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22q11.21 Deletion Syndromes: A Review of Proximal, Central, and Distal Deletions and Their Associated Features

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Abstract
Chromosome 22q11.21 contains a cluster of low-copy repeats (LCRs), referred to as LCR22A–H, that mediate meiotic non-allelic homologous recombination, resulting in either deletion or duplication of various intervals in the region. The deletion of the DiGeorge/velocardiofacial syndrome interval LCR22A–D is the most common recurrent microdeletion in humans, with an estimated incidence of ~1:4,000 births. Deletion of other intervals in 22q11.21 have also been described, but the literature is often confusing, as the terms 'proximal', 'nested', 'distal', and 'atypical' have all been used to describe various of the other intervals. Individuals with deletions tend to have features with widely variable expressivity, even among families. This review concisely delineates each interval and classifies the reported literature accordingly.

Recurrent copy number changes that occur throughout the genome are often flanked by repetitive DNA sequences referred to as segmental duplications or low-copy repeats (LCRs). These high-homology sequences mediate recurrent copy number changes (CNVs) via meiotic non-allelic homologous recombination [Shaikh et al., 2000; Stankiewicz and Lupski, 2002]. Several genomic disorders resulting from recurrent CNVs have been described for chromosomes 2, 7, 15, 16, 17, and 22 [Shaffer and Lupski, 2000; Stankiewicz and Lupski, 2002]. The proximal long arm of chromosome 22 contains a cluster of LCRs (LCR22A–H) which predispose to various combinations of recurrent CNVs, the most common of which is the deletion of ~3 Mb spanning LCR22A–D (A–D) leading to DiGeorge syndrome (DGS)/velocardiofacial syndrome. This is also the most common recurrent microdeletion in humans, with an incidence of ~1:4,000 births, although this may be underestimated due to the phenotypic variability and ascertainment bias in reported cases [McDonald-McGinn et al., 1999; Rosenfeld et al., 2013]. Approximately 85–90% of individuals with DGS have the ~3-Mb A–D deletion, while 8–10% have a nested ~1.5-Mb LCR22A–B (A–B) deletion, and individuals with atypical deletions with at least 1 breakpoint not in an LCR have also been reported [Edelmann et al., 1999; McDonald-McGinn et al., 1999; Shaikh et al., 2000; Nogueira et al., 2008; Beaujard et al., 2009; Weisfeld-Adams et al., 2012]. Both A–B and A–D deletions result in similar phenotypes, presumably due to loss of common critical genes. The characteristic phenotype of DGS includes car-

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diac defects (primarily conotruncal anomalies), velopharyngeal insufficiency, immune deficiency due to thymic hypo-/aplasia, and hypocalcemia due to parathyroid gland hypoplasia [McDonald-McGinn et al., 1999]. Deletions of more distal regions have also been reported extensively, and many of those individuals were referred for suspicion of DGS, highlighting the similarity of phenotypic features for these CNVs [Kurahashi et al., 1996; Rauch et al., 1999, 2005; Saitta et al., 1999; Shaikh et al., 2000; Garcia-Miñaur et al., 2002; Wieser et al., 2005; Jackson et al., 2007; Mikhail et al., 2007, 2014; Ben-Shachar et al., 2008; Jalali et al., 2008; Rødningen et al., 2008; Xu et al., 2008; Lafay-Cousin et al., 2009; Ogilvie et al., 2009; Bruce et al., 2010; Madan et al., 2010; Beddow et al., 2011; Bourdeaut et al., 2011; Eaton et al., 2011; Garavelli et al., 2011; Nik-Zainal et al., 2011; Tan et al., 2011; Toth et al., 2011; Verhoeven et al., 2011; Yu et al., 2011; Breckpot et al., 2012; Pebrel-Richard et al., 2012; Verhagen et al., 2012; Fagerberg et al., 2013; Zhao et al., 2013; Rump et al., 2014; Racedo et al., 2015]. The literature for these other CNVs is not uniform with respect to the designation of particular intervals, and previous reviews have grouped proximal and distal CNVs together [Tan et al., 2010; Yu et al., 2011].

The purpose of this review is to systematically classify each of the regions of CNV in order to standardize the nomenclature and provide details of the clinical features of patients reported in the literature, as well as our own cohort of postnatal and prenatal cases. We conducted a thorough search of available literature with regard to CNVs in 22q11.2 with the exception of the proximal A–D region. For this CNV, we used the GeneReviews® entry as a primary source (http://www.ncbi.nlm.nih.gov/books/NBK1523/). Primary literature was queried with respect to A–B versus A–D deletions, as these are grouped together in the GeneReviews entry.

New Cohort Included in This Study

From December 2008 to December 2014, our laboratory reported ~82,000 postnatal microarrays, and from November 2010 to December 2014, we reported ~22,000 prenatal microarrays. Reports that described a CNV in 22q11.2 were included in this study. These individuals were further divided into proximal, central, and distal CNVs, as shown in figure 1. While individuals for whom we had no clinical information were included in the total, these individuals were excluded from the phenotypic analysis. It should be noted that ascertainment bias is inevitable in this cohort, and that clinical information provided may not be complete.

