CHROMOSOMAL ABNORMALITIES ASSOCIATED WITH NEURAL TUBE DEFECTS (II): PARTIAL ANEUPLOIDY

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SUMMARY

Fetuses with neural tube defects (NTDs) carry a risk of chromosomal abnormalities. The risk varies with maternal age, gestational age at diagnosis, association with other structural abnormalities, and family history of chromosome aberrations. This article provides a comprehensive review of structural chromosomal abnormalities associated with NTDs, such as del(13q), r(13), dup(2p), del(2q), del(1p), del(1q), dup(1q), del(3p), dup(3p), del(3q), dup(3q), del(4p), dup(4p), del(4q), dup(4q), del(5p), del(6p), dup(6q), del(6q), dup(7p), del(7q), dup(8q), del(9p), del(10q), del(11q), dup(11q), dup(12p), dup(14q), del(14q), del(15q), dup(16q), del(18q), r(18), dup(20p), +i(20p), del(22q), del(Xp), and dup(Xq). NTDs may be associated with aneuploidy. Perinatal identification of NTDs should alert one to the possibility of chromosomal abnormalities and prompt a thorough cytogenetic investigation and genetic counseling. [*Taiwan J Obstet Gynecol* 2007;46(4):336–351]

Key Words: chromosomal abnormalities, neural tube defects, partial aneuploidy

Introduction

Neural tube defects (NTDs) have an incidence of 1–2 per 1,000 births and are considered to be a heterogeneous condition resulting from failure of normal neural tube closure between the third and fourth week of embryonic development. The three common types of NTDs are anencephaly, spina bifida, and encephalocele. The uncommon types of NTDs include amniotic band syndrome, limb–body wall complex, cloacal exstrophy or OEIS complex, and other types of spinal abnormalities. The incidence of NTDs varies with race, geographic variation, socioeconomic classes, nutritional status, and multiple predisposing factors such as single gene disorders (Meckel syndrome, median cleft face syndrome, Roberts syndrome, Jarcho-Levin syndrome and HARD [hydrocephalus, agyria, retinal dysplasia] syndrome), chromosomal abnormalities (trisomy 18, trisomy 13, triploidy and other structural abnormalities), teratogens (valproic acid, aminopterin/amethopterin and thalidomide), maternal diabetes, family history of NTDs, thermolabile mutation in the *MTHFR* gene, and others [1]. There is considerable evidence that genetics contributes to the etiology of NTDs. Fetuses with NTDs carry a risk of chromosomal abnormalities. The risk varies with maternal age, gestational age at diagnosis, association with other structural abnormalities, and family history of chromosome aberrations.

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Partial Aneuploidy

Structural chromosomal abnormalities associated with NTDs include del(13q), r(13), dup(2p), del(2q), del(1p), del(1q), dup(1q), del(3p), dup(3p), del(3q), dup(3q), del(4p), dup(4p), del(4q), dup(4q), del(5p), del(6p), dup(6q), del(6q), dup(7p), del(7q), dup(8q), del(9p), del(10q), del(11q), dup(11q), dup(12p), dup(14q), del(14q), del(15q), dup(16q), del(18q), r(18), dup(20p), +i(20p), del(22q), del(Xp), and dup(Xq).

Del(13q) and r(13)

The reported NTDs associated with del(13q) and r(13) include spina bifida, encephalocele, anencephaly, atelencephaly, exencephaly, and aprosencephaly [2–20] (Table 1). Schmid et al [3] first reported the prenatal diagnosis of ring chromosome 13 by amniocentesis at 33 weeks' gestation in a fetus with anencephaly, limb deformities, and congenital heart defects. Rudelli et al [8] reported the pathologic characteristics of two 18-week gestation fetuses with anencephaly, exencephaly, multiple limb defects, and urogenital defects carrying chromosome 13q deletions (distal to bands q13 and q22, respectively). Benn et al [7] reported the prenatal diagnosis of ring chromosome 13 (46,XY,r(13)(p11q13)) by amniocentesis at 20 weeks' gestation in a fetus with anencephaly, imperforate anus and urethral meatus, severe talipes, syndactyly, cardiac defects, and other anomalies. Palmer et al [9] reported the prenatal diagnosis of ring chromosome 13 (46,XX,r(13)) by amniocentesis at 18 weeks' gestation in a fetus with anencephaly. Brown et al [13] reported prenatal diagnosis of chromosome 13q deletion (46,XX,del(13)(q31.2q34)) by amniocentesis at 25 weeks' gestation in a fetus with a large occipital encephalocele, severe microcephaly, anteriorly displaced anus, and bilaterally absent thumbs. Chen et al [16] reported the prenatal diagnosis of a chromosome 13q deletion (46,XX,del(13)(q21)) by amniocentesis at 20 weeks' gestation in a fetus with severe intrauterine growth restriction, cardiomegaly, an occipital encephalocele, and a calvarial defect. Chen et al [17] reported the prenatal diagnosis of mosaic ring chromosome 13 (46,XX,r(13)(p11q32)/45,XX,–r(13); 77%/23%) by amniocentesis at 23 weeks' gestation in a fetus with intrauterine growth restriction and anencephaly. Molecular genetic analysis of the case reported by Chen et al [17] revealed that the breakpoint was distal to the *ZIC2* gene on 13q32, suggesting the association of other genes on 13q32–q34 with

Table 1. Reported neural tube defect (NTD) cases with partial aneuploidy of chromosome 13

