

Copy Number Variation and Inherited Disease

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Genome ResearchCNV and nervous system diseases –
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Abstract. Several new genomic disorders caused by copy number variation (CNV) of genes whose dosage is critical for the physiological function of the nervous system have been recently identified. Dup(7)(q11.23) patients carry duplications of the genomic region deleted in Williams-Beuren syndrome, they are characterized by prominent speech delay. The phenotypes of Potocki-Lupski syndrome and *MECP2* duplication syndrome were neuropsychologically examined in detail, which revealed autism as an endophenotype and a prominent behavioral feature of these disorders. Tandem duplication of *LMNB1* was reported to

cause adult-onset autosomal dominant leukodystrophy. *PAFAH1B1/LIS1* and *YWHAE*, which were deleted in isolated lissencephaly (*PAFAH1B1/LIS1* alone) and Miller-Dieker syndrome (both genes), were found to be duplicated in patients with developmental delay. Finally, two novel microdeletion syndromes affecting 17q21.31 and 15q13.3, as well as their reciprocal duplications, were also identified. In this review, we provide an overview of the phenotypic manifestation of these syndromes and the rearrangements causing them.

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Much progress has been made in the research on CNV and neurological diseases since our last review on this topic (Lee and Lupski, 2006) two years ago. Some known disorders were further characterized and several new genomic disorders with major neurological manifestations were identified, some of which are caused by rearrangements of genomic regions which were not related to any genomic disorder and others caused by rearrangements reciprocal to genomic intervals of known disorders. A few of these new findings are summarized and discussed in this review. Both autism and schizophrenia have been shown to be genomic disorders, they will be discussed elsewhere in this issue.

Williams-Beuren region reciprocal duplication

A significant recent finding in neurogenetics is the characterization of the reciprocal duplication involving the Williams-Beuren syndrome (WBS, MIM194050) region. WBS is caused by genomic deletions in 7q11.23 that typically encompass 25–30 genes. WBS has the prevalence of 1/7,500 to 1/20,000 and is among the most well-characterized microdeletion syndromes (Greenberg, 1990; Osborne, 1999; Tassabehji, 2003). The majority of WBS patients carry a common recurrent 1.55 Mb deletion, which apparently occurs via non-allelic homologous recombination (NAHR) (Stankiewicz and Lupski, 2002; Bayes et al., 2003). The reciprocal duplication of this deletion has long been expected; but it was not until 2005 that this duplication was finally identified in a single patient with severe speech delay (Somerville et al., 2005). Since then, 16 further duplications in the WBS critical region (WBCR) have been reported (Somerville et al., 2005; Kriek et al., 2006; Berg et al., 2007; Depienne et al., 2007; Kirchoff et al., 2007a; Torniero et al., 2007, 2008; Merritt and Lindor, 2008; Orellana et al., 2008), enabling the definition and the first characterizations of the dup(7)(q11.23) syndrome (MIM 609757).

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and Klein-Tasman, 2000). This contrast is of extraordinary interest, as it indicates the existence of one or more genes in WBCR that are highly dosage sensitive (in case of both increased and decreased gene amount) for the development of the neuronal circuits and pathways involved in human speech and language ability (Fisher, 2005; Tassabehji and Donnai, 2006). Moreover, speech delay is such a common general pediatric problem; other than sometimes being related to hearing impairment, there are relatively few insights into its biological causes.

Mechanisms for the deletions and duplications in dup(7)(q11.23)

The WBS region displays a highly complex genomic structure; it contains three groups (A, B, C) of low copy repeats (LCRs) (Stankiewicz and Lupski, 2002) ranging from 44 to 146 kb in size. Each group includes at least three highly (up to 99.5%) homologous copies of LCRs which are localized in three different modules (centromeric, medial and telomeric) (Cusco et al., 2008) (Fig. 1). In 89% of WBS cases, the deletions are 1.55 Mb in length and arise via NAHR between the two LCRs Bc and Bm (Bayes et al., 2003; Cusco et al., 2008). An uncommon but recurrent deletion of 1.84 Mb has also been identified in 8% of WBS patients (Cusco et al., 2008); this deletion is caused by NAHR between an alternative LCR pair Ac and Am (Bayes et al., 2003) (Fig. 1).

Besides these two recurrent deletions, a number of non-recurrent deletions of atypical sizes have also been identified (Wu et al., 1998; Botta et al., 1999; Tassabehji et al., 1999, 2005; Korenberg et al., 2000; Gagliardi et al., 2003; Heller et al., 2003; Karmiloff-Smith et al., 2003; Howald et al., 2006; Schubert and Laccone, 2006). These atypical deletions, and the differences in their phenotypic manifestations, have been very informative in delineating the WBS endophenotypes and especially in searching for genes associated with language and cognition (Tassabehji, 2003). Different from the two recurrent deletions, most of these nonrecurrent deletions do not have both breakpoints localized in LCRs, so they could have occurred via either non homologous end joining (NHEJ) (Shaw and Lupski, 2005) or replication fork stalling and template switching (FoSTeS) (Lee et al., 2007), as well as NAHR mediated by elements other than LCRs (such as the *Alu* repeats; Babcock et al., 2003; Shaw and Lupski, 2005). As little information on the exact breakpoints of these nonrecurrent deletions is available, no conclusion can be drawn yet as to which mechanism indeed causes these deletions.

Sixteen duplications in the WBS region have been reported to date. The breakpoints of the two duplications described by Somerville et al. and Torniero et al. are localized in Bm and Bc (Fig. 1); these two duplications are thus the bona fide reciprocal duplications of the 1.55 Mb WBS common recurrent deletion. The breakpoints of the duplications described in Kriek et al. (2006), Berg et al. (2007), Depienne et al. (2007), Kirchhoff et al. (2007a), Merritt and Lindor (2008), Orellana et al. (2008) and Torniero et al. (2008) were not exactly mapped. They could be in any LCR or in the non-duplicated region between the LCRs Am and Bt; the duplica-

tions could thus be reciprocal to the common recurrent deletion, uncommon recurrent deletion (if the breakpoints are in Ac and Am), or perhaps some may represent nonrecurrent duplications. The two duplications carried by case 4 reported in Berg et al. (2007) and case 2 in Kriek et al. (2006) are clearly NOT reciprocal to the recurrent WBS deletions; one of them extends beyond WBCS into the telomeric direction, another one affects only one single gene *FKBP6* in WBCS. The identification of more duplications and the mapping of their breakpoints will help us further understand the mechanisms for these rearrangements. Furthermore, the phenotypic comparison among duplications with different sizes, as well as between reciprocal deletions and duplications will be very useful in further delineation of the dup(7)(q11.23) syndrome and understanding the substrates and pathways of the dosage sensitivity in the WBS critical region.

Using a PCR-based sperm typing assay, Turner et al. (2008) mapped the frequency of the 1.55 Mb common WBS deletion and its reciprocal duplication in meiosis; they observed a two deletion to one duplication ratio in the frequencies of the reciprocal events. Considering the prevalence of WBS and the fact that the overwhelming majority of the WBS deletions are indeed due to the 1.55 Mb deletion, one should expect more duplication cases to be found soon. However, the phenotype of dup(7)(q11.23) syndrome seems to be much milder and does not include the multiple organ anomalies observed in WBS; the chance that these individuals are medically ascertained and receive comprehensive genetic tests is thus lower than that for the WBS patients.

Flanking CNVs and SVs associated with the deletions and duplications in dup(7)(q11.23)

Only a few cases of parental inheritance have been reported for the WBS deletion; otherwise, almost all WBS deletions are sporadic de novo events occurring in the meiosis of one of the parents (the transmitting progenitor) (Cusco et al., 2008). Several structural variants of the WBS region were observed to be frequently associated with the transmitting progenitors. A 2 Mb inversion mediated by the inversely oriented centromeric and telomeric LCR modules, and including the whole WBCR, occurs more frequently in the transmitting parents than non-transmitting parents and control persons (Osborne et al., 2001; Bayes et al., 2003). An inversion does not change the copy number of genes and is not a true copy number variation (CNV); it is, however, a very important and frequent element of genomic structural variation (SV), as also observed by disease-independent genome-wide analyses of structural variations (Flores et al., 2007; Korbelt et al., 2007; Kidd et al., 2008). Most recently, Cusco et al. (2008) identified several CNV polymorphisms of the LCR blocks, the most frequent ones being deletion and duplication of the centromeric LCRs mediated by NAHR between Cc and Cm. The deletion allele was found to be significantly more frequent in transmitting progenitors than non-transmitting progenitors and control individuals.

