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REVIEW ARTICLE

Balanced translocations in mental retardation

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Abstract Over the past few decades, the knowledge on genetic defects causing mental retardation has dramatically increased. In this review, we discuss the importance of balanced chromosomal translocations in the identification of genes responsible for mental retardation. We present a database-search guided overview of balanced translocations identified in patients with mental retardation. We divide those in four categories: (1) balanced translocations that helped to identify a causative gene within a contiguous gene syndrome, (2) balanced translocations that led to the identification of a mental retardation gene confirmed by independent methods, (3) balanced translocations disrupting candidate genes that have not been confirmed by independent methods and (4) balanced translocations not reported to disrupt protein coding sequences. It can safely be concluded that balanced translocations have been instrumental in the identification of multiple genes that are involved in mental retardation. In addition, many more candidate genes were identified with a suspected but (as yet?) unconfirmed role in mental retardation. Some balanced translocations do not disrupt a protein coding gene and it can be speculated that in the light of recent findings concerning ncRNA's and ultra-conserved regions, such findings are worth further investigation as these potentially may lead us to the discovery of novel disease mechanisms.

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Introduction

Mental retardation is predominantly characterized by an overall intelligence coefficient (IQ) under 70 (Luckasson et al. 2002). It is a common, lifelong disorder, with an estimated frequency of 1–3% of the human population (Leonard and Wen 2002; Roeleveld et al. 1997; WHO 2001). Approximately 0.4% of the population is reported to be moderate/severely handicapped with an IQ < 50. The cause of the mental handicap remains unknown in at least half of the cases. Since genetic causes attributes to about half of the known aetiologies, it is generally believed that about 50% of all mental retardation cases have a genetic origin (Curry et al. 1997; Stevenson et al. 2003; Winnepenninckx et al. 2003). Mutations in several genes have been reported to cause mental retardation, but it has been estimated that the disruption of thousands of different genes may result in mental retardation and the great majority of those are unknown as yet (Ropers 2007).

With the exception of families showing X-linked or recessive inheritance, familial clustering is relatively rare in mental retardation pedigrees due to the fact that patients seldom reproduce. Linkage studies that have been so helpful in providing candidate regions to look for disease genes in other types of disorders are therefore rarely feasible in mental retardation research. In order to identify novel genes, we are thus dependent on other hints where to look for disease genes in the genome. One of those leads are balanced translocations, the product of a recombination event between two chromosomes, without loss of any chromosomal material (Fig. 1). These have been postulated to play a causative role in mental retardation disorders a long time ago (Breg et al. 1972), a hypothesis that has been verified by subsequent studies (Jacobs 1974). Balanced translocations are found as de novo events in 1/2,000 live births and

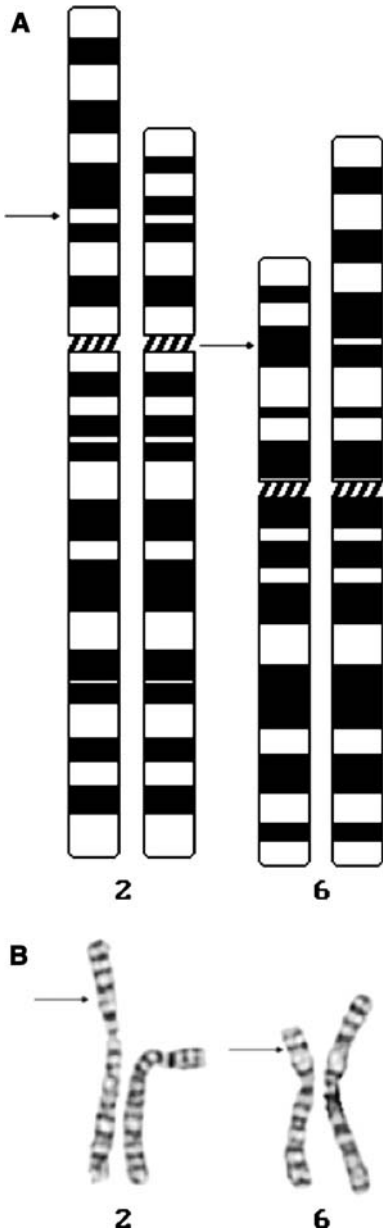

Fig. 1 A balanced t(2;6)(p15;p22.3). Translocation breakpoints are indicated by *black arrows*. Normal Chromosomes are on the left, derivatives on the *right*

are associated with a two- to three-fold increase in risk of inborn abnormalities (Warburton 1991). There are no recent reports on the frequency of balanced translocations in the mentally handicapped, but in one study from 1977, 7 balanced de novo translocations were found in a population of 455 handicapped patients, suggesting that a balanced translocation is responsible for 1.5% of cases of mental retardation (Funderburk et al. 1977). This frequency is in line with a second study reporting that 41 out of 153 balanced translocations were associated with MR and/or congenital malformations (Fryns et al. 1986). A translocation may disrupt a single gene only, and identification of the disrupted sequences may point to a candidate mental retardation gene. A number of genes have been cloned after analysis of such breakpoints in carriers of a balanced translocation (listed in Tables 1a, b, 2). Seemingly contradictory, many balanced translocations have been cloned where no conclusive evidence on the role of the disrupted gene in the aetiology of mental retardation could be obtained or where no gene has been identified at any of the breakpoints (listed in Tables 3, 4).