Authors	Chromosome aberration	Deletion or duplication extent	NTDs and brain anomalies
Del(13q) and r(13)			
Fear and Briggs [4]	der(13)t(3;13)(q21;q34)mat	13q34 → qter 3q21 → qter	Lumbar meningomyelocele
Kennedy et al [18]	der(13)t(11;13)(q23.1;q34)mat	13q34 → qter 11q23.1 → qter	Lumbosacral meningomyelocele
Jones et al [6]	r(13)(p11q34)/–r(13) (84.5%/6.5%)	13q34 → qter	Lumbar spina bifida
Luo et al [20]	del(13)(q33.2)	13q33.2 → qter	Lumbosacral meningomyelocele
Chen et al [17]	r(13)(p11q32)/–r(13) (77%/23%)	13q32 → qter	Anencephaly
Telfer et al [5]	del(13)(q32)	13q32 → qter	Parietal encephalocele
Brown et al [14]	der(13)t(13;22)(q31.2;q13.3)pat	13q31.2 → qter 22q13.3 → qte	Partial anencephaly, posterior encephalocele
Kennedy et al [18]	der(13)t(13;22)(q31.2;q13.3)pat	13q31.2 → qter 22q13.3 → qter	Anencephaly
Brown et al [13]	del(13)(q31.2q34)	13q31.2 → qter	Occipital encephalocele
Brown et al [13]	der(13)t(13;15)(q22;q26)pat	13q22 → qter 15q26 → qter	Anencephaly
Rudelli et al [8]	del(13)(q22)	13q22 → qter	Anencephaly
Towfighi et al [10]	del(13)(q22q31)	13q22 → q31	Atelencephaly
Lam et al [19]	der(13)t(4;13)(p15.2;q21.2)pat	13q21.2 → qter 4p15.2 → pter	Exencephaly
Brandt et al [12]	r(13)(p11q21.1)/–r(13) (92%/8%)	13q21.1 → qter	Anencephaly
Chen et al [16]	del(13)(q21)	13q21 → qter	Occipital encephalocele
Drugan et al [11]	del(13)(q13)	13q13 → qter	Anencephaly
Benn et al [7]	r(13)(p11q13)	13q13 → qter	Anencephaly
Rudelli et al [8]	del(13)(q13)	13q13 → qter	Anencephaly
Goldsmith et al [15]	r(13)/–r(13) (67%/37%)	Unknown	Aprosencephaly
Palmer et al [9]	r(13)	Unknown	Anencephaly
Schmid et al [3]	r(13)/–r(13) (93%/7%)	Unknown	Anencephaly
Allderdice et al [2]	r(13)	Unknown	Encephalocele

Del = deletion; r = ring chromosome; der = derivative chromosome; mat = maternal origin; –r(13) = monosomy 13 with absence of r(13); pat = paternal origin.

NTDs. The *ZIC2* gene is well known to be responsible for human holoprosencephaly (HPE) [21]. Recent studies, however, found no supporting evidence for an association between *ZIC2* and the risks of NTDs [22,23]. The human *ZIC5* on 13q32 has been proposed as a strong candidate gene responsible for NTDs [24]. Inoue et al [24] found that mice with disrupted *ZIC5* manifested incomplete neural tube closure and suggested that *ZIC5* is involved in the generation of the neural tube tissue in mouse development. Other possible candidate genes of NTDs in the involved segment of chromosome 13q include *MAB21L1* (13q13). *Cdx2* maps to 13q12.3 and is essential for axial elongation in mouse development [25].

Dup(2p)

The reported central nervous system anomalies associated with dup(2p) include spina bifida, anencephaly, encephalocele, atelencephaly, and agenesis of corpus callosum [26–38] (Table 2). Walbaum et al [31] reported a fetus with anencephaly and truncus arteriosus as the unbalanced product of a translocation carrier mother with t(2;5)(p13;p15) and a previous child with spina bifida. The fetus had dup(2)(pter → p13) and del(5)(pter → p15). Singer et al [32] reported the prenatal diagnosis of a duplication of 2p (2p24 → pter) by amniocentesis in the third pregnancy of a woman with fetal anencephaly and congenital cystic disease of the right kidney. The maternal karyotype was

Table 2. Reported neural tube defect (NTD) cases with partial aneuploidy of chromosome 2

Authors	Chromosome aberration	Duplication or deletion extent	NTDs
Dup(2p)			
Singer et al [32]	der(10)t(2;10)(p24;q26)mat	2p24 → pter 10q26 → qter	Anencephaly
Wellesley and Boyle [36]	der(3)t(2;3)(p23.1;q29)pat	2p23.1 → pter 3q29 → qter	Sacral meningomyelocele
Carriere [27]	der(10)t(2;10)(p23;q26)mat*	2p23 → pter 10q26 → qter	Encephalocele
Francke and Jones [28]	der(7)t(2;7)(p23;q36)mat*	2p23 → pter 7q36 → qter	Anencephaly
Cassidy et al [29]	der(3)t(2;3)(p23;p27)*	2p23 → pter 3p27 → pter	Anencephaly
Winsor et al [34] two cases	der(5)t(2;5)(p23;p15)mat	2p23 → pter 5p15 → pter	Anencephaly
Thangavelu et al [38]	dup(2)(p25.3p22)	2p22 → p25.3	Anencephaly
	dup(2)(p25p22)	2p22 → p25	Anencephaly
Doray et al [37]	der(15)t(2;15)(p22;q26)mat	2p22 → pter 15q26 → qter	Craniorachischisis
	der(15)t(2;15)(p22;q26)mat	2p22 → pter 15q26 → qter	Anencephaly
Hahm et al [35]	der(15)t(2;15)(p21;q26)	2p21 → pter 15q26 → qter	Anencephaly
Therkelsen et al [26] two cases	ins(2)(q34p13p24)pat	2p13 → p24	Spina bifida
Fineman et al [30]	der(9)t(2;9)(p13;p24)mat	2p13 → pter 9p24 → pter	Spina bifida
Walbaum et al [31]	der(5)t(2;5)(p13;p15)mat	2p13 → pter 5p15 → pter	Anencephaly
Sarda et al [33]	der(X)t(X;2)(q27;p13)mat	2p13 → pter Xq27 → qter	Lumbar meningomyelocele
Del(2q)			
Melnyk and Muraskas [43]	del(2)(q36q36)	2q36	Lumbar meningomyelocele
Nye et al [45]	del(2)(q35q36.2)	2q35 → q36.2	Lumbosacral meningomyelocele
Chinen et al [44]	del(2)(q24.2q31)	2q24.2 → q31	Occipital encephalocele
McConnell et al [42]	del(2)(q22q31)	2q22 → q31	Occipital encephalocele

**Presumed rearrangement. Dup = duplication; der = derivative chromosome; mat = maternal origin; pat = paternal origin; ins = insertion; del = deletion.*

