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Recurrent Duplications of 17q12 Associated with Variable Phenotypes

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The ability to identify the clinical nature of the recurrent duplication of chromosome 17q12 has been limited by its rarity and the diverse range of phenotypes associated with this genomic change. In order to further define the clinical features of affected patients, detailed clinical information was collected in the largest series to date (30 patients and 2 of their siblings) through a multi-institutional collaborative effort. The majority of patients presented with developmental delays varying from mild to severe. Though dysmorphic features were commonly reported, patients do not have consistent and recognizable features. Cardiac, ophthalmologic, growth, behavioral, and other abnormalities were each present in a subset of patients. The

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newly associated features potentially resulting from 17q12 duplication include height and weight above the 95th percentile, cataracts, microphthalmia, coloboma, astigmatism, tracheomalacia, cutaneous mosaicism, pectus excavatum, scoliosis, hypermobility, hypospadias, diverticulum of Kommerell, pyloric stenosis, and pseudohypoparathryoidism. The majority of duplications were inherited with some carrier parents reporting learning disabilities or microcephaly. We identified additional, potentially contributory copy number changes in a subset of patients, including one patient each with 16p11.2 deletion and 15q13.3 deletion. Our data further define and expand the clinical spectrum associated with duplications of 17q12 and provide support for the role of genomic modifiers contributing to phenotypic variability. © 2015 Wiley Periodicals, Inc.

Key words: CNV; genotype phenotype; duplication

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INTRODUCTION

The introduction of chromosomal microarrays to clinical and research laboratories has led to the rapid discovery of novel and recurrent genomic rearrangements associated with disease. Some of these alterations are now known to manifest phenotypes for both the deletion and duplication of the same region. This reciprocal nature is consistent with generation of these rearrangements through a nonallelic homologous recombination (NAHR) mechanism mediated by complimentary segmental duplications or low-copy repeats at the breakpoints. A recent example of this phenomenon is the deletion of multiple genes including *HNF1B* (*TCF2*) at chromosome 17q12. Features associated with this deletion include renal anomalies, maturity-onset diabetes of the young type 5 (MODY5), epilepsy, and others [Bellanne-Chantelot et al., 2005; Decramer et al., 2007; Mefford et al., 2007; Edghill et al., 2008; Nagamani et al., 2010]. The clinical significance of the reciprocal 17q12 duplication was subsequently discovered, but a recognizable phenotype has not been described.

First reported in a single patient in 2006 [Sharp et al., 2006], there are now 14 individuals or families described in the literature with 17q12 duplications overlapping *HNF1B* [Sharp et al., 2006; Mefford et al., 2007; Mencarelli et al., 2008; Nagamani et al., 2010; Faguer et al., 2011; Brandt et al., 2012; Bierhals et al., 2013; Girirajan et al., 2013; Hardies et al., 2013; Smigiel et al., 2014]. The reports include both *de novo* cases and rearrangements inherited from normal or affected parents of either gender. The majority of these duplications minimally involve a 1.4 Mb segment that includes 15 genes (approximately chr17:34,820,000–36,250,000; genome build hg19). The region is flanked by segmental duplications that are polymorphic in copy number in the general population and contain genes in the chemokine (C-C motif) ligand and TBC1 domain families with no known clinically significant dosage sensitivity. The phenotypes of patients with 17q12 duplication can include any combination of cognitive impairment, speech and motor developmental delay, brain anomalies, dysmorphic facial features, behavioral abnormalities (such as aggression or self-injury), esophageal atresia, renal anomalies, epilepsy, and others [Sharp et al., 2006; Mefford et al., 2007; Mencarelli et al., 2008; Nagamani et al., 2010; Faguer et al., 2011; Bierhals et al., 2013; Brandt et al., 2012; Girirajan et al., 2013; Hardies et al., 2013; Smigiel et al., 2014].

Here, we present the clinical features of 30 new unrelated patients and two affected siblings collected through a multi-institution collaboration with nearly identical duplications of 17q12, the largest series assembled to date. The results expand the associated phenotypes and reveal a complex clinical syndrome with variable expressivity, which may, in part, be explained by additional rare copy number variants (CNVs) in the affected individuals.