The aim of this review is to highlight the importance of balanced, gene disrupting translocations in the identification of mental retardation genes. To achieve this, a restrictive search was performed on three major databases of genetic diseases. The Decipher database collects clinical information about submicroscopic imbalances, such as microdeletions, microduplications, microinversions and translocations. The database was accessed on 26 March 2008 and referenced literature for the described syndromes were screened at that time for description of cases with mental retardation and balanced translocations. The term "developmental delay" was intentionally left out of the criteria, because of the much broader definition compared to "mental retardation". The "Online Mendelian Inheritance In Men" database, provided by NCBI, contains descriptions and research history on most known genetic diseases in humans. It was queried on 24 April 2008 for the terms 'mental retardation' AND 'translocation'. The resulting 230 hits were screened for relevance and redundancy. As a final repository of cytogenetic information, the 'Mendelian Cytogenetics Network Online Database' (MCNdb) was accessed on 12 May 2008. With 'Mental Retardation' as criterion, 95 entries were retrieved, out of which the de novo, simple balanced translocations were retained. In addition, a few recent individual studies that were not retrieved were included. All cases thus identified are listed in Tables 1, 2, 3, and 4, where multiple translocations through the same gene have been grouped.

Results

A total of 92 individual balanced translocations in patients with a mental handicap were identified. Based on the phenotypic information provided, the cases were split into four categories. A first category was created of patients with a balanced translocation localized within regions of known microdeletion syndromes (Table 1a, b). A second category consists of balanced translocations that led to the unambiguous identification of mental retardation genes, as confirmed by independent methods (Table 2). A third category was created for balanced translocations where candidate genes have been identified at the breakpoints, but where the role of

Table 1 (a) Genes confirmed to be causative for (part of) a microdeletion syndrome phenotype, identified through balanced translocations, (b) Genes not confirmed by mutations, thought to be causative for (part of) a microdeletion syndrome phenotype, identified through balanced translocations

Region	Gene	Translocations	Syndrome	Function	Publication	Confirmation
(a)						
2q22	ZEB2	t(2;11)(q22.2;q21)	Mowat–Wilson	Embryonic development of neural structures (ZNF)	Wakamatsu et al. (2001)	Wakamatsu et al. (2001)
5q35	NSD1	t(5;8)(q35;q24.1)	Sotos	Transcription regulation	Kurotaki et al. (2002)	Kurotaki et al. (2002)
9q34.3	EHMT1	t(X;9)(p11.23;q34.3)	Del(9qter)	Cellcycle g_0/g_1 transition	Kleefstra et al. (2005)	Kleefstra et al. (2006)
7q11.23	ELN	t(7;16)(q11.23;q13)	WB/SVAS	Component of elastic fibers	Duba et al. (2002)	Li et al. (1997)
16p13.2	CREBBP	t(2;16)(q36.3;p13.3)	Rubinstein–Taybi	Transcription regulation	Petrij et al. (2000); Petrij et al. (1995)	Petrij et al. (1995)

Region	Gene	Translocations	Syndrome	Function	Publication
(b)					
3p25	SRGAP3	t(X;3)(p22.1;p25)	Del(3pter)	Role in Slit-Robo signal transduction Pathway	Endris et al. (2002)
3p26.1	CALL	t(X;3)(p22.1;p26.3)		Neural cell adhesion (signal transduction)	Frints et al. (2003)
3p26.2-p26.3	CNTN4	t(3;10)(p26;q26)		Synaptogenesis	Fernandez et al. (2004)
15q12	HBII-85 C/D box snoRNA cluster	t(15;19)(q12;q13.41) t(4;15)(q27;q11.2) t(9;15)(q21;q12-13) t(X;15)(q28;q12) t(4;15)(q27;q11.2)	Prader–Willi	Several (e.g.,: site-specific modifications of ribosomal RNA's and snoRNA's by 2'-*O*-methylation)	Conroy et al. (1997; Kuslich et al. (1999); Schüle et al. (2005); Schulze et al. (1996); Sun et al. (1996); Wirth et al. (2001)
21q22.2	DYRK1A	t(9;21)(p12;q22) t(2;21)(q22;q22)	Partial monosomy 21	Protein kinase	Moller et al. (2008a)
22q11.2	CLTCL1	t(21;22)(p12;q11)	DiGeorge /VCFS	Major protein of coated pits	Holmes et al. (1997)
22q13.3	SHANK3	t(12;22)(q24.1;q13.3)	Del(22q13.3)	Structural protein of postsynaptic density	Bonaglia et al. (2001)

these genes in mental retardation has not been confirmed by independent methods (Table 3). Finally, balanced translocations in patients where no candidate genes were identified at the breakpoints remain as a fourth category (Table 4).