46,XX,t(2;10)(p24;q26) and the fetal karyotype was 46,XY,der(10)t(2;10)(p24;q26)mat. The woman's first pregnancy resulted in a female fetus with anencephaly and left hydronephrosis. Pedigree analysis revealed that the woman had a maternal aunt with spina bifida. Hahm et al [35] reported the prenatal diagnosis of partial trisomy 2p (2p21 → pter) and partial monosomy 15q (15q26 → qter) by amniocentesis at 19 weeks' gestation in a fetus with minor facial anomalies, musculoskeletal defects, postaxial polydactyly, and anencephaly. The fetal karyotype was 46,XY,der(15)t(2;15)(p21;q26). Winsor et al [34] reported recurrent anencephaly with partial trisomy 2p (2p23 → pter). The maternal karyotype was 46,XX,t(2;5)(p23;p15). Her first pregnancy resulted in a male fetus with anencephaly, lumbosacral dysraphism at L3–S1, left microphthalmia, preauricular skin tags, absent pituitary gland and left adrenal gland, rocker-bottom feet, bilateral simian creases, hypoplastic penis and scrotum, undescended testes, and the karyotype of 46,XY,der(5)t(2;5)(p23;p15)mat. Her third pregnancy resulted in a fetus with anencephaly, polydactyly, and the karyotype of 46,XY,der(5)t(2;5)(p23;p15)mat. Her fifth pregnancy resulted in a fetus with the karyotype of 46,XY,der(5)t(2;5)(p23;p15)mat, and multiple anomalies but no anencephaly or gross central nervous system abnormalities. Wellesley and Boyle [36] reported the prenatal diagnosis of partial trisomy 2p (2p23.1 → pter) in a fetus with anencephaly and sacral meningomyelocele by amniocentesis at 15 weeks' gestation. The fetal karyotype was 46,XX,der(3)t(2;3)(p23.1;q29)pat. Thangavelu et al [38] reported dup(2)(p25.3p22) in a fetus with anencephaly diagnosed at 16 weeks' gestation, and dup(2)(p25p22) in another fetus with anencephaly diagnosed at 17 weeks' gestation. Doray et al [37] reported the prenatal diagnosis of partial trisomy 2p (2p22 → pter) in two male sib fetuses by chorionic villus sampling. Both fetuses had NTDs, with craniorachischisis in the first fetus and anencephaly in the second fetus, and the karyotype of 46,XY,der(15)t(2;15)(p22;q26)mat. Doray et al [37] reviewed 64 cases with partial trisomy 2p and found that 15 cases (23.44%) had NTDs, including spina bifida, anencephaly and encephalocele. Lurie et al [39] suggested that the common triplicated region of chromosome 2p associated with NTDs is the band 2p24. Chromosome 2p24 contains the two genes *GDF7* (growth/differentiation factor 7) and *DDEF2* (development and differentiation enhancing factor 2) that are important for neural tube development. *GDF7* is involved in the generation of a discrete class of commissural interneurons in the mouse spinal cord [40], and *DDEF2* is involved in cell communication and structure [41].

Del(2q)

Deletions of 2q have been associated with spina bifida and encephalocele [42–45] (Table 2). McConnell et al [42] reported a partial deletion of chromosome 2, del(2)(q22q31), in a newborn with a prominent occiput, a short mandible, a short sternum, overlapping fingers, rocker-bottom feet, cleft palate, a heart defect, and occipital meningomyelocele. Chinen et al [44] reported a female infant with an interstitial deletion involving 2q24.3 or del(2)(q24.2q31), micrognathia, facial dysmorphism, ocular ptosis, low-set ears, a beaked nose, congenital heart defects, and occipital encephalocele. Melnyk and Muraskas [43] reported an infant with a *de novo* deletion of 2q36, multiple minor anomalies, lumbar meningomyelocele, hydrocephalus, and congenital heart defects. Nye et al [45] reported lumbosacral myelomeningocele and Waardenburg syndrome in patients with an interstitial deletion of 2q35 and the *PAX3* gene. The *PAX3* gene was mapped to chromosome 2q35. In humans, neural tube defects have occasionally been associated with Waardenburg syndrome [46–56]. Hol et al [55] reported a girl with spina bifida, mild signs of Waardenburg syndrome, and a frameshift mutation in the gene for *PAX3*. Shim et al [57] reported a 6-year-old boy with bilateral sensorineural deafness, lateral displacement of inner canthi, a bulbous nasal tip, synophrys, cryptorchidism, Waardenburg syndrome type I, a lumbar spina bifida, and the karyotype of 46,XY,der(2)inv(2)(q13q21)inv(2)(q21q24.2)ins(2)(q24.2q33q35). Fluorescence *in situ* hybridization study showed a breakpoint at 2q35 being proximal to and without involvement of the *PAX* gene. Kujat et al [56] reported the prenatal diagnosis of spina bifida in a fetus, leading to the initial diagnosis of Waardenburg syndrome type I in the members of a four-generation family and a novel splice site mutation within the *PAX3* gene in intron 5 in all affected family members but in none of the unaffected relatives. Stamm et al [58] used a high-density single nucleotide polymorphism screen and identified linkage to loci at 7p21.1–pter and 2q33.1–q35 in a large multiplex NTD family. Other possible candidate genes of NTDs in the involved segment of chromosome 2q include *HOXD* (2q31–q32).

Del(1p), del(1q), and dup(1q)

Partial deletions and duplications of chromosome 1 can be associated with spina bifida and encephalocele [59–66] (Table 3). Thauvin-Robinet et al [65] reported the prenatal diagnosis of anhydramnios, occipital encephalocele, and enlarged bladder at 12 weeks' gestation in a fetus with the karyotype of 46,XY,der(1)t(1;14)(p35;q32)mat, a 1p35–pter deletion and a

Table 3. Reported neural tube defect (NTD) cases with partial aneuploidy of chromosome 1

Authors	Chromosome aberration	Deletion or duplication extent	NTDs
Del(1p)			
Thauvin-Robinet et al [65]	der(1)t(1;14)(p35;q32)mat	1p35 → pter 14q32 → qter	Occipital encephalocele
Del(1q)			
Golabi et al [60] Case 1 and 2	der(1)t(1;12)(q43;p13)mat	1q43 → qter 12p13 → pter	Occipital encephalocele, lumbar spina bifida
Ribeiro and Brunoni [62]	del(1)(q43)	1q43 → qter	Occipital meningocele
Wen et al [66]	del(1)(q42)	1q42 → qter	Encephalocele
Al-Awadi et al [61]	del(1)(q32q42)	1q32 → q42	Encephalocele
Takano et al [63]	del(1)(q24q25.3)	1q24 → q25.3	Spina bifida, meningomyelocele
Dup(1q)			
Dagna Bricarelli et al [59]	der(6)t(1;6)(q32;q26)mat*	1q32 → qter 6q26 → qter	Occipital meningomyelocele
Pettenati et al [64]	der(14)t(1;14)(q11;p11.1)†	1q11 → qter 14p11.1 → pter	Parietal encephalocele