Proximal Deletions (A–B, A–D, A–E, A–F)

The proximal deletions of 22q (fig. 1) most typically have a common proximal breakpoint in LCR22A, and either span A–D or A–B. Deletion of either results in one of the most prevalent microdeletion syndromes in humans, DGS/velocardiofacial syndrome [McDonald-McGinn et al., 1999]. The most common features for DGS are summarized in table 1 and include postnatal growth restriction, congenital heart defects, palatal abnormalities, microcephaly, intellectual disability, psychiatric and/or behavioral problems, developmental delay, language delay, hypotonia, feeding problems/gastrointestinal abnormalities, and renal anomalies [McDonald-McGinn et al., 1999]. Other features may also be present, such as skeletal issues and ocular anomalies, but are found in fewer individuals overall. Hypocalcemia that can lead to seizures is also a common feature unique to individuals with proximal 22q deletions.

It is generally accepted that >90% of proximal deletions are de novo, and studies have demonstrated enrichment of a maternal origin of these de novo deletions, attributed to higher rates of meiotic crossover in females [Delio et al., 2013]. However, familial cases with variable expressivity have been well documented [McDonald-McGinn et al., 1999], and inheritance of proximal deletions, both A–D and A–B, has been observed to be as high as 28% [Fernández et al., 2005]. Fernández et al. [2005] reported that the nested A–B deletions tended to be found more in families, a finding supported by Adeyinka et al. [2004]. Adeyinka et al. [2004] described a cohort of 10 families with at least 2 members testing positive for DGS deletions and found that 70% of the inherited deletions in their study were the nested A–B region. These authors also reported that most transmitting parents of the A–B deletion were female, consistent with previous studies of inherited deletions, although whether those were A–B or A–D deletions in those studies is not always provided [Ryan et al., 1997; McDonald-McGinn et al., 2001; Adeyinka et al., 2004; Delio et al., 2013]. One hypothesis for this apparent difference in inheritance rates between the A–B and A–D deletions is that the smaller deletion may result in an overall milder phenotype and therefore be observed more frequently in families, but individuals with more severe phenotypes having the A–B deletion have also been reported [Digilio et al., 2003; Fernández et al., 2005]. Another hypothesis is that individuals, particularly males, with the 3-Mb A–D deletion are less fecund, perhaps due to loss of gene(s) important for gamete development, although this hypothesis is also controversial

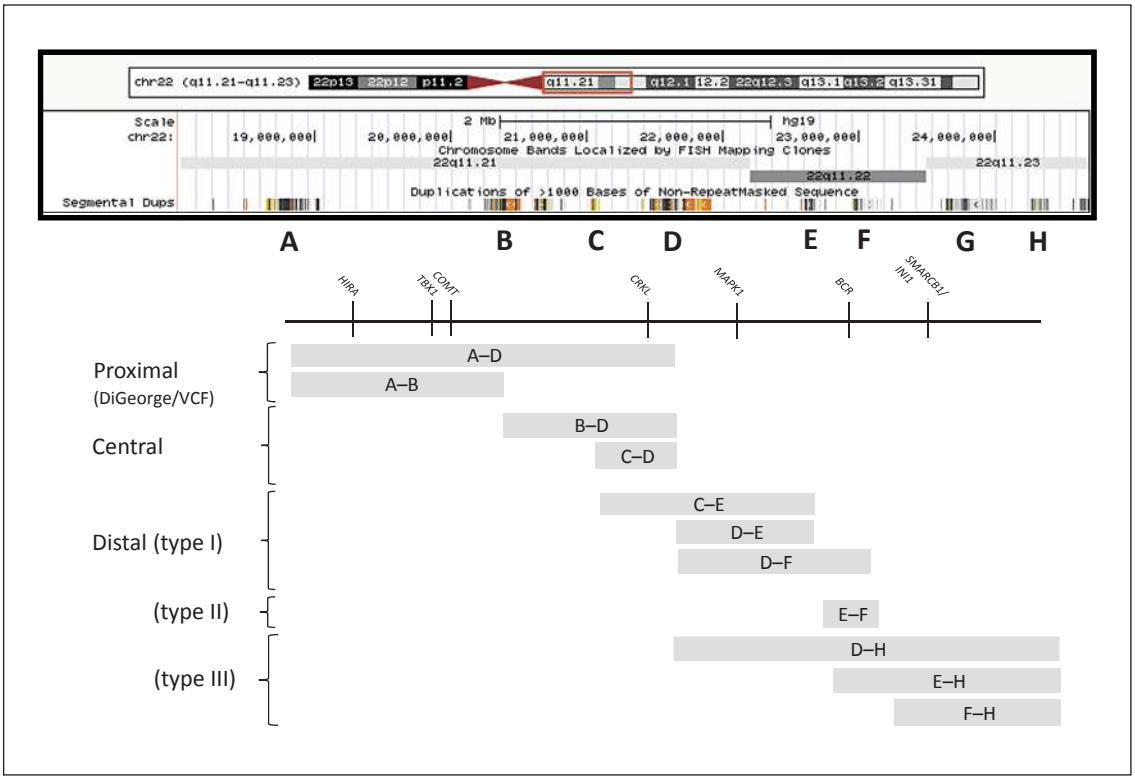

Fig. 1. Proximal 22q11.2 region from the UCSC Genome Browser (http://genome.ucsc.edu/cgi-bin/hgTracks?db=hg19&position=chr22%3A18000000–24500000&hgsid=427040253_tbGHNQ83ZO1oFT0Xb7uDyhyZYwIU). LCR22A–H are labeled, and key genes in each interval are noted.

