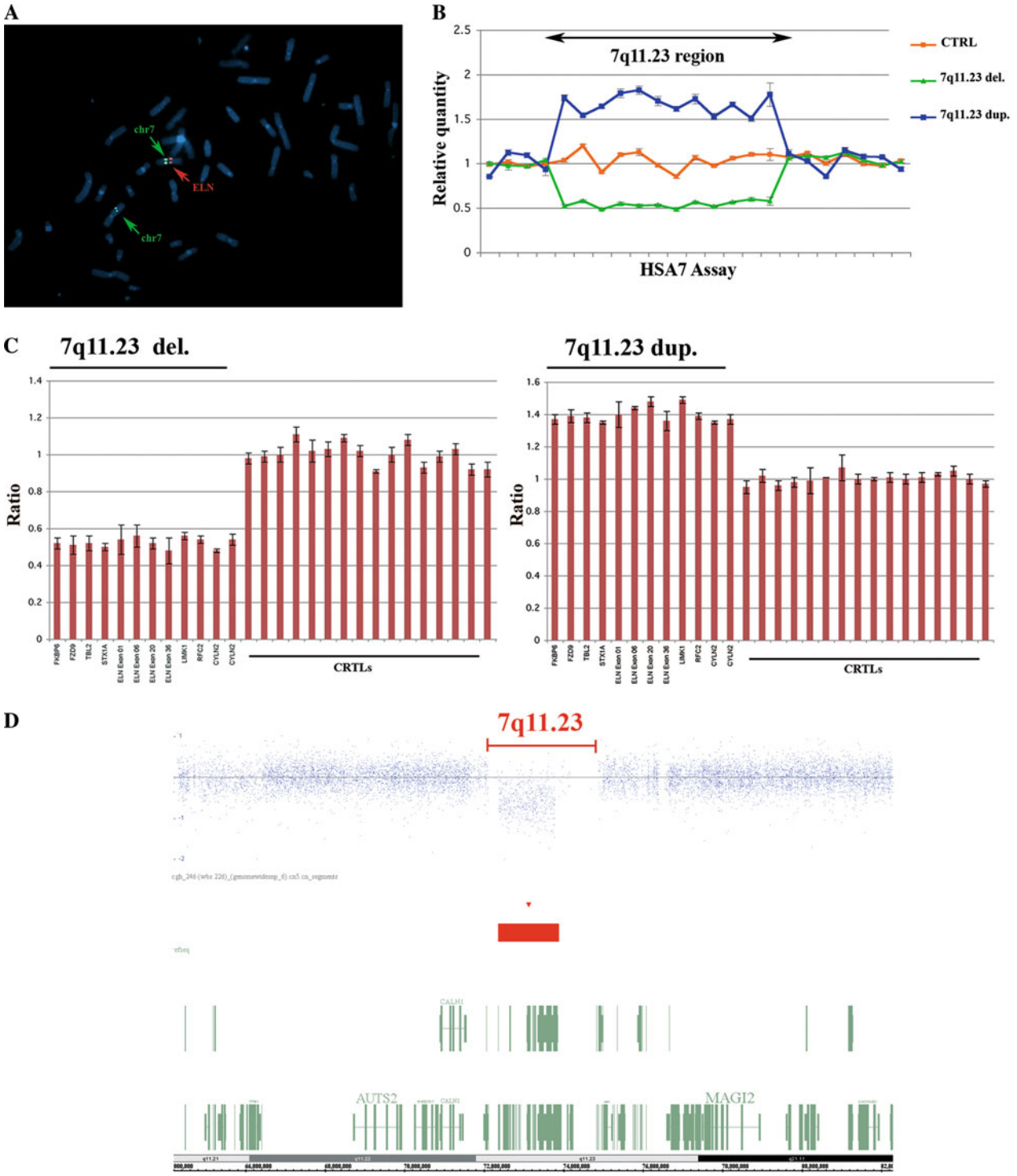

Fig. 2 **a** Methods to detect 7q11.23 copy number variants. Metaphase FISH in a WBS patient. Normal non-deleted chromosome 7 has two hybridization signals relative to *ELN* gene (*red signals*) and two *green signals* corresponding to the control probes on the same chromosome. The deleted chromosome 7 shows only the two hybridization *green signals* corresponding to the control probe, indicating that *ELN* gene is deleted. **b** Mapping WBS typical deletion and duplication by qPCR. Relative DNA quantity of assays from the 7q11.23 region and control region was quantified as previously reported (Ferrero et al. 2010; Howald et al. 2006). Schematic representation of a classical WBS-deleted patient (wbs-del, *green triangles*), and a patient carrying the 7q11.23 duplication (wbs-dup, *blue squares*) compared to a control (CTRL, *red squares*). **c** MLPA analysis of deletion and duplication in 7q11.23 region. The *graph on the left* shows a deletion of the *FKBP6*, *FZD9*, *TBL2*, *STX1A*, *ELN*, *LIMK1*, *RFC2*, and *CYLN2*/*CLIP2* genes on chromosome 7. The *graph on the right* shows the duplication of the same region. **d** Results of array comparative genomic hybridization (aCGH) showing a 1.5-Mb (*top*) and a 1.8-Mb loss in the WBS region

the regions comprises between the LCR blocks (Schubert 2009). Haplotype analysis indicated that two-thirds of the deletions arise from crossover events between chromosome 7 homologs during meiosis, while intrachromatid rearrangements occur in one-third of cases (Cusco et al. 2008). Interchromosomal recombination appears to be the most common mechanism responsible for the duplications (Hannes et al. 2009). Interestingly, the molecular characterization of deletion junctions in some atypical patients suggests that mechanisms other than NAHR, such as non-homologous end joining or fork stalling and template switching should be considered as responsible for some of the rearrangements at 7q11.23 (Antonell et al. 2010; Lee et al. 2007).

Using a sperm-based assay to measure the rate of de novo reciprocal deletions and duplications, it has been shown that 7q11.23 deletions are generated at a higher rate than their reciprocal duplications (Turner et al. 2008). This may occur because intrachromatid NAHR generates only deleted gametes (Turner et al. 2008). However, the ultimate reasons underlining this difference are yet unclear.

The edges of the LCR blocks of 7q11.23 region are GC rich (50.1%) and contain an unusually high abundance of repetitive elements consisting primarily of Alu sequences (Martindale et al. 2000); the presence of such Alu elements may be the mechanism predisposing to large segmental duplications (Antonell et al. 2005).

Inversion of the 7q11.23 region has been found in 27% of affected individuals with an atypical WBS phenotype and in 33% of transmitting parents (Osborne et al. 2001). The inversion is generated by meiotic or mitotic intrachromatid misalignment between the inverted homologous centromeric and telomeric LCR blocks, resulting in NAHR between paired LCR blocks. This event can occur at each of the LCR blocks, thus resulting in variable sized (1.8–2.9 Mb) paracentric inversions (Bayes et al. 2003). Inversion is considered a benign polymorphism because carriers are phenotypically normal (Tam et al. 2008). However, inversion carriers are at risk for generating gametes harboring the WBS deletion because of an increase likelihood of chromosome 7 mispairing events in meiosis (Scherer et al. 2005; Tam et al. 2008).

Role of genes within 7q11.23 region: functional studies and animal models

Although the commonly deleted region in WBS has been characterized in detail and a clear role of haploinsufficiency of *ELN* on connective tissue and cardiovascular abnormalities has been established (Curran et al. 1993; Ewart et al. 1993), the contributions of the remaining genes in the critical region to the various features of WBS remain open. Complementary strategies involving clinical, neuropsychological, and molecular analyses of patients with both typical and atypical WBS, mouse models and functional gene studies have been pursued to delineate the individual and/or combined contribution of these genes to the spectrum of WBS abnormalities. These studies focus exclusively on the single-copy genes, while no information have been so far reported on the possible role of genes within the LCRs.

The three blocks A, B, and C are mainly composed of truncated copies of pseudogenes, while the region comprised between LCR blocks C-mid and B-mid contains single-copy genes.

The block A consists of four different pseudogenes: *STAG3L*, *PMS2L*, *GATS-L*, *WBSCR16*, and a genetic fragment of *WBSCR19* gene.

STAG3L

Stromalin 3 (*STAG3*) on 7q22 is the ancestral gene of a family of truncated homologous genes likely originating through genomic duplications. This family includes STAG3-like (*STAG3L*) 1, 2, and 3 that map to 7q11.23, and STAG3-like 4 and 5 on chromosomal region 7q22. The ancestral gene *STAG3* encodes for a component of the axial/lateral element of the synaptonemal complex that is specifically expressed in germinal cells, and has a role in sister chromatid arm cohesion during mammalian meiosis (Prieto et al. 2001).

STAG3L genes are transcribed, normally processed, and result in messengers of distinct sizes which are detected ubiquitously. The longest ORF of *STAG3L1*, *STAG3L2*, and *STAG3L3* cDNAs predicts the generation of identical 134 amino acid proteins, which share 85% similarity to the middle part of *STAG3*. It is not known whether any of these transcripts encode a functional protein (Pezzi et al. 2000).

PMS2L

There are 15 pseudogene loci of *PMS2* (*PMS2L*), some of them located in the LCR block A of WBS region (Nicolaides et al. 1995; Osborne et al. 1997). These pseudogenes are homologous to *PMS2* the gene mutated in mismatch repair cancer syndrome (OMIM 276300) and hereditary non-polyposis colon cancer (HNPCC; OMIM 120435).

GATS-L

The medial and telomeric part of block A contains *GATS* sequences related to the ancestral *GATS* gene on chromosome 7q22. A part of these sequences shows a high degree of homology to the 5′ end of the pseudogene of *GTF2I* on LCR block B. The function of the ancestral *GATS* gene is still unclear (Valero et al. 2000).

WBSCR19

Within the block A is present a genetic fragment with high similarity to *WBSCR19* located on chromosome 7p13. The role of *WBSCR19* still remains undefined.

Finally, a pseudogene of *WBSCR16* gene maps within the telomeric part of block A. The functional copy of *WBSCR16* is localized between the medial part of block A and telomeric part of block B; it encodes a RCC1-like G-exchanging factor ubiquitously expressed with a yet unknown function (Merla et al. 2002).

The block B contains three genes: *GTF2I*, *NCF1*, and *GTF2IRD2*.

GTF2I

General transcription factor 2-I (*GTF2I*) and GTF2I repeat domain containing protein 2 (*GTF2IRD2*) belong to the TFII-I gene family encoding transcription factors with multiple helix-loop-helix (HLH)-like domains, also known as I-repeats (Bayarsaihan et al. 2002; Hinsley et al. 2004). The functional copy of *GTF2I* is localized in the B-mid. The centromeric and telomeric copies of *GTF2I* are expressed as truncated proteins (Perez Jurado et al. 1998; Wang et al. 1998). A third member of this gene family, *GTF2IRD1*, is one of the single-copy genes located within WBS region. Genomic alignments suggest that *GTF2IRD2* is a truncated version of *GTF2I*, containing its 5′ coding region. *GTF2I* interacts with *GTF2IRD1* (Hinsley et al. 2004) and appears to be the product of *GTF2IRD1* duplication (Makeyev et al. 2004). While *GTF2IRD2* is deleted only in WBS patients with the rarer 1.84-Mb deletions, *GTF2IRD1* and *GTF2I* are invariably deleted in all cases with canonical deletions (Bayes et al. 2003).

GTF2I is ubiquitously expressed, with high levels observed during tooth development (Ohazama and Sharpe 2007); it interacts promiscuously with multiple proteins and DNA, linking signal transduction to transcription. *GTF2I* acts as a multifunctional transcription factor that can bind enhancer (E-box) and core promoter (Inr) elements in response to upstream signaling events (Roy et al. 1997). Therefore, it could potentially affect a broad range of physiological and developmental pathways. Interestingly, the expression of *GTF2I* in WBS patients is dependent on the parental origin of the transmitted allele, supporting the presence of an epigenetic control mechanism and the hypothesis that *GTF2I* is paternally imprinted (Collette et al. 2009). Moreover, post-transcriptional silencing of this gene results in reduced expression of two genes essential for osteoblast differentiation and for Runx2-induced transcription of osteocalcin (Lazebnik et al. 2009). In line with these findings, heterozygous deletion of *Gtf2i* in mice results in craniofacial and skeletal defects (Enkhmandakh et al. 2009).

NCF1

The neutrophil cytosolic factor 1 (*NCF1*) encodes $p47^{phox}$, a cytosolic subunit of the NADPH oxidase (NOX) complex, which is mutated in an autosomal recessive form of chronic granulomatous disease (OMIM 233700) (Gorlach et al. 1997). Only the gene copy located in the medial block B is functional, whereas the other two copies, located in the centromeric and telomeric blocks, respectively, are pseudogenes with truncating mutations (Gorlach et al. 1997). Recent findings suggest a role of *NCF1* in hypertension of WBS patients as increased blood pressure occurs with lower frequency in individuals with deletion including the functional copy of the gene. Therefore, hemizygosity for *NCF1* may be a protective factor against hypertension possibly mediated by a reduced angiotensin II-mediated oxidative stress. Increased *NCF1* gene-copy number (three copies), which has been found in a number of WBS patients, does not result neither in increased prevalence of hypertension nor in greater activation of the NOX complex, despite increased $p47^{phox}$ protein expression (Del Campo et al. 2006).

