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The duplication 17p13.3 phenotype: Analysis of 21 families delineates developmental, behavioral and brain abnormalities, and rare variant phenotypes

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URLs

DECIPHER: Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources, <http://decipher.sanger.ac.uk>;

UCSC Genome Browser, <http://genome.ucsc.edu>.

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Abstract

Chromosome 17p13.3 is a gene rich region that when deleted is associated with the well-known Miller-Dieker syndrome. A recently described duplication syndrome involving this region has been associated with intellectual impairment, autism and occasional brain MRI abnormalities. We report 34 additional patients from 21 families to further delineate the clinical, neurological, behavioral, and brain imaging findings. We found a highly diverse phenotype with inter- and intrafamilial variability, especially in cognitive development. The most specific phenotype occurred in individuals with large duplications that include both the *YWHAE* and *LIS1* genes. These patients had a relatively distinct facial phenotype and frequent structural brain abnormalities involving the corpus callosum, cerebellar vermis and cranial base. Autism spectrum disorders were seen in a third of duplication probands, most commonly in those with duplications of *YWHAE* and flanking genes such as *CRK*. The typical neurobehavioral phenotype was usually seen in those with the larger duplications. We did not confirm the association of early overgrowth with involvement of *YWHAE* and *CRK*, or growth failure with duplications of *LIS1*. Older patients were often overweight. Three variant phenotypes included cleft lip/palate (CLP), split hand/foot with long bone deficiency (SHFLD), and a connective tissue phenotype resembling Marfan syndrome. The duplications in patients with clefts appear to disrupt *ABR*, while the SHFLD phenotype was associated with duplication of *BHLHA9* as noted in two recent reports. The connective tissue phenotype did not have a convincing critical region. Our experience with this large cohort expands knowledge of this diverse duplication syndrome.

Keywords

17p13.3; Microarray; autism; Cleft lip/palate; marfanoid; split hand foot long bone deficiency; *ABR*; *LIS 1*; *YWHAE*; *BHLHA9*

INTRODUCTION

Human chromosome 17 is a small, gene rich chromosome associated with several well-known deletion and duplication syndromes. The first recognized was Miller-Dieker syndrome (MDS), caused by large deletions of 17p13.3 [Dobyns et al., 1983]. We previously showed that the severe brain phenotype is caused by deletion of both *LISI* (designated *PAFAH1B1* in the UCSC browser and other genome databases) and the modifying gene *YWHAE* [Cardoso et al., 2003], but have not determined which genes are responsible for the MDS facial phenotype or Chiari malformation [Cardoso et al., 2003; Nagamani et al., 2009].

Several small series adding to 16 patients with dup 17p13.3 have been reported in the past 3 years that have begun to define the phenotypes associated with duplications of this region [Bi et al., 2009; Bruno et al., 2010; Hyon et al., 2011; Roos et al., 2009; Shimojima et al., 2010]. Duplications of the telomeric portion containing *YWHAE* were linked to high birth weight, large body size, dysmorphic facial appearance, mild developmental delay, autism, and behavior disorders such as increased aggression and preoccupation with food. Duplications of the centromeric region were associated with small body size, microcephaly, moderate to severe developmental delay and mild brain malformations – but not dysmorphic features – and duplication of *LISI* was suggested as the cause [Bi et al., 2009]. Brain-imaging studies were reported to show variable abnormalities of the corpus callosum and cerebellum in three of six imaged patients, with the remaining three scans reported as normal. Another approximately 70 individuals from 20 families with small duplications of distal 17p13.3 and split-hand/foot malformation and long bone deficiency (SHFLD) have been reported. However, none have had developmental delay, intellectual disability (ID) or autism [Armour et al., 2011; Klopocki et al., 2012].

Given the variable phenotype and genomic regions involved, we hypothesized that multiple genes were likely to contribute to the phenotype and that a larger group of patients would be required for accurate genotype-phenotype analysis. Our initial review of several patients with dup 17p13.3 suggested that the phenotypes were variable and that the association of specific genes with discrete phenotypes – including *YWHAE* and *LISI* – was probably premature. We have now ascertained 34 patients from 21 families with dup 17p13.3 by contacting colleagues directly or through two large clinical testing laboratories (Signature Genomic Laboratories and GeneDx), as well as from the DECIPHER database. All duplications included *YWHAE*, *LISI* or both, as well as varying combinations of 48 known genes located between the 17p telomere and *LISI* (data downloaded 11/25/2012 from the UCSC gene track in the UCSC genome browser). We critically assessed patients with respect to their developmental history, neurological and behavioral presentation, craniofacial phenotype, and medical complications. We also reviewed available brain imaging studies on 18 patients.