MATERIALS AND METHODS

Patient Samples

Collection and reporting of clinical data and/or photographs were carried out after approval by human subjects review boards at the participating centers, including University of Washington, Seattle, WA; Mayo Clinic, Rochester, MN; Ghent University, Ghent, Belgium; Payton Manning Childrens Hospital, Indianapolis, IN; University of Siena, Italy, Siena; and IRCCS Associazione Oasi Maria Santissima, Troina, Italy.

High-Resolution Chromosomal Microarray Analysis

After initial identification of the 17q12 duplication, which occurred through a variety of clinical and research arrays depending on the lab of origin for the patient, a subset of cases (n = 17) were further characterized on high-density oligonucleotide arrays. Specifically, a custom Agilent whole genome array with one million probes and average probe spacing of 3–4 bp in the 17q12 region was used for additional evaluation of 12 patients. Samples were hybridized against pooled male control DNA. Data were processed using custom in-house scripts and post-processed using DNA analytics software (Agilent, Santa Clara, CA). Result calls >50 kb were further

TABLE I. Phenotypes of Patients With 17q12 Duplications

Case	1	2	3	4	5	6	7	8	9	10^	11	12	13^	13a^*
Decipher	2843	NA	248324	249155	249156	NA	NA	NA	NA	NA	249291	NA	248538	NA
Gender	F	M	F	M	M	M	M	M	M	F	M	F	F	F
Age	7 years	26 months	16 months	6 years	9 years	25 years	24 years	14 years	15 years	8 years	17 months	2.5 months	18 years	18 years
Inheritance														
Inheritance	Pat	Pat	Mat	Pat	Mat	Unk	Unk	Unk	Unk	Mat GM	D.N.	Pat	Mat	Mat
Affected parent?	+	−	+	+	+	−	−	−	−	+	−	−	−	−
Growth														
Weight (centile)	10–25	<3	50	−0.5 SD	+0.5 SD	>>97	NR	10–25	95–97	80	<3	NR	75	NR
Height (centile)	10–25	<3	−1.5 SD	−0.5 SD	+0.5 SD	NR	NR	<<3	50	50	10–25	NR	75–91	NR
OFC (centile)	<<2 SD	<3	−2 SD	−2 SD	−1 SD	90–97	75–90	50	50–75	NR	−3 SD	5–10	47	11
Development														
Walked >18 m	+	−	NR	NR	+	−	NR	+	+	+	−	NR	+	NR
Speech delay	NR	+	NR	+	+	+	NR	NR	+	+	+	NR	NR	NR
Intellectual disability	+	−	+	+	+	+	+	+	+	+	NR	NR	+	+
Seizures	NR	−	NR	NR	NR	+	NR	NR	NR	NR	NR	NR	NR	NR
Hypotonia	NR	NR	NR	NR	+	NR	NR	NR	NR	NR	NR	NR	+	+
Other neurological	+	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	+	+
Behavioral abnormalities	NR	NR	NR	NR	NR	NR	+	NR	NR	+	NR	NR	NR	NR
Other														
Dysmorphic features	+	+	+	NR	+	+	NR	+	+	−	+	+	+	+
Vision	NR	−	NR	NR	−	NR	NR	+	−	−	NR	+	−	+
Cardiac	−	NR	NR	NR	NR	NR	NR	−	−	−	NR	+	−	NR
Renal	−	NR	−	NR	NR	NR	NR	−	−	−	NR	+	+	+
Skeletal	NR	−	NR	NR	NR	+	NR	NR	NR	−	NR	NR	+	+
Endocrine	+	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	+	+
Other	NR	+	NR	NR	NR	NR	NR	NR	NR	NR	NR	+	NR	NR