GTF2IRD2

GTF2IRD2 appears to be fully transcribed by the medial and the telomeric copies of block B, whereas the B-cen copy lacking exons 1 and 2 is not expressed (Tipney et al. 2004). The function of GTF2IRD2 is still unknown although the presence of regions of homology to regulatory factors, such as leucine zipper and Cys-2/His-2 zinc finger domains, suggests that the encoded protein has DNA and protein binding properties (Hinsley et al. 2004; Makeyev et al. 2004). *GTF2IRD2* is ubiquitously expressed and higher levels are observed in fetal tissues (Makeyev et al. 2004; Tipney et al. 2004). *GTF2IRD2* which is variably included in WBS deletions is a candidate to modulate the effects of the other *GTF2I* genes on WBS phenotype (Bayes et al. 2003). Four genes are present in the LCR block C: *POM121*, *NSUN5*, *TRIM50*, and *FKBP6*.

POM121

POM121 is one of the integral membrane components of the nuclear pore complex (NPC), which mediates the bidirectional transport of macromolecules between nucleus and cytoplasm. Human cells possess multiple *POM121* gene loci on chromosome 7q11.23, as a consequence of complex segmental-duplications occurred during human evolution. Studies in HeLa cells have demonstrated that two full-length *POM121* are transcribed and translated by both centromeric and telomeric loci. POM121 depletion induces clustering of NPCs, indicating an important role of this

protein on maintenance of NPC structure and organization (Funakoshi et al. 2007).

NSUN5

This gene (alias *WBSCR20A*) encodes a member of the evolutionarily conserved nucleolar protein 1 (NOL1)/NOP2/SUN domain family. NSUN5 may function as a DNA methyltransferase in the nucleus (Doll and Grzeschik 2001; Merla et al. 2002). The ancestral gene of *NSUN5* is located in the medial part of block C; other two copies *NSUN5C* and *NSUN5B* flanking the WBS deletion at the centromeric and telomeric sides are transcribed as truncated copies with a shorter open reading frame (ORF). All three *NSUN5* genes are ubiquitously expressed although the truncated copies have tissue-specific patterns (Antonell et al. 2005).

TRIM50

Recently, three tripartite motif-containing protein 50 (*TRIM50*)-*like* copies were identified in the human genome, *TRIM74* (*TRIM50C*), *TRIM50* (also known as *TRIM50A*), and *TRIM73* (*TRIM50B*). All three copies are expressed as demonstrated by the identification of spliced ESTs specific to each transcript. *TRIM50* maps between *NSUN5* and *FKBP6* within repeated block C-mid, *TRIM74* maps to the block C-cen interval, between *NSUN5C* and *FKBP6T1*, and *TRIM73* between *FKBPT2* and *NSUN5B* in block C-tel (Fig. 1). Therefore, WBS patients are hemizygotes for *TRIM50* but not for *TRIM73* and *TRIM74* (Merla et al. 2002). TRIM50 belongs to the TRIM family which harbors, from their N- to their C-terminal, a Ring (R), a B-box type 2 (B2), a Coiled-Coil (CC), and an RFP-like/B30.2 domain. *TRIM73* and *TRIM74* encode almost identical putative proteins containing only the R, B2, and CC domains. As many other members of this family, *TRIM50* encodes for an E3-ubiquitin-ligase with a role in the ubiquitin-mediated proteasome degradation pathway (Micale et al. 2008).

FKBP6

The functional copy of the FK506-binding protein 6 (*FKBP6*) is located in the medial part of block C, whereas the centromeric and telomeric pseudogene copies of *FKBP6* are truncated copies harboring the first four exons of the ancestral gene (Meng et al. 1998). FKBP6 belongs to the immunophilins FKBP family and contains a three-unit tetratricopeptide repeat motif and a peptidyl-prolyl *cis–trans* isomerase activity (Meng et al. 1998). This protein is a component of the synaptonemal complex, an elaborate meiosis-specific supramolecular protein structure involved in pairing and recombination of homologous chromosomes during meiosis (Heyting 1996). Loss of *Fkbp6* results in abnormal pairing and misalignment of homologous chromosomes, non-homologous partner switches, and autosynapsis of the X chromosome cores in meiotic spermatocytes. In addition, loss of *Fkbp6* results in aspermia and absence of normal pachytene spermatocytes in male mice but normal fertility and no apparent abnormalities in females (Crackower et al. 2003). Interestingly, one of the 7q11.23 duplication patients with congenital heart defect carried a small 0.3–0.4 Mb microduplication encompassing only *FKBP6* (Kriek et al. 2006).

The single-copy gene inside the critical region

At the present, 22 single-copy genes have been mapped between the LCR blocks C-mid and B-mid (Fig. 1).

FZD9

Frizzled drosophila homolog of 9 (*FZD9*) encodes for a transmembrane receptor of Wnt signaling proteins. The binding of Fzd receptors results in inhibition of β-catenin pathway involved in development, lymphoid maturation, tumorigenesis, and maintenance of stem cell populations in various tissues (Huelsken et al. 2000, 2001; Korinek et al. 1998). *FZD9* is selectively expressed in the hippocampus throughout life (Zhao and Pleasure 2004, 2005), and *Fzd9* null mutants have defects in learning and memory reflecting hippocampal functional deficits (Zhao and Pleasure 2005). Moreover, *Fzd9* null and heterozygous mice have increased apoptotic cell deaths and increased precursor proliferation during hippocampal development. These evidences suggested that *Fzd9* has an important role in hippocampal development, and therefore, may be a candidate for the neurodevelopmental and behavioral phenotype of WBS individuals. However, in another study, no WBS development and morphologic features abnormalities were observed in *Fzd9* knockout mice (Ranheim et al. 2005). Homozygous mice lacking *Fzd9* showed immune and hematologic abnormalities including splenomegaly, thymic atrophy, lymphoadenopathy, and abnormalities of B cells in the bone marrow (Ranheim et al. 2005). Hence, more studies are needed to ascertain the precise contribution of FZD9 to neurodevelopmental and behavioral features.

BAZ1B

Bromodomain adjacent to zinc finger domain 1B (*BAZ1B*), also known as Williams syndrome transcription factor (WSTF), is one of the components of the multifunctional ATP-dependent chromatin-remodeling complex named 'WSTF including nucleosome assembly complex' (WINAC) and involved in multiple functions such as DNA

transcription, DNA replication, and DNA repair (Kitagawa et al. 2003). Core components of the WINAC are essential for embryonic development, whereas coregulatory subunits appear to support the spatiotemporal function of the complexes (Bultman et al. 2000; de la Serna et al. 2006). These evidences may suggest that certain features of WBS could be the resultant of chromatin-remodeling dysfunction due to *BAZ1B* haploinsufficiency (Kitagawa et al. 2003).

Experimental data suggest that BAZ1B regulates the expression of enzymes involved in both synthesis and catabolism of vitamin D (Kitagawa et al. 2003). Therefore, *BAZ1B* haploinsufficiency has been hypothesized to be responsible for the hypercalcemia of WBS. Nevertheless, to date, no gene has been proven to be involved in the hypercalcemia. Interestingly, the calcitonin receptor (*CALCR*) gene, which was originally hypothesized to be important in the pathogenesis of WBS-associated hypercalcemia, is just outside the WBS deletion interval (Perez Jurado et al. 1995). Given the recently recognized role of positional effect on the expression of genes outside the critical region, the contribution of this gene to the hypercalcemia could be reconsidered (Henrichsen et al. 2009a, b; Merla et al. 2006).

BAZ1B is important in the developing heart, and is required for normal function of cardiac transcriptional regulators. Consistent with this role, all *BAZ1B*−/− and 10% of *BAZ1B*+/− mice exhibit cardiovascular defects, such as multiple atrial and muscular ventricular septal abnormalities, hypertrophy of both ventricles, and double-outlet right ventricles (Yoshimura et al. 2009). However, these congenital heart malformations are rarely observed in WBS patients.

BCL7B

B-cell CLL/lymphoma 7B (*BCL7B*) belongs to a family of highly conserved genes expressed in early embryonic development. *BCL7A*, another member of the family, is a putative tumor suppressor gene with a role in the pathogenesis of non-Hodgkin lymphoma (Zani et al. 1996). Hemizygous loss of 7q11.23, including *BCL7B* and its reduced expression, has been found in pilocytic astrocytomas (Potter et al. 2008). Despite these data, there is no evidence to suggest an increased tumor risk in WBS (Pober and Morris 2007) although a formal estimate of the cancer incidence in WBS has not yet been calculated.

TBL2

The transducing-β-like 2 (*TBL2*) gene encodes a member of the β-transducin protein family with four putative WD40-repeats. Expression studies showed a ubiquitous lower level expression of *TBL2* mainly in testis, skeletal muscle, and heart (Perez Jurado et al. 1999). The role of *TBL2* in the pathophysiology of WBS has not been resolved so far.

MLXIPL

The Max-like protein (MLX)-interacting protein-like (*MLXIPL*) gene (also known as *WBSCR14* or *CHREBP*) encodes a member of the basic-helix-loop-helix leucine (bHLH) family of transcription factors (Cairo et al. 2001). It dimerizes with MLX to bind and activate, in a glucose-dependent manner, carbohydrate responsive element motifs in the promoter of several genes involved in hepatic glycolysis, lipogenesis, and gluconeogenesis (Iizuka and Horikawa 2008; Uyeda et al. 2002). When glucose availability is low, WBSCR14 is maintained in an inactive, phosphorylated status in the cytosol (Kawaguchi et al. 2001; Merla et al. 2004; Uyeda et al. 2002; Yamashita et al. 2001). Conversely, high glucose level results in WBSCR14 dephosphorylation, nuclear translocation, and transcriptional activation (Kabashima et al. 2003). *Wbscr14*−/− mice are viable with a normal lifespan, but they show decreased serum triglyceride and increased hepatic glycogen content compared to wild-type mice (Iizuka et al. 2004). Therefore, *WBSCR14* haploinsufficiency may be involved in the impaired glucose tolerance and diabetes mellitus of WBS individuals (Cherniske et al. 2004).

VPS37D

Vacuolar protein sorting 37 (*VPS37D*; alias *WBSCR24*) is homologous to proteins of the conserved endosomal sorting complex for transport, which performs three distinct but related functions: (1) recognition of ubiquitinated cargoes and prevention of their recycling and retrograde trafficking; (2) deformation of the endosomal membrane, allowing cargo to be sorted into endosomal invaginations; (3) catalyzation of final abscission of the endosomal invaginations (Raiborg and Stenmark 2009).

DNAJC30

The intronless *DNAJC30* (alias *WBSCR18*) gene encodes for a member of the DNAJ/HSP40 molecular chaperones, which regulate chaperone activity by stimulating ATPase activity. *WBSCR18* is expressed in multiple tissues, but its function remains unknown (Merla et al. 2002).

WBSCR22

This gene encodes a putative protein containing a nuclear localization signal and an *S*-adenosyl-L-methionine binding motif typical of methyltransferases. It is strongly expressed

in heart, skeletal muscle, kidney, and testis (Doll and Grzeschik 2001; Merla et al. 2002).

STX1A

Syntaxin 1A (*STX1A*) encodes for a plasma membrane protein abundantly expressed in neurons. It forms a complex with the 25-kDa synaptosomal-associated protein (SNAP-25) and vesicle-associated membrane protein 2 (VAMP-2; also known as synaptobrevin), two proteins involved in synaptic vesicle exocytosis. *Stx1a*+/− mice are viable with no apparent phenotype, but they exhibit impaired long-term potentiation (LTP) in the hippocampal slice and impaired memory consolidation and extinction in the conditioned fear memory test. Because these functions rely on synaptic plasticity and given its role in synaptic exocitosis, *STX1A* could play a role in the neurocognitive phenotype of WBS (Fujiwara et al. 2006). Most of the *Stx1a*−/− mice die in utero (McRory et al. 2008). However, few homozygous animals were born alive and exhibited reduced body size (McRory et al. 2008).

Transgenic mice expressing increased levels of *Stx1a* and *Stx1a*+/− mice display a reduced insulin secretion and impaired glucose tolerance, possibly mediated by altered function of pancreatic β-cell ion channels and of the exocytic machinery. Therefore, alteration of *STX1A* gene dosage might also contribute to impaired glucose metabolism and diabetes of WBS patients (Lam et al. 2005).

WBSCR26

The function of this gene is unknown. It is highly expressed in testis, skin, kidney, liver, and small intestine (Doll and Grzeschik 2001; Merla et al. 2002).

ABHD11

The abhydrolase domain containing 11 (*ABHD11*; alias *WBSCR21*) gene encodes a ubiquitously expressed protein harboring an α/β hydrolase domain. Five alternatively spliced forms have been identified in human. *WBSCR21* form B, form C, and form E encode truncated WBSCR21 proteins without the hydrolase domain (Merla et al. 2002). *ABHD11* function is unknown.