In four of the 16 dup(7)(q11.23) cases described to date, not enough information on inheritance pattern is available.

Quite different from the sporadic nature of WBS, among the remaining 12 informative dup(7)(q11.23) cases, one inherited the duplication from his father (Kriek et al., 2006); three from their mothers (Berg et al., 2007; Torniero et al., 2008); 4/12 (33%) is astonishingly high compared to the familial WBS cases. This difference may be related to the milder phenotype of dup(7)(q11.23) compared to WBS (Berg et al., 2007). It will be very interesting to investigate if the CNV alleles associated with the transmission of the deletions also occur in higher frequency in the transmitting progenitors of the duplications. The theoretical answer would be yes.

MECP2 duplication syndrome

The X-linked gene *MECP2* located in Xq28 encodes the methyl-CpG-binding protein 2 (MeCP2). By functioning as both a transcription activator and repressor, MeCP2 regulates the expression of a wide range of genes in CNS (Chahrour et al., 2008). Point mutations and intragenic deletions in *MECP2* have been found to be the major cause of the neurodevelopmental disorder Rett syndrome (RTT, MIM312750). In females, the manifestation of Rett syndrome includes stereotypic hand wringing, loss of speech, acquired microcephaly, mental retardation with autistic features, seizures, ataxia, and breathing dysrhythmias. The only males manifesting *bona fide* Rett syndrome when carrying the same mutations are those with an 47, XXY karyotype (reviewed in Moretti and Zoghbi, 2006). Males with normal karyotype and carrying the same mutations causing Rett syndrome in females suffer from severe encephalopathy and infantile death (Zeev et al., 2002). Hypomorphic mutations barely causing any phenotype in females cause mental retardation, tremors and a variety of neuropsychiatric features in males (Meloni et al., 2000; Cohen et al., 2002; Kleefstra et al., 2002).

A number of deletions involving *MECP2* have been identified in female patients with Rett syndrome and one male patient with severe neonatal encephalopathy (Schollen et al., 2003; Laccone et al., 2004; Ravn et al., 2005; Hardwick et al., 2007; Scala et al., 2007). Skewed X inactivation (SCI) was identified in some, but not all informative deletion patients. Although some deletions include a part of the downstream flanking gene *IRAK1* (Laccone et al., 2004; Pan et al., 2006; Hardwick et al., 2007; Scala et al., 2007), most of them are intragenic and involve parts of exon 3 and/or exon 4 of *MECP2* (Ravn et al., 2005); none of the larger (>1 kb) deletions has been reported to be recurrent. Interestingly, 12 of 21 nonrecurrent deletions with precisely mapped boundaries have one of their breakpoints in a 150 bp genomic region, which is also a hotspot for the smaller deletions (20–500 bp) confined within exon 4 (reviewed in Hardwick et al., 2007). This phenomenon was named breakpoint grouping (Lee et al., 2006), it has been described for the nonrecurrent duplications at the Pelizaeus-Merzbacher Disease (PMD, MIM312080) locus (Lee et al., 2006) and the nonrecurrent deletions at the Smith-Magenis syndrome (SMS; MIM182290) locus (Stankiewicz et al., 2003). Similar to

these loci, the *MECP2* locus also occurs in a region with highly complex genomic architecture characterized through multiple LCRs (del Gaudio et al., 2006). The occurrence of breakpoint grouping further highlights the important roles of genomic architecture in the formation of genomic rearrangements.

Recently, a number of genomic duplications involving *MECP2* have also been identified in males manifesting a progressive neurodevelopmental syndrome (Van Esch et al., 2005; Meins et al., 2005; del Gaudio et al., 2006; Friez et al., 2006; Bauters et al., 2008; Carvalho et al., submitted). The common phenotypes include severe to profound mental retardation, poor speech development, infantile hypotonia, recurrent infections, epilepsy and progressive spasticity. Tavyev et al. (submitted), for the first time, performed detailed neuropsychiatric examinations including Autism Diagnostic Observation Schedule (ADOS) and Autism Diagnostic Interview-Revised (ADI-R) on nine males carrying *MECP2* duplication and demonstrated that autism is a defining feature of the *MECP2* duplication syndrome (Tavyev et al., submitted). The neuronal phenotype of *MECP2* duplication (MIM 300260) is thus remarkably similar to that of Rett Syndrome caused by loss of function of *MECP2* with both disorders displaying mental retardation and autism. Analyses at cellular and molecular levels, however, showed that the detailed pathomechanisms underlying the two syndromes are completely different (Chahrour et al., 2008). Interestingly, neuropsychological examination of the mothers of the duplication patients, who are carriers of the duplication, showed that they display significant psychiatric symptoms including generalized anxiety, depression, and compulsion that preceded the birth of their children, although a nearly 100% skewing of X inactivation favoring the duplication chromosome was observed (Tavyev et al., submitted). However, the skewed X inactivation was measured in the blood and does not necessarily reflect what is occurring in the brain.

No recurrent *MECP2* duplication has been observed yet, the boundaries of the duplications are scattered around a 3 Mb region flanking *MECP2*. High-resolution array CGH and subsequent PCR experiments revealed that some of the duplications have complex structure (Bauters et al., 2008; Carvalho et al., submitted) and may have arisen via the FoSTeS mechanism. FoSTeS has also been observed for rearrangements at the PMD locus, similarly localized in a highly complex genomic region (Lee et al., 2007). Surprisingly, the duplications in the *MECP2* region always encompass much larger genomic fragments than the deletions. The smallest duplication in the *MECP2* region identified to date is 154 kb (Carvalho et al., submitted) and involves at least the complete open reading frames of *IRAK1* and *MECP2*. This smallest duplication already exceeds the largest *MECP2* region deletions reported to date (Ravn et al., 2005; Hardwick et al., 2007).

The difference in the size of *MECP2* region duplications and deletions is curious. It might be due to the different mechanisms underlying the origin of these rearrangements and reflects a true difference in the size of the deletions and

duplication in this region; alternatively, it can be related to phenotypic selection, as has been postulated for the PMD associated *PLP1* (proteolipid protein 1) duplications (Inoue et al., 2002). The rearrangements not observed may have an early lethal or extremely mild phenotype, keeping the carriers from being medically ascertained. Skewed-X inactivation, which has been observed in all duplication carriers and some deletion patients, may also play a role in the phenotypic manifestation of these rearrangements.

ADLD and *LMNB1* duplication

After Charcot-Marie-Tooth disease type 1A (CMT1A, MIM118220) (Lupski et al., 1991; Raeymaekers et al., 1991) and Pelizeaus-Merzbacher Disease (PMD, MIM312080) (Inoue, 2005), the adult-onset autosomal dominant leukodystrophy (ADLD, MIM169500) became the third member in the group of demyelinating disorders that can be caused by abnormal gene dosage (Padiath et al., 2006). ADLD is a very rare (only five families have been reported worldwide), slowly progressive and fatal condition which manifests in the fourth to sixth decade of life (Schwankhaus et al., 1994). The characteristic early autonomic abnormalities include bowel/bladder dysfunction, impotence in male patients, decreased sweating and others. Later in the course of their disease, ADLD patients develop ataxia and signs of pyramidal tract involvement (Brown et al., 1987). Symmetrical demyelination in the CNS can be found in MRI scans and neuropathological examination (Schwankhaus et al., 1988). If not for the symmetry, such lesions could be mistaken for those observed in multiple sclerosis.

