Letter to the Editor

Cytogenetic and Genome Research

Cytogenet Genome Res 2014;144:28–30
DOI: 10.1159/000367908

Accepted: May 9, 2014
by M. Schmid
Published online: October 14, 2014

Clinical Manifestations of Partial Trisomy 2p

Iosif W. Lurie

Chromosome Disorder Outreach, Boca Raton, Fla., USA

Sir,

Martínez-Juárez et al. [2014] reported 2 siblings with trisomy 2p caused by maternal translocation t(2;12)(p22.3q24.3). Neither of these siblings nor several other patients with pure trisomy 2p cited by these authors had congenital diaphragmatic hernia (CDH), neuroblastoma or neural tube defects (NTD). Almost 20 years ago, we [Lurie et al., 1995] suggested that these findings are causally related to trisomy 2p. Martínez-Juárez et al. state that our conclusion was false and that these findings actually are caused by associated chromosomal imbalances.

CDH was reported in 7 patients with trisomy 2p (table 1). Four of these patients had associated deletions for other chromosomes, 1 had mosaic trisomy for the whole 2p and proximal part of 2q (from centromere to 2q11.2) [Kan et al., 2014], and 2 had pure trisomy 2p [Heathcote et al., 1991; Blassnig-Ezeh et al., 2013]. In the latter observation, absence of any associated imbalance was confirmed by molecular methods. Blassnig-Ezeh et al. [2013] narrowed down the critical segment for CDH to approximately 8 Mb (between 42.3 and 50.0 Mb) on 2p21. In that context, there are no reasons to relate the origin of CDH to any chromosomal abnormalities that accompanied trisomy 2p.

Table 1. CDH in individuals with partial trisomy 2p

Reference	Trisomic segment	Associated imbalance
Kan et al., 2014	2cen–pter (mosaic)	dup 2cen–q11.2 (mosaic)
Sarda et al., 1992	2p13pter	del Xp13pter
Blassnig-Ezeh et al., 2013	2p16.3p21	–
Mosca et al., 2011	2p16.3pter	del 15q26.2qter
Heathcote et al., 1991	2p21p25	–
León León et al., 2011	2p21pter	del 18p11pter
Bender et al., 1969	2p23pter	del 6p25pter

Table 2. Neuroblastoma in individuals with partial trisomy 2p

Reference	Trisomic segment	Associated imbalance
Say et al., 1980	2p21p25	–
Dowa et al., 2006	2p21pter	del 8p23.2pter
Stephane et al., 2003	2p22pter	del 8p23pter
Nagano et al., 1980	2p22.3pter	del 16p13.3pter
Patel et al., 1997	2p23pter	del 13q34qter
Yüksel et al., 2002	2p23pter	del 17q25qter
Morgenstern et al., 2014	2p23pter	del 16p13.3pter
Nowaczyk et al., 2000	2p23.2pter	del 7q36.1qter
Warad et al., 2012	2p24.1p25.3	–
Lipska et al., 2013	2p24.1pter	del 18q22.3qter
Van Mater et al., 2013	2p24.3 (1 Mb)	dup 3q29 (0.144 Mb) del 20p12.1 (0.219 Mb)

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1424–8581/14/1441–0028$39.50/0

Iosif W. Lurie
913 Rachel Jordan Court
Owings Mills, MD 21117 (USA)
E-Mail iosifw@gmail.com

Table 3. NTD in individuals with partial trisomy 2p

Reference	Trisomic segment	Associated imbalance	Type of defect
Therkelsen et al., 1973	2p13p24	–	spina bifida
Fineman et al., 1983	2p13pter	del 9p24pter	spina bifida
Walbaum et al., 1984	2p13pter	del 5p15pter	anencephaly
Sarda et al., 1992	2p13pter	del Xp13pter	spina bifida
Mosca et al., 2011	2p16.3pter	del 15q26.2qter	spina bifida
Hahm et al., 1999	2p21pter	del 15q26qter	anencephaly, spina bifida
Kim et al., 2007	2p21pter	del 5p15pter	exencephaly
Thangavelu et al., 2004, case 1	2p22p25	–	anencephaly
Thangavelu et al., 2004, case 2	2p22p25.3	–	anencephaly
Doray et al., 2003, case 1	2p22pter	del 15q26qter	anencephaly, spina bifida
Doray et al., 2003, case 2	2p22pter	del 15q26qter	anencephaly
Winsor et al., 1997, case 1	2p23pter	del 5p15pter	anencephaly
Winsor et al., 1997, case 2	2p23pter	del 5p15pter	anencephaly
Stallworth et al., 2008	2p23pter	del 9p24pter	anencephaly, spina bifida
Wellesley and Boyle, 2000	2p23.1pter	del 3q29qter	anencephaly, spina bifida
Singer et al., 1987	2p24pter	del 10q26qter	anencephaly
Cain et al., 2008	2p25.1pter	del 13q32qter	occipital encephalocele
Gregory et al., 2000, case 1	2p25.2pter	del 10q26.3qter	anencephaly
Gregory et al., 2000, case 2	2p25.2pter	del 10q26.3qter	anencephaly
Poulose et al., 2007	2p25.2pter	del 10q26.3qter	'exencephaly-anencephaly'

At least 11 patients with trisomy 2p developed neuroblastoma (table 2). Two of these patients had pure trisomy 2p [Say et al., 1980; Warad et al., 2012], another had an additional 0.144-Mb duplication of 3q29 and a 0.219-Mb deletion of 20p12.1 [Van Mater et al., 2013]. In the opinion of Martínez-Juárez et al. [2014], a person with an imbalance of this size may be classified as pure duplication 2p. Eight others had an associated imbalance. New data show that duplication of the *MYCN* locus at 2p24.3 is responsible for the origin of neuroblastoma in patients with trisomy 2p [Lipska et al., 2013].

NTD were found in 20 published patients with trisomy 2p (table 3). There are no other partial trisomies where NTD were reported in such a large number of persons. In at least 3 patients [Therkelsen et al., 1973; Thangavelu et al., 2004], anencephaly or spina bifida was found without any associated imbalance.

Of course, several reports of the above-mentioned abnormalities in individuals with pure trisomy 2p were published in the 'pre-molecular era', and a tiny associated imbalance for other chromosomal segments could not be completely excluded. However, neither of the partial monosomies associated with neuroblastoma (deletions of the distal parts of 7q, 8p, 13q, 16p, 17q, or 18q) are known as causative factors for the origin or this tumor. The same is true for partial monosomies in patients with trisomy 2p and NTD, because these deletions (with the exception of del 13q) are not known as being associated with anencephaly or spina bifida. These facts suggest that trisomy 2p itself but not the associated imbalances are responsible for the origin of NTD.

So, there is strong evidence that all 3 groups of the above-mentioned defects are caused by trisomy 2p, but not by the associated imbalance.

Martínez-Juárez et al. [2014] state that a horseshoe kidney observed in one of their patients is a 'previously unrecognized defect associated with this syndrome'. Actually, however, horseshoe kidney was reported both in patients with pure trisomy 2p [Cummings et al., 1997] and in association with another imbalance [Larson et al., 1982].

Also, both siblings reported by Martínez-Juárez et al. [2014] were presented by Quintana Palma et al. [2010] at the 35th annual meeting of the Mexican Society of Human Genetics. The published abstract of their presentation states that the boy had unilateral renal agenesis and hypospadias (although in the article they describe these defects as horseshoe kidney and overriding scrotum).

Precise description of the phenotype, thorough and critical review of the literature, as well as care in drawn conclusions are important issues to consider in the writing of any scientific paper.

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