CLDN3 and *CLDN4*

Claudin proteins are important in the formation of tight junctions of epithelial and endothelial cells, and their expression is altered in various cancers such as ovarian, breast, prostate, and pancreatic tumors (Morin 2005). Higher expression of CLDN3 and CLDN4 are associated with increased cellular motility and survival of ovarian tumor cells. *CLDN3* gene silencing suppresses ovarian tumor growth and metastasis (Huang et al. 2009). Interestingly, the occurrence of ovarian cancer in WBS has been reported in one review article (Pober and Morris 2007).

WBSCR27 and *WBSCR28*

Little is known about the proteins encoded by these genes. WBSCR27 protein belongs to the ubiE/COQ5 methyltransferase family with unknown function. Androgen receptor-mediated *WBSCR28* repression may be involved in prostate cancer (Prescott et al. 2007).

ELN

ELN haploinsufficiency is unequivocally responsible for SVAS and other connective tissue abnormalities of WBS patients (Ewart et al. 1993). The elastin forms the elastic fibers of the extracellular matrix of connective tissue throughout the body. Elastin haploinsufficiency in WBS results in an arteriopathy involving medium- and large-sized arteries leading to lumen narrowing. Hypertension is observed commonly in WBS patients with and without renal artery stenosis (Broder et al. 1999; Giordano et al. 2001), and its etiology is still a matter of debate. Reduction of vascular elasticity, due to elastin haploinsufficiency, may increase the hemodynamic stress to the endothelium, leading to intimal proliferation of smooth muscle and fibroblasts, fibrosis, and luminal narrowing of the vessels (Karnik et al. 2003). However, the pathogenesis of the arteriopathy in WBS may be more complex, and is possibly related to other genes in the WBS critical region such as *NCF1* (Del Campo et al. 2006).

Eln−/− mice die in the perinatal period with exuberant vascular smooth muscle cell overgrowth. *Eln*+/− mice, instead synthesizing ~50% of normal elastin protein, survive beyond the neonatal period. These mice exhibit cardiovascular features resembling those found in patients with WBS although there are some notable differences, such as the absence of focal areas of stenosis (Li et al. 1998).

Interestingly, in contrast to other studies (Urban et al. 2000, 2002), relative expression levels of *ELN* gene in skin fibroblasts from WBS patients was found to be highly variable with values overlapping to those of non-affected (Merla et al. 2006). This discrepancy might be due to the different number of samples examined and/or to the different sensitivity of the used methods.

Therefore, it is possible that the gene expression changes are not always directly correlated to copy number, suggesting that other factors, such as size of the deletion, changes in chromatin, dosage compensation mechanisms, or a combination of these factors, may influence the transcription levels. It is also possible that incomplete penetrance of

SVAS correlates with *ELN* mRNA levels and patients activating compensatory mechanism(s) of expression are less likely to develop the obstruction (Merla et al. 2006). In addition, it remains to be investigated whether ELN expression in fibroblasts recapitulates the expression of affected cells (i.e. smooth muscle or connective tissue cells).

LIMK1

LIM kinase 1 (LIMK1) is a serine protein kinase involved in organization of the actin cytoskeleton by phosphorylation and inactivation of cofilin, a protein which depolymerizes actin (Proschel et al. 1995). *LIMK1* is prominently expressed in the central nervous system and accumulates at the level of mature synapses, suggesting that it may be involved in synapse formation and/or maintenance (Scott and Olson 2007). Actin remodeling has been suggested to be crucial for the establishment and modification of dendritic spines that make up the majority of the synaptic connections within the hippocampus and are associated with the formation and maintenance of memory and learning (Nimchinsky et al. 2002). *Limk1−/−* mice exhibit significant abnormalities in dendritic spine morphology and development and in synaptic structures. Consistent with these alterations, the mice show behavioral abnormalities, including impaired fear conditioning and spatial learning (Frangiskakis et al. 1996; Meng et al. 2002), reminiscent of impaired visuospatial constructive cognition seen in WBS patients. However, hemizygous deletion of *LIMK1* does not appear to be sufficient to account for the spatial deficits associated with WBS (Smith et al. 2009).

EIF4H

Eukaryotic initiation factor 4H (*EIF4H*) gene is ubiquitously expressed, and is involved in translation initiation and RNA duplex unwinding (Richter et al. 1999). Interestingly, the hsa-miR-590, the only known miRNA within the WBS-deleted region, maps within the intron 4–5 of the *EIF4H* gene (Merla et al., unpublished results).

LAT2

Linker for activation of T cells 2 (*LAT2*) encodes for a Na^+-independent neutral amino acid transporter. Functional studies have indicated that *LAT2* plays a role in mast cell activation, but this function requires further clarification (Iwaki et al. 2007).

RFC2

RFC2 is a subunit of the replication factor C (RFC) that plays a key role in chromosome replication in eukaryotic cells (Peoples et al. 1996). The elongation of primed DNA templates by DNA polymerase δ and ε requires the action of the accessory proteins, proliferating cell nuclear antigen (PCNA) and RFC complex. Unbound to DNA, PCNA promotes localization of replication factors with a consensus PCNA-binding domain to replication factories. When bound to DNA, PCNA organizes various proteins involved in DNA replication, DNA repair, DNA modification, and chromatin remodeling (Majka and Burgers 2004). RFC2 is ubiquitinated by the RAD6–RAD18 complex in vitro, and its modification is inhibited in the presence of the replication protein A in response to a DNA damage (Tomida et al. 2008). Interestingly, WBS patient-derived cell lines were found to exhibit a defective ATR-pathway activity similar to other syndromes with defective DNA damage response (O'Driscoll et al. 2007). Cardinal clinical features of this group of disorders include microcephaly and growth failure, which are also common in WBS. Hence, defective ATR-pathway in WBS could be responsible for microcephaly and growth retardation which are typically seen in DNA damage response and repair deficiency syndromes, such as for example ataxia–telengectasia (OMIM 208900) and Seckel syndrome (OMIM 210600) (Kerzendorfer and O'Driscoll 2009).

CLIP2

CAP-Gly domain-containing linker protein 2 (*CLIP2*) belongs to a family of cytoplasmic linker proteins mediating interactions between organelles and microtubules. CLIP2 is abundantly expressed in neurons of the hippocampus, piriform cortex, olfactory bulb, and inferior olive (Hoogenraad et al. 2002), and has been implicated in regulation of microtubule dynamics (De Zeeuw et al. 1997). *Clip2* knockout mice have features reminiscent of WBS, including growth deficiency, altered hippocampal synaptic functioning, and specific deficits affecting motor coordination but not locomotor activity. *CLIP2* haploinsufficiency might contribute to the cerebellar and hippocampal dysfunctions involved in the motor and cognitive features of WBS patients (Hoogenraad et al. 2002). Absence of *CLIP2* also leads to increased levels of CLIP-170 (a closely related cytoplasmic linker protein) and dynactin at the tips of growing microtubules. Patients with partial deletions of the WBS region not including the *CLIP2* gene exhibit mild–absent visuospatial impairment and relatively spared fine motor and gross motor skills. These findings suggest a role for *CLIP2* in motor and cognitive phenotypes (Dai et al. 2009; Ferrero et al. 2010).

GTF2IRD1

GTF2IRD1 binds regulatory elements of genes involved in development and differentiation. A combination of

comparative sequence analyses and binding assays has defined a highly conserved DNA element, defined as GTF2IRD1 upstream control element (GUCE) which is present in the three genes *HOXC8*, *Goosecoid*, and *Troponin I slow*, all regulated by *GTF2IRD1* in vivo (Thompson et al. 2007). Similar to other members of the TFII-I gene family, *GTF2IRD1* is highly expressed during odontogenesis, and therefore, may be involved in WBS tooth abnormalities (Ohazama and Sharpe 2007). During development *Gtf2ird1* is predominantly expressed in musculoskeletal and craniofacial tissues, whereas in adult mice it is expressed in neurons of the central and peripheral nervous system, spiral ganglion of the cochlea, smooth muscle, retina, and olfactory epithelium. A mouse model harboring a deletion between *Clip2* and *Gtf2ird1* showed craniofacial abnormalities involving a misaligned jaw, a twisted snout, and dental abnormalities (Tassabehji et al. 2005). *Gtf2ird1* knockout mice, instead, do not exhibit craniofacial or dental abnormalities (Palmer et al. 2007). Finally, mice haploinsufficient for both *Gtf2ird1* and *Gtf2i* are often growth retarded, and show hypoplasia of the mandible, as well as other craniofacial defects resembling the defects and dental problems of WBS individuals (Enkhmandakh et al. 2009).

Several studies showed that *GTF2IRD1* transcript levels in WBS patients are not significantly different from controls, whereas transcription levels from the flanking genes *CLIP2* and *GTF2I* are as expected ~50% of health control levels (Antonell et al. 2010; Collette et al. 2009; Merla et al. 2006; Palmer et al. 2009). The unexpected result of *GTF2IRD1* was recently explained by the demonstration of a negative auto-regulatory mechanism controlling the level of *GTF2IRD1* transcription via direct binding of the GTF2IRD1 protein to a highly conserved region on its promoter. Protein–DNA interaction is critically dependent upon multiple interactions between separate domains of the protein and at least two of the three DNA binding sites of the *GTF2IRD1* promoter. This auto-regulatory mechanism results into dosage compensation of *GTF2IRD1* transcription in WBS patients (Palmer et al. 2009).

Analyses of the phenotypes of patients with partial deletions of WBS region suggest that *GTF2I* and *GTF2IRD1* have overlapping functions and may contribute to at least some of the craniofacial features, global intellectual deficit, and the cognitive-behavioral profile, such as visuospatial skills, cognition, and hypersociability (Edelmann et al. 2007; Howald et al. 2006; Morris et al. 2003).

WBSCR23

WBSCR23 is intronless, and its mRNA is transcribed on the same strand of *GTF2IRD1* gene. The function of this transcript is unknown, and the putative protein has no significant similarity to any so far characterized protein (Merla et al. 2002).

Mouse models for the WBS genomic deletions

Dissection of the molecular mechanisms underlying the unique features of WBS have been improved with the recent generation of a knockout mouse model for the WBS region generated by Uta Francke's group (Li et al. 2009). Using chromosome-engineering techniques, they generated three strains of mice with complementary half-deletions of the conserved WBS syntenic region on mouse chromosome 5G2: proximal deletion (Prox-del) mice lack *Gtf2i* to *Limk1*, distal deletion (Dist-del) mice lack *Limk1* to *Fkbp6*, and the double heterozygote (Dist-del/Prox-del) mice carry the complete human deletion (Fig. 3).

Dist-del and Dist-del/Prox-del mice showed craniofacial abnormalities similar to those observed in WBS individuals, such as the reduction of the posterior width of the skulls and reduced brain volumes, and indicate that genes within the Dist-del are the main contributors to the craniofacial

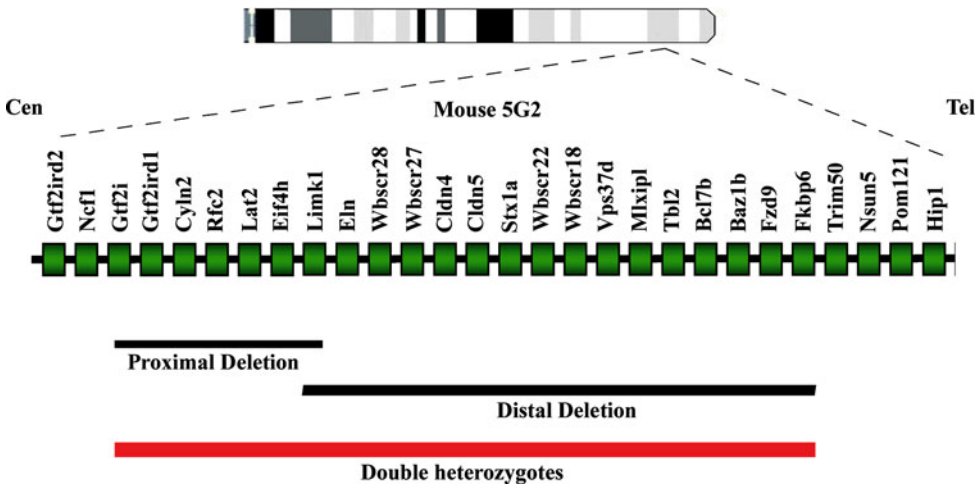

Fig. 3 Genomic organization of WBS syntenic region in mouse chromosome 5G2. Schematic representation of proximal deletion mice lacking *Gtf2i* to *Limk1*, distal deletion mice lacking *Limk1* to *Fkbp6*, and double heterozygotes model lacking the full human deletion, as reported in (Li et al. 2009). The two partial deletions are depicted as *black lines* and the double heterozygote as a *red line*. *Cen* centromere; *Tel* telomere

abnormalities seen in WBS individuals. Typical WBS connective tissue abnormality such as hernia was observed in Dist-del and Dist-del/Prox-del mice, while females developed rectal or vaginal prolapse.