Balanced translocations pinpoint causative genes in contiguous gene syndromes

Microdeletion syndromes are caused by cytogenetically invisible deletions at specific positions in the genome. Classical examples of such mental retardation microdeletion syndromes include the Prader–Willi/Angelman Syndromes (del 15q11-q13), the DiGeorge/velocardiofacial Syndrome (del 22q11.2) and the Williams–Beuren Syndrome (del 7q11.23). On the genomic level, these recurrent deletions are often caused by non-allelic homologous recombination (NAHR) between nearly identical repeat blocks flanking the disease region. More recently, several new microdeletion syndromes have been identified as a result of the rapid development of whole genome copy number variation analysis platforms (Ballif et al. 2007; Koolen et al. 2006; Sharp et al. 2006, 2008; Shaw-Smith et al. 2006). Microdeletion syndromes near the telomeres are commonly referred to as subtelomeric disorders (de Vries et al. 2003). Subtelomeric deletions have the deletion of a series of genes in common with the remainder of the microdeletion syndromes, but the chromosome rearrangements are caused by much more diverse mechanisms and generally result in a more variable size of the deletion (Rooms et al. 2007). Balanced translocations have led to the identification of causative genes within some of the critical deletion regions (Table 1).

Prader–Willi is clinically associated with mental retardation, decreased foetal activity, neonatal hypotonia and feeding difficulties, hyperphagia with obesity, hypogonadism, short stature and small hands and feet (Sun et al. 1996). About 70% of PWS patients have a microdeletion of 3–4 Mb on the paternally derived chromosome 15q11.2 (maternal deletions result in Angelman Syndrome due to the fact that this chromosomal region is

Table 2 Confirmed mental retardation genes identified through balanced translocations

Region	Gene	Translocations	Phenotype	Function	Publication	Confirmation
7p13	GLI3	t(3;7)(p21.1;p13) t(6;7)(q27;p13)	GCPS/PHS	DNA-binding transcription factor in the S. Hedgehog pathway	Tommerup and Nielsen(1983) Kruger et al. (1989)	Johnston et al. (2005)
Xp11.22-21	SMC1A	t(X;8)(p11.2;q24.3)	X-linked Cornelia De Lange Syndrome	Mitosis/DNA-repair	Egemen et al. (2005)	Musio et al. (2006)
Xp11-p22.1	ZNF81	t(X;9)(p11.23;q34.3)	nsMRX	Down-regulates expression of chemokine receptor	Kleefstra et al. (2004a)	Kleefstra et al. (2004a)
Xp11.2	KIAA1202	t(X;8)(p11.2;p22.3) t(X;19)(p11.2;p13.3)	MR + others congenital abnormalities	Assembly of protein complexes at cell membrane, or remodelling of actin cytoskeleton	Hagens et al. (2006)	Hagens et al. (2006)
Xp11.3	ZNF41	t(X;7)(p11.3;q11.21)	nsMRX	Transcriptional regulation	Shoichet et al. (2003)	Shoichet et al. (2003)
Xp22.3	CDKL5	t(X;7)(p22.3;p15) t(X;6)(p22.3;q14	RTT/ISSX2	Protein kinase activity	Kalscheuer et al. (2003)	Tao et al. (2004; Weaving et al. (2004)
Xq11.4	TM4SF2	t(X;2)(p11.4;21.3)	nsMRX	Signal transduction in neurite outgrowth	Zemni et al. (2000)	Zemni et al. (2000)
Xq12	OPHN1	t(X;12)(q11;q15)	nsMRX	Rho hydrolysis/targets with functions in axons/dendrites outgrowth	Bienvenu et al. (1997) Billuart et al. (1998)	Billuart et al. (1998)
Xq22.3-q23	DCX	t(X;2)(q22;p21)	LISX1	Direct neuronal migration	Ross et al. (1997)	des Portes et al. (1998)
Xq24-q25	GRIA3	t(X;12)(q25;q15)	MR + seizures, bipolar disorder	Neurotransmitter receptor	Gecz et al. (1999)	Wu et al. (2007)
Xq26.1	OCRL1	t(X;3)(q25;q27)	Lowe oculo-cerebrorenal Syndrome	Actin polymerisation	Attree et al. (1992); Reilly et al. (1988)	Lin et al. (1997)
Xq26	ARHGEF6	t(X;21)(q26;p11)	nsMRX	Rho-dependent signalling	Kutsche et al. (2000)	Kutsche et al. (2000)

subject to genomic imprinting). Most of the remaining cases are due to maternal uniparental disomy, and a few sporadic cases have imprinting defects due to mutations in the imprinting centre.

No intact SNRP mRNA, a gene within the critical region, was detected in a patient with a de novo balanced translocation, and it was thus suggested that full mRNA was necessary for a normal phenotype (Sun et al. 1996) (Fig. 2). Since SNRP expression was unaffected in a second patient with a translocation just downstream of the SNRP-gene (Schulze et al. 1996), the focus of attention shifted downstream to IPW/PAR1, a gene that was silenced in this patient. Expression of SNURF/SNRP, consisting of the SNRP gene together with newly identified exons, extending the original transcript was detected in a translocation patient with PWS, but expression of IPW and PAR1 as well as a novel C/D box snoRNA were absent. Together with atypical microdeletions in this region, these findings put the C/D box snoRNA's forward as the main candidate (Wirth et al. 2001). Subsequently, the SNRPN locus was shown to consist of 148 exons, spanning from the imprinting centre 5′ of SNURF to the UBE3 gene. The transcript was shown to contain IPW as well as PAR1, besides several snoRNA's inside its introns. The snoRNA genes are present as two multi-snoRNA gene clusters (PWCR1/HBII-85 and HBII-52), three single-copy snoRNA genes (HBII-436/13/437) and two copies of an additional snoRNA gene (HBII-438A/B) (Runte et al. 2001).