METHODS AND PATIENTS

Subject ascertainment

We ascertained 42 patients from 29 families personally, or by query of the Signature Genomics, GeneDx and DECIPHER databases for duplications in 17p13.3 that contained

either *YWHAE* or *LISI*. We eliminated six families from further analysis due to other genomic imbalances predicted to impact the phenotype. We eliminated another two families with chromosome rearrangements predicted to result in loss (rather than gain) of function. One had a small intragenic duplication within *YWHAE*, while the other had breakpoints in both *YWHAE* and *CRK*. We included two previously reported children (Patients 2 and 3 in their report), as unpublished brain imaging data became available [Roos et al., 2009]. We kept two unrelated patients with a second duplication in 17p13.2 consisting of 454 kb and 410 kb, as their phenotypes were typical of 17p13.3 duplication. The occurrence of more than one chromosome 17 rearrangement has been reported before and likely reflects the large number of segmental duplications and related propensity for instability on 17p [Shchelochkov et al., 2010]. We also kept one patient with the common dup 16p13.11, as it has been found in normal individuals although it is a risk factor for schizophrenia and other neuropsychiatric disorders [Hannes et al., 2009; Ingason et al., 2011; Ramalingam et al., 2011].

We thus included 34 patients from 21 families in our analysis. Clinicians (including geneticists, neurologists and behavioral pediatricians) supplied clinical data, brain imaging studies and photographs with parental consent. The Institutional Review Boards of Community Hospitals Central California, the University of Chicago, and Seattle Children's Hospital approved this study.

Phenotype data

The clinical, brain magnetic resonance imaging (MRI), and chromosome microarray data were entered in a spreadsheet without identifying information. MRI's were reviewed by WBD and re-reviewed without knowledge of clinical or array data by AJB. Facial photographs were analyzed for dysmorphic features by CJC and WBD, supplemented by clinical descriptions from referring physicians. We followed one subject and evaluated her facial features over 5 years; others were generally seen and described in one or two clinic visits. We specifically looked for evidence of facial hypotonia and an elongated face, as well as other features such as a prominent chin as this was mentioned as a frequent finding in other series [Bi et al., 2009; Bruno et al., 2010; Roos et al., 2009]. Growth was plotted on standard CDC growth charts, with data confined to a single time point for most patients. Developmental status was assessed from referring physician reports and, for a few patients, from detailed psychological studies outlined by the referring physician. The diagnosis of an autistic spectrum disorder was listed only if the referring physician noted this specifically in the records.

Chromosome microarrays

Arrays reported in this study utilized several different platforms as they were performed in different laboratories over several years during which time the resolution increased. The most common platforms used were oligonucleotide arrays: SignatureChipOS version 1 (105K- manufactured by Agilent Technologies, Santa Clara, CA) and SignatureChipOS version 2 (135K, manufactured by Roche NimbleGen, Madison WI).

RESULTS AND DISCUSSION

Subject groups

Due to heterogeneous duplication sizes and locations, we identified no subgroups with common breakpoints. However, our 34 subjects and all previously reported subjects fell into three size groups, and we divided our cohort into these 3 subgroups for genotype-phenotype analysis (Figure 1). These subsets included small telomeric duplications involving chr17:800,000-1,600,000 that include *YWHAE* and flanking genes (Group 1); larger duplications that involved most of 17p13.3 (Group 2), and small centromeric duplications involving chr17:2,000,000-3,000,000 that include *LISI* and flanking genes (Group 3).

Prior reports implicated *YWHAE* and *LISI* as contributing to the duplication 17p13.3 phenotype [Bi et al., 2009; Bruno et al., 2010; Roos et al., 2009], and limited data from mouse (plus our unpublished data) suggest a possible role for *HICI* [Carter et al., 2000]. These genes are separated by 656 kb (*YWHAE-HICI*) and 535 kb (*HICI-LISI*), and serve as sentinel genes for the telomeric (Group 1), large (Group 2) and centromeric (Group 3) regions. We recognize that these 3 sentinel genes may or may not be the pathogenic genes in these overlapping regions, so our data should not be interpreted to implicate these genes specifically. Given the 48 genes in the 17p13.3 region and evidence of incomplete penetrance, we hypothesized that multiple genes contribute to key components of the phenotype. After separating patients into these three groups, we examined sets of features emphasizing growth and development including autism, dysmorphic features and medical and neurological complications, and compared them between groups. For analysis of less common phenotypes including cerebellar vermis hypoplasia (CBVH), cleft lip/palate (CLP), SHFLD and marfanoid habitus, we evaluated all patients as a single group.

Overview and demographics

We analyzed data on 34 individuals from 21 families with dup 17p13.3, separated into groups as noted above. The probands presented with developmental disorders from infancy to 4–5 years of age (N=12), congenital anomalies (N=3), family history of a developmental disorder such as autism (N=1), failure-to-thrive (N=3), or abnormal fetal ultrasound (N=2). The demographics of these families did not differ substantially from the clinic populations where they were seen (Supplementary Table I). Multiple ethnicities were represented including African-American, Caucasian (16 families), Hispanic, East Indian and Asian. Parental ages were not increased. Our index patients were first evaluated between 6 months and 28 years of age. Several carrier parents were identified and included, although information regarding phenotype and behavior was limited for most. Data on the three affected fetuses in this cohort was also limited. With the exception of one child delivered prematurely at 33 weeks, all other index patients were delivered between 37 and 40 weeks gestation. Pregnancies were generally uncomplicated, except that one mother was in an automobile accident and another was diagnosed with hyperthyroidism during the pregnancy. Five of 17 patients for whom information was available were delivered by cesarean section, a rate similar to the general population.