[Leana-Cox et al., 1996; Fernández et al., 2005]. The reason(s) for the apparent differences in the rate of inheritance between the 2 deletion intervals remains to be determined conclusively.

For the time frame of December 2008 to December 2014, our lab reported 426 proximal deletions from ~82,000 postnatal microarrays performed. Of those, 35 (8%) were nested A–B deletions. Clinical information was provided for 23 individuals with A–B deletions: 4 (17%) had a cardiac defect, 2 (9%) were referred for suspicion of velocardiofacial syndrome, and 19 (83%) were referred for developmental delays and/or intellectual disabilities. Of those 35 A–B deletions reported postnatally, 8 had follow-up studies with 5 being de novo, 2 that were maternally inherited, and 1 which is known to be familial since 2 siblings have the deletion, but the parental carrier is not known.

From November 2010 to December 2014, we reported 92 proximal deletions from ~22,000 prenatal microarrays, 8 of which were A–B deletions. Two of those have had familial follow-up studies, and both were maternally inherited. In total, our data include 43 A–B deletions of a total of 518 proximal events (8%).

Deletions spanning LCR22B–D (B–D) or LCR22C–D (C–D) at the distal end of the 3-Mb DGS region have been described in the context of nested and/or atypical proximal deletions in most reports, but as these regions do not include the critical genes for DGS, *HIRA* and *TBX1*, it is more appropriate to classify these intervals differently. Rump et al. [2014] have proposed 'central' 22q deletions, a terminology which is adopted in this review. As such, these CNVs are discussed in the next section.

Central Deletions (B–D, C–D)

Central deletions span either B–D or C–D, nested at the distal end of the larger 3-Mb DGS interval, but not including the DGS critical genes *HIRA* or *TBX1*. In the studies by Rump et al. [2014], Breckpot et al. [2012], Ogilvie et al. [2009], and Garavelli et al. [2011], the authors also included individuals with deletions spanning

Table 1. Common phenotypic features for individuals with deletion of each interval in 22q11.21q11.23

Phenotypic features	Deletion				
	proximal[a] (A–B, A–D)	central[b] (B–D, C–D)	distal		
			type I[c] (C–E, D–E, D–F)	type II[d] (E–F)	type III[e] (any incl. *SMARCB1*)
Number of individuals reported[f]	incidence ~1:4,000 births	76	45	8	17 (14 begin at D)
Follow-up: origin	93% DN	35: 14 fam, 13 unk, 8 DN	45: 1 fam, 16 unk, 28 DN	5: 1 fam, 4 DN	6: 6 DN
Growth restriction/short stature	growth lag in childhood, adults mostly normal	16/68 (24%)	25/45 (56%)	2/8 (25%)	2/17 (12%)
Immune deficiency/recurrent infections	77%	10/68 (15%)	9/45 (20%)	none reported	1/17 (6%)
Hypocalcemia	50%	none reported	1 borderline/45 (2%)	none reported	none reported
CNS anomalies/seizures	<20%	11/68 (16%)	3/45 (7%)	2/8 (25%)	1/17 (6%)
Hypotonia	common	6/68 (9%)	3/45 (7%)	1/8 (13%)	none reported
Developmental delay	common	16/68 (24%)	21/45 (47%)	7/8 (88%)	6/17 (35%)
Macro-/microcephaly	micro, up to 50%	micro, 5/68 (7%) macro, 1/68 (1%)	micro, 17/45 (38%) macro, 1/45 (2%)	micro, 2 relative macro, 1	micro, 4/17 (24%)
Skeletal anomalies	>15%	12/68 (18%)	22/45 (49%)	2/8 (25%)	3/17 (18%)
Intellectual disability/learning problems	70–90%	17/68 (25%)	18/45 (40%)	4/8 (50%)	2/17 (12%)
Language delay	common	15/68 (22%)	6/45 (13%)	3/8 (38%)	1/17 (6%)
Ocular anomalies	<50%	4/68 (6%)	4/45 (9%)	none reported	2/17 (12%)
Cardiovascular defects	74%	20/101* (20%)	24/45 (53%)	1/8 (13%)	5/17 (29%)
Psychiatric/behavior problems	~60%	12/68 (18%)	13/45 (29%)	2/8 (25%)	2/8 (25%)
Genitourinary anomalies	31%	13/68 (19%)	7/45 (16%)	1/8 (13%)	1/17 (6%)
Palatal anomalies	69%	5/68 (7%)	5/45 (11%)	1/8 (13%)	3/17 (18%)
Feeding problems/GI anomalies	36%	3/68 (4%)	10/45 (22%)	1/8 (13%)	2/17 (12%)
Dysmorphic features (see table 2)	common (esp. among Caucasians)	31/68 (46%)	26/45 (58%)	7/8 (88%)	5/17 (29%)
Rhabdoid tumor					16/17 (94%)

DN = De novo; fam = familial; GI = gastrointestinal; unk = unknown (not the parent tested).