Identification of this long and extremely complex transcribed region subsequently forced a re-evaluation of the previously described cases. The cases described by Conroy, Schulze, Wirth and Kuslich (after reassessment) were in accordance with a critical involvement of the snoRNA clusters, showing no expression of elements downstream of the

Table 3 Unconfirmed mental retardation genes at balanced translocation breakpoints

Region	Gene	Translocations	Phenotype	Function	Publication
1p22	NTNG1	t(1:7)(p22;q32)	Rett Syndrome	Axon guiding molecule	Borg et al. (2005)
2p24 9q32	ZNF 462 ASXL2	t(2;9)(p24;q32)	MR + absence of corpus callosum and ocular colobomas	Putative role in CNS development	Ramocki et al. (2003) Talisetti et al. (2003)
2q24.1	GPD2	t(2;7)(q24.1;q36.1)	nsMR	Mitochondrial glycerophosphate dehydrogenase	Daoud et al. (2009)
2q32	SATB2	t(2;7)(q32;p21) t(2;11)(q32;p14)	CPI	Transcription regulation (associated with CP, not with MR)	FitzPatrick et al. (2003)
4q21	JNK3	t(Y;4)(q11.2;q21)	Developmental epileptic encephalopathy	Role in neuronal differentiation and apoptosis	Shoichet et al. (2006)
5q31.1	CDKL3	t(X;5)(p11.1;q31.1)	Non specific MR	Protein kinase activity	Dubos et al. (2008)
6q21	SNX3	t(6;13)(q21;q12)	MCOPS8	Intracellular traffic	Vervoort et al. (2002)
6q22.3	TCBA1	t(1;6)(q32.2;q22.3)	MR + recurrent infections	Possible role in tumorigenesis	Yue et al. (2006)
7q11.2	AUTS2	t(7;20)(q11.2;p11.2) t(3;7)(p21.3;q11.2) t(7;11)(q11.2;p11) t(7;13)(q11.2;q22)	MR + autism, seizures, dismorfisms	Unknown	Sultana et al. (2002) Kalscheuer et al. (2007)
9p22	MLLT3	t(4;9)(q34;p22)	MR + dysmorphisms + epilepsy	Oncogene	Striano et al. (2005)
9p24.3	DOCK8	t(X;9)(q13.1;p24)	MR + dismorfisms, seizures, speech delay	GTP/GTPase binding/GEF	Griggs et al. (2008)
16p13	FOX1	t(14;16)(q32;p13.3) + inv(p13.3;p12.1) t(1;16)(q12;p13.2)	MR + autism, seizures, dismorfisms	ATXN2-binding (RNA-binding)	Bhalla et al. (2004)
19q13.1	PAFAH1B3	t(1;19)(q21.3;q13.2)	Lissencephaly 1	Brain development: inactivates PAF	Nothwang et al. (2001)
Xp21.2-p22.3	GRPR	t(X;8)(p22.13;q22.1)	MR + autism, epilepsy, exostoses	Membrane receptor, in GIS and CNS	Ishikawa-Brush et al. 1997)
Xq13.1	ZNF261	t(X;13)(q13.1;q31)	nsMRX	Subunit of BHC histone deacetylase complex	van der Maarel et al. (1996)
Xq13.3	ZDHHC15	t(X;15)(q13.3;cen)	nsMRX	Palmytoyl transferase	Mansouri et al. (2005)

original SNRP transcript (Conroy et al. 1997; Gallagher et al. 2002; Kuslich et al. 1999; Schulze et al. 1996; Wirth et al. 2001). These observations, together with the assumption of a fusion product in the patient described by Sun et al. (1996) in combination with findings from a deletion case (Greger et al. 1993), allowed a new critical region of 121 kb to be defined, containing the PWCR1/HBII-85 snoRNA cluster and the HBII-438A snoRNA as the only putative functional genes (Gallagher et al. 2002). A translocation detected in a PWS patient, disrupting intron 17 and abolishing PWCR1/HBII-85 and HBII-438A expression (Schüle et al. 2005), and an atypical deletion in another patient, ranging from IPW, which is just 3′ of HBII-85, to UBE3A, without PWS (Runte et al. 2001) confirmed the involvement of these snoRNA's in the core phenotype of PWS. Conclusive evidence was recently published by Sahoo et al. (2008), describing a PWS patient with a small 174-Kb deletion involving only the PWCR1/HBII-85 cluster. This concluded a search started more than a decade ago, guided by six balanced translocations and leading towards new discoveries in what is considered one of the most complex regions in the human genome.