Via linkage analysis, Fu and colleagues identified a locus on 5q31 which is linked to ADLD in a five-generation kindred (Coffeen et al., 2000). In another segregating kindred, ADLD was reported as being linked to 5q23 (Marklund et al., 2006). Later, Fu and colleagues detected a tandem duplication of a 170 kb genomic fragment at 5q31 that segregates with the disease in the ADLD family (Padiath et al., 2006). The duplication does not disrupt any known gene and encompasses the complete ORF of two genes, of them only *LMNB1* (encoding Lamin B1) is expressed in the brain. Indeed, increased expression of *LMNB1*, at both RNA and protein levels, was found in brain tissue of the patients bearing the duplication. Also, overexpressing human *LMNB1* or its *Drosophila* orthologue resulted in neurodegenerative phenotypes in flies. It is thus highly likely that the duplication of *LMNB1* is causative for ADLD.

Lamin B1 is a member of the intermediate filament family of proteins and is part of the nuclear lamina underlying the nuclear envelope of eukaryotic cells (Worman and Bonne, 2007). Mutations in its close paralogue, *LMNA/C*, have been found to be causative for more than ten different disorders. Interestingly, some of the conditions result from haploinsufficiency of *LMNA* (Worman and Bonne, 2007). Time-lapse videomicroscopy showed that the protein Lamin B1 serves a fundamental role within the nuclear envelope by anchoring the nucleus to the cytoskeleton (Ji et al.,

2007). Silencing of *LMNB1* via siRNA causes cell death in human cells and *C. elegans* (Liu et al., 2000; Harborth et al., 2001). Homozygous *Lmnb1* knockout mice die at birth, with defects in lung and bone (Vergnes et al., 2004). Intriguingly, the heterozygous knockout mice were reported to be fertile and 'phenotypically indistinguishable from wildtype mice' (Vergnes et al., 2004). It is not known how the increased dosage of Lamin B1 causes the phenotypes in ADLD.

Duplication in the 17p13 lissencephaly and Miller-Dieker syndrome region

Heterozygote deletions in the chromosomal region 17p13 have long been known to cause two distinct disorders with partially overlapping phenotypes: isolated lissencephaly sequence (ILS, MIM607432) and Miller-Dieker syndrome (MDS, MIM 247200). Analyses of the phenotype-genotype associations of these two disorders (Cardoso et al., 2003) have highlighted the importance of two genes for the phenotypic manifestation of the deletion: *PAFAH1B1/LIS1* and *YWHAE* (coding for the protein 14-3-3 ϵ). The deletions involving only *PAFAH1B1/LIS1* (Reiner et al., 1993) but not *YWHAE* cause ILS, characterized by lissencephaly and minimal or no other dysmorphic features (Cardoso et al., 2003). ILS can be also caused by point mutations in the *PAFAH1B1/LIS1* gene (Uyanik et al., 2007). When the deletion encompasses both *PAFAH1B1/LIS1* and *YWHAE*, MDS is manifested, with lissencephaly plus significant facial dysmorphism, as well as occasionally other congenital anomalies (Dobyns et al., 1991). In addition, the lissencephaly phenotype in MDS is in general more severe than in ILS (Dobyns et al., 1991; Cardoso et al., 2003). Interestingly, two patients carrying deletions of only *YWHAE* but not *PAFAH1B1/LIS1* have also been reported, who have no lissencephaly, but only mental retardation (Cardoso et al., 2003).

PAFAH1B1/LIS1 encodes a 45-kDa noncatalytic subunit of platelet-activating factor acetylhydrolase 1B (Hattori et al., 1994). *YWHAE*, or 14-3-3 ϵ , encodes the ϵ isoform of the 14-3-3 proteins, which bind to phosphoserine/phosphothreonine motifs in numerous binding partners and play important roles in a multitude of cellular functions (Kjarland et al., 2006). *PAFAH1B1/LIS1* and *YWHAE/14-3-3 ϵ* function in the same physiological pathway affecting neuronal migration (Toyo-oka et al., 2003; Wynshaw-Boris, 2007). Reduced dosage of either *Pafah1b1/Lis1* or *Ywhae/14-3-3 ϵ* in mouse results in neuronal migration defects and development impairments. The phenotypes are more severe in double heterozygous knockout mice (*Pafah1b1 +/-, Ywhae +/-*) when the dosage of both genes is decreased (Toyo-oka et al., 2003), which is consistent with the human data.

Interestingly, Mei et al. also reported a heterozygous duplication in *PAFAH1B1/LIS1* in a patient with lissencephaly grade 2 (Mei et al., 2008). This duplication only includes exon 3–5 of *PAFAH1B1/LIS1* and likely disrupts its ORF and reduces the effective gene dosage. The pathological effect of this duplication would be thus probably similar to that of the loss-of-function deletions in *PAFAH1B1/LIS1*. Duplica-

tions truly increasing gene dosages were only detected very recently. Applying array CGH techniques, Bi et al. (2009) detected heterozygote duplication of either *PAFAH1B1/LIS1* or *YWHAE/14-3-3ε* alone, as well as a large duplication involving both *YWHAE/14-3-3ε* and *PAFAH1B1/LIS1* in seven unrelated cases. RT-PCR confirmed the enhanced expression level of these two genes at increased gene dosage. Increased *PAFAH1B1/LIS1* dosage causes failure to thrive, moderate to severe developmental delay, small brain and mild brain structural abnormalities. Duplication of *YWHAE/14-3-3ε* is associated with dysmorphic faces, macrosomia and developmental delay. None of the duplication patients showed a lissencephaly phenotype. Bi et al. also showed that transgenic mice overexpressing *Pafah1b1/Lis1* mimicked part of the phenotypes observed in human, confirming the dosage-sensitivity of *PAFAH1B1/LIS1* at both decreased and increased expression.

The size and localization of most ILS and MDS deletions were analyzed via FISH (Cardoso et al., 2003; Chabchoub et al., 2006; Mei et al., 2008) and sequence-tag mapping (Cardoso et al., 2003), only one case was analyzed with BAC-array (Chabchoub et al., 2006). These methods are not optimal for detecting complex rearrangements or to map the exact boundaries of the rearrangements. It is thus not possible to conclude if the cases with similar deletions (Cardoso et al., 2003) indeed represent recurrent rearrangements. Mei et al. obtained the breakpoints of deletions in four lissencephaly patients via long-range PCR (Mei et al., 2008). All obtained breakpoints are localized in or adjacent to *Alu* sequence. Sequence analysis showed that two of the deletions probably occurred via *Alu*-mediated NAHR, with one of them found in two patients, as has been previously shown for nonrecurrent SMS deletions in 17p11.2 (Shaw and Lupski, 2005). It is not clear from the reported data if it is a true recurrent deletion or if these two patients inherited this deletion from a common ancestor. Another deletion apparently resulted from an NHEJ mechanism, with no homology found at the junction but a piece of 'filler-DNA' of 24 bp (Mei et al., 2008). The high-density oligo array with 2–3 oligos interrogating each kb DNA as well as subsequent PCR reactions enabled Bi et al. to observe several complex rearrangements with the duplications interrupted by triplication or normal copy number. These complex rearrangements are likely the result of the recently proposed replication Fork Stalling and Template Switching (FoSTeS) mechanism (Lee et al., 2007). Breakpoint analyses are being performed for further information regarding the mechanisms underlying these rearrangements.