[a] Statistics in percentages for proximal deletions are taken from McDonald-McGinn et al., 1999.

[b] Data from Kurahashi et al., 1996; Garcia-Miñaur et al., 2002; Rauch et al., 2005; D'Angelo et al., 2007; Jalali et al., 2008; Fernández et al., 2009; Yu et al., 2011; Verhagen et al., 2012; Zhao et al., 2013; Rump et al., 2014; and this study. * Includes cases of Racedo et al., 2015 who only examined cardiac features of 25 individuals.

[c] Data from Rauch et al., 1999, 2005; Saitta et al., 1999; Mikhail et al., 2007, 2014; Ben-Shachar et al., 2008; Jalali et al., 2008; Rødningen et al., 2008; Xu et al., 2008; Ogilvie et al., 2009; Bruce et al., 2010; Madan et al., 2010; Garavelli et al., 2011; Tan et al., 2011; Verhoeven et al., 2011; Yu et al., 2011; Breckpot et al., 2012; Fagerberg et al., 2013; Molck et al., 2013; Rump et al., 2014.

[d] Data from Shaikh et al., 2000; Rauch et al., 2005; Nik-Zainal et al., 2011; Yu et al., 2011; Mikhail et al., 2014.

[e] Data from Wieser et al., 2005; Jackson et al., 2007; Lafay-Cousin et al., 2009; Beddow et al., 2011; Bourdeaut et al., 2011; Tan et al., 2011; Toth et al., 2011.

[f] Index cases and familial carriers.

LCR22C–E (C–E) in the central group. Given the similarity between those individuals and individuals with distal type I deletions as described in Mikhail et al. [2014], we propose that deletions spanning C–E be classified as distal type I deletions and have included them in the next section.

Central deletions are reported in the literature for 45 individuals including familial carriers [Kurahashi et al., 1996; Garcia-Miñaur et al., 2002; Rauch et al., 2005; D'Angelo et al., 2007; Jalali et al., 2008; Fernández et al., 2009; Yu et al., 2011; Verhagen et al., 2012; Zhao et al., 2013; Rump et al., 2014]. Postnatally, our laboratory has reported 31 central deletions. Of those, sufficient clinical information was provided for 23, resulting in a total of 68 individuals with clinical information (table 1). The study by Racedo et al. [2015] only examined cardiac features of 25 individuals with central deletion, so that total is only included in the cardiac category in table 1, and those 25 are not included in the 45 reported individuals. Seven of the 31 individuals reported from our lab had follow-up studies performed, and 4 deletions were de novo, 2 were familial and 1 unknown. Combined with 28 index cases in the literature, 35 total probands had follow-up studies and 14/35 (40%) were inherited, not unlike the reported higher inheritance rate for the A–B proximal deletions [Adeyinka et al., 2004; Fernández et al., 2005]. Taken together, it is interesting to note that each of the individual nested regions of the 3-Mb DGS interval has a high rate of inheritance, while loss of the entire region is predominantly de novo.

Overall, the most common features of central deletions include growth restriction [16/68 (24%)], developmental delay [16/68 (24%)], intellectual disability [17/68 (25%)], language delay [15/68 (22%)], and dysmorphic features [31/68 (46%)]. The most common dysmorphic features noted were abnormal ears (8), upslanting palpe-

Table 2. Common facial features associated with each interval compared to those commonly found in patients with proximal deletions

Feature	Deletion				
	proximal (A–B, A–D)	central (B–D, C–D)	distal		
			type I (C–E, D–E, D–F)	type II (E–F)	type III (any incl. *SMARCB1*)
Abnormal ears	+	8/68 (12%)	16/45 (36%)	2/7 (29%)	3/17 (18%)
Smooth philtrum		–	13/45 (29%)	–	2/17 (12%)
Short philtrum		2/68	2/45	–	–
Thin upper lip		2/68	9/45 (20%)	–	2/17 (12%)
Hypoplastic alae nasi	+	1/68	8/45 (18%)	–	–
Long face	+	2/68	1/47	–	1/17
High nasal bridge		2/68	7/45 (16%)	–	1/17
Pointed chin		–	5/45 (11%)	–	–
Asymmetric face	+	5/68	–	–	2/17 (12%)
Triangular face		4/68	5/45 (11%)	–	–
Square face		2/68	–	–	1/17
Prominent forehead		6/68	3/45	1/7 (14%)	–
Narrow palpebral fissures		1/68	1/45	1/7 (14%)	–
Upslanting palpebral fissures		6/68	7/45 (16%)	–	3/17 (18%)
Short palpebral fissures		2/68	–	–	1/17
Bitemporal narrowing		2/68	2/45	–	1/17
Synophrys		2/68	2/45	–	–
Short upturned nose		–	1/45	–	1/17
Full lips		2/68	1/45	–	–
Arched eyebrows		–	7/45 (16%)	–	–
Broad nasal root/nose	+	1/68	6/45 (13%)	–	–
Hyperopia		–	1/45	1/7 (14%)	–
Ear tags/pits	+	1/68	4/45	1/7 (14%)	3/17 (18%)
Hypertelorism	+	–	2/45	1/7 (14%)	–
Micro-/retrognathia		3/68	7/45 (16%)	–	1/17
Downturned mouth		–	3/45	–	2/17 (12%)
Deep-set eyes		1/68	4/45	1/7 (14%)	–
Epicanthic folds	+	2/68	2/45	–	1/17
Hypotelorism		4/68	2/45	–	–
Malar flattening	+	3/68	2/45	–	2/17 (12%)