**Presumed rearrangement; †12% (3/25) aberrant cells/analyzed cells in cord blood. Del = deletion; der = derivative chromosome; mat = maternal origin; dup = duplication.*

14q32–qter duplication. Golabi et al [60] reported double NTDs of occipital encephalocele and lumbar spina bifida in two sibs with del(1)(q43 → qter), dup(12)(p13 → pter), and the karyotype of 46,XX, der(1)t(1;12)(q43;p13)mat. Ribeiro and Brunoni [62] reported a newborn with hydrocephalus, occipital meningocele, and a terminal deletion 1q43 → qter. Wen et al [66] reported a case with encephalocele and del(1)(q42). Al-Awadi et al [61] reported a malformed infant with a *de novo* interstitial deletion of 1q (1q32 → q42), microcephaly, encephalocele, small eyes with unilateral esotropia, hypertelorism, highly arched palate, micrognathia, low-set ears, a short neck, congenital heart defects, and single umbilical artery. Takano et al [63] reported a 12-month-old boy with the karyotype of 46,XY,del(1)(q24q25.3), spina bifida, meningomyelocele, hydrocephalus, anal atresia, an atrial septal defect, left renal agenesis, bilateral cryptorchidism, talipes equinovarus, low birth weight, growth/developmental retardation, and minor anomalies. Dagna Bricarelli et al [59] reported occipital myelomeningocele in a case with partial trisomy 1q (1q32 → qter) and partial monosomy 6q (6q26 → qter) because of unbalanced translocation inherited from maternal t(1;6)(q32;q26). Pettenati et al [64] reported the prenatal diagnosis of mosaic trisomy 1q in a fetus with mosaic der(14)t(1;14)(q11;p11.1) with nuchal thickening, bitemporal narrowing, a single choroid plexus cyst, mild ventriculomegaly, hyperechoic bowel, hydrops fetalis, and left parietal encephalocele. Possible candidate genes of NTDs in the involved segments of chromosome 1 include *CRABP2* (1q21.3), *PRKACB* (1p36.1), *PAX7* (1p36.2–p36.12), *MTHFR* (1p36.3) and *MTR* or *MS* (1q43).

Del(3p), dup(3p), del(3q), and dup(3q)

Partial deletions and duplications of chromosome 3 can be associated with spina bifida and encephalocele [4,67–73] (Table 4). Allderdice et al [67] reported spina bifida or sacral dimple in the rec(3)dup(3)(q21 → qter) del(p25 → pter) children of known inv(3)(p25q21) carriers. Fear and Briggs [4] reported absence of the right eye and lumbar spina bifida in an infant with the karyotype of 46,XX,der(13)t(3;13)(q21;q34), and partial trisomy 3q (3q21 → qter) and partial monosomy 13q (13q34 → qter) born to a carrier mother with t(3;13)(q21;q34). Schinzel [72] reported recurrent NTDs in two unbalanced offsprings with dup(3)(q21 → qter) and del(5)(pter → p15.2). The first underweight girl had lumbar myelomeningocele, Arnold-Chiari malformation, agenesis of the corpus callosum, anal stenosis, intestinal malrotation, Meckel's diverticulum, and uterus bicornis. The following prenatally diagnosed fetus had gastroschisis, posterior encephalocele, and uterus bicornis. Kennedy et al [71] reported lumbosacral meningomyelocele, holoprosencephaly, premaxillary agenesis, tetralogy of Fallot, ventricular septal defect, and pulmonary stenosis in a fetus with the karyotype of 46,XY,der(3)del(3)(p26) dup(3)(p26p21.3). Suzumori et al [68] reported the prenatal diagnosis of partial trisomy 3p (3p21 → pter) in a fetus with cleft lip and palate, absent genitalia, lumbosacral

Table 4. Reported neural tube defect (NTD) cases with partial aneuploidy of chromosome 3

Authors	Chromosome aberration	Deletion or duplication extent	NTDs
Del(3p)			
Bader et al [69]	der(3)t(3;11)(p26;q21)mat	3p26 → pter 11q21 → qter	Lumbosacral meningomyelocele
Dup(3q) and del(3p)			
Allderdice et al [67] Case 1, 7, 8 and 13	rec(3)dup(3)(q21qter)del(3)(p25)	3q21 → qter 3p25 → pter	Spina bifida or sacral dimple
Dup(3q)			
Fear and Briggs [4]	der(13)t(3;13)(q21;q34)mat	3q21 → qter 13q34 → qter	Lumbar meningomyelocele
Schinzel [72]	dup(3)(q21qter), del(5)(p15.2)	3q21 → qter 5p15.2 → pter	Lumbar meningomyelocele
	dup(3)(q21qter), del(5)(p15.2)	3q21 → qter 5p15.2 → pter	Posterior encephalocele
Dup(3p) and del(3p)			
Kennedy et al [71]	der(3)del(3)(p26)dup(3)(p26p21.3)	3p21.3 → p26 3p26 → pter	Lumbosacral meningomyelocele, holoprosencephaly
Dup(3p)			
Suzumori et al [68]	der(11)t(3;11)(p21;q25)mat	3p21 → pter 11q25 → qter	Lumbosacral spina bifida
Del(3q)			
Kosaki et al [73]	del(3)(q12.2q13.2)	3q12.2 → q13.2	Spina bifida, OEIS complex
Jokiaho et al [70]	del(3)(q27)	3q27 → qter	Parietal meningocele

Del = deletion; der = derivative chromosome; mat = maternal origin; dup = duplication; rec = recombinant chromosome; OEIS = omphalocele-exstrophy-imperforate anus-spinal defects.

spina bifida, and the karyotype of 46,XX,der(11) t(3;11)(p21;q25)mat. Kosaki et al [73] reported an infant with del(3)(q12.2q13.2), spina bifida and omphalocele-exstrophy-imperforate anus-spinal defects (OEIS) complex. Jokiaho et al [70] reported a deletion of 3q27 → qter in an infant with mild dysmorphism, parietal meningocele, and neonatal miliaria rubra-like lesion. Possible candidate genes of NTDs in chromosome 3 include *TERC* (telomerase RNA component) (3q21–q28), *DVL3* (Dishevelled 3) (3q27), *ZIC1* (3q24), and *hOGG1* (3p26.2). Dup(3)(q21 → qter) has been associated with spina bifida and encephalocele [4,67]. The region of 3q21–qter contains the *ZIC1*, *TERC* and *DVL3* genes, and the region of chromosome 3p contains the genes of cell adhesion molecules *CNTN4* and *CNTN6* (3p25–p26) [74], and *CHL1* (3p26.1) [75].