17q21.31 microdeletion syndrome

A new genomic disorder affecting the nervous system, the microdeletion syndrome 17q21.31 (MIM 610443) was identified by three groups simultaneously in 2006 (Koolen et al., 2006; Sharp et al., 2006; Shaw-Smith et al., 2006), after several single cases with similar deletions had been reported earlier (Park et al., 1992; Khalifa et al., 1993; Varela et al.,

2006). In a recent multi-center clinical and molecular study on 22 patients, Koolen et al. (2008) estimated the prevalence of the 17q21.31 microdeletion syndrome to be 1/16,000. Common phenotypes observed in almost all affected individuals include developmental delay, hypotonia, a friendly/ amiable behavior and mild but characteristic dysmorphic facial features (Koolen et al., 2006, 2008; Sharp et al., 2006; Shaw-Smith et al., 2006). The deletions are of 500–650 kb in size; the minimal critical region was refined to a 424 kb genomic segment (Sharp et al., 2006; Koolen et al., 2008) and encompasses six genes including *CRHR1* (coding for corticotrophin releasing hormone receptor 1) and *MAPT* (coding for microtubule-associated protein tau), both highly expressed in brain (Sharp et al., 2006). Gain-of-function mutations in *MAPT* are known to cause autosomal dominant forms of frontal temporal dementia with parkinsonism (MIM 600274) (Hutton et al., 1998; D'Souza et al., 1999; Rademakers et al., 2004); common genetic variation of *MAPT* is associated with progressive supranuclear palsy (PSNP, MIM 601104) (Pittman et al., 2005) and Alzheimer's disease (Myers et al., 2005). Haploinsufficiency of *MAPT* has never been reported in humans before (Koolen et al., 2006). Interestingly, in mice lacking the *Tau/Mapt* gene (Harada et al., 1994), muscle weakness, hyperactivity in a novel environment and impairment of contextual fear conditioning were found (Ikegami et al., 2000), in parallel to the motor developmental defect and learning disability observed in del(17)(q21.31) patients (Koolen et al., 2006; Shaw-Smith et al., 2006). These data render a possible role of *MAPT* in the pathomechanisms underlying this new genomic disorder microdeletion 17q21.31.

The deletions in 17q21.31 always occur de novo; their breakpoints were mapped in large flanking LCR blocks of highly complex structure (Koolen et al., 2006; Sharp et al., 2006; Shaw-Smith et al., 2006). Two major haplotypes named H1 and H2 exist for this region (Stefansson et al., 2005). The H2 lineage harbors a 900 kb inversion covering the 17q21.31 deletion region and is under positive selection in European populations, where it has a frequency of 20%. One of the profound differences between these two haplotypes is that the inversion places the two LCRs directly mediating the 17q21.31 deletions in the same orientation and thus facilitates/enables the NAHR rearrangements (Stankiewicz and Lupski, 2002) which delete the flanked interval (Lupski, 2006; Sharp et al., 2006). Indeed, haploype analyses in all three reports found that the transmitting parent of the deletion patient obligatorily carries either H1/H2 heterozygote or H2/H2 homozygote genotype. No transmitting parent without the H2 haplotype has ever been identified.

Interestingly, a duplication of the critical region deleted in the 17q21.31 deletion syndrome has also been identified in a girl with severe psychomotor developmental delay and dysmorphic craniofacial features (Kirchhoff et al., 2007b). Like the transmitting parents of the deletion patients, the transmitting father of this girl also carries the H2 haplotype (H1/H2 heterozygote) (Kirchhoff et al., 2007b). It would be very interesting to compare the phenotype of the duplication patients with the patients carrying isolated gain-of-

function mutations in *MAPT* in detail, to evaluate the contribution of *MAPT* to the duplication phenotypes. However, this comparison would be much more informative after more duplication patients are described and more precise knowledge can be gained about the phenotypic manifestation of the 17q21.31 duplication.

15q13.3 microdeletion syndrome

Using their BAC array specifically designed to interrogate genome-wide 130 NAHR candidate sites flanked by LCRs (Sharp et al., 2005, 2006), Sharp et al. (2008) identified another new genomic disorder, the microdeletion syndrome 15q13.3 (MIM612001), which is associated with mild to moderate mental retardation, seizure and/or abnormal EEG findings, mild and variable facial and digital dysmorphism. The recurrent deletion is 1.5 Mb long and encompasses six genes. The proximal and distal breakpoints of the deletions are localized in two large LCR/SD blocks designated BP4 and BP5, respectively (Sharp et al., 2008). These data, and the apparent recurrent nature of the deletions both suggest that these deletions in 15q13.3 are caused by NAHR mediated by BP4 and BP5.

Although the genomic localization of the deleted region is adjacent to the common deletion region in Prader-Willi syndrome (PWS, MIM176270) and Angelman syndrome (AS, MIM105830), none of the six included genes is known to be imprinted (Sharp et al., 2008). One of these genes, *CHRNA7* (cholinergic receptor, neuronal nicotinic, alpha polypeptide 7), encodes the alpha7 subunit of an ion channel, nicotinic acetylcholine receptor, that mediates neuronal signal transmission (Berg and Conroy, 2002). *CHRNA7* has been an interesting candidate gene for genetic epilepsies for many years; it is the paralogue of *CHRNA4*, the first gene ever found to be mutated in an idiopathic epilepsy syndrome, autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE, MIM600513) (Steinlein et al., 1995). Mutations in the gene coding for another subunit of the nicotinic acetylcholine receptors, *CHRNA2* (De Fusco et al., 2000; Phillips et al., 2001) and another paralogue of *CHRNA7*, *CHRNA2* (Aridon et al., 2006), were also found to cause epilepsy syndromes. Linkage studies pinpointed *CHRNA7* as a possible susceptibility factor for both juvenile myoclonic epilepsy type 2 (EJM2, MIM604827) (Elmslie et al., 1997) and benign epilepsy of childhood with centrotemporal spikes (MIM 117100) (Neubauer et al., 1997). Furthermore, knockout mice lacking *Chrna7* show a hypersynchronous neocortical EEG phenotype (Orr-Urtreger et al., 1997). However, pathological point mutations of *CHRNA7* have not been found in any epilepsy syndromes (Taske et al., 2002; Ortrud Steinlein, personal communication). The finding of the microdeletion 15q13.3 syndrome now sheds new light onto *CHRNA7* and its possible role in epileptogenesis. Interestingly, a partial pseudogene of *CHRNA7*, *CHRFAM7A* is located less than 2 Mb away (Steinlein and Bertrand, 2008), not only adding difficulties to mutational analyses of *CHRNA7*, but also rendering the genomic archi-

tecture of this locus even more complex, as these two genes *CHRNA7* and *CHRFAM7A* can function as substrates for NAHR themselves.

Theoretically, the occurrence of the reciprocal duplication can be mostly expected for the region undergoing an NAHR-mediated recurrent deletion (Stankiewicz and Lupski, 2002). Indeed, Sharp et al. identified an apparent reciprocal duplication of the 1.5 Mb deletion in a healthy control individual, indicating that the increased copy number of the critical genes in this region may not affect the neuronal system in a way as dramatic as the decreased copy number (Sharp et al., 2008). Interestingly, the LCR/SDs in the two NAHR-mediating LCR blocks BP4 and BP5 have inverted orientation in the draft sequence of the UCSC sequence browser (www.genome.ucsc.edu). According to the mechanisms of NAHR (Lupski, 1998; Stankiewicz and Lupski, 2002), there is probably also an inverted haplotype in this region, which would place BP4 and BP5 into the same orientation and facilitate the NAHR rearrangements. Indeed, this inversion was found in the transmitting progenitors of both 15q13.3 microdeletion carrying patients whose parent of origin could be determined. Further investigations are still needed for a statistically relevant conclusion because of the high frequency of this inversion in the normal population.

Conclusions

Since the 1998 review that coined and defined the term genomic disorders (Lupski, 1998), a multitude of genomic disorders caused by genomic rearrangements instead of the traditional Watson-Crick base pair changes have been identified. Many of these disorders are due to altered gene dosage, or copy number variation (CNV), of one or more dosage-sensitive genes inside the rearranged region. The recent development of new techniques such as array-CGH to observe the rearrangements and their breakpoints with a higher resolution have greatly facilitated and catalyzed the identification and characterization of CNVs and novel genomic disorders; they have also yielded insights into molecular mechanisms for the rearrangements as well as the biological nature of the dosage-sensitivity of the rearranged regions which result in diseases (reviewed by Lupski and Stankiewicz, 2005; Emanuel and Saitta, 2007; Stankiewicz and Beaudet, 2007; Gu et al., 2008).