Case	14	15^	16	17	18^	18a^**	19	20	21^	22	23	24	25^	26	27	28	29	30
Decipher	NA	NA	NA	250103	NA	NA	NA	NA	NA	NA	NA	NA	253870	NA	NA	270302	NA	NA
Gender	M	M	F	M	M	F	M	M	M	M	M	M	F	F	F	F	M	M
Age	3.5 years	4.5 years	13 years	11 years	9 years	16 years	3 years	3 years	14 years	15 years	7 years	4 years	11 years	8 months	5 years	16 months	9 years	9 years
Inheritance																		
Inheritance	Unk	Unk	Pat	Mat	Pat***	Pat***	Unk	Mat	Pat	Mat	Pat	Mat	Unk	Pat	Pat	Pat	Mat	D.N.
Affected parent?	−	−		−	NR	NR	−		−	+	−	+	−	−	+	−	+	−
Growth																		
Weight (centile)	3	50–75	NR	NR	94	90	5–10	50–75	<3	<3	75	98–99	98–99	<1	50	9	NR	9
Height (centile)	20	25–50	NR	−0.4 SD	7	3	5–10	25	<3	5	>97	75–91	94	<1	85	2	NR	9
OFC (centile)	<5	50	NR	−1.9 SD	NR	NR	<3	50	<3	2	75	9–25	NR	<1	75	<1	NR	9
Development																		
Walked >18 m	+	−	NR	−	+	NR	−	−	+	−	+	NR	+	NR	+	−	NR	−
Speech delay	NR	+	NR	−	+	+	−	+	+	+	+	+	+	NR	+	+	+	+
Intellectual disability	+	NR	+	−	+	+	+	+	+	+	+	+	+	NR	+	NR	+	+
Seizures	NR	+	NR	−	NR	+	+	−	+	+	+	NR	NR	NR	NR	+	NR	+
Hypotonia	+	NR	NR	NR	−	NR	NR	−	−	+	+	NR	NR	NR	+	NR	NR	NR
Other neurological	NR	+	+	NR	NR	NR	NR	+	+	NR	+	NR	NR	NR	NR	NR	NR	NR
Behavioral abnormalities	NR	NR	NR	NR	NR	NR	NR	NR	+	+	NR	+	+	NR	+	−	+	+

TABLE I. (*Continued*)

Case	14	15^	16	17	18^	18a^**	19	20	21^	22	23	24	25^	26	27	28	29	30
Other systems																		
Dysmorphic features	+	−	NR	+	−	−	−	+	+	+	+	−	NR	+	+	+	−	−
Vision	NR	NR	NR	+	NR	NR	−	+	+	NR	+	−	−	−	−	−	NR	−
Cardiac	NR	NR	NR	+	+	+	−	−	NR	NR	NR	−	NR	NR	−	−	NR	−
Renal	NR	NR	NR	NR	NR	NR	−	−	−	−	+	−	−	−	−	−	NR	NR
Skeletal	+	NR	NR	+	+	NR	−	−	+	+	NR	NR	+	+	+	NR	NR	NR
Endocrine	+	NR	NR	NR	NR	NR	NR	NR	NR	NR	+	NR	NR	NR	−	NR	NR	NR
Other	+	NR	+	+	NR	NR	NR	+	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

^ has a second large CNV (see Table III); * identical twin of case 13; ** sibling of case 18; *** assumed paternal due to affected siblings and lack of maternal inheritance; NA, not applicable; NR, not reported but unknown whether the feature was specifically assessed; +, when the feature was present based on clinical report; −, when the feature was assessed but not present based on clinical report.

considered and filtered for known CNVs and segmental duplications. Another five patients were evaluated using a commercially available oligonucleotide array (Agilent) with one million probes, average spacing 3 kb, and processed using manufacturer's software. All clinical reports were reviewed to determine whether additional CNVs of uncertain or clinical significance were identified.

RESULTS

Phenotypes of Patients With 17q12 Duplication

Here, we report the identification of 30 unrelated patients with nearly identical duplications of chromosome 17q12 (Tables I and II, Supplemental Tables SI and SII), along with data for two affected siblings of two patients, one of which is an identical twin. The breakpoints for each duplication lie within segmental duplications, and the unique regions duplicated in each patient include the same ~1.4-Mb region (chr17:34,820,000–36,250,000; genome build hg19). Ten patients are female and 20 are male. Two patients were initially identified because of a history of multiple congenital anomalies while the remaining 28 were ascertained due to developmental delays and/or intellectual disability. Gross motor development was variable with 12 patients walking at or after 18 months of age while 10 walked prior to this age. Nineteen patients were reported to have delayed speech development; of note, the identical twins diverged on the presence of speech delay.