Del(4p), dup(4p), del(4q), and dup(4q)

Partial deletions and duplications of chromosome 4 can be associated with spina bifida and encephalocele [19,76–80] (Table 5). Of interest is the association of Wolf-Hirschhorn syndrome with NTDs. Tachdjian et al [77] reported three fetuses with distal 4p deletions of 4p14 → pter, 4p15 → pter or 4p16 → pter, Wolf-Hirschhorn syndrome, and sacral dimples. Carbonell et al [76] reported Wolf-Hirschhorn syndrome, cleft lip and palate, polydactyly, multicystic kidneys, and occipital encephalocele in a fetus with a deletion of 4p (4p15 → pter) mimicking Meckel syndrome. Lam et al [19] reported a fetus with exencephaly, dup(4)(p15.2 → pter), and del(13)(q21.2 → qter). The *SLIT2* gene maps to 4p15.2. In *Drosophila* embryogenesis, the *slit* gene has been shown to play a critical role in central nervous system midline formation; and in humans, *Slit-2* mRNA is expressed exclusively in the spinal cord [81]. Quadrelli et al [79] reported a 5-year-old girl with del(4)(q33), facial and digital dysmorphism, a complex congenital heart defect, a large occipital encephalocele, and postnatal growth deficiency. Mikelsaar et al [78] reported a 7-year-old girl with a duplication of 4q (4q25 → qter), mental retardation, facial dysmorphism, a small umbilical hernia, and spina bifida occulta of the 10th and 11th thoracic vertebrae. Nowaczyk et al [80] reported a male infant with an interstitial deletion of chromosome 4,

Table 5. Reported neural tube defect (NTD) cases with partial aneuploidy of chromosomes 4–12, 14–16, 18, 20, 22, and X

Authors	Chromosome aberration	Deletion or duplication extent	NTDs
Del(4p)			
Tachdjian et al [77]			
Case 1	del(4)(p14)	4p14 → pter	Sacral dimple
Case 2	del(4)(p16)	4p16 → pter	Sacral dimple
Case 3	del(4)(p15)	4p15 → pter	Sacral dimple
Carbonell et al [76]	del(4)(p15)	4p15 → pter	Occipital encephalocele
Dup(4p)			
Lam et al [19]	der(13)t(4;13)(p15.2;q21.2)pat	4p15.2 → pter 13q21.2 → qter	Exencephaly
Del(4q)			
Quadrelli et al [79]	del(4)(q33)	4q33 → qter	Occipital encephalocele
Nowaczyk et al [80]	del(4)(q13.2q23)	4q13.2 → q23	Occipital encephalocele
Dup(4q)			
Mikelsaar et al [78]	der(22)t(4;22)(q25;p11)	4q25 → qter	Spina bifida occulta
Del(5p)			
Schinzel [72]	del(5)(p15.2),dup(3)(q21qter)	5p15.2 → pter 3q21 → qter	Lumbar meningomyelocele
	del(5)(p15.2),dup(3)(q21qter)	5p15.2 → pter 3q21 → qter	Posterior encephalocele
Schinzel [72]	del(5)(p15)	5p15 → pter	Lumbosacral meningocele
Mita et al [82]	del(5p)	5p	Lumbosacral meningomyelocele
Winsor et al [34] two cases	der(5)t(2;5)(p23;p15)mat	5p15 → pter 2p23 → pter	Anencephaly
Walbaum et al [31]	der(5)t(2;5)(p13;p15)mat	5p15 → pter 2p13 → pter	Anencephaly
Del(6p)			
Wright et al [85]	der(6)t(6;11)(p?;q?)pat	6p 11q	Craniorachischisis
Dup(6q)			
Stamberg et al [86]	der(22)t(6;22)(q21;p13)mat	6q21 → qter	Occipital encephalocele
Del(6q)			
Lukusa et al [87]	del(6)(q25.3)	6q25.3→qter	Lumbar spina bifida
Dagna Bricarelli et al [59]	der(6)t(1;6)(q32;q26)mat*	6q26 → qter 1q32 → qter	Occipital meningomyelocele
Dup(7p)			
Carnevale et al [90]	der(14)t(7;14)(p11;p11)mat	7p11 → pter	Frontoethmoidal encephalocele

Del(7q)			
Rodríguez et al [93]	del(7)(q36)	7q36 → qter	Anterior meningomyelocele, sacral agenesis
Drugan et al [11]	del(7)(q32)	7q32 → qter	Encephalocele
Bogart et al [92] Case 4	del(7)(q32)	7q32 → qter	Anencephaly, craniorachischisis
Stevenson et al [91]	del(7)(q22.1q22.3)	7q22.1 → q22.3	Anencephaly
Dup(8q)			
Williams et al [98] Case 3	rec(8)dup q, inv(8)(p23q22)	8q22 → qter	Occipital encephalocele
Schinzel [97]			
Case 1	der(18)t(8;18)(q23;p11.3)mat	8q23 → qter	Frontal meningocele of the skull, lower thoracic and lumbar spina bifida
Case 2	der(18)t(8;18)(q23;p11.3)mat	8q23 → qter	Lower thoracic spina bifida
Del(9p)			
Fineman et al [30]	der(9)t(2;9)(p13;p24)mat	9p24 → pter 2p13 → pter	Spina bifida
Del(10q)			
Singer et al [32]	der(10)t(2;10)(p24;q26)mat	10q26 → qter 2p24 → pter	Anencephaly
Carriere [27]	der(10)t(2;10)(p23;q26)mat*	10q26 → qter 2p23 → pter	Encephalocele
Del(11q)			
Suzumori et al [68]	der(11)t(3;11)(p21;q25)mat	11q25 → qter 3p21 → pter	Lumbosacral spina bifida
Dup(11q)			
Wright et al [85]	der(6)t(6;11)(p?;q?)pat	11q 6p	Craniorachischisis
Kennedy et al [18]	der(13)t(11;13)(q23.1;q34)mat	11q23.1 → qter 13q34 → qter	Lumbosacral meningomyelocele
Park et al [100]	+der(13)t(11;13)(q21;q14)mat	11q21 → qter 13pter → q14	Sacral spina bifida
Bader et al [69]	der(3)t(3;11)(p26;q21)mat	11q21 → qter 3p26 → pter	Lumbosacral meningomyelocele
Dup(12p)			
Golabi et al [60] Case 1 and 2	der(1)t(1;12)(q43;p13)mat	12p13 → pter 1q43 → qter	Occipital encephalocele, lumbar spina bifida
Dup(14q)			
Thauvin-Robinet et al [65]	der(1)t(1;14)(p35;q32)mat	14q32 → qter 1p35 → pter	Occipital encephalocele