In this review, we summarized some of the most recently defined genomic disorders affecting the nervous system. These disorders can be neurodevelopmental (as WBS and the reciprocal duplication), neurodegenerative (as ADLD), or neuropsychiatric diseases (as autism; Sebat et al., 2007; Kumar et al., 2008; Weiss et al., 2008; and schizophrenia: Lupski, 2008; Stefansson et al., 2008; The International Schizophrenia Consortium, 2008; Walsh et al., 2008; Xu et al., 2008) which are described elsewhere in this issue). From the rearrangement point of view, CNV-based genomic disorders could be due to duplication, deletion or sometimes complex rearrangements including both events in different

genomic segments (Lee et al., 2007). The mechanisms underlying these pathological rearrangements, as for any other genomic rearrangements, can be NAHR, NHEJ or FoSTeS (Lupski and Stankiewicz, 2005; Lee et al., 2007; Gu et al., 2008). Not many publications have reported NHEJ or FoSTeS as the presumptive mechanism underlying a pathological rearrangement, which is partially because the characteristics of NHEJ and FoSTeS are not resolved by many traditional techniques and are not yet as well known among the geneticists as NAHR and are often not recognized, as in the case of the atypical nonrecurrent deletions in WBS described in the first part of this review. High resolution genome analysis tools and direct sequencing of breakpoints are often required to reveal complex rearrangements. We expect to see more NHEJ- or FoSTeS-mediated pathological rearrangements reported in the future, especially in the analyses of the 'atypical' or nonrecurrent rearrangements.

It should be emphasized that the identification of a new genomic disorder is by no means accomplished after the original finding of overlapping genomic rearrangements and common phenotypes at a certain genomic locus. The reciprocal duplications to the Smith-Magenis Syndrome deletions were already described by Potocki et al. (2000) as a new genomic disorder identified in seven individuals in 2000, but it was not until 2007 that the same group and their collaborators have recruited more patients and performed comprehensive, multidisciplinary clinical and molecular analyses on 35 patients bearing this duplication, thus giving the first comprehensive clinical description of this disorder, now named the Potocki-Lupski syndrome (PTLS, MIM610883) (Potocki et al., 2007). The clinical data refined the key phenotypes of PTLS, which include infantile hypotonia, failure to thrive, mild to moderate mental retardation and autism spectrum disorders. It was not until this comprehensive clinical study with 35 patients that the autistic features and structural cardiovascular anomalies were also

identified to be among the key manifestations of PTLS. The number of patients and the state-of-art array CGH technique also enabled the precise mapping of the rearrangements and further delineations of the phenotypes, which narrowed down the critical region of PTLS to a 1.3 Mb region containing *RAI1*, the critical dosage-sensitive gene for SMS (Slager et al., 2003; Bi et al., 2004, 2006; Girirajan et al., 2005). We look forward to similar developments in the research of all newly defined genomic disorders, to the new clinical and biological insight that the future studies of these disorders will bring us.

For many genomic disorders with distinct abnormalities, the reciprocal rearrangements have partially milder phenotypes (such as the facial dysmorphism in the reciprocal duplication of the WBS) or a reduced penetrance (as in the reciprocal duplication of the WBS deletion and the microdeletion 15q13.3 syndrome), implicating that dosage sensitivity does not always apply for both increased or decreased dosage of the same gene. In some other cases, the reciprocal rearrangements have partially opposite or reciprocal endophenotype (as the difference in the speech vs. visuospatial development between WBS and dup(7)(q11.23) syndrome), indicating a quantitative read out system downstream of a critical gene. There are also instances when duplications and deletions involving the same gene manifest similar phenotypes, although through completely different molecular pathways, as in deletions and duplications of *MECP2*. Whether and how too much or too little gene product will be recognized and/or tolerated by the organism is not a trivial fact, it reflects the function and regulation of an individual gene and the pathways in which it is involved. Careful analysis and comparison of the phenotypes of reciprocal genomic disorders/conditions would thus likely provide interesting insight into the biology of the genes underlying their pathomechanisms.

References

- Aridon P, Marini C, Di Resta C, Brilli E, De Fusco M, et al: Increased sensitivity of the neuronal nicotinic receptor alpha 2 subunit causes familial epilepsy with nocturnal wandering and ictal fear. *Am J Hum Genet* 79:342–350 (2006).
- Babcock M, Pavlicek A, Spiteri E, Kashork CD, Ioshikhes I, et al: Shuffling of genes within low-copy repeats on 22q11 (LCR22) by *Alu*-mediated recombination events during evolution. *Genome Res* 13:2519–2532 (2003).
- Bauters M, Van Esch H, Friez MJ, Boespflug-Tanguy O, Zenker M, et al: Nonrecurrent *MECP2* duplications mediated by genomic architecture-driven DNA breaks and break-induced replication repair. *Genome Res* 18:847–858 (2008).
- Bayes M, Magano LF, Rivera N, Flores R, Perez Jurado LA: Mutational mechanisms of Williams-Beuren syndrome deletions. *Am J Hum Genet* 73:131–151 (2003).
- Berg DK, Conroy WG: Nicotinic alpha 7 receptors: Synaptic options and downstream signaling in neurons. *J Neurobiol* 53:512–523 (2002).
- Berg JS, Brunetti-Pierri N, Peters SU, Kang SH, Fong CT, et al: Speech delay and autism spectrum behaviors are frequently associated with duplication of the 7q11.23 Williams-Beuren syndrome region. *Genet Med* 9:427–441 (2007).
- Bi W, Saifi GM, Shaw CJ, Walz K, Fonseca P, et al: Mutations of *RAI1*, a PHD-containing protein, in nondeletion patients with Smith-Magenis syndrome. *Hum Genet* 115:515–524 (2004).
- Bi W, Saifi GM, Girirajan S, Shi X, Szomju B, et al: *RAI1* point mutations, CAG repeat variation, and SNP analysis in non-deletion Smith-Magenis syndrome. *Am J Med Genet A* 140:2454–2463 (2006).
- Bi W, Sapir T, Shchelochkov OA, Zhang F, Withers MA, et al: Increased *LIS1* expression affects human and mouse brain development. *Nat Genet*, Epub ahead of print (2008).
- Botta A, Novelli G, Mari A, Novelli A, Sabani M, et al: 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 (1999).
- Brown RT, Polinsky RJ, Schwankhaus J, Eldridge R, McFarland H, et al: Adrenergic dysfunction in hereditary adult-onset leukodystrophy. *Neurology* 37:1421–1424 (1987).
- Cardoso C, Leventer RJ, Ward HL, Toyo-Oka K, Chung J, et al: Refinement of a 400-kb critical region allows genotypic differentiation between isolated lissencephaly, Miller-Dieker syndrome, and other phenotypes secondary to deletions of 17p13.3. *Am J Hum Genet* 72:918–930 (2003).
- Chabchoub E, de Ravel T, Thoelen R, Vermeesch JR, Frysns JP, Van Esch H: Detection of an unusual 17p13.3 microdeletion by array comparative genomic hybridisation in a patient with lissencephaly. *Clin Genet* 70:535–537 (2006).