Motor coordination and motor skill assessment showed that Dist-del/Prox-del mice had the greatest impairment in motor skills and coordination compared to the other genotypes, thus showing that both genes in the proximal and distal region contribute to sensory and motor dysfunction (Li et al. 2009). Interestingly, Prox-del mice showed a set of abnormal social interactions, including increased sociability and acoustic startle response, while Dist-del mice showed cognitive defects (Li et al. 2009), providing evidence that some dosage-sensitive genes in the Prox-del region are responsible for WBS behavioral phenotype.

This study has tremendously improved our understanding of how WBS features generate; it provides insights about the contribution of individual genes or sets of genes for WBS phenotypes and then represents a useful model for any future studies on WBS.

Lessons from atypical patients

The study of affected individuals with atypical (smaller or larger) deletions and duplications allows inference on genotype–phenotype correlations. Clinical versus molecular analyses provide a unique opportunity to investigate the individual contribution of genes within the 7q11.23 interval to the clinical phenotypes. A certain number of WBS individuals with atypical deletions (Antonell et al. 2010; Botta et al. 1999; Dai et al. 2009; Edelmann et al. 2007; Ferrero et al. 2010; Gagliardi et al. 2003a; Hirota et al. 2003, 2006; Karmiloff-Smith et al. 2003; Korenberg et al. 2000; Morris et al. 2003; Schubert and Laccone 2006; Tassabehji et al. 1999) and one with a duplication involving only the *FKBP6* gene have been reported (Kriek et al. 2006).

Based on two families presenting with cardiovascular manifestations and partial features of the WBS cognitive profile associated with atypical deletions encompassing only *ELN* and *LIMK1*, it was suggested that *LIMK1* hemizygosity contributes to impairment of visuospatial construction (Frangiskakis et al. 1996). However, this claim turned out to be inconsistent with the finding of three individuals with similar deletions including *LIMK1* who also showed SVAS but not the WBS cognitive abnormalities (Tassabehji et al. 1999).

There have been reports of several WBS individuals with deletions extending from the centromeric LCR to the *CYLN2* or *GTF2IRD1* presenting with SVAS, milder facial features, and unusual cognitive profile with preserved visuospatial skills (see Fig. 1). The clinical and molecular evaluations imply that the genes affected by those deletions have contributed modestly to the WBS phenotype and even less to neurocognition (Ferrero et al. 2010; Gagliardi et al. 2003b; Howald et al. 2006; Tassabehji et al. 2005; van Hagen et al. 2007). Consistently, recent studies reinforce the concept that *LIMK1* deletion alone would not be sufficient to cause the impairment of visuospatial and construction abilities as initially proposed (Tassabehji et al. 1999). *GTF2IRD1* hemizygosity alone is not sufficient to cause the visuospatial construction deficit, but may contribute to the hypersociable personality (Antonell et al. 2010). Combined clinical and molecular results suggest that hemizygosity of the *GTF2I* family of transcription factors is sufficient to produce multiple aspects of the WBS cognitive and behavioral profiles, including impaired visuospatial construction abilities, an over friendly personality accompanied by excessive non-social anxiety and language delay (Dai et al. 2009; Edelmann et al. 2007). In summary, although further studies are clearly needed, the analyses of atypical deletion patients points to *LIMK1*, *CYLN2*, and *GTF2I* as the most likely candidates for the neurodevelopmental phenotype of WBS.

The number of atypical deletions in patients is still small, and detailed deletion size mapping at nucleotide level and expression data of deleted and flanking genes performed by MLPA, qPCR, or aCGH on a larger number of patients will help to shed light on the pathogenic role of genes within the deleted region.

Conclusions and future directions

The WBS and its reciprocal 7q11.23 duplication syndrome share few phenotypic similarities such as joint laxity, infantile hypotonia, developmental delay/mental retardation, and ADHD (Table 1). However, they are strikingly different with respect to their cognitive and behavioral profiles. The expressive language delay with sparing of visuospatial cognition in patients with duplication of the WBS region is in direct contrast to the well-characterized cognitive profile seen in typical WBS patients, while the relative behavioral withdrawal is the converse of the typically outgoing personality profile observed in patients with WBS. The molecular and neuroanatomical substrates of these features are of great interest, and it is possible that genes both within and/or immediately outside the critical region are expressed in brain structures important for language, visuospatial cognition, anxiety, and social behavior in such a way that changes in gene dosage have different classes of effects. For such dosage-sensitive genes, alleles with varying degrees of activity on the normal chromosome (in the case of deletion) or on either chromosome (in the case of duplication) could modify the effect of the genomic rearrangement, thus explaining the variability on expressivity observed in both

conditions. One class of dosage-sensitive genes could affect pathways in reciprocal fashion, resulting in converse phenotypes in deletion and duplication patients. A different class of dosage-sensitive genes could disrupt the same pathway, resulting in features shared between the two syndromes, such as anxiety and ADHD.

The majority of the studies aiming at elucidation of genotype/phenotype correlation in WBS have been focused on the role of genes inside the deleted/duplicated interval. However, multiple other factors such as regulatory sequences, parental origin of the CNV, and variations in the non-deleted/duplicated allele may be also involved.

Of interest is also the potential importance of the genes and expressed pseudogenes within LCRs. Do the non-deleted genes/pseudogenes in the LCRs contribute to the 7q11.23 CNV phenotypes? For instance, we showed that WBS patients are hemizygous for *TRIM50*, but not for the paralogous *TRIM73* and *TRIM74* located within the blocks C (Micale et al. 2008). Both paralogous genes lack the C-terminal region responsible for proper protein localization, therefore we can speculate that their roles may be somewhat different from the one of TRIM50; hence, the LCR-located genes may exert own contribution for WBS phenotype. Unfortunately, to date, no studies have addressed this question.

All these factors, which have been largely neglected until recently, likely play an important role in determining the variable expressivity of WBS phenotype (Collette et al. 2009; Merla et al. 2006). Likely, comprehensive genome-wide and transcriptome analyses of WBS-affected individuals and of the recently developed mouse model will provide a testable list of candidate pathways dysregulated in WBS and possibly involved in the wide range of associated clinical findings.

Acknowledgments We thank members of Drs. Merla and Brunetti-Pierri's laboratories for helpful discussion. We are grateful to Dr. Savino Calvano for providing with FISH picture, Massimo Carella and Orazio Palmieri for aCGH analysis. This work was in part supported by grants from the Jérôme Lejeune Foundation, the Italian Ministry of Health (Ricerca Corrente 2008-10), the Fondazione Banca del Monte di Foggia "Domenico Siniscalco Ceci", the Italian Telethon Foundation (Grant No. GGP06122), and with the contribution of Ministero degli Affari Esteri, Direzione Generale per la Promozione e la Cooperazione Culturale (2009–2010) to GM. NBP is supported by grant of the Italian Telethon Foundation (Grant No. TCBP37TELC).

References

American Academy of Pediatrics Committee on Genetics (2001) Health care supervision for children with Williams syndrome. Pediatrics 107:1192–1204

Amenta S, Sofocleous C, Kolialexi A, Thomaidis L, Giouroukos S, Karavitakis E, Mavrou A, Kitsiou S, Kanavakis E, Fryssira H (2005) Clinical manifestations and molecular investigation of 50 patients with Williams syndrome in the Greek population. Pediatr Res 57:789–795

Antonell A, de Luis O, Domingo-Roura X, Perez-Jurado LA (2005) Evolutionary mechanisms shaping the genomic structure of the Williams-Beuren syndrome chromosomal region at human 7q11.23. Genome Res 15:1179–1188

Antonell A, Del Campo M, Magano LF, Kaufmann L, Martinez de la Iglesia J, Gallastegui F, Flores R, Schweigmann U, Fauth C, Kotzot D, Perez-Jurado LA (2010) Partial 7q11.23 deletions further implicate GTF2I and GTF2IRD1 as the main genes responsible for the Williams-Beuren syndrome neurocognitive profile. J Med Genet. doi:10.1136/jmg.2009.071712

Axelsson S, Bjornland T, Kjaer I, Heiberg A, Storhaug K (2003) Dental characteristics in Williams syndrome: a clinical and radiographic evaluation. Acta Odontol Scand 61:129–136

Bailey JA, Gu Z, Clark RA, Reinert K, Samonte RV, Schwartz S, Adams MD, Myers EW, Li PW, Eichler EE (2002) Recent segmental duplications in the human genome. Science 297:1003–1007

Bayarsaihan D, Dunai J, Greally JM, Kawasaki K, Sumiyama K, Enkhmandakh B, Shimizu N, Ruddle FH (2002) Genomic organization of the genes Gtf2ird1, Gtf2i, and Ncf1 at the mouse chromosome 5 region syntenic to the human chromosome 7q11.23 Williams syndrome critical region. Genomics 79:137–143

Bayes M, Magano LF, Rivera N, Flores R, Perez Jurado LA (2003) Mutational mechanisms of Williams-Beuren syndrome deletions. Am J Hum Genet 73:131–151

Beckmann JS, Estivill X, Antonarakis SE (2007) Copy number variants and genetic traits: closer to the resolution of phenotypic to genotypic variability. Nat Rev Genet 8:639–646

Bellugi U, Bihrle A, Jernigan T, Trauner D, Doherty S (1990) Neuropsychological, neurological, and neuroanatomical profile of Williams syndrome. Am J Med Genet Suppl 6:115–125

Berg JS, Brunetti-Pierri N, Peters SU, Kang SH, Fong CT, Salamone J, Freedenberg D, Hannig VL, Prock LA, Miller DT, Raffalli P, Harris DJ, Erickson RP, Cunniff C, Clark GD, Blazo MA, Peiffer DA, Gunderson KL, Sahoo T, Patel A, Lupski JR, Beaudet AL, Cheung SW (2007) Speech delay and autism spectrum behaviors are frequently associated with duplication of the 7q11.23 Williams-Beuren syndrome region. Genet Med 9:427–441

Beunders G, van de Kamp JM, Veenhoven RM, van Hagen JM, Nieuwint AW, Sistermans EA (2010) A triplication of the Williams Beuren Syndrome region in a patient with mental retardation, a severe expressive language delay, behavioural problems and dysmorfisms. J Med Genet 47:271–275

Beuren AJ, Apitz J, Harmjanz D (1962) Supravalvular aortic stenosis in association with mental retardation and a certain facial appearance. Circulation 26:1235–1240

Bird LM, Billman GF, Lacro RV, Spicer RL, Jariwala LK, Hoyme HE, Zamora-Salinas R, Morris C, Viskochil D, Frikke MJ, Jones MC (1996) Sudden death in Williams syndrome: report of ten cases. J Pediatr 129:926–931

Black JA, Carter RE (1963) Association between aortic stenosis and facies of severe infantile hypercalcaemia. Lancet 2:745–749

Botta A, Novelli G, Mari A, Novelli A, Sabani M, Korenberg J, Osborne LR, Digilio MC, Giannotti A, Dallapiccola B (1999) Detection of an atypical 7q11.23 deletion in Williams syndrome patients which does not include the STX1A and FZD3 genes. J Med Genet 36:478–480

Bouchireb K, Boyer O, Bonnet D, Brunelle F, Decramer S, Landthaler G, Liutkus A, Niaudet P, Salomon R (2010) Clinical features and management of arterial hypertension in children with Williams-Beuren syndrome. Nephrol Dial Transplant 25(2):434–438

Broder K, Reinhardt E, Ahern J, Lifton R, Tamborlane W, Pober B (1999) Elevated ambulatory blood pressure in 20 subjects with Williams syndrome. Am J Med Genet 83:356–360

Brunetti-Pierri N, Berg JS, Scaglia F, Belmont J, Bacino CA, Sahoo T, Lalani SR, Graham B, Lee B, Shinawi M, Shen J, Kang SH, Pursley A, Lotze T, Kennedy G, Lansky-Shafer S, Weaver C,

Roeder ER, Grebe TA, Arnold GL, Hutchison T, Reimschisel T, Amato S, Geragthy MT, Innis JW, Obersztyn E, Nowakowska B, Rosengren SS, Bader PI, Grange DK, Naqvi S, Garnica AD, Bernes SM, Fong CT, Summers A, Walters WD, Lupski JR, Stankiewicz P, Cheung SW, Patel A (2008) Recurrent reciprocal 1q21.1 deletions and duplications associated with microcephaly or macrocephaly and developmental and behavioral abnormalities. Nat Genet 40:1466–1471

Bultman S, Gebuhr T, Yee D, La Mantia C, Nicholson J, Gilliam A, Randazzo F, Metzger D, Chambon P, Crabtree G, Magnuson T (2000) A Brg1 null mutation in the mouse reveals functional differences among mammalian SWI/SNF complexes. Mol Cell 6:1287–1295

Cairo S, Merla G, Urbinati F, Ballabio A, Reymond A (2001) WBSCR14, a gene mapping to the Williams–Beuren syndrome deleted region, is a new member of the Mlx transcription factor network. Hum Mol Genet 10:617–627

Cambiaso P, Orazi C, Digilio MC, Loche S, Capolino R, Tozzi A, Faedda A, Cappa M (2007) Thyroid morphology and subclinical hypothyroidism in children and adolescents with Williams syndrome. J Pediatr 150:62–65

Chapman CA, du Plessis A, Pober BR (1996) Neurologic findings in children and adults with Williams syndrome. J Child Neurol 11:63–65