Features observed in at least 10% of all individuals, not including proximal deletion carriers, are highlighted in dark grey; features observed in 5–10% of all individuals, not including proximal deletion carriers, are highlighted in light grey. Percentages are only listed for frequencies >10%.

bral fissures (6), and a prominent forehead (6) (table 2). Growth restriction was observed in children but not adults, consistent with the early growth lag reported for proximal deletions. Genitourinary anomalies were noted in 13/68 (19%) of the individuals, again consistent with the incidence of these features in individuals with proximal deletions. Cardiac defects [20/101 (20%)] and psychiatric/behavior problems [12/68 (18%)] were also commonly reported (table 1). Frequent infections, particularly otitis media, were noted for several individuals. Skeletal abnormalities were observed in 10 individuals with scoliosis, long fingers and 2–3-toe syndactyly described in 2 individuals each [Verhagen et al., 2012; Rump et al., 2014].

With regard to cardiac defects, Rump et al. [2014] described 1 index case and 1 parental carrier with septal defects. The index case of Garcia-Miñaur et al. [2002] was noted to have tetralogy of Fallot (TOF), and 2 index cases in Verhagen et al. [2012] were observed with cardiac defects [TOF in patient 1, ventricular septal defect (VSD) with complex defects in patient 2]. Patient 3 of Jalali et al. [2008] had a conotruncal heart defect, but it is not noted whether patient 4 (the parent of patient 3) has the same defect. Zhao et al. [2013] reported on a cohort specifically with cardiac defects, and identified a single individual with a central deletion, but the types of cardiac defects are not specified. In Racedo et al. [2015], 8/20 B–D deletion subjects and 1/5 C–D deletion subjects had cardiac

Table 3. Prenatal ultrasound findings and delivery information reported in the literature compared to the ultrasound findings in the new cohort in this study

	Deletion				
	proximal (A–B, A–D)	central (B–D, C–D)	distal		
			type I (C–E, D–E, D–F)	type II (E–F)	type III (any incl. *SMARCB1*)
Previous literature		Garcia-Miñaur et al., 2002; D'Angelo et al., 2007; Verhagen et al., 2012; Rump et al., 2014	Saitta et al., 1999; Ben-Shachar et al., 2008; Xu et al., 2008; Ogilvie et al., 2009; Garavelli et al., 2011; Tan et al., 2011; Verhoeven et al., 2011; Breckpot et al., 2012; Fagerberg et al., 2013; Molck et al., 2013; Mikhail et al., 2014; Rump et al., 2014	Mikhail et al., 2014	Jackson et al., 2007; Tan et al., 2011; Toth et al., 2011
Reported ultrasound abnormalities	common findings include cardiac defects, CL/P	IUGR (2); renal agenesis (2); decreased fetal movements (2); absent renal artery; VSD; complex cardiac defect; right inguinal hernia; spina bifida; ventriculomegaly; oligohydramnios; increased NT; CPC; echogenic intracardiac focus; clubfoot	truncus arteriosus ; VSD; abnormal bowel by US; possible diaphragmatic hernia; IUGR; CL; cardiac defects; single umbilical artery; growth restriction; placental insufficiency		polyhydramnios; bilateral CL/P
Reported delivery and gestational age	N/A	CS at term; CS for fetal distress; CS for cephalopelvic disproportion; CS at 31 weeks for placental insufficiency; CS for decreased fetal movements and IUGR	25/36 with GA at delivery provided delivered prior to 37 weeks; 14 delivered via CS	CS at 32 weeks	delivered at 34 weeks; delivered at 35 weeks, 4 days; CS at 37 weeks
This study					
Number of cases	93	16 (3 are sibs)	2	3	0
Follow-up	31 f/u; 27 DN (87%)	10 f/u (sibs counted as 1); 3 DN (33%)	2 f/u; 1 DN (50%)	1 f/u; 0 DN	
Abnormal ultrasound findings		**abnormal US in 13/16:** CPC (3); lumbar spina bifida/ myelomeningocele (3); left echogenic kidney with hydroureter (2); echogenic bowel (2); enlarged cisterna magna; heart defect; pyelectasis; obstructed kidney unilaterally; polycystic kidney unilaterally; clubfoot; persistent right umbilical vein; gastroschisis; 2-vessel cord	none	**abnormal US in 2/3** cardiac defect; increased NT	