- Chahrouh M, Jung SY, Shaw C, Zhou X, Wong ST, et al: *MeCP2*, a key contributor to neurological disease, activates and represses transcription. *Science* 320:1224–1229 (2008).
- Coffeen CM, McKenna CE, Koeppe AH, Plaster NM, Maragakis N, et al: Genetic localization of an autosomal dominant leukodystrophy mimicking chronic progressive multiple sclerosis to chromosome 5q31. *Hum Mol Genet* 9:787–793 (2000).
- Cohen D, Lazar G, Couvert P, Desportes V, Lippe D, et al: *MECP2* mutation in a boy with language disorder and schizophrenia. *Am J Psychiatry* 159:148–149 (2002).
- Cusco I, Corominas R, Bayes M, Flores R, Rivera-Brugues N, et al: Copy number variation at the 7q11.23 segmental duplications is a susceptibility factor for the Williams-Beuren syndrome deletion. *Genome Res* 18:683–694 (2008).
- D'Souza I, Poorkaj P, Hong M, Nochlin D, Lee VM, et al: Missense and silent tau gene mutations cause frontotemporal dementia with Parkinsonism-chromosome 17 type, by affecting multiple alternative RNA splicing regulatory elements. *Proc Natl Acad Sci USA* 96:5598–5603 (1999).
- De Fusco M, Becchetti A, Patrignani A, Annesi G, Gambardella A, et al: The nicotinic receptor beta 2 subunit is mutant in nocturnal frontal lobe epilepsy. *Nat Genet* 26:275–276 (2000).
- del Gaudio D, Fang P, Scaglia F, Ward PA, Craigen WJ, et al: Increased *MECP2* gene copy number as the result of genomic duplication in neurodevelopmentally delayed males. *Genet Med* 8:784–792 (2006).
- Depienne C, Heron D, Betancur C, Benyahia B, Trouillard O, et al: Autism, language delay and mental retardation in a patient with 7q11 duplication. *J Med Genet* 44:452–458 (2007).
- Dobyns WB, Curry CJ, Hoyne HE, Turlington L, Ledbetter DH: Clinical and molecular diagnosis of Miller-Dieker syndrome. *Am J Hum Genet* 48:584–594 (1991).
- Elmslie FV, Rees M, Williamson MP, Kerr M, Kjeldsen MJ, et al: Genetic mapping of a major susceptibility locus for juvenile myoclonic epilepsy on chromosome 15q. *Hum Mol Genet* 6:1329–1334 (1997).
- Emanuel BS, Saitta SC: From microscopes to microarrays: Dissecting recurrent chromosomal rearrangements. *Nat Rev Genet* 8:869–883 (2007).
- Fisher SE: On genes, speech, and language. *N Engl J Med* 353:1655–1657 (2005).
- Flores M, Morales L, Gonzaga-Jauregui C, Dominguez-Vidana R, Zepeda C, et al: Recurrent DNA inversion rearrangements in the human genome. *Proc Natl Acad Sci USA* 104:6099–6106 (2007).
- Friez MJ, Jones JR, Clarkson K, Lubs H, Abuelo D, et al: Recurrent infections, hypotonia, and mental retardation caused by duplication of *MECP2* and adjacent region in Xq28. *Pediatrics* 118:e1687–1695 (2006).
- Gagliardi C, Bonaglia MC, Selicorni A, Borgatti R, Giorda R: Unusual cognitive and behavioural profile in a Williams syndrome patient with atypical 7q11.23 deletion. *J Med Genet* 40:526–530 (2003).
- Girirajan S, Elsas LJ, 2nd, Devriendt K, Elsea SH: *RAI1* variations in Smith-Magenis syndrome patients without 17p11.2 deletions. *J Med Genet* 42:820–828 (2005).
- Greenberg F: Williams syndrome professional symposium. *Am J Hum Genet* 6:85–88 (1990).
- Gu W, Zhang F, Lupski JR: Mechanisms for human genomic rearrangements. *Pathogenetics* 1:4 (2008).
- Harada A, Oguchi K, Okabe S, Kuno J, Terada S, et al: Altered microtubule organization in small-calibre axons of mice lacking tau protein. *Nature* 369:488–491 (1994).
- Harborth J, Elbashir SM, Bechert K, Tuschl T, Weber K: Identification of essential genes in cultured mammalian cells using small interfering RNAs. *J Cell Sci* 114:4557–4565 (2001).
- Hardwick SA, Reuter K, Williamson SL, Vasudevan V, Donald J, et al: Delineation of large deletions of the *MECP2* gene in Rett syndrome patients, including a familial case with a male proband. *Eur J Hum Genet* 15:1218–1229 (2007).
- Hattori M, Adachi H, Tsujimoto M, Arai H, Inoue K: Miller-Dieker lissencephaly gene encodes a subunit of brain platelet-activating factor acetylhydrolase [corrected]. *Nature* 370:216–218 (1994).
- Heller R, Rauch A, Luttgens S, Schroder B, Winterpacht A: Partial deletion of the critical 1.5 Mb interval in Williams-Beuren syndrome. *J Med Genet* 40:e99 (2003).
- Howald C, Merla G, Digilio MC, Amenta S, Lyle R, et al: Two high throughput technologies to detect segmental aneuploidies identify new Williams-Beuren syndrome patients with atypical deletions. *J Med Genet* 43:266–273 (2006).
- Hutton M, Lendon CL, Rizzu P, Baker M, Froelich S, et al: Association of missense and 5'-splice-site mutations in *tau* with the inherited dementia FTDP-17. *Nature* 393:702–705 (1998).
- Ikegami S, Harada A, Hirokawa N: Muscle weakness, hyperactivity, and impairment in fear conditioning in tau-deficient mice. *Neurosci Lett* 279:129–132 (2000).
- Inoue K: *PLP1*-related inherited demyelinating disorders: Pelizaeus-Merzbacher disease and spastic paraplegia type 2. *Neurogenetics* 6:1–16 (2005).
- Inoue K, Osaka H, Thurston VC, Clarke JT, Yoneyama A, et al: Genomic rearrangements resulting in *PLP1* deletion occur by nonhomologous end joining and cause different demyelinating phenotypes in males and females. *Am J Hum Genet* 71:838–853 (2002).
- Ji JY, Lee RT, Vergnes L, Fong LG, Stewart CL, et al: Cell nuclei spin in the absence of lamin B1. *J Biol Chem* 282:20015–20026 (2007).
- Karmiloff-Smith A, Grant J, Ewing S, Carette MJ, Metcalfe K, et al: Using case study comparisons to explore genotype-phenotype correlations in Williams-Beuren syndrome. *J Med Genet* 40:136–140 (2003).
- Khalifa MM, MacLeod PM, Duncan AM: Additional case of de novo interstitial deletion del(17)(q21.3q23) and expansion of the phenotype. *Clin Genet* 44:258–261 (1993).
- Kidd JM, Cooper GM, Donahue WF, Hayden HS, Sampas N, et al: Mapping and sequencing of structural variation from eight human genomes. *Nature* 453:56–64 (2008).
- Kirchhoff M, Bisgaard AM, Bryndorf T, Gerdes T: 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 (2007a).
- Kirchhoff M, Bisgaard AM, Duno M, Hansen FJ, Schwartz M: A 17q21.31 microduplication, reciprocal to the newly described 17q21.31 microdeletion, in a girl with severe psychomotor developmental delay and dysmorphic craniofacial features. *Eur J Med Genet* 50:256–263 (2007b).
- Kjarland E, Keen TJ, Kleppe R: Does isoform diversity explain functional differences in the 14-3-3 protein family? *Curr Pharm Biotechnol* 7:217–223 (2006).
- Kleefstra T, Yntema HG, Oudakker AR, Romein T, Sijdermans E, et al: De novo *MECP2* frameshift mutation in a boy with moderate mental retardation, obesity and gynaecomastia. *Clin Genet* 61:359–362 (2002).
- Koolen DA, Vissers LE, Pfundt R, de Leeuw N, Knight SJ, et al: A new chromosome 17q21.31 microdeletion syndrome associated with a common inversion polymorphism. *Nat Genet* 38:999–1001 (2006).
- Koolen DA, Sharp AJ, Hurst JA, Firth HV, Knight SJ, et al: Clinical and molecular delineation of the 17q21.31 microdeletion syndrome. *J Med Genet* 45:710–720 (2008).
- Korbel JO, Urban AE, Affourtit JP, Godwin B, Grubert F, et al: Paired-end mapping reveals extensive structural variation in the human genome. *Science* 318:420–426 (2007).
- Korenberg JR, Chen XN, Hirota H, Lai Z, Bellugi U, et al: VI. Genome structure and cognitive map of Williams syndrome. *J Cogn Neurosci* 12 Suppl 1:89–107 (2000).
- Kriek M, White SJ, Szuhai K, Knijnenburg J, van Ommen GJ, et al: 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 (2006).
- Kumar RA, KaraMohamed S, Sudi J, Conrad DF, Brune C, et al: Recurrent 16p11.2 microdeletions in autism. *Hum Mol Genet* 17:628–638 (2008).
- Laccone F, Junemann I, Whately S, Morgan R, Butler R, et al: Large deletions of the *MECP2* gene detected by gene dosage analysis in patients with Rett syndrome. *Hum Mutat* 23:234–244 (2004).
- Lee JA, Lupski JR: Genomic rearrangements and gene copy-number alterations as a cause of nervous system disorders. *Neuron* 52:103–121 (2006).
- Lee JA, Inoue K, Cheung SW, Shaw CA, Stankiewicz P, Lupski JR: Role of genomic architecture in *PLP1* duplication causing Pelizaeus-Merzbacher disease. *Hum Mol Genet* 15:2250–2265 (2006).
- Lee JA, Carvalho CM, Lupski JR: A DNA replication mechanism for generating nonrecurrent rearrangements associated with genomic disorders. *Cell* 131:1235–1247 (2007).
- Liu J, Rolef Ben-Shahar T, Riemer D, Treinin M, Spann P, et al: Essential roles for *Caenorhabditis elegans* lamin gene in nuclear organization, cell cycle progression, and spatial organization of nuclear pore complexes. *Mol Biol Cell* 11:3937–3947 (2000).
- Lupski JR: Genomic disorders: Structural features of the genome can lead to DNA rearrangements and human disease traits. *Trends Genet* 14:417–422 (1998).
- Lupski JR: Genome structural variation and sporadic disease traits. *Nat Genet* 38:974–976 (2006).
- Lupski JR: Schizophrenia: Incriminating genomic evidence. *Nature* 455:178–179 (2008).
- Lupski JR, Stankiewicz P: Genomic disorders: Molecular mechanisms for rearrangements and conveyed phenotypes. *PLoS Genet* 1:e49 (2005).
- Lupski JR, de Oca-Luna RM, Slaugenhaupt S, Pentao L, Guzzetta V, et al: DNA duplication associated with Charcot-Marie-Tooth disease type 1A. *Cell* 66:219–232 (1991).