Cherniske EM, Carpenter TO, Klaiman C, Young E, Bregman J, Insogna K, Schultz RT, Pober BR (2004) Multisystem study of 20 older adults with Williams syndrome. Am J Med Genet A 131:255–264

Collette JC, Chen XN, Mills DL, Galaburda AM, Reiss AL, Bellugi U, Korenberg JR (2009) William's syndrome: gene expression is related to parental origin and regional coordinate control. J Hum Genet 54:193–198

Crackower MA, Kolas NK, Noguchi J, Sarao R, Kikuchi K, Kaneko H, Kobayashi E, Kawai Y, Kozieradzki I, Landers R, Mo R, Hui CC, Nieves E, Cohen PE, Osborne LR, Wada T, Kunieda T, Moens PB, Penninger JM (2003) Essential role of Fkbp6 in male fertility and homologous chromosome pairing in meiosis. Science 300:1291–1295

Curran ME, Atkinson DL, Ewart AK, Morris CA, Leppert MF, Keating MT (1993) The elastin gene is disrupted by a translocation associated with supravalvular aortic stenosis. Cell 73:159–168

Cusco I, Corominas R, Bayes M, Flores R, Rivera-Brugues N, Campuzano V, Perez-Jurado LA (2008) Copy number variation at the 7q11.23 segmental duplications is a susceptibility factor for the Williams-Beuren syndrome deletion. Genome Res 18:683–694

Dai L, Bellugi U, Chen XN, Pulst-Korenberg AM, Jarvinen-Pasley A, Tirosh-Wagner T, Eis PS, Graham J, Mills D, Searcy Y, Korenberg JR (2009) Is it Williams syndrome? GTF2IRD1 implicated in visual-spatial construction and GTF2I in sociability revealed by high resolution arrays. Am J Med Genet A 149A:302–314

de la Serna IL, Ohkawa Y, Imbalzano AN (2006) Chromatin remodelling in mammalian differentiation: lessons from ATP-dependent remodellers. Nat Rev Genet 7:461–473

De Zeeuw CI, Hoogenraad CC, Goedknegt E, Hertzberg E, Neubauer A, Grosveld F, Galjart N (1997) CLIP-115, a novel brain-specific cytoplasmic linker protein, mediates the localization of dendritic lamellar bodies. Neuron 19:1187–1199

Del Campo M, Antonell A, Magano LF, Munoz FJ, Flores R, Bayes M, Perez Jurado LA (2006) Hemizygosity at the NCF1 gene in patients with Williams-Beuren syndrome decreases their risk of hypertension. Am J Hum Genet 78:533–542

Del Pasqua A, Rinelli G, Toscano A, Iacobelli R, Digilio C, Marino B, Saffirio C, Mondillo S, Pasquini L, Sanders SP, de Zorzi A (2009) New findings concerning cardiovascular manifestations emerging from long-term follow-up of 150 patients with the Williams-Beuren-Beuren syndrome. Cardiol Young 19:563–567

Depienne C, Heron D, Betancur C, Benyahia B, Trouillard O, Bouteiller D, Verloes A, LeGuern E, Leboyer M, Brice A (2007) Autism, language delay and mental retardation in a patient with 7q11 duplication. J Med Genet 44:452–458

Doll A, Grzeschik KH (2001) Characterization of two novel genes, WBSCR20 and WBSCR22, deleted in Williams-Beuren syndrome. Cytogenet Cell Genet 95:20–27

Dykens EM (2003) Anxiety, fears, and phobias in persons with Williams syndrome. Dev Neuropsychol 23:291–316

Eckert MA, Hu D, Eliez S, Bellugi U, Galaburda A, Korenberg J, Mills D, Reiss AL (2005) Evidence for superior parietal impairment in Williams syndrome. Neurology 64:152–153

Edelmann L, Prosnitz A, Pardo S, Bhatt J, Cohen N, Lauriat T, Ouchanov L, Gonzalez PJ, Manghi ER, Bondy P, Esquivel M, Monge S, Delgado MF, Splendore A, Francke U, Burton BK, McInnes LA (2007) An atypical deletion of the Williams-Beuren syndrome interval implicates genes associated with defective visuospatial processing and autism. J Med Genet 44:136–143

Einfeld SL, Tonge BJ, Florio T (1997) Behavioral and emotional disturbance in individuals with Williams syndrome. Am J Ment Retard 102:45–53

Enkhmandakh B, Makeyev AV, Erdenechimeg L, Ruddle FH, Chimge NO, Tussie-Luna MI, Roy AL, Bayarsaihan D (2009) Essential functions of the Williams-Beuren syndrome-associated TFII-I genes in embryonic development. Proc Natl Acad Sci USA 106:181–186

Ensenauer RE, Adeyinka A, Flynn HC, Michels VV, Lindor NM, Dawson DB, Thorland EC, Lorentz CP, Goldstein JL, McDonald MT, Smith WE, Simon-Fayard E, Alexander AA, Kulharya AS, Ketterling RP, Clark RD, Jalal SM (2003) Microduplication 22q11.2, an emerging syndrome: clinical, cytogenetic, and molecular analysis of thirteen patients. Am J Hum Genet 73:1027–1040

Eronen M, Peippo M, Hiippala A, Raatikka M, Arvio M, Johansson R, Kahkonen M (2002) Cardiovascular manifestations in 75 patients with Williams syndrome. J Med Genet 39:554–558

Ewart AK, Morris CA, Atkinson D, Jin W, Sternes K, Spallone P, Stock AD, Leppert M, Keating MT (1993) Hemizygosity at the elastin locus in a developmental disorder, Williams syndrome. Nat Genet 5:11–16

Ferrero GB, Biamino E, Sorasio L, Banaudi E, Peruzzi L, Forzano S, di Cantogno LV, Silengo MC (2007) Presenting phenotype and clinical evaluation in a cohort of 22 Williams-Beuren syndrome patients. Eur J Med Genet 50:327–337

Ferrero GB, Howald C, Micale L, Biamino E, Augello B, Fusco C, Turturo MG, Forzano S, Reymond A, Merla G (2010) An atypical 7q11.23 deletion in a normal IQ Williams-Beuren syndrome patient. Eur J Hum Genet 18:33–38

Francke U (1999) Williams-Beuren syndrome: genes and mechanisms. Hum Mol Genet 8:1947–1954

Frangiskakis JM, Ewart AK, Morris CA, Mervis CB, Bertrand J, Robinson BF, Klein BP, Ensing GJ, Everett LA, Green ED, Proschel C, Gutowski NJ, Noble M, Atkinson DL, Odelberg SJ, Keating MT (1996) LIM-kinase1 hemizygosity implicated in impaired visuospatial constructive cognition. Cell 86:59–69

Fujiwara T, Mishima T, Kofuji T, Chiba T, Tanaka K, Yamamoto A, Akagawa K (2006) Analysis of knock-out mice to determine the role of HPC-1/syntaxin 1A in expressing synaptic plasticity. J Neurosci 26:5767–5776

Funakoshi T, Maeshima K, Yahata K, Sugano S, Imamoto F, Imamoto N (2007) Two distinct human POM121 genes: requirement for the formation of nuclear pore complexes. FEBS Lett 581:4910–4916

Gagliardi C, Bonaglia MC, Selicorni A, Borgatti R, Giorda R (2003a) Unusual cognitive and behavioural profile in a Williams syndrome patient with atypical 7q11.23 deletion. J Med Genet 40:526–530

Gagliardi C, Frigerio E, Burt DM, Cazzaniga I, Perrett DI, Borgatti R (2003b) Facial expression recognition in Williams syndrome. Neuropsychologia 41:733–738

Giannotti A, Tiberio G, Castro M, Virgilii F, Colistro F, Ferretti F, Digilio MC, Gambarara M, Dallapiccola B (2001) Coeliac disease in Williams syndrome. J Med Genet 38:767–768

Gillberg C, Rasmussen P (1994) Brief report: four case histories and a literature review of Williams syndrome and autistic behavior. J Autism Dev Disord 24:381–393

Giordano U, Turchetta A, Giannotti A, Digilio MC, Virgilii F, Calzolari A (2001) Exercise testing and 24-hour ambulatory blood pressure monitoring in children with Williams syndrome. Pediatr Cardiol 22:509–511

Glessner JT, Wang K, Cai G, Korvatska O, Kim CE, Wood S, Zhang H, Estes A, Brune CW, Bradfield JP, Imielinski M, Frackelton EC, Reichert J, Crawford EL, Munson J, Sleiman PM, Chiavacci R, Annaiah K, Thomas K, Hou C, Glaberson W, Flory J, Otieno F, Garris M, Soorya L, Klei L, Piven J, Meyer KJ, Anagnostou E, Sakurai T, Game RM, Rudd DS, Zurawiecki D, McDougle CJ, Davis LK, Miller J, Posey DJ, Michaels S, Kolevzon A, Silverman JM, Bernier R, Levy SE, Schultz RT, Dawson G, Owley T, McMahon WM, Wassink TH, Sweeney JA, Nurnberger JI, Coon H, Sutcliffe JS, Minshew NJ, Grant SF, Bucan M, Cook EH, Buxbaum JD, Devlin B, Schellenberg GD, Hakonarson H (2009) Autism genome-wide copy number variation reveals ubiquitin and neuronal genes. Nature 459:569–573

Gorlach A, Lee PL, Roesler J, Hopkins PJ, Christensen B, Green ED, Chanock SJ, Curnutte JT (1997) A p47-phox pseudogene carries the most common mutation causing p47-phox-deficient chronic granulomatous disease. J Clin Invest 100:1907–1918

Greenberg F, Lewis RA (1988) The Williams syndrome. Spectrum and significance of ocular features. Ophthalmology 95:1608–1612

Hannes FD, Sharp AJ, Mefford HC, de Ravel T, Ruivenkamp CA, Breuning MH, Fryns JP, Devriendt K, Van Buggenhout G, Vogels A, Stewart H, Hennekam RC, Cooper GM, Regan R, Knight SJ, Eichler EE, Vermeesch JR (2009) Recurrent reciprocal deletions and duplications of 16p13.11: the deletion is a risk factor for MR/MCA while the duplication may be a rare benign variant. J Med Genet 46:223–232

Henrichsen CN, Chaignat E, Reymond A (2009a) Copy number variants, diseases and gene expression. Hum Mol Genet 18:R1–R8

Henrichsen CN, Vinckenbosch N, Zollner S, Chaignat E, Pradervand S, Schutz F, Ruedi M, Kaessmann H, Reymond A (2009b) Segmental copy number variation shapes tissue transcriptomes. Nat Genet 41:424–429

Herguner S, Mukaddes NM (2006) Autism and Williams syndrome: a case report. World J Biol Psychiatry 7:186–188

Heyting C (1996) Synaptonemal complexes: structure and function. Curr Opin Cell Biol 8:389–396

Hill ID, Dirks MH, Liptak GS, Colletti RB, Fasano A, Guandalini S, Hoffenberg EJ, Horvath K, Murray JA, Pivor M, Seidman EG (2005) Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 40:1–19

Hillier LW, Fulton RS, Fulton LA, Graves TA, Pepin KH, Wagner-McPherson C, Layman D, Maas J, Jaeger S, Walker R, Wylie K, Sekhon M, Becker MC, O'Laughlin MD, Schaller ME, Fewell GA, Delehaunty KD, Miner TL, Nash WE, Cordes M, Du H, Sun H, Edwards J, Bradshaw-Cordum H, Ali J, Andrews S, Isak A, Vanbrunt A, Nguyen C, Du F, Lamar B, Courtney L, Kalicki J, Ozersky P, Bielicki L, Scott K, Holmes A, Harkins R, Harris A, Strong CM, Hou S, Tomlinson C, Dauphin-Kohlberg S, Kozlowicz-Reilly A, Leonard S, Rohlfing T, Rock SM, Tin-Wollam AM, Abbott A, Minx P, Maupin R, Strowmatt C, Latreille P, Miller N, Johnson D, Murray J, Woessner JP, Wendl MC, Yang SP, Schultz BR, Wallis JW, Spieth J, Bieri TA, Nelson JO, Berkowicz N, Wohldmann PE, Cook LL, Hickenbotham MT, Eldred J, Williams D, Bedell JA, Mardis ER, Clifton SW, Chissoe SL, Marra MA, Raymond C, Haugen E, Gillett W, Zhou Y, James R, Phelps K, Iadanoto S, Bubb K, Simms E, Levy R, Clendenning J, Kaul R, Kent WJ, Furey TS, Baertsch RA, Brent MR, Keibler E, Flicek P, Bork P, Suyama M, Bailey JA, Portnoy ME, Torrents D, Chinwalla AT, Gish WR et al (2003) The DNA sequence of human chromosome 7. Nature 424:157–164

Hinsley TA, Cunliffe P, Tipney HJ, Brass A, Tassabehji M (2004) Comparison of TFII-I gene family members deleted in Williams-Beuren syndrome. Protein Sci 13:2588–2599

Hirota H, Matsuoka R, Chen XN, Salandanan LS, Lincoln A, Rose FE, Sunahara M, Osawa M, Bellugi U, Korenberg JR (2003) Williams syndrome deficits in visual spatial processing linked to GTF2IRD1 and GTF2I on chromosome 7q11.23. Genet Med 5:311–321