Eight patients and one sibling reported a seizure disorder whereas six patients and one identical twin reported hypotonia. An additional patient was found to have increased muscle tone. Five abnormal MRI findings were reported including one case each of periventricular leukomalacia, cerebral calcification on frontal lobes, small supratentorial hemorrhage, agenesis of the corpus callosum and widespread cortical dysplasia with heterotopic gray matter, and likely schizencephaly.

Nine patients were noted to have behavioral abnormalities. Two of these patients have explosive behaviors or become easily frustrated. An additional two have repetitive behaviors or preference for routine. One patient was described as having psychosis and auditory hallucinations.

The majority of patients have dysmorphic features, although no features were reported in all patients (Fig. 1, Supplemental Table SII). Trigonocephaly, plagiocephaly, thick lips, deep set eyes, short philtrum, and low hairline were each reported in two cases. Features reported in three cases each include a bulbous nose and prominent ears. Slanting palpebral features were found in five cases, with three cases described as upsplanting and two cases as downslanting. Three cases had long eyelashes, two of which also demonstrated synophorys/thick eyebrows. Numerous dysmorphic features were reported in one case each. Eleven cases and one sibling had no known dysmorphic features. Six of the 30 patients showed ophthalmic abnormalities: two with astigmatism, one with exotropia with amblyopia, one with bilateral cataracts, one with strabismus, and one with unilateral microophthalmia and coloboma of the iris, retina, and optic nerve.

Growth parameters were also variable (Table I). Seven patients had weight below the 5th percentile whereas four patients had weight above the 95th percentile. For height, eight cases and one

TABLE II. Frequency of Phenotypes in Current Study and Previously Published cases

	New Cases (# with phenotype/# reporting)	Total Number In New Cases (# with phenotype/total # of cases)	Previously Published (# with phenotype/# reporting)	Total Number in Previously Reported Cases (# with phenotype/total # of cases)	Combined Cohort (# with phenotype/# of those reporting)	Combined Cohort (# with phenotype/total # of cases)
Weight <5 centile	7/25	7/30	1/5	1/14	8/30	8/44
Weight >95 centile	4/25	4/30	0/5	0/14	4/30	4/44
Height <5 centile	8/25	8/30	1/5	1/14	9/30	9/44
Height >95 centile	2/25	2/30	0/5	0/14	2/30	2/44
OFC <5 centile	13/25	13/30	2/5	2/14	15/30	15/44
Gross motor delay	12/22	12/30	4/5	4/14	16/27	16/44
Speech delay	19/21	19/30	4/5	4/14	23/26	23/44
Intellectual disability	23/25	23/30	6/7	6/14	29/32	29/44
Seizures/Epilepsy	8/11	8/30	4/4	4/14	12/15	12/44
Hypotonia	6/9	6/30	5/6	5/14	11/15	11/44
Other neurological abn	7/7	7/30	3/5	3/14	10/12	10/44
Behavioral abn	9/10	9/30	4/4	4/14	13/14	13/44
Dysmorphic features	19/26	19/30	6/7	6/14	25/33	25/44
Ophthalmologic abn	6/18	6/30	2/2	2/14	8/20	8/44
Cardiac abn	3/14	3/30	2/5	2/15	519	5/44
Renal abn	3/17	3/30	1/3	1/14	4/20	4/44
Skeletal abn	10/14	10/30	5/5	5/14	15/19	15/44
Endocrine abn	4/5	4/30	1/1	1/14	5/6	5/44

Gray shading indicates that the phenotype is present in at least 33% of cases; the cases with additional large CNVs are included in the frequency calculations where applicable.