- Marklund L, Melin M, Melberg A, Giedraitis V, Dahl N: Adult-onset autosomal dominant leukodystrophy with autistic symptoms restricted to 1.5 Mbp on chromosome 5q23. *Am J Med Genet B Neuropsychiatr Genet* 141:608–614 (2006).
- Mei D, Lewis R, Parrini E, Lazarou LP, Marini C, et al: High frequency of genomic deletions and duplication in the *LISI* gene in lissencephaly: Implications for molecular diagnosis. *J Med Genet* 45:355–361 (2008).
- Meins M, Lehmann J, Gerresheim F, Herchenbach J, Hagedorn M, et al: Submicroscopic duplication in Xq28 causes increased expression of the *MECP2* gene in a boy with severe mental retardation and features of Rett syndrome. *J Med Genet* 42:e12 (2005).
- Meloni I, Bruttini M, Longo I, Mari F, Rizzolio F, et al: A mutation in the Rett syndrome gene, *MECP2*, causes X-linked mental retardation and progressive spasticity in males. *Am J Hum Genet* 67:982–985 (2000).
- Merritt JL, Lindor NM: Further clinical description of duplication of Williams-Beuren region presenting with congenital glaucoma and brachycephaly. *Am J Med Genet A* 146A:1055–1058 (2008).
- Mervis CB, Klein-Tasman BP: Williams syndrome: Cognition, personality, and adaptive behavior. *Ment Retard Dev Disabil Res Rev* 6:148–158 (2000).
- Moretti P, Zoghbi HY: MeCP2 dysfunction in Rett syndrome and related disorders. *Curr Opin Genet Dev* 16:276–281 (2006).
- Morris CA, Mervis CB: Williams syndrome and related disorders. *Annu Rev Genomics Hum Genet* 1:461–484 (2000).
- Myers AJ, Kaleem M, Marlowe L, Pittman AM, Lees AJ, et al: The H1c haplotype at the *MAPT* locus is associated with Alzheimer's disease. *Hum Mol Genet* 14:2399–2404 (2005).
- Neubauer BA, Moises HW, Lassker U, Waltz S, Diebold U, Stephani U: Benign childhood epilepsy with centrotemporal spikes and electroencephalography trait are not linked to EBN1 and EBN2 of benign neonatal familial convulsions. *Epilepsia* 38:782–787 (1997).
- Orellana C, Bernabeu J, Monfort S, Rosello M, Oltra S, et al: Duplication of the Williams-Beuren critical region: Case report and further delineation of the phenotypic spectrum. *J Med Genet* 45:187–189 (2008).
- Orr-Urtreger A, Goldner FM, Saeki M, Lorenzo I, Goldberg L, et al: Mice deficient in the alpha7 neuronal nicotinic acetylcholine receptor lack alpha-bungarotoxin binding sites and hippocampal fast nicotinic currents. *J Neurosci* 17:9165–9171 (1997).
- Osborne LR: Williams-Beuren syndrome: Unraveling the mysteries of a microdeletion disorder. *Mol Genet Metab* 67:1–10 (1999).
- Osborne LR, Li M, Pober B, Chitayat D, Bodurtha J, et al: A 1.5 million-base pair inversion polymorphism in families with Williams-Beuren syndrome. *Nat Genet* 29:321–325 (2001).
- Padiath QS, Saigoh K, Schiffmann R, Asahara H, Yamada T, et al: Lamin B1 duplications cause autosomal dominant leukodystrophy. *Nat Genet* 38:1114–1123 (2006).
- Pan H, Li MR, Nelson P, Bao XH, Wu XR, Yu S: Large deletions of the *MECP2* gene in Chinese patients with classical Rett syndrome. *Clin Genet* 70:418–419 (2006).
- Park JP, Moeschler JB, Berg SZ, Bauer RM, Wurster-Hill DH: A unique de novo interstitial deletion del(17)(q21.3q23) in a phenotypically abnormal infant. *Clin Genet* 41:54–56 (1992).
- Phillips HA, Favre I, Kirkpatrick M, Zuberi SM, Goudie D, et al: *CHRNA2* is the second acetylcholine receptor subunit associated with autosomal dominant nocturnal frontal lobe epilepsy. *Am J Hum Genet* 68:225–231 (2001).
- Pittman AM, Myers AJ, Abou-Sleiman P, Fung HC, Kaleem M, et al: Linkage disequilibrium fine mapping and haplotype association analysis of the *tau* gene in progressive supranuclear palsy and corticobasal degeneration. *J Med Genet* 42:837–846 (2005).
- Potocki L, Chen KS, Park SS, Osterholm DE, Withers MA, et al: Molecular mechanism for duplication 17p11.2 – the homologous recombination reciprocal of the Smith-Magenis microdeletion. *Nat Genet* 24:84–87 (2000).
- Potocki L, Bi W, Treadwell-Deering D, Carvalho CM, Eifert A, et al: 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 (2007).
- Rademakers R, Cruts M, van Broeckhoven C: The role of tau (*MAPT*) in frontotemporal dementia and related tauopathies. *Hum Mutat* 24:277–295 (2004).
- Raeymaekers P, Timmerman V, Nelis E, De Jonghe P, Hoogendijk JE, et al: Duplication in chromosome 17p11.2 in Charcot-Marie-Tooth neuropathy type 1a (CMT 1a). The HMSN Collaborative Research Group. *Neuromuscul Disord* 1:93–97 (1991).
- Ravn K, Nielsen JB, Skjeldal OH, Kerr A, Hulthen M, Schwartz M: Large genomic rearrangements in *MECP2*. *Hum Mutat* 25:324 (2005).
- Reiner O, Carrozzo R, Shen Y, Wehnert M, Faustinella F, et al: Isolation of a Miller-Dieker lissencephaly gene containing G protein beta-subunit-like repeats. *Nature* 364:717–721 (1993).
- Scala E, Longo I, Ottimo F, Speciale C, Sampieri K, et al: *MECP2* deletions and genotype-phenotype correlation in Rett syndrome. *Am J Med Genet A* 143A:2775–2784 (2007).
- Schollen E, Smeets E, Deflem E, Fryns JP, Matthijs G: Gross rearrangements in the *MECP2* gene in three patients with Rett syndrome: Implications for routine diagnosis of Rett syndrome. *Hum Mutat* 22:116–120 (2003).
- Schubert C, Laccone F: Williams-Beuren syndrome: Determination of deletion size using quantitative real-time PCR. *Int J Mol Med* 18:799–806 (2006).
- Schwankhaus JD, Patronas N, Dorwart R, Eldridge R, Schlesinger S, McFarland H: Computed tomography and magnetic resonance imaging in adult-onset leukodystrophy. *Arch Neurol* 45:1004–1008 (1988).
- Schwankhaus JD, Katz DA, Eldridge R, Schlesinger S, McFarland H: Clinical and pathological features of an autosomal dominant, adult-onset leukodystrophy simulating chronic progressive multiple sclerosis. *Arch Neurol* 51:757–766 (1994).
- Sebat J, Lakshmi B, Malhotra D, Troge J, Lese-Martin C, et al: Strong association of de novo copy number mutations with autism. *Science* 316:445–449 (2007).
- Sharp AJ, Locke DP, McGrath SD, Cheng Z, Bailey JA, et al: Segmental duplications and copy-number variation in the human genome. *Am J Hum Genet* 77:78–88 (2005).
- Sharp AJ, Hansen S, Selzer RR, Cheng Z, Regan R, et al: Discovery of previously unidentified genomic disorders from the duplication architecture of the human genome. *Nat Genet* 38:1038–1042 (2006).
- Sharp AJ, Mefford HC, Li K, Baker C, Skinner C, et al: A recurrent 15q13.3 microdeletion syndrome associated with mental retardation and seizures. *Nat Genet* 40:322–328 (2008).
- Shaw CJ, Lupski JR: Non-recurrent 17p11.2 deletions are generated by homologous and non-homologous mechanisms. *Hum Genet* 116:1–7 (2005).
- Shaw-Smith C, Pittman AM, Willatt L, Martin H, Rickman L, et al: Microdeletion encompassing *MAPT* at chromosome 17q21.3 is associated with developmental delay and learning disability. *Nat Genet* 38:1032–1037 (2006).
- Slager RE, Newton TL, Vlangos CN, Finucane B, Elsea SH: Mutations in *RAI1* associated with Smith-Magenis syndrome. *Nat Genet* 33:466–468 (2003).
- Somerville MJ, Mervis CB, Young EJ, Seo EJ, del Campo M, et al: Severe expressive-language delay related to duplication of the Williams-Beuren locus. *N Engl J Med* 353:1694–1701 (2005).
- Stankiewicz P, Beaudet AL: Use of array CGH in the evaluation of dysmorphology, malformations, developmental delay, and idiopathic mental retardation. *Curr Opin Genet Dev* 17:182–192 (2007).
- Stankiewicz P, Lupski JR: Genome architecture, rearrangements and genomic disorders. *Trends Genet* 18:74–82 (2002).
- Stankiewicz P, Shaw CJ, Dapper JD, Wakui K, Shaffer LG, et al: Genome architecture catalyzes nonrecurrent chromosomal rearrangements. *Am J Hum Genet* 72:1101–1116 (2003).
- Stefansson H, Helgason A, Thorleifsson G, Steinthorsdottir V, Masson G, et al: A common inversion under selection in Europeans. *Nat Genet* 37:129–137 (2005).
- Stefansson H, Rujescu D, Cichon S, Pietilainen OP, Ingason A, et al: Large recurrent microdeletions associated with schizophrenia. *Nature* 455:232–236 (2008).
- Steinlein OK, Bertrand D: Neuronal nicotinic acetylcholine receptors: From the genetic analysis to neurological diseases. *Biochem Pharmacol* 76:1175–1183 (2008).
- Steinlein OK, Mulley JC, Propping P, Wallace RH, Phillips HA, et al: A missense mutation in the neuronal nicotinic acetylcholine receptor alpha 4 subunit is associated with autosomal dominant nocturnal frontal lobe epilepsy. *Nat Genet* 11:201–203 (1995).
- Taske NL, Williamson MP, Makoff A, Bate L, Curtis D, et al: Evaluation of the positional candidate gene *CHRNA7* at the juvenile myoclonic epilepsy locus (*EJM2*) on chromosome 15q13-14. *Epilepsy Res* 49:157–172 (2002).
- Tassabehji M: Williams-Beuren syndrome: A challenge for genotype-phenotype correlations. *Hum Mol Genet* 12 Spec No 2:R229–237 (2003).
- Tassabehji M, Donnai D: Williams-Beuren syndrome: More or less? Segmental duplications and deletions in the Williams-Beuren syndrome region provide new insights into language development. *Eur J Hum Genet* 14:507–508 (2006).
- Tassabehji M, Metcalfe K, Karmiloff-Smith A, Carette MJ, Grant J, et al: Williams syndrome: Use of chromosomal microdeletions as a tool to dissect cognitive and physical phenotypes. *Am J Hum Genet* 64:118–125 (1999).
- Tassabehji M, Hammond P, Karmiloff-Smith A, Thompson P, Thorgerisson SS, et al: GTF2IRD1 in craniofacial development of humans and mice. *Science* 310:1184–1187 (2005).
- The International Schizophrenia Consortium: Rare chromosomal deletions and duplications increase risk of schizophrenia. *Nature* 455:237–241 (2008).