Hoogenraad CC, Koekkoek B, Akhmanova A, Krugers H, Dortland B, Miedema M, van Alphen A, Kistler WM, Jaegle M, Koutsourakis M, Van Camp N, Verhoye M, van der Linden A, Kaverina I, Grosveld F, De Zeeuw CI, Galjart N (2002) Targeted mutation of Cyln2 in the Williams syndrome critical region links CLIP-115 haploinsufficiency to neurodevelopmental abnormalities in mice. Nat Genet 32:116–127

Howald C, Merla G, Digilio MC, Amenta S, Lyle R, Deutsch S, Choudhury U, Bottani A, Antonarakis SE, Fryssira H, Dallapiccola B, Reymond A (2006) Two high throughput technologies to detect segmental aneuploidies identify new Williams-Beuren syndrome patients with atypical deletions. J Med Genet 43:266–273

Huang YH, Bao Y, Peng W, Goldberg M, Love K, Bumcrot DA, Cole G, Langer R, Anderson DG, Sawicki JA (2009) Claudin-3 gene silencing with siRNA suppresses ovarian tumor growth and metastasis. Proc Natl Acad Sci USA 106:3426–3430

Huelsken J, Vogel R, Brinkmann V, Erdmann B, Birchmeier C, Birchmeier W (2000) Requirement for beta-catenin in anterior-posterior axis formation in mice. J Cell Biol 148:567–578

Huelsken J, Vogel R, Erdmann B, Cotsarelis G, Birchmeier W (2001) beta-Catenin controls hair follicle morphogenesis and stem cell differentiation in the skin. Cell 105:533–545

Iafrate AJ, Feuk L, Rivera MN, Listewnik ML, Donahoe PK, Qi Y, Scherer SW, Lee C (2004) Detection of large-scale variation in the human genome. Nat Genet 36:949–951

Iizuka K, Horikawa Y (2008) ChREBP: a glucose-activated transcription factor involved in the development of metabolic syndrome. Endocr J 55:617–624

Iizuka K, Bruick RK, Liang G, Horton JD, Uyeda K (2004) Deficiency of carbohydrate response element-binding protein (ChREBP) reduces lipogenesis as well as glycolysis. Proc Natl Acad Sci USA 101:7281–7286

Ino T, Nishimoto K, Iwahara M, Akimoto K, Boku H, Kaneko K, Tokita A, Yabuta K, Tanaka J (1988) Progressive vascular lesions in Williams-Beuren syndrome. Pediatr Cardiol 9:55–58

Iwaki S, Jensen BM, Gilfillan AM (2007) Ntal/Lab/Lat2. Int J Biochem Cell Biol 39:868–873

Jernigan TL, Bellugi U (1990) Anomalous brain morphology on magnetic resonance images in Williams syndrome and Down syndrome. Arch Neurol 47:529–533

Jernigan TL, Bellugi U, Sowell E, Doherty S, Hesselink JR (1993) Cerebral morphologic distinctions between Williams and Down syndromes. Arch Neurol 50:186–191

Jones KL, Smith DW (1975) The Williams elfin facies syndrome. A new perspective. J Pediatr 86:718–723

Kabashima T, Kawaguchi T, Wadzinski BE, Uyeda K (2003) Xylulose 5-phosphate mediates glucose-induced lipogenesis by xylulose 5-phosphate-activated protein phosphatase in rat liver. Proc Natl Acad Sci USA 100:5107–5112

Kaplan P, Kirschner M, Watters G, Costa MT (1989) Contractures in patients with Williams syndrome. Pediatrics 84:895–899

Kapp ME, von Noorden GK, Jenkins R (1995) Strabismus in Williams syndrome. Am J Ophthalmol 119:355–360

Karmiloff-Smith A, Grant J, Ewing S, Carette MJ, Metcalfe K, Donnai D, Read AP, Tassabehji M (2003) Using case study comparisons to explore genotype-phenotype correlations in Williams-Beuren syndrome. J Med Genet 40:136–140

Karnik SK, Brooke BS, Bayes-Genis A, Sorensen L, Wythe JD, Schwartz RS, Keating MT, Li DY (2003) A critical role for elastin signaling in vascular morphogenesis and disease. Development 130:411–423

Kawaguchi T, Takenoshita M, Kabashima T, Uyeda K (2001) Glucose and cAMP regulate the L-type pyruvate kinase gene by phosphorylation/dephosphorylation of the carbohydrate response element binding protein. Proc Natl Acad Sci USA 98:13710–13715

Kerzendorfer C, O'Driscoll M (2009) Human DNA damage response and repair deficiency syndromes: linking genomic instability and cell cycle checkpoint proficiency. DNA Repair 8:1139–1152

Kirchhoff M, Bisgaard AM, Bryndorf T, Gerdes T (2007) MLPA analysis for a panel of syndromes with mental retardation reveals imbalances in 5.8% of patients with mental retardation and dysmorphic features, including duplications of the Sotos syndrome and Williams-Beuren syndrome regions. Eur J Med Genet 50:33–42

Kitagawa H, Fujiki R, Yoshimura K, Mezaki Y, Uematsu Y, Matsui D, Ogawa S, Unno K, Okubo M, Tokita A, Nakagawa T, Ito T, Ishimi Y, Nagasawa H, Matsumoto T, Yanagisawa J, Kato S (2003) The chromatin-remodeling complex WINAC targets a nuclear receptor to promoters and is impaired in Williams syndrome. Cell 113:905–917

Klein-Tasman BP, Mervis CB (2003) Distinctive personality characteristics of 8-, 9-, and 10-year-olds with Williams syndrome. Dev Neuropsychol 23:269–290

Korenberg JR, Chen XN, Hirota H, Lai Z, Bellugi U, Burian D, Roe B, Matsuoka R (2000) VI. Genome structure and cognitive map of Williams syndrome. J Cogn Neurosci 12(Suppl 1):89–107

Korinek V, Barker N, Willert K, Molenaar M, Roose J, Wagenaar G, Markman M, Lamers W, Destree O, Clevers H (1998) Two members of the Tcf family implicated in Wnt/beta-catenin signaling during embryogenesis in the mouse. Mol Cell Biol 18:1248–1256

Kriek M, White SJ, Szuhai K, Knijnenburg J, van Ommen GJ, den Dunnen JT, Breuning MH (2006) Copy number variation in regions flanked (or unflanked) by duplicons among patients with developmental delay and/or congenital malformations; detection of reciprocal and partial Williams-Beuren duplications. Eur J Hum Genet 14:180–189

Lai CS, Fisher SE, Hurst JA, Vargha-Khadem F, Monaco AP (2001) A forkhead-domain gene is mutated in a severe speech and language disorder. Nature 413:519–523

Lakusta L, Dessalegn B, Landau B (2010) Impaired geometric reorientation caused by genetic defect. Proc Natl Acad Sci USA 107(7):2813–2817

Lam PP, Leung YM, Sheu L, Ellis J, Tsushima RG, Osborne LR, Gaisano HY (2005) Transgenic mouse overexpressing syntaxin-1A as a diabetes model. Diabetes 54:2744–2754

Lazebnik MB, Tussie-Luna MI, Hinds PW, Roy AL (2009) Williams-Beuren syndrome-associated transcription factor TFII-I regulates osteogenic marker genes. J Biol Chem 284:36234–36239

Lee JA, Carvalho CM, Lupski JR (2007) A DNA replication mechanism for generating nonrecurrent rearrangements associated with genomic disorders. Cell 131:1235–1247

Levitin DJ (2005) Musical behavior in a neurogenetic developmental disorder: evidence from Williams Syndrome. Ann N Y Acad Sci 1060:325–334

Levitin DJ, Cole K, Chiles M, Lai Z, Lincoln A, Bellugi U (2004) Characterizing the musical phenotype in individuals with Williams Syndrome. Child Neuropsychol 10:223–247

Levitin DJ, Cole K, Lincoln A, Bellugi U (2005) Aversion, awareness, and attraction: investigating claims of hyperacusis in the Williams syndrome phenotype. J Child Psychol Psychiatry 46:514–523

Leyfer OT, Woodruff-Borden J, Klein-Tasman BP, Fricke JS, Mervis CB (2006) Prevalence of psychiatric disorders in 4 to 16-year-olds with Williams syndrome. Am J Med Genet B Neuropsychiatr Genet 141B:615–622

Li DY, Faury G, Taylor DG, Davis EC, Boyle WA, Mecham RP, Stenzel P, Boak B, Keating MT (1998) Novel arterial pathology in mice and humans hemizygous for elastin. J Clin Invest 102:1783–1787

Li HH, Roy M, Kuscuoglu U, Spencer CM, Halm B, Harrison KC, Bayle JH, Splendore A, Ding F, Meltzer LA, Wright E, Paylor R, Deisseroth K, Francke U (2009) Induced chromosome deletions cause hypersociability and other features of Williams-Beuren syndrome in mice. EMBO Mol Med 1:50–65

Lupski JR (1998) Genomic disorders: structural features of the genome can lead to DNA rearrangements and human disease traits. Trends Genet 14:417–422

Lupski JR (2009) Genomic disorders ten years on. Genome Med 1:42

Majka J, Burgers PM (2004) The PCNA-RFC families of DNA clamps and clamp loaders. Prog Nucleic Acid Res Mol Biol 78:227–260

Makeyev AV, Erdenechimeg L, Mungunsukh O, Roth JJ, Enkhmandakh B, Ruddle FH, Bayarsaihan D (2004) GTF2IRD2 is located in the Williams-Beuren syndrome critical region 7q11.23 and encodes a protein with two TFII-I-like helix-loop-helix repeats. Proc Natl Acad Sci USA 101:11052–11057

Marler JA, Elfenbein JL, Ryals BM, Urban Z, Netzloff ML (2005) Sensorineural hearing loss in children and adults with Williams syndrome. Am J Med Genet A 138:318–327

Martindale DW, Wilson MD, Wang D, Burke RD, Chen X, Duronio V, Koop BF (2000) Comparative genomic sequence analysis of the Williams syndrome region (LIMK1-RFC2) of human chromosome 7q11.23. Mamm Genome 11:890–898

McCarroll SA, Kuruvilla FG, Korn JM, Cawley S, Nemesh J, Wysoker A, Shapero MH, de Bakker PI, Maller JB, Kirby A, Elliott AL, Parkin M, Hubbell E, Webster T, Mei R, Veitch J, Collins PJ, Handsaker R, Lincoln S, Nizzari M, Blume J, Jones KW, Rava R, Daly MJ, Gabriel SB, Altshuler D (2008) Integrated detection and population-genetic analysis of SNPs and copy number variation. Nat Genet 40:1166–1174

McRory JE, Rehak R, Simms B, Doering CJ, Chen L, Hermosilla T, Duke C, Dyck R, Zamponi GW (2008) Syntaxin 1A is required for normal in utero development. Biochem Biophys Res Commun 375:372–377

Meng X, Lu X, Morris CA, Keating MT (1998) A novel human gene FKBP6 is deleted in Williams syndrome. Genomics 52:130–137

Meng Y, Zhang Y, Tregoubov V, Janus C, Cruz L, Jackson M, Lu WY, MacDonald JF, Wang JY, Falls DL, Jia Z (2002) Abnormal spine morphology and enhanced LTP in LIMK-1 knockout mice. Neuron 35:121–133

Mercuri E, Atkinson J, Braddick O, Rutherford MA, Cowan FM, Counsell SJ, Dubowitz LM, Bydder G (1997) Chiari I malformation in asymptomatic young children with Williams syndrome: clinical and MRI study. Eur J Paediatr Neurol 1:177–181

Merla G, Ucla C, Guipponi M, Reymond A (2002) Identification of additional transcripts in the Williams-Beuren syndrome critical region. Hum Genet 110:429–438

Merla G, Howald C, Antonarakis SE, Reymond A (2004) The subcellular localization of the ChoRE-binding protein, encoded by the Williams-Beuren syndrome critical region gene 14, is regulated by 14–3-3. Hum Mol Genet 13:1505–1514

Merla G, Howald C, Henrichsen CN, Lyle R, Wyss C, Zabot MT, Antonarakis SE, Reymond A (2006) Submicroscopic deletion in patients with Williams-Beuren syndrome influences expression levels of the nonhemizygous flanking genes. Am J Hum Genet 79:332–341

Merritt JL, Lindor NM (2008) Further clinical description of duplication of Williams-Beuren region presenting with congenital glaucoma and brachycephaly. Am J Med Genet A 146A:1055–1058

Mervis CB (2006) Williams-Beuren syndrome: research, evaluation, and treatment. Johns Hopkins University Press, Baltimore

Mervis CB, Klein-Tasman BP (2000) Williams syndrome: cognition, personality, and adaptive behavior. Ment Retard Dev Disabil Res Rev 6:148–158

Mervis CB, Robinson BF, Bertrand J, Morris CA, Klein-Tasman BP, Armstrong SC (2000) The Williams syndrome cognitive profile. Brain Cogn 44:604–628