(continued on next page)

Table 5. *(continued)*

Authors	Chromosome aberration	Deletion or duplication extent	NTDs
Del(14q)			
Claussen et al [105]	del(14)(q31)	14q31 → qter	Encephalocele
Del(15q)			
Doray et al [37]	der(15)t(2;15)(p22;q26)mat	15q26 → qter 2p22 → pter	Craniorachischisis
	der(15)t(2;15)(p22;q26)mat	15q26 → qter 2p22 → pter	Anencephaly
Hahm et al [35]	der(15)t(2;15)(p21;q26)	15q26 → qter 2p21 → pter	Anencephaly
Dup(16q)			
Gustavsson et al [106]	der(11)ins(11;16)(q13;q12.1q22.1)	16q12.1 → q22.1	Lumbosacral meningomyelocele
Del(18q)			
Dowton et al [107]	del(18)(q22.2)	18q22.2 → qter	Thoracolumbar meningomyelocele
r(18)			
Bird et al [109]	r(18)(p11q12)	18p11 → pter 18q12 → qter	Anencephaly
Cohen et al [108]	r(18)	18p	Encephalocele, cyclopia
Dup(20p)			
Zumel et al [112]	der(15)t(15;20)(p11.2;p12)	20p12 → pter	Anencephaly
+i(20p)			
Wu et al [113]	+i(20)(p10)	tetrasomy 20p	Occipital encephalocele
Del(22q)			
Nickel et al [116] three cases	del(22)(q11.21q11.23)	22q11.21 → q11.23	Lumbar or lumbosacral meningomyelocele
Forrester et al [117] two cases	del(22)(q11.2q11.2)	22q11.2	Lumbosacral meningomyelocele
Seller et al [118]	del(22)(q11.2q11.2)	22q11.2	Sacral spina bifida
Maclean et al [119] two cases	del(22)(q11.2q11.2)	22q11.2	Sacral meningomyelocele
Del(Xp)			
Plaja et al [124]	del(X)(p22.1)	Xp22.1 → pter	Acrania, cervicodorsal rachischisis
Dup(Xq)			
Hol et al [125]	dup(X)(q26q27)	Xq26 → q27	Lower lumbar spina bifida
	dup(X)(q26q27)	Xq26 → q27	Lumbosacral meningomyelocele

**Presumed rearrangement. Del = deletion; dup = duplication; der = derivative chromosome; pat = paternal origin; mat = maternal origin; rec = recombinant chromosome; ins = insertion; r = ring chromosome; i = isochromosome.*

del(4)(q13.2q23), occipital encephalocele, cleft palate, short limbs, and congenital heart defects.

Del(5p)

Distal 5p deletion or cri du chat syndrome can be associated with spina bifida and anencephaly [31,34, 72,82] (Table 5). Schinzel [72] reported a 3-week-old girl with large lumbosacral meningocele, cri du chat syndrome, and del(5)(pter → p15). Mita et al [82] reported a 48-day-old girl with deletion of 5p, cri du chat syndrome, characteristic cry, mental retardation, microcephaly, facial dysmorphism, umbilical hernia, prolapsus ani, dislocation of the hip joint, and lumbosacral meningomyelocele. Of interest is the occurrence of NTDs in concomitant dup(2p) and del(5p), and in concomitant dup(3q) and del(5p). Walbaum et al [31] reported recurrent anencephaly in sib fetuses with partial trisomy 2p (2p13 → pter) and partial monosomy 5p (5p15 → pter). Winsor et al [34] reported recurrent anencephaly in sib fetuses with partial trisomy 2p (2p23 → pter) and partial monosomy 5p (5p15 → pter). Schinzel [72] reported recurrent NTDs in two unbalanced offsprings with dup(3)(q21 → qter) and del(5)(pter → p15.2). The first underweight girl had lumbar myelomeningocele, Arnold-Chiari malformation, agenesis of the corpus callosum, anal stenosis, intestinal malrotation, Meckel's diverticulum, and uterus bicornis. The following prenatally diagnosed fetus had gastroschisis, posterior encephalocele, and uterus bicornis. Chromosome 5p contains the two genes *CDH18* (cadherin-18) (5p15.2–p15.1) and *IRX1* (5p15.3) that are important for neural morphogenesis. CDH18 is expressed through the central nervous system [83], and *IRX1* is involved in neurogenesis [84].