- Torniero C, Dalla Bernardina B, Novara F, Vetro A, Ricca I, et al: 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 (2007).
- Torniero C, Dalla Bernardina B, Novara F, Cerini R, Bonaglia C, et al: Dysmorphic features, simplified gyral pattern and 7q11.23 duplication reciprocal to the Williams-Beuren deletion. *Eur J Hum Genet* 16:880–887 (2008).
- Toyo-oka K, Shionoya A, Gambello MJ, Cardoso C, Leventer R, et al: 14-3-3epsilon is important for neuronal migration by binding to NUDEL: A molecular explanation for Miller-Dieker syndrome. *Nat Genet* 34:274–285 (2003).
- Turner DJ, Miretti M, Rajan D, Fiegler H, Carter NP, et al: Germline rates of de novo meiotic deletions and duplications causing several genomic disorders. *Nat Genet* 40:90–95 (2008).
- Uyanik G, Morris-Rosendahl DJ, Stiegler J, Klappecki J, Gross C, et al: Location and type of mutation in the *LIS1* gene do not predict phenotypic severity. *Neurology* 69:442–447 (2007).
- Van Esch H, Bauters M, Ignatius J, Jansen M, Raynaud M, et al: Duplication of the *MECP2* region is a frequent cause of severe mental retardation and progressive neurological symptoms in males. *Am J Hum Genet* 77:442–453 (2005).
- Varela MC, Krepischi-Santos AC, Paz JA, Knijnenburg J, Szuhai K, et al: A 17q21.31 microdeletion encompassing the *MAPT* gene in a mentally impaired patient. *Cytogenet Genome Res* 114: 89–92 (2006).
- Vergnes L, Peterfy M, Bergo MO, Young SG, Reue K: Lamin B1 is required for mouse development and nuclear integrity. *Proc Natl Acad Sci USA* 101:10428–10433 (2004).
- Walsh T, McClellan JM, McCarthy SE, Addington AM, Pierce SB, et al: Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. *Science* 320:539–543 (2008).
- Weiss LA, Shen Y, Korn JM, Arking DE, Miller DT, et al: Association between microdeletion and microduplication at 16p11.2 and autism. *N Engl J Med* 358:667–675 (2008).
- Worman HJ, Bonne G: 'Laminopathies': A wide spectrum of human diseases. *Exp Cell Res* 313: 2121–2133 (2007).
- Wu YQ, Sutton DR, Nickerson E, Lupski JR, Potocki L, et al: Delineation of the common critical region in Williams syndrome and clinical correlation of growth, heart defects, ethnicity, and parental origin. *Am J Med Genet* 78:82–89 (1998).
- Wyshaw-Boris A: Lissencephaly and *LIS1*: Insights into the molecular mechanisms of neuronal migration and development. *Clin Genet* 72: 296–304 (2007).
- Xu B, Roos JL, Levy S, van Rensburg EJ, Gogos JA, Karayiorgou M: Strong association of de novo copy number mutations with sporadic schizophrenia. *Nat Genet* 40:880–885 (2008).
- Zeev BB, Yaron Y, Schanen NC, Wolf H, Brandt N, et al: Rett syndrome: Clinical manifestations in males with *MECP2* mutations. *J Child Neurol* 17:20–24 (2002).