A more straightforward illustration of the importance of balanced translocations in the identification of mental

Table 4 Reported balanced translocations without clear candidate genes

Translocations	Phenotype	Publication
t(4;9)(q22;q24)	MR + epilepsy + dysmorphism	Skovby and Niebuhr (1974)
t(12;19)(q15;q13)	MR + dysmorphism	Histinx et al. (1975)
t(1;15)(p22;q26)	MR + dysmorphism	van Hemel et al. (1975)
t(4;13)(q31;q14)	MR + congenital malformations	Jenkins et al. (1975)
t(1;13)(q24;q32)	MR + congenital malformations	Wilbur et al. (1977)
t(X;9)(p22;q12)	MR + dysmorphism	Mattei et al. (1978)
t(6;17)(p22;q22)	MR + dysmorphism	Ayme et al. (1979)
t(2;10)(q14;q23)	MR + dysmorphism	Ayme et al. (1979)
t(5;15)(q13;q25)	MR + Enuresis type 2	Nielsen and Krag-Olsen (1981)
t(12;17)(q15;q25)	MR + dysmorphisms	Coco and Penchaszadeh (1982)
t(13;18)(q21;q21)	MR + dysmorphisms	Coco and Penchaszadeh (1982)
t(6;14)(q13;q32)	'MR of any degree'	Friedrich et al. (1982)
t(9;17)(q34;q11)	Ehlers-Danlos	Dockery et al. (1982)
t(4;7)(q34;q31)	'MR of any degree'	Rasmussen et al. (1982)
t(1;16)(q12;p13)	MR + behaviour disorder	Rasmussen et al. (1982)
t(1;2)(p36;q23)	'MR of any degree'	Rasmussen et al. (1982)
t(1;16)(q32;q22)	MR + dysmorphisms	Garcia-Sagredo et al. (1983)
t(X;15)(q12;p11)	MR + Café au lait + dysmorphism	Kleczkowska et al. (1985)
t(1;6)(q44;q27)	MR + Retinal cone dysfunction	Tranebjaerg et al. (1986)
t(1;4)(q42;p16)	'MR of any degree'	Kähkönen et al. (1986)
t(12;14)(q24;q32)	Coffin–Siris Syndrome	Patel et al. (1987)
t(1;2)(p22;q22)	MR + congential anomalies	Chitayat et al. (1989)
t(5;7)(q33.1;p15.1)	Cohen Syndrome	Fryns et al. (1990)
t(Y;19)(q11;q13)	Bannayan-Zonana	Israel et al. (1991)
t(12;15)(q22;q22)	'MR of any degree'	Speleman et al. (1992)
t(2;9)(q35;q34)	MR + dysmorphisms	Prieto-Carrasquero et al. (1995)
t(17;19)(q25;q12)	'MR of any degree'	Prieto-Carrasquero et al. (1995)
t(3;4)(q23;q21)	MR + microcephaly + micrognathia	Prieto-Carrasquero et al. (1995)
t(8;16)(q24;q24)	'MR of any degree'	Prieto-Carrasquero et al. (1995)
t(9;13)(q32;q22)	MR + dysmorphism	Fryns and Hendrickx (1996)
t(X;16)(q28;q11.2)	Pai Syndrome	Masuno et al. (1997)
t(1;7)(q21.3;q34) t(7;22)(q32;q11.2)	Coffin–Siris Syndrome	McPherson et al. (1997) McGhee et al. (2000)
t(6;13)(q25q22)	MR + dysmorphisms	Wirth et al. (1999)
t(3;13)(q21;q22.2)	MR + Kyphoscoliosis of the spine	Wirth et al. (1999)
t(4;13)(p14;q32)	MR + epilepsy + stereotypic movements'	Wirth et al. (1999)
t(6;13)(p21.2;q33.3)	MR + dysmorphism + epilepsy	Wirth et al. (1999)
t(2;10)(q24;q22)	MR + behavioural problems	Santos et al. (2003)
t(17;20)(p13.3;q13.33)	MR + dysmorphism + transient homocysteinemia	Walter et al. (2004)

retardation genes is the identification of the causative gene in the 9q subtelomeric deletion syndrome. After thorough clinical investigation, it was noticed that the phenotype of a patient with a t(X;9)(p11.23;q34.3) showed a striking similarity with that of patients with the subtelomeric del(9qter) syndrome. EHMT1, one of the candidate genes in the commonly deleted region of patients with a subtelomeric deletion was disrupted by the translocation, and considered a good candidate gene (Kleefstra et al. 2005). Twenty-three patients without detectable chromosomal abnormalities and with phenotypic characteristics of the 9q subtelomeric deletion syndrome were further screened for EHMT1 aberrations and mutations were identified in two patients (Kleefstra et al. 2006). This confirmed haploinsufficiency of EHMT1 as the main cause of the del(9q) syndrome. Similarly, studying patients with a syndromic