FIG. 1. Fontal and profile facial photographs for cases 11 (A), 15 (B), 20 (C), 21 (D). Most patients exhibit minor dysmorphic features, though none are consistent across all patients. Patient 11 (A) has a prominent metopic suture and trigonocephaly; patient 15 (B) has a broad forehead, wide nasal tip and low columella, similar to patient 20 (C). Patient 21 (D) has a long face with prominent ears, square chin, and deep set eyes.

sibling were below the 5th percentile with two patients being above the 95th percentile. Microcephaly as defined by an OFC of less than the 5th percentile was reported in 13 of the 30 patients whereas one patient had an OFC between the 90th and 97th percentile.

Seven patients reportedly had a normal echocardiogram whereas cardiac abnormalities were noted in three cases and one sibling. These abnormalities included two cases with a ventricular septal defect, one case with a leaky heart valve, and one patient who had a small muscular ventricular septal defect with a vascular ring around the trachea and diverticulum of Kommerell.

Fourteen patients reportedly had a normal renal ultrasound. One patient was found to have mildly echogenic kidneys and hypoechoic pyramids versus hydronephrosis. Both identical twins had renal tubular acidosis with one twin also having a horseshoe kidney. An additional patient had bilateral renal cysts.

Additional features reported in one or two of the 30 patients and/or their siblings each include small hands and feet, brachydactyly, 2/3 toe syndactyly, pectus excavatum, asymmetric thorax, scoliosis, sacral dimple, tracheomalacia, hyponatremia and hyperkalemia, hypoglycemia, hyporeflexia, hypospadias, cutaneous mosaicism, arthrogryposis, and joint dislocation. Two patients and a concordant identical twin had pseudohypoparathyroidism.

Frequency of Duplication

Five of the patients in our study came from two cohorts of 2,034 patients who were tested by chromosomal microarray due to intellectual or developmental disability. Compared to three published control studies [The International Schizophrenia Consortium, 2008; Itsara et al., 2009; Shaikh et al., 2009] in which there was sufficient coverage to identify the same duplication, we find a significant enrichment of the duplication in affected individuals (5/2,034 affected vs. 3/7,700 controls; $P = 0.012$, Fisher's Exact test), suggesting that the duplication is associated with abnormal phenotypes. In a large clinical laboratory setting where the reasons for referral are more varied, the frequency of the duplication was much lower (19/22,231 = 0.085% of cases ascertained between 3/2008 and 10/2013, Mayo Clinic Laboratories).

Inheritance of Duplication

Both parents were available for analysis in 21 cases. The duplication was inherited in 19 of these cases from the mother (n = 9) or father (n = 10) while it was *de novo* in two cases. The mother of the sibling set (cases 18 and 18a) did not carry the duplication and so paternal inheritance is assumed, although germline mosaicism in either parent cannot be ruled out. Although detailed phenotype information is not available for all parents, nine carrier parents are reported to have learning disabilities or microcephaly and one carrier father was treated for seizures as a teenager but is currently seizure free.

Additional Rare Copy Number Variants

High-density oligonucleotide chromosomal microarrays were performed in a subset (n = 17) of patients in order to determine whether additional rare CNVs might contribute to the phenotype. For those patients where additional DNA was not available, clinical array reports were reviewed. Notably, in 5/30 (17%) cases, the proband carried a second CNV that is >500 kb (Table III), two of which are recurrent CNVs associated with neurodevelopmental disorders. In case 13, the proband and identical twin both have a 15q13.3 deletion in addition to the 17q12 duplication. Patient 18 and his affected sister each have a 16p11.2 deletion. Three cases have large nonrecurrent CNVs. Patient 15 carries a 800 kb duplication of 18q22 and case 10 has a 1.5 Mb deletion of 4q35. Case 25 has a 5.2 Mb deletion of 14q21 of unknown inheritance. In 4/5 cases, the second CNV is maternally inherited.

DISCUSSION

We report detailed phenotype information for 32 individuals from 30 unrelated families with 17q12 duplication (Tables I and II, Supplemental Tables SI and SII). The patients in our series have a wide range of phenotypic features consistent with the spectrum reported in the 14 cases previously published in the literature [4–13]. Though variable between patients and even amongst affected family members, multiple systems can be involved including growth, neurological and behavioral abnormalities, cardiac, endocrine, renal, dysmorphic features, and others.