Metcalfe K, Rucka AK, Smoot L, Hofstadler G, Tuzler G, McKeown P, Siu V, Rauch A, Dean J, Dennis N, Ellis I, Reardon W, Cytrynbaum C, Osborne L, Yates JR, Read AP, Donnai D, Tassabehji M (2000) Elastin: mutational spectrum in supravalvular aortic stenosis. Eur J Hum Genet 8:955–963

Micale L, Fusco C, Augello B, Napolitano LM, Dermitzakis ET, Meroni G, Merla G, Reymond A (2008) Williams-Beuren syndrome TRIM50 encodes an E3 ubiquitin ligase. Eur J Hum Genet 16(9):1038–1049

Mizugishi K, Yamanaka K, Kuwajima K, Kondo I (1998) Interstitial deletion of chromosome 7q in a patient with Williams syndrome and infantile spasms. J Hum Genet 43:178–181

Morimoto M, An B, Ogami A, Shin N, Sugino Y, Sawai Y, Usuku T, Tanaka M, Hirai K, Nishimura A, Hasegawa K, Sugimoto T (2003) Infantile spasms in a patient with Williams syndrome and craniosynostosis. Epilepsia 44:1459–1462

Morin PJ (2005) Claudin proteins in human cancer: promising new targets for diagnosis and therapy. Cancer Res 65:9603–9606

Morris CA, Carey JC (1990) Three diagnostic signs in Williams syndrome. Am J Med Genet Suppl 6:100–101

Morris CA, Demsey SA, Leonard CO, Dilts C, Blackburn BL (1988) Natural history of Williams syndrome: physical characteristics. J Pediatr 113:318–326

Morris CA, Leonard CO, Dilts C, Demsey SA (1990) Adults with Williams syndrome. Am J Med Genet Suppl 6:102–107

Morris CA, Thomas IT, Greenberg F (1993) Williams syndrome: autosomal dominant inheritance. Am J Med Genet 47:478–481

Morris CA, Mervis CB, Hobart HH, Gregg RG, Bertrand J, Ensing GJ, Sommer A, Moore CA, Hopkin RJ, Spallone PA, Keating MT, Osborne L, Kimberley KW, Stock AD (2003) GTF2I hemizygosity implicated in mental retardation in Williams syndrome: genotype-phenotype analysis of five families with deletions in the Williams syndrome region. Am J Med Genet A 123:45–59

Nakamoto S, Saga T, Shinohara T (2003) Williams syndrome associated with complete atrioventricular septal defect. Heart 89:e15

Nicolaides NC, Kinzler KW, Vogelstein B (1995) Analysis of the 5′ region of PMS2 reveals heterogeneous transcripts and a novel overlapping gene. Genomics 29:329–334

Nimchinsky EA, Sabatini BL, Svoboda K (2002) Structure and function of dendritic spines. Annu Rev Physiol 64:313–353

O'Driscoll M, Dobyns WB, van Hagen JM, Jeggo PA (2007) Cellular and clinical impact of haploinsufficiency for genes involved in ATR signaling. Am J Hum Genet 81:77–86

Ohazama A, Sharpe PT (2007) TFII-I gene family during tooth development: candidate genes for tooth anomalies in Williams syndrome. Dev Dyn 236:2884–2888

Orellana C, Bernabeu J, Monfort S, Rosello M, Oltra S, Ferrer I, Quiroga R, Martinez-Garay I, Martinez F (2008) Duplication of the Williams-Beuren critical region: case report and further delineation of the phenotypic spectrum. J Med Genet 45:187–189

Osborne LR, Herbrick JA, Greavette T, Heng HH, Tsui LC, Scherer SW (1997) PMS2-related genes flank the rearrangement breakpoints associated with Williams syndrome and other diseases on human chromosome 7. Genomics 45:402–406

Osborne LR, Li M, Pober B, Chitayat D, Bodurtha J, Mandel A, Costa T, Grebe T, Cox S, Tsui LC, Scherer SW (2001) A 1.5 million-base pair inversion polymorphism in families with Williams-Beuren syndrome. Nat Genet 29:321–325

Ou Z, Berg JS, Yonath H, Enciso VB, Miller DT, Picker J, Lenzi T, Keegan CE, Sutton VR, Belmont J, Chinault AC, Lupski JR, Cheung SW, Roeder E, Patel A (2008) Microduplications of 22q11.2 are frequently inherited and are associated with variable phenotypes. Genet Med 10:267–277

Ounap K, Laidre P, Bartsch O, Rein R, Lipping-Sitska M (1998) Familial Williams-Beuren syndrome. Am J Med Genet 80:491–493

Palmer SJ, Tay ES, Santucci N, Cuc Bach TT, Hook J, Lemckert FA, Jamieson RV, Gunnning PW, Hardeman EC (2007) Expression of Gtf2ird1, the Williams syndrome-associated gene, during mouse development. Gene Expr Patterns 7:396–404

Palmer SJ, Santucci N, Widagdo J, Bontempo SJ, Tay ES, Hook J, Lemckert F, Gunning PW, Hardeman EC (2009) Negative autoregulation of GTF2IRD1 in Williams-Beuren syndrome via a novel DNA binding mechanism. J Biol Chem 285(7):4715–4724

Pankau R, Partsch CJ, Gosch A, Oppermann HC, Wessel A (1992) Statural growth in Williams-Beuren syndrome. Eur J Pediatr 151:751–755

Pankau R, Gosch A, Wessel A (1993) Radioulnar synostosis in Williams-Beuren syndrome: a component manifestation. Am J Med Genet 45:783

Pankau R, Partsch CJ, Winter M, Gosch A, Wessel A (1996) Incidence and spectrum of renal abnormalities in Williams-Beuren syndrome. Am J Med Genet 63:301–304

Pankau R, Siebert R, Kautza M, Schneppenheim R, Gosch A, Wessel A, Partsch CJ (2001) Familial Williams-Beuren syndrome showing varying clinical expression. Am J Med Genet 98:324–329

Partsch CJ, Dreyer G, Gosch A, Winter M, Schneppenheim R, Wessel A, Pankau R (1999) Longitudinal evaluation of growth, puberty, and bone maturation in children with Williams syndrome. J Pediatr 134:82–89

Partsch CJ, Japing I, Siebert R, Gosch A, Wessel A, Sippell WG, Pankau R (2002) Central precocious puberty in girls with Williams syndrome. J Pediatr 141:441–444

Partsch CJ, Siebert R, Caliebe A, Gosch A, Wessel A, Pankau R (2005) Sigmoid diverticulitis in patients with Williams-Beuren syndrome: relatively high prevalence and high complication rate in young adults with the syndrome. Am J Med Genet A 137:52–54

Peoples R, Perez-Jurado L, Wang YK, Kaplan P, Francke U (1996) The gene for replication factor C subunit 2 (RFC2) is within the 7q11.23 Williams syndrome deletion. Am J Hum Genet 58:1370–1373

Perez Jurado LA, Li X, Francke U (1995) The human calcitonin receptor gene (CALCR) at 7q21.3 is outside the deletion associated with the Williams syndrome. Cytogenet Cell Genet 70:246–249

Perez Jurado LA, Wang YK, Peoples R, Coloma A, Cruces J, Francke U (1998) A duplicated gene in the breakpoint regions of the 7q11.23 Williams-Beuren syndrome deletion encodes the initiator binding protein TFII-I and BAP-135, a phosphorylation target of BTK. Hum Mol Genet 7:325–334

Perez Jurado LA, Wang YK, Francke U, Cruces J (1999) TBL2, a novel transducin family member in the WBS deletion: characterization of the complete sequence, genomic structure, transcriptional variants and the mouse ortholog. Cytogenet Cell Genet 86:277–284

Pernot C, Worms AM, Marcon F, Admant P (1984) Williams-Beuren facies with mental retardation and tetralogy of Fallot. Pediatrie 39:53–58

Pezzi N, Prieto I, Kremer L, Perez Jurado LA, Valero C, Del Mazo J, Martinez AC, Barbero JL (2000) STAG3, a novel gene encoding a protein involved in meiotic chromosome pairing and location of STAG3-related genes flanking the Williams-Beuren syndrome deletion. FASEB J 14:581–592

Pittschieler K, Morini G, Crepaz R (1993) Williams syndrome and coeliac disease. Acta Paediatr 82:iv

Pober BR (2010) Williams-Beuren syndrome. N Engl J Med 362:239–252

Pober BR, Filiano JJ (1995) Association of Chiari I malformation and Williams syndrome. Pediatr Neurol 12:84–88

Pober BR, Morris CA (2007) Diagnosis and management of medical problems in adults with Williams-Beuren syndrome. Am J Med Genet C Semin Med Genet 145C:280–290

Pober BR, Lacro RV, Rice C, Mandell V, Teele RL (1993) Renal findings in 40 individuals with Williams syndrome. Am J Med Genet 46:271–274

Potocki L, Bi W, Treadwell-Deering D, Carvalho CM, Eifert A, Friedman EM, Glaze D, Krull K, Lee JA, Lewis RA, Mendoza-Londono R, Robbins-Furman P, Shaw C, Shi X, Weissenberger G, Withers M, Yatsenko SA, Zackai EH, Stankiewicz P, Lupski JR (2007) Characterization of Potocki-Lupski syndrome (dup(17)(p11.2p11.2)) and delineation of a dosage-sensitive critical interval that can convey an autism phenotype. Am J Hum Genet 80:633–649

Potter N, Karakoula A, Phipps KP, Harkness W, Hayward R, Thompson DN, Jacques TS, Harding B, Thomas DG, Palmer RW, Rees J, Darling J, Warr TJ (2008) Genomic deletions correlate with underexpression of novel candidate genes at six loci in pediatric pilocytic astrocytoma. Neoplasia 10:757–772

Prescott J, Jariwala U, Jia L, Cogan JP, Barski A, Pregizer S, Shen HC, Arasheben A, Neilson JJ, Frenkel B, Coetzee GA (2007) Androgen receptor-mediated repression of novel target genes. Prostate 67:1371–1383

Prieto I, Suja JA, Pezzi N, Kremer L, Martinez AC, Rufas JS, Barbero JL (2001) Mammalian STAG3 is a cohesin specific to sister chromatid arms in meiosis I. Nat Cell Biol 3:761–766

Proschel C, Blouin MJ, Gutowski NJ, Ludwig R, Noble M (1995) Limk1 is predominantly expressed in neural tissues and phosphorylates serine, threonine and tyrosine residues in vitro. Oncogene 11:1271–1281

Raiborg C, Stenmark H (2009) The ESCRT machinery in endosomal sorting of ubiquitylated membrane proteins. Nature 458:445–452

Ranheim EA, Kwan HC, Reya T, Wang YK, Weissman IL, Francke U (2005) Frizzled 9 knock-out mice have abnormal B-cell development. Blood 105:2487–2494

Redon R, Ishikawa S, Fitch KR, Feuk L, Perry GH, Andrews TD, Fiegler H, Shapero MH, Carson AR, Chen W, Cho EK, Dallaire S, Freeman JL, Gonzalez JR, Gratacos M, Huang J, Kalaitzopoulos D, Komura D, MacDonald JR, Marshall CR, Mei R, Montgomery L, Nishimura K, Okamura K, Shen F, Somerville MJ, Tchinda J, Valsesia A, Woodwark C, Yang F, Zhang J, Zerjal T, Zhang J, Armengol L, Conrad DF, Estivill X, Tyler-Smith C, Carter NP, Aburatani H, Lee C, Jones KW, Scherer SW, Hurles ME (2006) Global variation in copy number in the human genome. Nature 444:444–454

Richter NJ, Rogers GW Jr, Hensold JO, Merrick WC (1999) Further biochemical and kinetic characterization of human eukaryotic initiation factor 4H. J Biol Chem 274:35415–35424

Rose C, Wessel A, Pankau R, Partsch CJ, Bursch J (2001) Anomalies of the abdominal aorta in Williams-Beuren syndrome—another cause of arterial hypertension. Eur J Pediatr 160:655–658

Roy AL, Du H, Gregor PD, Novina CD, Martinez E, Roeder RG (1997) Cloning of an inr- and E-box-binding protein, TFII-I, that interacts physically and functionally with USF1. EMBO J 16:7091–7104

Sadler LS, Robinson LK, Verdaasdonk KR, Gingell R (1993) The Williams syndrome: evidence for possible autosomal dominant inheritance. Am J Med Genet 47:468–470

Santer R, Pankau R, Schaub J, Burgin-Wolff A (1996) Williams-Beuren syndrome and celiac disease. J Pediatr Gastroenterol Nutr 23:339–340

Santos A, Silva C, Rosset D, Deruelle C (2010) Just another face in the crowd: Evidence for decreased detection of angry faces in children with Williams syndrome. Neuropsychologia 48(4):1071–1078

Sarimski K (1996) Specific eating and sleeping problems in Prader-Willi and Williams-Beuren syndrome. Child Care Health Dev 22:143–150

Scherer SW, Gripp KW, Lucena J, Nicholson L, Bonnefont JP, Perez-Jurado LA, Osborne LR (2005) Observation of a parental inversion variant in a rare Williams-Beuren syndrome family with two affected children. Hum Genet 117:383–388

Schlesinger BE, Butler NR, Black JA (1956) Severe type of infantile hypercalcaemia. Br Med J 1:127–134