Del(6p), dup(6q), and del(6q)

Partial deletions and duplications of chromosome 6 can be associated with spina bifida, encephalocele, and craniorachischisis [59,85–87] (Table 5). Wright et al [85] reported craniorachischisis in a fetus with partial trisomy 11q and partial monosomy 6p due to an unbalanced translocation inherited from a carrier father with a reciprocal translocation, t(6p+;11q–). The human *TFAP2A* (transcription factor AP-2α) gene maps to 6p24 and the *AP-2* knockout mice have been shown to exhibit anencephaly, craniofacial abnormalities, thoraco-abdominoschisis, and skeletal defects [88]. *JUMONJI*, the human homologue of the mouse *jumonji* gene, is required for the closure of the neural tube and maps to 6p23–p24 [89]. Stamberg et al [86] reported a stillborn infant with occipital encephalocele, ambiguous genitalia, imperforate anus, omphalocele, unilateral hydronephrosis, and the karyotype of 46,*XY*,der(22) t(6;22)(q21;p13) or (q21;pter)mat and partial trisomy 6q (6q21 → qter). Lukusa et al [87] reported a 10-year-old mentally retarded boy with terminal 6q25.3 deletion, dysmorphism, abnormal behavior, and lumbar spina bifida. Dagna Bricarelli et al [59] reported occipital myelomeningocele in a case with partial trisomy 1q (1q32 → qter) and partial monosomy 6q (6q26 → qter) because of unbalanced translocation inherited from maternal t(1;6)(q32;q26). Other possible candidate genes of NTDs in the involved segments of chromosome 6 include *Cited 2* (6q23.3), *MACS* (6q22.2), and *T box* (human analogue of Brachyury gene in mice) (6q27).

Dup(7p) and del(7q)

Partial duplications of chromosome 7p can be associated with encephalocele, and partial deletions of chromosome 7q can be associated with spina bifida, encephalocele, and anencephaly [11,90–93] (Table 5). Carnevale et al [90] reported frontoethmoidal encephalocele in an infant with dup(7)(p11 → pter) due to der(14)t(7;14)(p11;p11)mat. Stevenson et al [91] reported a male fetus with anencephaly, a beaked nose, bifid thumbs, hypoplastic genitalia, and the karyotype of 46,*XY*,del(7)(q22.1q22.3). Rodríguez et al [93] reported an 18-month-old boy with mental retardation, microcephaly, a distinctive face, bilateral coloboma, café-au-lait spot in the abdomen, sacral agenesis, anterior myelomeningocele, and a terminal deletion of the long arm of chromosome 7 (7q36 → qter). Drugan et al [11] reported encephalocele in a case with del(7)(q32). Bogart et al [92] reported a 16-week gestation fetus with anencephaly, complete craniorachischisis, and del(7)(q32). The human *HLXB9* gene maps to 7q36 and is involved in Currarino syndrome with autosomal dominant sacral agenesis and the associated features of anorectal malformation, a presacral mass, and urogenital malformation [94]. *SHH* gene also maps to 7q36 and is responsible for holoprosencephaly 3 (HPE3) [95,96]. Another possible candidate gene of NTDs in the segment involved in chromosome 7 is *HOXA1* (7p15.3).

Dup(8q)

Partial duplications of chromosome 8q can be associated with encephalocele and spina bifida [97,98] (Table 5). Schinzel [97] reported frontal meningocele of the skull and spina bifida of the lower thoracic and lumbar spine, bilateral talipes equinovarus, mental retardation in a girl, and lower thoracic spina bifida in her half-sister, both with dup(8)(q23 → qter) due to der(18)t(8;18)(q23;p11.3)mat. Williams et al [98] reported occipital encephalocele in an infant with

recombinant chromosome 8 syndrome, atrial septal defect, patent ductus arteriosus, bilateral abdominal cryptorchidism, polycystic kidneys and hypoplastic ureters, hydrocephalus, prominent pons, valgus deformity of foot, and dup(8)(q22 → qter) due to paternal inv(8)(p23q22).

Del(9p)

Fineman et al [30] reported spina bifida associated with del(9)(p24 → pter) and dup(2)(p13 → pter) due to der(9)t(2;9)(p13;p24)mat.

Del(10q)

Singer et al [32] reported prenatal diagnosis of del(10)(q26 → qter) and dup(2)(2p24 → pter) by amniocentesis in the third pregnancy of a woman with fetal anencephaly and congenital cystic disease of the right kidney. The maternal karyotype was 46,*XX*,t(2;10)(p24;q26) and the fetal karyotype was 46,*XY*,der(10)t(2;10)(p24;q26)mat. The woman's first pregnancy resulted in a female fetus with anencephaly and left hydronephrosis. Pedigree analysis revealed that the woman had a maternal aunt with spina bifida.

Del(11q) and dup(11q)

Suzumori et al [68] reported the prenatal diagnosis of del(11)(q25 → qter) and dup(3)(p21 → pter) in a fetus with cleft lip and palate, absent genitalia, lumbosacral spina bifida, and the karyotype of 46,*XX*,der(11)t(3;11)(p21;q25)mat. Craniorachischisis and spina bifida have been described in dup(11q) [18,69,85,99,100]. Rott et al [99] first observed familial NTDs and possible duplication of distal 11q in three cases with myelomeningocele, spina bifida, and spina bifida with meningocele, respectively. Kennedy et al [18] reported a duplication of 11q and a deletion of 13q associated with spina bifida. Wright et al [85] reported a duplication of 11q and a deletion of 6p associated with craniorachischisis. Bader et al [69] reported a fetus with a duplication of the segment 11q21 → qter and a deletion of the segment 3p26 → pter associated with lumbosacral meningomyelocele. Park et al [100] reported the prenatal diagnosis of an 18-week gestation fetus with prominent scoliosis involving the lumbar to sacral regions, sacral rachischisis aperta (spina bifida) with myeloschisis, low-set ears, micrognathia, occipital hypoplasia, a large left congenital diaphragmatic hernia, and dup(11)(q21 → qter) and dup(13)(pter → q14) due to unbalanced 3:1 disjunction of a maternal t(11;13)(q21;q14) translocation. Chromosome 11q contains *NAP1L2* (11q23.1), which is a possible NTD candidate gene, and other genes such as *FOLR1* and *FOLR2* (11q13.3–q13.5) for human folate receptor [101,102], *MKS2* (11q13) [103], and *Barx2* (11q25) [104].

Dup(12p)

Golabi et al [60] reported double NTDs of occipital encephalocele and lumbar spina bifida in two sibs with dup(12)(p13 → pter) and del(1)(q43 → qter) due to 46,*XX*,der(1)t(1;12)(q43;p13)mat.

Del(14q) and dup(14q)

Thauvin-Robinet et al [65] reported the prenatal diagnosis of anhydramnios, occipital encephalocele, and enlarged bladder in a 12-week gestation fetus with the karyotype of 46,*XY*,der(1)t(1;14)(p35;q32)mat, a 1p35–pter deletion and a 14q32–qter duplication. Claussen et al [105] reported encephalocele in a 34-week gestation fetus with del(14)(q31 → qter). The DNA repair gene *XRCC3* maps to 14q32.3.