CL/P = Cleft lip/palate; CPC = choroid plexus cyst; CS = cesarean section; DN = de novo; f/u = follow-up; GA = gestational age; IUGR = intrauterine growth restriction; NT = nuchal translucency; US = ultrasound; VSD = ventricular septal defect.

defects. These included conotruncal defects in 4/25, TOF in 3/25, interrupted aortic arch in 1/25, VSD in 4/25, and atrial septal defect (ASD) in 2/25. Only 1 individual in our postnatal cohort was noted to have cardiac issues (a benign murmur), although it is possible that the clinical information was incomplete or that this feature was not specifically looked at in individuals prior to diagnosis. In total, septal defects (4/101), TOF (4/101), and conotruncal defects (5/101) were observed most commonly in the central deletion cohort. While the types of cardiac defects described in individuals with central deletions are not different from those in individuals with proximal deletion, the incidence tends to be lower.

Prenatally, we have reported 16 central deletions. Thirteen of 16 were referred for microarray testing because of ultrasound abnormalities which often included CNS and renal anomalies (table 3). These findings are consistent with what has been reported for other individuals who were ascertained prenatally [Garcia-Miñaur et al., 2002; Verhagen et al., 2012; Rump et al., 2014]. An unspecified cardiac defect was noted in only 1 of our cases. Deletions were inherited in 9/12 (75%) of our prenatal cases with follow-up studies, consistent with the apparent higher rate of inheritance for this region.

Key differences between central and proximal deletions include much lower incidences of immune deficiency, hypotonia, palatal abnormalities, and behavior problems in the central group (table 1). Although several individuals were noted to have recurrent infections, thymic development in these individuals was not noted to be abnormal, suggestive of a gene(s) in the proximal A–B region important for thymic development.

Distal Deletions

Type I (C–E, D–E, D–F)

Based on the classification system of Mikhail et al. [2014] and the clinical issues unique to distal type I deletion carriers, we include deletions spanning LCR22C–E (C–E) with the type I group [Ogilvie et al., 2009; Garavelli et al., 2011; Breckpot et al., 2012; Mikhail et al., 2014; Rump et al., 2014]. The reported deletions have largely been de novo and fetuses/neonates having distal type I deletions tended to require pregnancy and delivery management that individuals with the other types of deletions typically do not (table 3). A total of 45 individuals have been reported with distal type I deletions, including an atypical B–F deletion observed by Molck et al. [2013] [Rauch et al., 1999, 2005; Saitta et al., 1999; Mikhail et al., 2007, 2014; Ben-Shachar et al., 2008; Jalali et al., 2008; Rødningen et al., 2008; Xu et al., 2008; Ogilvie et al., 2009; Bruce et al., 2010; Madan et al., 2010; Garavelli et al., 2011; Tan et al., 2011; Verhoeven et al., 2011; Yu et al., 2011; Breckpot et al., 2012; Fagerberg et al., 2013; Molck et al., 2013; Rump et al., 2014]. The individuals reported in Ravnan et al. [2006] are described as deleted for *BCR*, but it is not known to what extent those deletions extend proximally. Therefore, those individuals have been excluded from table 1.

As reported in Mikhail et al. [2014], most type I deletions are de novo [28/45 (62%)] (table 1). This is similar to the high rate of de novo deletion for the ~3-Mb proximal A–D interval [McDonald-McGinn et al., 1999]. Other major findings of distal type I deletions include preterm birth [25/36 mentioned (69%)], growth restriction [25/45 (56%)], cardiac defects [24/45 (53%)], dysmorphic features [26/45 (58%)], minor skeletal anomalies [22/45 (49%)], microcephaly [17/45 (38%)], and developmental delay [21/45 (47%)] (tables 1, 3).

Cardiac defects were observed in 24/45 (53%) and were primarily septal defects. Specific cardiac findings noted for more than 1 individual with a distal type I deletion include VSD (8), ASD (4), truncus arteriosus (4), persistent ductus arteriosus (3), interrupted aortic arch (2), and bicuspid aortic valve (2) [Rauch et al., 1999, 2005; Saitta et al., 1999; Ben-Shachar et al., 2008; Ogilvie et al., 2009; Garavelli et al., 2011; Tan et al., 2011; Verhoeven et al., 2011; Breckpot et al., 2012; Fagerberg et al., 2013; Mikhail et al., 2014].