Schmitt JE, Eliez S, Warsofsky IS, Bellugi U, Reiss AL (2001) Corpus callosum morphology of Williams syndrome: relation to genetics and behavior. Dev Med Child Neurol 43:155–159

Schubert C (2009) The genomic basis of the Williams-Beuren syndrome. Cell Mol Life Sci 66:1178–1197

Schubert C, Laccone F (2006) Williams-Beuren syndrome: determination of deletion size using quantitative real-time PCR. Int J Mol Med 18:799–806

Scott RW, Olson MF (2007) LIM kinases: function, regulation and association with human disease. J Mol Med 85:555–568

Sebat J, Lakshmi B, Troge J, Alexander J, Young J, Lundin P, Maner S, Massa H, Walker M, Chi M, Navin N, Lucito R, Healy J, Hicks J, Ye K, Reiner A, Gilliam TC, Trask B, Patterson N, Zetterberg A, Wigler M (2004) Large-scale copy number polymorphism in the human genome. Science 305:525–528

Sellner LN, Taylor GR (2004) MLPA and MAPH: new techniques for detection of gene deletions. Hum Mutat 23:413–419

Sforzini C, Milani D, Fossali E, Barbato A, Grumieri G, Bianchetti MG, Selicorni A (2002) Renal tract ultrasonography and calcium homeostasis in Williams-Beuren syndrome. Pediatr Nephrol 17:899–902

Shaffer LG, Kennedy GM, Spikes AS, Lupski JR (1997) Diagnosis of CMT1A duplications and HNPP deletions by interphase FISH: implications for testing in the cytogenetics laboratory. Am J Med Genet 69:325–331

Sharp AJ, Mefford HC, Li K, Baker C, Skinner C, Stevenson RE, Schroer RJ, Novara F, De Gregori M, Ciccone R, Broomer A, Casuga I, Wang Y, Xiao C, Barbacioru C, Gimelli G, Bernardina BD, Torniero C, Giorda R, Regan R, Murday V, Mansour S, Fichera M, Castiglia L, Failla P, Ventura M, Jiang Z, Cooper GM, Knight SJ, Romano C, Zuffardi O, Chen C, Schwartz CE, Eichler EE (2008) A recurrent 15q13.3 microdeletion syndrome associated with mental retardation and seizures. Nat Genet 40:322–328

Smith AD, Gilchrist ID, Hood B, Tassabehji M, Karmiloff-Smith A (2009) Inefficient search of large-scale space in Williams syndrome: further insights on the role of LIMK1 deletion in deficits of spatial cognition. Perception 38:694–701

Somerville MJ, Mervis CB, Young EJ, Seo EJ, del Campo M, Bamforth S, Peregrine E, Loo W, Lilley M, Perez-Jurado LA, Morris CA, Scherer SW, Osborne LR (2005) Severe expressive-language delay related to duplication of the Williams-Beuren locus. N Engl J Med 353:1694–1701

Stagi S, Bindi G, Neri AS, Lapi E, Losi S, Jenuso R, Salti R, Chiarelli F (2005) Thyroid function and morphology in patients affected by Williams syndrome. Clin Endocrinol 63:456–460

Stankiewicz P, Lupski JR (2002) Genome architecture, rearrangements and genomic disorders. Trends Genet 18:74–82

Stinton C, Elison S, Howlin P (2010) Mental health problems in adults with Williams syndrome. Am J Intellect Dev Disabil 115:3–18

Stromme P, Bjornstad PG, Ramstad K (2002) Prevalence estimation of Williams syndrome. J Child Neurol 17:269–271

Tam E, Young EJ, Morris CA, Marshall CR, Loo W, Scherer SW, Mervis CB, Osborne LR (2008) The common inversion of the Williams-Beuren syndrome region at 7q11.23 does not cause clinical symptoms. Am J Med Genet A 146A:1797–1806

Tassabehji M (2003) Williams-Beuren syndrome: a challenge for genotype-phenotype correlations. Hum Mol Genet 12(Spec No 2):R229–R237

Tassabehji M, Metcalfe K, Karmiloff-Smith A, Carette MJ, Grant J, Dennis N, Reardon W, Splitt M, Read AP, Donnai D (1999) Williams syndrome: use of chromosomal microdeletions as a tool to dissect cognitive and physical phenotypes. Am J Hum Genet 64:118–125

Tassabehji M, Hammond P, Karmiloff-Smith A, Thompson P, Thorgeirsson SS, Durkin ME, Popescu NC, Hutton T, Metcalfe K, Rucka A, Stewart H, Read AP, Maconochie M, Donnai D (2005) GTF2IRD1 in craniofacial development of humans and mice. Science 310:1184–1187

Thompson PD, Webb M, Beckett W, Hinsley T, Jowitt T, Sharrocks AD, Tassabehji M (2007) GTF2IRD1 regulates transcription by binding an evolutionarily conserved DNA motif 'GUCE'. FEBS Lett 581:1233–1242

Tipney HJ, Hinsley TA, Brass A, Metcalfe K, Donnai D, Tassabehji M (2004) Isolation and characterisation of GTF2IRD2, a novel fusion gene and member of the TFII-I family of transcription factors, deleted in Williams-Beuren syndrome. Eur J Hum Genet 12:551–560

Tomaiuolo F, Di Paola M, Caravale B, Vicari S, Petrides M, Caltagirone C (2002) Morphology and morphometry of the corpus callosum in Williams syndrome: a T1-weighted MRI study. Neuroreport 13:2281–2284

Tomida J, Masuda Y, Hiroaki H, Ishikawa T, Song I, Tsurimoto T, Tateishi S, Shiomi T, Kamei Y, Kim J, Kamiya K, Vaziri C, Ohmori H, Todo T (2008) DNA damage-induced ubiquitylation of RFC2 subunit of replication factor C complex. J Biol Chem 283:9071–9079

Torniero C, dalla Bernardina B, Novara F, Vetro A, Ricca I, Darra F, Pramparo T, Guerrini R, Zuffardi O (2007) Cortical dysplasia of the left temporal lobe might explain severe expressive-language delay in patients with duplication of the Williams-Beuren locus. Eur J Hum Genet 15:62–67

Torniero C, Dalla Bernardina B, Novara F, Cerini R, Bonaglia C, Pramparo T, Ciccone R, Guerrini R, Zuffardi O (2008) Dysmorphic features, simplified gyral pattern and 7q11.23 duplication reciprocal to the Williams-Beuren deletion. Eur J Hum Genet 16:880–887

Trauner DA, Bellugi U, Chase C (1989) Neurologic features of Williams and Down syndromes. Pediatr Neurol 5:166–168

Tsao CY, Westman JA (1997) Infantile spasms in two children with Williams syndrome. Am J Med Genet 71:54–56

Turner DJ, Miretti M, Rajan D, Fiegler H, Carter NP, Blayney ML, Beck S, Hurles ME (2008) Germline rates of de novo meiotic deletions and duplications causing several genomic disorders. Nat Genet 40:90–95

Udwin O, Yule W (1991) A cognitive and behavioural phenotype in Williams syndrome. J Clin Exp Neuropsychol 13:232–244

Urban Z, Helms C, Fekete G, Csiszar K, Bonnet D, Munnich A, Donis-Keller H, Boyd CD (1996) 7q11.23 deletions in Williams syndrome arise as a consequence of unequal meiotic crossover. Am J Hum Genet 59:958–962

Urban Z, Michels VV, Thibodeau SN, Davis EC, Bonnefont JP, Munnich A, Eyskens B, Gewillig M, Devriendt K, Boyd CD (2000) Isolated supravalvular aortic stenosis: functional haploinsufficiency of the elastin gene as a result of nonsense-mediated decay. Hum Genet 106:577–588

Urban Z, Riazi S, Seidl TL, Katahira J, Smoot LB, Chitayat D, Boyd CD, Hinek A (2002) Connection between elastin haploinsufficiency and increased cell proliferation in patients with supravalvular aortic stenosis and Williams-Beuren syndrome. Am J Hum Genet 71:30–44

Uyeda K, Yamashita H, Kawaguchi T (2002) Carbohydrate responsive element-binding protein (ChREBP): a key regulator of glucose metabolism and fat storage. Biochem Pharmacol 63:2075–2080

Valero MC, de Luis O, Cruces J, Perez Jurado LA (2000) Fine-scale comparative mapping of the human 7q11.23 region and the orthologous region on mouse chromosome 5G: the low-copy repeats that flank the Williams-Beuren syndrome deletion arose at breakpoint sites of an evolutionary inversion(s). Genomics 69:1–13

Van der Aa N, Rooms L, Vandeweyer G, van den Ende J, Reyniers E, Fichera M, Romano C, Delle Chiaie B, Mortier G, Menten B, Destree A, Maystadt I, Mannik K, Kurg A, Reimand T, McMullan D, Oley C, Brueton L, Bongers EM, van Bon BW, Pfund R, Jacquemont S, Ferrarini A, Martinet D, Schrander-Stumpel C, Stegmann AP, Frints SG, de Vries BB, Ceulemans B, Kooy RF (2009) Fourteen new cases contribute to the characterization of the 7q11.23 microduplication syndrome. Eur J Med Genet 52:94–100

van Hagen JM, van der Geest JN, van der Giessen RS, Lagers-van Haselen GC, Eussen HJ, Gille JJ, Govaerts LC, Wouters CH, de Coo IF, Hoogenraad CC, Koekkoek SK, Frens MA, van Camp N, van der Linden A, Jansweijer MC, Thorgeirsson SS, De Zeeuw CI (2007) Contribution of CYLN2 and GTF2IRD1 to neurological and cognitive symptoms in Williams Syndrome. Neurobiol Dis 26:112–124

Wain LV, Armour JA, Tobin MD (2009) Genomic copy number variation, human health, and disease. Lancet 374:340–350

Wang PP, Jernigan TL (1994) Morphometric studies using neuroimaging. Neurol Clin 12:789–802

Wang PP, Hesselink JR, Jernigan TL, Doherty S, Bellugi U (1992) Specific neurobehavioral profile of Williams' syndrome is associated with neocerebellar hemispheric preservation. Neurology 42:1999–2002

Wang PP, Doherty S, Rourke SB, Bellugi U (1995) Unique profile of visuo-perceptual skills in a genetic syndrome. Brain Cogn 29:54–65

Wang YK, Perez-Jurado LA, Francke U (1998) A mouse single-copy gene, Gtf2i, the homolog of human GTF2I, that is duplicated in the Williams-Beuren syndrome deletion region. Genomics 48:163–170

Wessel A, Gravenhorst V, Buchhorn R, Gosch A, Partsch CJ, Pankau R (2004) Risk of sudden death in the Williams-Beuren syndrome. Am J Med Genet A 127A:234–237

Williams JC, Barratt-Boyes BG, Lowe JB (1961) Supravalvular aortic stenosis. Circulation 24:1311–1318

Wilson DI, Goodship JA, Burn J, Cross IE, Scambler PJ (1992) Deletions within chromosome 22q11 in familial congenital heart disease. Lancet 340:573–575

Winter M, Pankau R, Amm M, Gosch A, Wessel A (1996) The spectrum of ocular features in the Williams-Beuren syndrome. Clin Genet 49:28–31

Wren C, Oslizlok P, Bull C (1990) Natural history of supravalvular aortic stenosis and pulmonary artery stenosis. J Am Coll Cardiol 15:1625–1630

Yamashita H, Takenoshita M, Sakurai M, Bruick RK, Henzel WJ, Shillinglaw W, Arnot D, Uyeda K (2001) A glucose-responsive transcription factor that regulates carbohydrate metabolism in the liver. Proc Natl Acad Sci USA 98:9116–9121

Yoshimura K, Kitagawa H, Fujiki R, Tanabe M, Takezawa S, Takada I, Yamaoka I, Yonezawa M, Kondo T, Furutani Y, Yagi H,

Yoshinaga S, Masuda T, Fukuda T, Yamamoto Y, Ebihara K, Li DY, Matsuoka R, Takeuchi JK, Matsumoto T, Kato S (2009) Distinct function of 2 chromatin remodeling complexes that share a common subunit, Williams syndrome transcription factor (WSTF). Proc Natl Acad Sci USA 106:9280–9285

Zani VJ, Asou N, Jadayel D, Heward JM, Shipley J, Nacheva E, Takasuki K, Catovsky D, Dyer MJ (1996) Molecular cloning of complex chromosomal translocation t(8;14;12)(q24.1;q32.3;q24.1) in a Burkitt lymphoma cell line defines a new gene (BCL7A) with homology to caldesmon. Blood 87:3124–3134

Zhang F, Gu W, Hurles ME, Lupski JR (2009) Copy number variation in human health, disease, and evolution. Annu Rev Genomics Hum Genet 10:451–481

Zhao C, Pleasure SJ (2004) Frizzled-9 promoter drives expression of transgenes in the medial wall of the cortex and its chief derivative the hippocampus. Genesis 40:32–39

Zhao C, Pleasure SJ (2005) Frizzled9 protein is regionally expressed in the developing medial cortical wall and the cells derived from this region. Brain Res Dev Brain Res 157:93–97