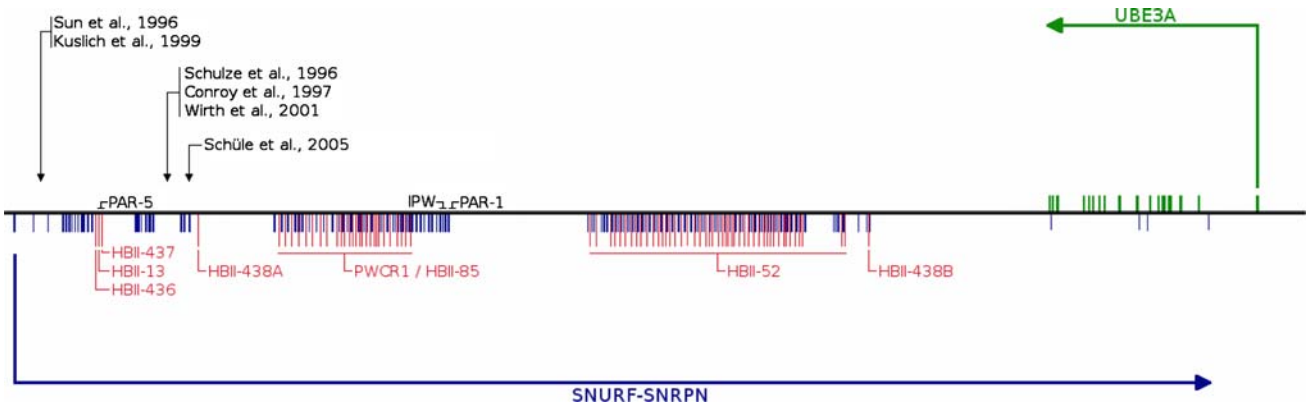

Fig. 2 Schematical overview of the Prader–Willi/Angelman region. SNURF-SNRPN exons are depicted in *blue*, snoRNA's in *red* and UBE3A exons in *green*. Described balanced translocations disrupting this region are visualised by *black arrows*. The locations of the incorporated transcripts PAR-5, IPW and PAR-1 are shown in *black*

form of Hirschprung disease known as Mowat–Wilson, two independent labs each found a balanced translocation disrupting the ZEB2 gene. During subsequent mutation screening in patients with the clinical symptoms of Mowat–Wilson, they both confirmed the gene's involvement in the phenotype of this microdeletion syndrome (Cacheux et al. 2001; Wakamatsu et al. 2001).

Identification of novel mental retardation genes through balanced translocations

One of the first identified mental retardation genes was characterized after studying a female patient with non-syndromic mental retardation and a balanced translocation t(X;12)(q11;q15) (Bienvenu et al. 1997). In contrast to syndromic patients, who are characterized by additional clinical or biochemical features, non-syndromic patients are characterized by mental retardation per se. In females, inactivation of one of the X-chromosomes by Lyonisation is usually a stochastic process. However, as a result of the X:autosome translocation, the intact X-chromosome is preferentially inactivated, silencing one copy of the gene by the X:autosome translocation, and the other by Lyonisation. A gene called oligophrenin-1 (OPHN1) was identified at the translocation breakpoint at Xq11 in the patient described before (Billuart et al. 1998). Disruption of the gene was considered a good indication for involvement in the mental retardation of the patient, but no conclusive evidence was found, and a search for mutations in this gene was initiated in additional patients. The search was facilitated by the availability of large families with X-linked mental retardation mapping to this chromosomal region (Chiurazzi et al. 2008). In one out of four families examined, a frameshift mutation was identified, proving the involvement of oligophrenin-1 in mental retardation. Following basically the same strategy, four additional non-syndromic mental retardation genes have been identified (see Table 2).

Examples of syndromic MRX gene identifications include the discovery of the DCX gene as the causative gene in lissencephaly. The identification of a patient with a balanced (X;2) translocation narrowed down the candidate region to 1 cM (Ross et al. 1997) and greatly facilitated cloning of the gene. The search for mutations in the candidate gene that mapped into this interval was successful in three out of three patients with an X-linked lissencephaly phenotype. However, it is of interest to note that not all cases of balanced autosome/X translocations are due to disruption of the gene that lies on the X-chromosome. The mental retardation in a female patient with a balanced t(X;9)(p11.23;q34.3) translocation that led to the discovery of EHMT1 as the causative gene in the 9q subtelomeric deletion syndrome, was originally proposed to be caused by ZNF81 deficiency, a gene located on the X-chromosome and disrupted by the same translocation (Kleefstra et al. 2004).

Only a handful of autosomal genes have been associated with MR phenotype, mostly involving syndromic forms. Two translocations disrupting the GLI3 gene in patients with Greig Syndrome, initiated mutation analysis on a cohort of patients with a phenotype suggestive of the disorder (Kruger et al. 1989; Tommerup and Nielsen 1983; Wild et al. 1997). Point mutations in GLI3 were shown to result in Greig Syndrome, while frameshift mutations result in a different phenotype, namely the Pallister–Hall Syndrome (Kang et al. 1997). While this is the only example of a new autosomal candidate gene identification, other translocations added to the mutation spectrum in known MR genes. Examples are a t(1;4)(q31;p15.3) translocation disrupting the ASPM gene involved in MCPH5, a t(2;5)(q24.3;q34) translocation disrupting SCN1A associated to MR and SMEI, a t(7;12)(q22;p13) translocation disrupting RELN leading to LIS2, or a t(18;20)(q21.1;q11.2) translocation causing the Pitt–Hopkins Syndrome by disruption of TCF4 (Kalscheuer et al. 2008a; Moller et al. 2008b; Pichon et al.

2004; Zaki et al. 2007). The identification of FOXL2, a transcription factor as the candidate gene responsible for the blepharophimosis/ptosis/epicanthus inversus syndrome (BPES) was identified partially based on translocation data (Boccone et al. 1994; de Almeida et al. 1993; Praphanphoj et al. 2000). Deletion of FOXL2 causes BPES with MR (De Baere et al. 2003), whereas point mutations in the same gene cause BPES without MR.