Dysmorphic features were observed in about half of the individuals [26/45 (58%)], including smooth philtrum in 13/45 (29%), and ear abnormalities in 16/45 (36%) (table 2). The ear abnormalities included low-set ears, posterior rotation, abnormal helices, ear tags, and ear pits. Other facial features included arched eyebrows (7), hypoplastic alae nasi (8), thin upper lip (9), micro-(3)/retrognathia (4), upslanting palpebral fissures (7), and pointed chin (5). Skeletal anomalies were noted for 22/45 (49%) individuals, primarily clinodactyly or other digit abnormalities (table 1) [Saitta et al., 1999; Ben-Shachar et al., 2008; Ogilvie et al., 2009; Garavelli et al., 2011; Tan et al., 2011; Verhoeven et al., 2011; Mikhail et al., 2014].

We have reported 2 distal type I deletions prenatally, 1 of which was de novo, and neither of which demonstrated ultrasound abnormalities. For the familial deletion, there were abnormalities in a previous child who also had a secondary pathogenic mutation, and the pregnancy for which we reported the deletion was terminated. For the de novo deletion, this baby was delivered preterm at 33 weeks 6 days with cleft lip/palate and achondroplasia. The mother was also affected with achondroplasia, and while cesarean section was planned for this pregnancy, early labor resulted in preterm delivery.

It is worth noting that of the reported individuals with distal type I deletions, over half were delivered prior to 37 weeks (table 3), and half of those infants were delivered via cesarean section [14/25 (56%)], often due to a pregnancy complication such as fetal distress, failure to progress, decreased fetal movement, premature rupture of membranes, or preeclampsia [Saitta et al., 1999; Rødningen et al., 2008; Ogilvie et al., 2009; Fagerberg et al., 2013; Mikhail et al., 2014]. This may be an underestimate as delivery information was not provided in all studies. This information has important prognostic significance in a prenatal diagnostic setting, as those pregnancies identified with distal type I deletions will require close management with respect to potential pregnancy complications and delivery. Abnormal ultrasound findings were not overly prevalent in this cohort, but of those who were reported with ultrasound abnormalities, cardiac defects were a common finding [Ogilvie et al., 2009; Garavelli et al., 2011; Tan et al., 2011; Breckpot et al., 2012].

Type II (E–F)

Distal type II deletions have been reported for 8 individuals [Shaikh et al., 2000; Rauch et al., 2005; Nik-Zainal et al., 2011; Yu et al., 2011; Mikhail et al., 2014]. Interestingly, of the 5 index cases with follow-up studies, 4 have been de novo. With such a limited number of reported cases, it is difficult to draw conclusions about typical phenotypic features or mode of inheritance. Seven of the 8 individuals (88%) exhibited developmental delay

and dysmorphic features, although features were specified only for 5/7 (table 2). Intellectual disability was noted in half (4/8) of the subjects.

Prenatally, we have reported 3 distal type II deletions. Only 1 has had follow-up studies and was found to be familial. Two were referred for ultrasound abnormalities, including increased nuchal translucency and an unspecified cardiac defect (table 3).

Type III (Any Including SMARCB1)

The distal type III deletion is defined by inclusion of *SMARCB1/INI1*, which significantly increases the risk for malignant rhabdoid tumors in these individuals [Bourdeaut et al., 2011; Eaton et al., 2011; Toth et al., 2011]. Seventeen individuals with type III deletions have been reported in the literature, most of which spanned proximally to LCR22D, and were frequently described with other congenital anomalies [Wieser et al., 2005; Jackson et al., 2007; Lafay-Cousin et al., 2009; Beddow et al., 2011; Bourdeaut et al., 2011; Tan et al., 2011; Toth et al., 2011]. Three individuals in Eaton et al. [2011] had deletions that span the entire *SMARCB1* gene, but it is not clear whether the deletions extend proximally into an LCR, although the authors do note that those deletions did not include the D–E region. Since the proximal breakpoints were not determined for those 3 individuals, they were excluded from table 1. Of the 6 individuals in the literature with follow-up studies, all were de novo deletions. Since these reports focus primarily on the propensity for malignancy in individuals with *SMARCB1* deletions, descriptions of congenital anomalies are not always provided. Of those subjects for whom clinical information is given, dysmorphic features [5/17 (29%)], cardiac defects [5/17 (29%)], developmental delay [6/17 (35%)], and microcephaly [4/17 (24%)] are the most prevalent features (table 1).

It is interesting to note that although these deletions often include the D–E interval, only a single subject was reported as being delivered prematurely; however, most reports did not include birth information (table 3) [Tan et al., 2011]. The report by Toth et al. [2011] did note that the index case was delivered by cesarean section at 37 weeks, but the reason for cesarean delivery was not provided. Only a single individual in the literature with a distal type III deletion did not present with a rhabdoid tumor when she was evaluated at 7 years of age (patient 2 in Tan et al. [2011]). Bourdeaut et al. [2011] have demonstrated that the strongest correlation with survival for individuals with *SMARCB1*-related malignancies is age, such that the older a patient is at diagnosis, the better the outcome. We have not reported any distal type III deletions.