Del(15q)

Doray et al [37] reported the prenatal diagnosis of del(15)(q26 → qter) and dup(2)(p22→pter) due to 46,*XY*,der(15)t(2;15)(p22;q26)mat in two male sib fetuses by chorionic villus sampling. Both fetuses had NTDs, with craniorachischisis in the first fetus and anencephaly in the second fetus. Hahm et al [35] reported the prenatal diagnosis of del(15)(q26 → qter) and dup(2)(p21 → pter) in a 19-week gestation fetus with minor facial anomalies, musculoskeletal defects, postaxial polydactyly, and anencephaly. The fetal karyotype was 46,*XY*,der(15)t(2;15)(p21;q26).

Dup(16q)

Gustavsson et al [106] reported a girl with a duplication of 16q12.1–q22.1, the karyotype of 46,*XX*,der(11)ins(11;16)(q13;q12.1q22.1), lumbosacral myelomeningocele, Arnold-Chiari II malformation, mental retardation, strabismus, micrognathia, epileptic seizures, and growth retardation.

Del(18q) and r(18)

Dowton et al [107] reported an infant with asymmetry of the left hemithorax, widely spaced nipples, scoliosis, a skin-covered thoracolumbar myelomeningocele, left talipes equinovarus, severe right paraxial fibular hemimelia and the karyotype of 46,*XX*,del(18)(q22.2). Anencephaly and encephalocele have been described in r(18) [108,109]. Cohen et al [108] reported cyclopia and encephalocele in a case with r(18). Bird et al [109] reported an infant with anencephaly, premaxillary agenesis and the karyotype of 46,*XX*,r(18)(p11q12). *TGIF* maps to 18p11.3 [110,111] and is responsible for HPE4.

Dup(20p) and +i(20p)

Zumel et al [112] reported prenatal diagnosis of dup(20)(p12 → pter) due to der(15)t(15;20)(p11.2; p12) in a 16-week gestation fetus with anencephaly. Wu et al [113] reported the prenatal diagnosis of pure tetrasomy 20p, or 47,XX,+i(20)(p10) by cord blood sampling in a 24-week gestation fetus with occipital encephalocele, mega-cisterna magna, mesomelic shortening, and clubfeet. Possible candidate genes of NTDs in chromosome 20p include *PAX1* (20p11.2). Helwig et al [114] reported a mouse with spina bifida and double heterozygosity for mutations in *PAX1* and *PGDFRA*. Hol et al [115] reported an amino acid substitution in *PAX1* in a patient with spina bifida.

Del(22q)

All reported NTDs associated with a 22q11.2 microdeletion are spina bifida [116–119]. Kousseff [120] first reported three sibs with sacral myelomeningocele, conotruncal cardiac defects, and minor head and neck anomalies. Toriello et al [121] reported an additional similar case and designated the disorder as "Kousseff syndrome". Nickel et al [116] reported three unrelated children with meningocele, one with DiGeorge syndrome, two with velocardiofacial syndrome, and all with a 22q11.2 deletion. Seller et al [118] reported a 22-week gestation fetus with sacral spina bifida, conotruncal cardiac defects, cleft palate, facial dysmorphism, Kousseff syndrome, and del(22)(q11.2q11.2). Forrester et al [117] studied the family described by Kousseff [120] and found a deletion of chromosome 22q11–q13 in the proband, his diseased brother, and his father. The proband, his brother and his sister had myelomeningocele and clinical findings consistent with DiGeorge syndrome/velocardiofacial syndrome. Maclean et al [119] reported two cases of sacral meningomyelocele, conotruncal cardiac anomalies, Kousseff syndrome, and a 22q11.2 microdeletion and suggested that Kousseff syndrome is a distinct clinical entity that is genetically heterogeneous. The region of chromosome 22q11 contains *DVL1L1*, which is expressed in several fetal and adult tissues including thymus and heart [122], and *MRPL40* (*NLVCF*), which is expressed in the first and second pharyngeal arches and the neural tube [123].

Del(Xp) and dup(Xq)

Partial deletions or duplications of chromosome X can be associated with anencephaly, spina bifida, and craniorachischisis [124,125] (Table 5). Plaja et al [124] reported an anencephalic fetus with acrania, cervicodorsal rachischisis, a left diaphragmatic hernia, ipsilateral lung hypoplasia, intestinal malrotation, horseshoe kidneys, adrenal gland hypoplasia, del(X)(p22.1 → pter), and the karyotype of 46,X,del(X)(p22.1). Hol et al [125] reported familial duplication of Xq26–q27 in two brothers, their mother, and their grandmother. The first brother had lower lumbar spina bifida occulta and deep sacral dimples, and the second brother had a large lumbosacral meningomyelocele. Cytogenetic analysis revealed the karyotype of 46,XY,dup(X)(q26q27), and fluorescence *in situ* hybridization analysis revealed that the duplication extended from Xq26.1 to Xq27.3. Fryns et al [126] reported a case of spina bifida with a *de novo* X/autosomal translocation of t(X;22)(q27;q12.1) pointing to a possible causative gene in Xq27. X-linked inheritance of NTDs has been postulated [127,128]. However, two studies of linkage analysis excluded linkage to the X chromosome [129,130]. *NLGN4* maps to Xq22.33 and is associated with X-linked mental retardation and autism [131]. *ZIC3* maps to Xq26.2 and is a possible candidate gene for NTDs [132,133].

Conclusion

This article provides a comprehensive review of structural chromosomal abnormalities associated with NTDs, such as del(13q), r(13), dup(2p), del(2q), del(1p), del(1q), dup(1q), del(3p), dup(3p), del(3q), dup(3q), del(4p), dup(4p), del(4q), dup(4q), del(5p), del(6p), dup(6q), del(6q), dup(7p), del(7q), dup(8q), del(9p), del(10q), del(11q), dup(11q), dup(12p), dup(14q), del(14q), del(15q), dup(16q), del(18q), r(18), dup(20p), +i(20p), del(22q), del(Xp), and dup(Xq). NTDs may be associated with aneuploidy. Perinatal identification of NTDs should alert one to the possibility of chromosomal abnormalities and prompt a thorough cytogenetic investigation and genetic counseling.

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