Having growth data available for 25 of the 30 patients in the new cohort allows for an expansion of knowledge regarding growth of individuals with this duplication. Although single individuals have been reported previously with weight or height less than the 5th percentile, the number reported in this new cohort is 7 and 8, respectively. Likewise, we can increase the total number of reported

TABLE III. Additional Rare, Large or Hotspot CNVs in Patients With 17q12 Duplications

Case	CNV		Size	Gene content	Inheritance
10	4q35 del	chr4: 186.8–188.3 (hg18)	1.5 Mb	10 genes	Maternal
13	15q13 del[a]	chr15: 28.4–30.3 (hg19)	1.9 Mb	Known NDD CNV	Maternal
15	18q22 dup	chr18: 63.9–64.7 (hg18)	805 kb	2 genes	Maternal
18 and 18a	16p11.2 del[a]	chr16: 29.5–30.2 (hg18)	700 kb	Known NDD CNV	Maternal
21	8q24.21 dup	chr8: 130.8–131.1 (hg19)	249 kb	2 genes	Paternal
25	14q21 del	chr14: 37.5–42.8 (hg19)	5.2 Mb	13 genes	Not maternal

[a]"Hotspot" rearrangement known to be associated with neurodevelopmental disorders.

patients with microcephaly from 2 to 15. Heights and weights on the other end of the spectrum have not been reported previously but two patients in our cohort have a height greater than the 95th percentile and four having a weight at the 95th percentile or greater.

Developmental and neurological abnormalities previously reported are also seen in the majority of patients in our series where the feature was assessed. These include gross motor delay, speech delay, intellectual disability, seizures, hypotonia, and other neurological or behavioral abnormalities. A high percentage of cases with dysmorphic features or skeletal abnormalities, when reported (19/26 for dysmorphic features and 10/14 for skeletal abnormalities), was confirmed in our cohort as well as the variable nature of these findings.

Abnormalities of many other systems have been reported previously and are expanded here. Newly identified ophthalmologic abnormalities are astigmatism and cataracts. Microphthalmia and strabismus are each now reported in an additional patient. For congenital heart defects, our cohort has two additional individuals with septal defects and one with a more complex cardiac anomaly including diverticulum of Kommerell. Two more patients with complex renal abnormalities are included in our cohort as well as a patient with bilateral renal cysts. In the genitourinary and trachea/esophageal systems, the potentially associated features are expanded to encompass hypospadias and tracheomalacia. Endocrine abnormalities reported in individuals with this duplication have been previously limited to one case with growth hormone deficiency; our cohort includes one patient with hypoglycemia and one with hyponatremia and hyperkalemia. Two patients and a sibling have pseudohypoaldosteronism.

In our series, 5/30 (17%) probands have a second large CNV that may contribute to the phenotypic presentation, all of which are maternally inherited. In two cases, the second CNV is already associated with neurodevelopmental disorders (15q13.3 deletion, 16p11.2 deletion) [Miller et al., 1993; van Bon et al., 1993]. A two-hit model has been proposed to explain the variable expressivity associated with some recurrent rearrangements [Girirajan et al., 2010, 2012]. Girirajan et al. reported a series of patients with a 520-kb deletion of 16p12.1 that is associated with variable phenotypes; in 6/20 cases, the proband was found to have a second large CNV. Similar to 17q12 duplications, in the majority of cases, the 16p12.1 deletion was inherited. A follow-up study investigating the role of "second hits" more broadly [Cooper et al., 2011] suggests that the phenotypic variation associated with some recurrent rearrangements may be partially explained by additional CNVs. Our results are consistent with this hypothesis and suggest that additional sequence or copy number variants may contribute to the phenotypic outcome in 17q12 duplication carriers. Other types of genetic variation that could contribute to phenotypic variability, including single nucleotide variants, epigenetic changes or overall effect of genetic background, have yet to be explored in this cohort.

In summary, we report the expanding phenotypic spectrum of patients with duplications of 17q12. Given that there is not a readily recognizable phenotype, the 17q12 duplication will most likely continue to be identified by genotype-first testing. Further investigation of genetic and genomic modifiers may lend insight into the basis of phenotypic variation and improve genetic and prognostic counseling in the future.

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