Variability of Phenotype

Candidate critical genes for major features of DGS are thought to include *HIRA*, *TBX1* and *COMT* [McDonald-McGinn et al., 1999; Lindsay et al., 2001; Kessler-Icekson et al., 2002; Bearden et al., 2004; Prasad et al., 2008; Chen et al., 2014; Ogata et al., 2014]. *CRKL* is considered a candidate critical gene for the central deletions [Racedo et al., 2015], and *MAPK1/ERK2* for the distal type I deletions [Saba-El-Leil et al., 2003; Binétruy et al., 2007; Newbern et al., 2008; Samuels et al., 2008]. Less is known about the potential effects of genes in the distal type II region. *SMARCB1* is the critical gene defining distal type III deletions due to the high rate of malignant rhabdoid tumors in individuals with this deletion.

Due to overlapping features of individuals with various 22q copy number changes, genotype-phenotype correlations cannot be accurately predicted. Which other factors are necessary to result in abnormal phenotypes in ascertained individuals with these CNVs remains to be determined. It is possible that phenotypic similarity and variability of 22q11.2 CNVs may be impacted by dysregulation of genes via loss of long-range regulatory sequences that could affect either common genes and/or common developmental pathways [Yamagishi and Srivastava, 2003; Zeitz et al., 2013]. Indeed, Zeitz et al. [2013] demonstrated long-range chromatin interaction of *COMT* in the proximal 22q11.2 region with genes on other chromosomes, as well as with *MAPK1* in the distal 22q11.2 region, supporting this interpretation.

Additionally, unmasking of other sequence variants throughout the genome and/or in the non-deleted allele that may affect the activities of the gene products has also been hypothesized to contribute to the variability of features for 22q11.2 deletions [Brzustowicz and Bassett, 2012; Zarchi et al., 2013; Carmel et al., 2014; Gothelf et al., 2014; Radoeva et al., 2014]. Other studies have suggested a possible gender effect in proximal deletion subjects, owing to the interaction of estrogen with *COMT*, but additional studies are needed to clarify whether there is indeed a relationship in DGS patients [Coman et al., 2010; Yu et al., 2012].

MicroRNA (miRNA) regulation has also been hypothesized to contribute to 22q11.2 deletion phenotypes. The nested proximal A–B region contains 6 putative miRNAs and the gene *DCGR8* which encodes Pasha, a component of the miRNA processing machinery. The potential role of miRNA in the pathogenesis of deletion phenotypes has been investigated and suggests a role, not only for the miRNAs in the regions themselves but also

for the dysregulation of miRNA processing due to the haploinsufficiency of *DCGR8* [Brzustowicz and Bassett, 2012; de la Morena et al., 2013; Merico et al., 2014]. Brzustowicz and Bassett [2012] propose that haploinsufficiency of *DGCR8* destabilizes developmental pathways by perturbing the miRNA regulatory network. This hypothesis, however, does not account for the variability and similarity of phenotypes in individuals with central and distal deletions who are disomic for *DGCR8*. In a study by Merico et al. [2014], the authors showed that the miRNAs in 22q11.2 are involved in the regulation of expression of genes in a number of developmental pathways which could be affected by reduced levels of these miRNAs. Using *Drosophila melanogaster* as a model system, Luhur et al. [2014] demonstrated that Pasha is involved in neuronal organization. Additionally, mouse models, haploinsufficient for the syntenic region of chromosome 16, demonstrated abnormal processing of brain-specific miRNAs, including *miR-185* which is localized to the A–B interval [Xu et al., 2013]. Even with an increased risk of developing schizophrenia in individuals with DGS, the incidence of this feature is also highly variable, with a lifetime risk of ~25% [Bassett et al., 2008; Fung et al., 2010].

Several authors have proposed that the *CRKL* gene may be involved in cardiac defects in individuals with central deletions [Ogilvie et al., 2009; Breckpot et al., 2012; Verhagen et al., 2012; Rump et al., 2014; Racedo et al., 2015]. Rump et al. [2014] highlight that loss of *CRKL* combined with loss of either *TBX1* or *MAPK1* in individuals with A–D or larger deletions results in higher rates of cardiac defects than in those individuals with central deletions haploinsufficient only for *CRKL*. In mice, *Crkl* has been shown to mediate *Fgf8* cell signaling via *Fgfr1/2*, supporting a modifying effect of 22q11.2 genes on other genes within developmental pathways [Moon et al., 2006]. Guris et al. [2006] have demonstrated an interaction between *Crkl* and *Tbx1* in retinoic acid metabolism resulting in a DGS phenotype in mice, such that compound heterozygosity for both results in increased penetrance and expressivity of the phenotypic features over heterozygous loss of either gene individually. Following this line of reasoning, individuals with proximal A–B deletions should present with cardiac defects about as often as those with central deletions and less often than those with proximal A–D deletions. This has not been specifically studied, and the clinical information provided for the proximal deletion patients in this study is insufficient to make this comparison.

Future Studies

Much has yet to be learned regarding the reasons for similarities and widely variable features for individuals with 22q11.2 deletions. Future studies comparing phenotypic features and inheritance rates of subjects with A–B and B–D deletions to those with A–D deletions may help uncover differences not yet fully appreciated. Additionally, studies of genes within the E–F interval should be investigated with respect to the high rate of de novo deletions to determine if the two are related.

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