Identification of candidate genes at breakpoints

In contrast to the causative genes identified at breakpoints that were mentioned above, numerous genes have been identified at translocation breakpoints in patients for which the role in disease could not be confirmed by mutation analysis as yet. Among those, the AUTS2 gene was found disrupted in four unrelated MR patients with balanced translocations (Kalscheuer et al. 2007; Sultana et al. 2002). This apparent correlation of a disruption to MR makes it a strong candidate for a critical role in normal brain function. However, no missense or nonsense mutations have been found in isolated patients. Another example includes the ARHGEF9 gene, encoding collybistin, a gene involved in cell signalling, that was found disrupted at a translocation breakpoint in a female with an X:autosome translocation (Kalscheuer et al. 2008b) The same gene was also found disrupted in a patient with a paracentric inversion of the X-chromosome (Marco et al. 2008). In the latter study, nearly 500 patients with unexplained mental retardation and suggestive X-linked inheritance were screened for mutations, but no unambiguous mutations were identified. A third example is the KIAA1202 gene, found disrupted in two independent female patients with balanced X:autosome translocations (Hagens et al. 2006). Again, a search for mutations in X-linked families revealed no evidence for a clear mutation, though sequence alterations were identified. Are AUTS2, ARHGEF9 and KIAA1202 mental retardation genes or not? For now, this remains a question on interpretation of the data. Some authors do include these genes in the listing for mental retardation genes, while others reserve the term mental retardation gene for genes that have been confirmed by mutation analysis. In addition to genes that have been reported disrupted in multiple patients, numerous reports exist on genes that have been found disrupted in a single case (Table 3). Examples include the DOCK8 gene on 9p24.3 and PAFAH1B3 on 19q13.1 (Griggs et al. 2008).

Many translocation breakpoints do not disrupt a candidate gene

The last and potentially largest category of balanced translocations, however, consists of breakpoints that have been identified, but where no coding gene has been identified at any of the breakpoints. This does not only apply to the cases that have been reported several years ago, when genomic maps and molecular technologies did not allow gene identification in many cases, but also to cases reported most recently. Published examples are listed in Table 4, but the number of reported cases is presumably only a fraction of the cases that are detected. The great majority of these class has likely not been reported as no gene was found interrupted and it is generally assumed that only disturbance of a protein coding gene can contribute to disease. Whether this assumption is correct is unknown at present. For instance, we ourselves recently cloned a balanced t(2;6)(p15;p22.3) de novo translocation in a patient with West Syndrome who showed no other chromosomal abnormalities. West Syndrome, also known as the "Infantile Spasms Syndrome" is a genetically heterogeneous mental retardation syndrome associated with epilepsy and hypsarithmia. Mutations in ARX and CDKL5 are both known to be causative, but no autosomal candidate genes have been identified so far (Kalscheuer et al. 2003; Kato 2006). Using marker analysis on flow-sorted derivatives, the breakpoint region provided by FISH analysis was refined and ultimately sequenced. Spanning the breakpoint on chromosome 6, a non coding RNA transcript, expressed in the foetal brain, was detected. Although such findings are hard to interpret at the moment, these should not be discarded.

Discussion

Over the past years, different labs have used balanced translocations to identify causative genes for mental retardation. The results ranged from the identification of mental retardation genes, like OPHN1, to characterisation of complex regulatory domains as seen for the Prader–Willi Syndrome. It can thus be safely concluded that balanced translocations are useful tools for the identification responsible for mental retardation genes including the identification of causative genes within regions deleted in contiguous gene syndromes. Some microdeletion syndromes have been "reduced" to a single gene disorder, with mutations in a single gene responsible for most of the clinical symptoms, while in other microdeletion syndromes, such genes have not been identified, neither through a balanced translocation nor through any other method. It can be questioned whether single candidate genes exist for all contiguous gene syndromes, or whether some microdeletion syndromes are truly contiguous, and as such the consequence of the combined absence of a multitude of genes.

Balanced translocations have been most successful in characterising candidate genes for X-linked non-syndromic mental retardation. Of the 16 genes identified for this specific type of a mental handicap, 5 identifications have been

guided by a balanced translocation (see Table 2) (Chiurazzi et al. 2008). Genes responsible for autosomal, syndromic mental retardation have also been identified at the position of translocation breakpoints observed in a single patient. In both cases, the identification of mutations in the causative genes was facilitated by an enrichment of the initial study population based on linkage data or phenotype, enabling selection of a population of patients significantly enriched for the specific phenotype, enormously increasing the odds ratio of finding a disease related mutation. In X-linked mental retardation, large collections of nuclear families have been assembled and the number of genes potentially involved in any specific X-linked disorder has been further reduced by linkage analysis (Chiurazzi et al. 2008). In syndromic disorders, a selection on the basis of the clinical phenotype seems a prerequisite for gene cloning, as only genes responsible for specific disorders characterized by a combination of mental retardation and a discriminating set of congenital abnormalities have been successfully identified up till now. Sometimes, mutations in genes involved in syndromic mental retardation were also found in patients with non-syndromic mental retardation. Thus, studying syndromal cases may also shed light on the diverse genetic defects that may lead to brain dysfunction in general.

In absence of clear selection criteria, mutations in very few, if any autosomal genes responsible for mental retardation have been reported despite the fact that numerous gene disrupting translocations have been identified. There are multiple plausible explanations for this discrepancy. First, rather than the gene disrupted by the balanced translocation, a positional effect affecting the dosage of a multitude of genes on the rearranged chromosomes is causative for the mental handicap. A second possibility is that disruption of the function of the gene, either by truncation or by fusion with a second transcript, is causative for the observed clinical symptoms, but mutations are extremely rare and can only be detected after screening populations of thousands and thousands of patients. Using current technologies, screening of such large populations is not feasible. Thirdly, there is the possibility that the balanced translocation might actually be coincidental, and the patient carries a causative mutation or microaberration somewhere else in the genome. Multiple studies on the nature of balanced chromosomal aberrations using array based methods have revealed that novel microaberrations occur in about one-third of the investigated subjects. In more than half of these cases, the aberrations are located at the seemingly balanced breakpoints and may take away a series of genes, making them less feasible for candidate gene identification (Baptista et al. 2008; Fantes et al. 2008; Gribble et al. 2005; Higgins et al. 2008). The remaining cases usually show no aberrations at the array level of analysis, but may contain imbalances of a few bases when sequenced (Higgins et al. 2008). Despite the fact that most of the reported balanced translocations are not analyzed at such a high resolution, it has to be stressed that candidate genes identified so far were directly disrupted by the breakpoint.

The last category, in which no coding gene has been identified at the breakpoints, may potentially become the most interesting one. Only 1–2% of the human genome encodes for proteins, and the function of the remaining DNA, if any, is largely unknown (Lander et al. 2001). For some time this remaining DNA was seen as junk, but with recent findings on ultra-conserved regions and ncRNA's, these noncoding regions are being intensely studied. So although this last category may have seemed uninteresting in the past, the findings on possible physiological roles of ncRNA's can place them back into the centre of attention (Mercer et al. 2008; Satterlee et al. 2007). Several forms of ncRNA's have been identified, and have been shown involved in neuronal development, gene expression and RNA editing. The mechanism on which their function is based is not yet fully understood, and the possibility of chromatin remodelling is currently under active investigation (Attanasio et al. 2008). Furthermore, the involvement of snoRNA's in the phenotype of PWS has stated a clear example of their putative role in MR syndromes. Characterisation of expressed RNA molecules spanning breakpoints in patients with specific phenotypes may help increase our understanding of this new family of potentially important genetic players.

Collecting the available knowledge on balanced translocations, we noticed that this information is scattered across different databases such as OMIM, DECIPHER, ECARUCA, MCNdb, or DGV and that some cases described in individual research papers accessible through PubMed are not listed in any of these. A comprehensive record curated by a central dedicated database of all known balanced disruptions, including high-resolution mapping of copy number variants, mapping data of the breakpoint and a detailed description of the clinical phenotype would be an enormous advantage. This should allow future researchers to relate the translocation breakpoints with aberrations found using high-resolution copy number analysis. Novel technology, including the array-CGH and dense SNP analysis is creating a continuous stream of new chromosomal aberrations involved in MR and to be able to correlate the aberrations found with these technologies with genes disrupted by translocation breakpoints would be of enormous help in the interpretation of these new findings. When correlating genomic imbalances to a phenotype, it is extremely important to have a close cooperation between the molecular laboratories and the clinic in order to be able to cluster patients according to their phenotype. This is clearly illustrated by the translocation that led to identification of EHMT1 in del(9q) as described before. As shown in Table 1b, three

genes are thought to be involved in the phenotype of the contiguous 3pter deletion syndrome based on translocations, and ITPN1 was proposed based on an atypical deletion patient (Cargile et al. 2002). Although all three gene disruptions seem to cause some aspects of the phenotype, none of them can explain the whole set of mental and growth retardation and dysmorphic features, and none of the three is confirmed by independent mutations in similar patients (Endris et al. 2002; Cargile et al. 2002; Frints et al. 2003; Fernandez et al. 2004). The observation of partial phenotypes for single gene disruptions points to a contiguous syndrome for del(3pter), but to the best of our knowledge, no explicit decision has been made for the 2q37 deletion syndrome, on the whether or not it is a contiguous syndrome. Nearly a 100 patients are characterized, and yet no general genotype to phenotype link has been established (Falk and Casas 2007).

With the development of recent techniques, the cloning of many more breakpoints can be awaited in the years to come. For instance, next generation sequencing technology has already been proven to be a reliable method to identify the breakpoints from flow-sorted or laser-dissected chromosomes in a single experiment (Kundakovic et al. 2008). This technique can thus substantially decrease the efforts necessary to clone translocation breakpoints. A further breakthough that can be anticipated is the massive parallel sequencing of multiple candidate genes in thousands of patients with mental retardation. This may enable the detection of mutations in genes that are mutated in a very low percentage of patients. Thus, novel technology in combination with an improved database annotation of disease related genomic abnormalities hold great promise for the elucidation of the role of the sequences interrupted in patients with mental retardation in the near future.

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