Microarray data

Our microarray data (Table I and Figure 1) demonstrated very heterogeneous breakpoints, which we expected as 17p13.3 contains no important segmental duplications, although it does contain interspersed repetitive elements such as SINEs that can function as recombination substrates for non-homologous end-joining (NHEJ) or fork stalling and template switching (FoSTeS) events [Bi et al., 2009; Shchelochkov et al., 2010]. The duplications in this cohort ranged in size from a small 231.4 kb duplication involving only four genes including *YWHAE* to a large 4.0 Mb duplication encompassing ~87 genes from the 17p telomere past *LISI*. In addition, three patients had second duplications in 17p13.2 (Patient 19, hereafter Pt19, and Pt21a1/a2), and one had a nested triplication within the dup (Pt9). These observations are consistent with the complex cytogenetic mechanisms previously reported with 17p rearrangements [Shchelochkov et al., 2010]. Another patient had a second duplication, dup 16p13.11 (pt17).

Inheritance

The duplication was *de novo* in 10/21 and familial in 10/21 probands (Table I). Only one parent was tested in Family 1. Generally, parents were less affected than their child. Reports of less affected carrier parents are common for several well-known microdeletion and microduplication syndromes such as deletion 15q13.3 [Hoppman-Chaney et al., 2012] and duplication 16p13.11 [Hannes et al., 2009]. This most likely reflects ascertainment bias, variable expressivity, or incomplete penetrance. The mother of an affected fetus diagnosed by array on amniotic fluid cells was mosaic for the duplication in 72% of her peripheral blood cells (Pt11a2). In another family, one parent was an obligate mosaic carrier based on two affected offspring (Pt4a1/4a2) and normal array and FISH results in both parents. One family with two affected siblings (Pt8a1/a2) had no parental testing, although one parent must carry the duplication.

We also recognize that phenotypes such as Kabuki syndrome have been erroneously attributed to copy number variants and acknowledge this possibility [Vermeesch et al., 2011], especially for our patients with the variant CLP, SHFLD and marfanoid phenotypes. However, the constancy of a core clinical and brain phenotype in individuals with 17p13.3 duplication leads us to conclude that the duplication is indeed causative. Although carrier parents were seldom evaluated clinically, the limited information available suggests that few were functioning entirely normally. This would support a relatively subtle phenotype with significant variability, or the effects of modifier genes and environment. In addition, a few probands had near normal intelligence on formal testing but had significant problems with behavior that interfered with school performance.

Duplication 17p13.3 – General Characteristics

A wide range of developmental and health abnormalities occur with dup 17p13.3 including prenatal and growth abnormalities, neurodevelopmental disorders including autism, dysmorphic facial features and other congenital anomalies, and other medical and neurologic problems. These are summarized in Tables II-V and Supplementary Table II.

Prenatal data—Eight patients had abnormal prenatal ultrasounds with findings summarized in Table II. All were referred for routine studies, except for one mother who had abnormal results on expanded AFP screening and another who was concerned about recurrence of duplication 17p13.3 diagnosed in a previous child. Potentially important findings included increased nuchal translucency (7.5 mm) in one fetus, fetal ventriculomegaly, renal anomalies and endocardial fibroelastosis.

Routine amniotic fluid karyotypes were all reported as normal, but subsequent microarrays revealed the duplication in three pregnancies. One mother was a heterozygous carrier of the duplication and another was a mosaic carrier. In a third family both parents had normal arrays and FISH consistent with germline mosaicism. Two mothers terminated affected pregnancies. In the remaining individuals with prenatal abnormalities the duplication was diagnosed sometime after birth.

Growth—Abnormal growth patterns have previously been reported in patients with dup 17p13.3 [Bi et al., 2009; Bruno et al., 2010; Roos et al., 2009; Shimojima et al., 2010]. We therefore reviewed available growth parameters in our cohort (Supplementary Table II). However, our data did not confirm previous reports of large size at birth or later tall stature with duplications involving *YWHAE*. We noticed a general tendency towards obesity from early childhood on in all three groups, but have insufficient data to define a critical region for this finding, or even separate our findings from those of the normal population. A recent report of a small deletion of *CRK* associated with postnatal growth deficiency suggests that this gene, located just centromeric to *YWHAE*, may be important in determining body size [Ostergaard et al., 2012]. Identification of further small duplications in this region will help clarify the genes important for the regulation of body size.

Dysmorphic facial features—We examined facial photographs in 20 patients (Table III and Figures 2–8). Patients in all three groups were mildly dysmorphic, but with subtle and inconsistent features most consistent with the secondary effects of generalized hypotonia, such as mildly myopathic face, open mouthed expression and mildly increased facial length. In infants and young children, facial changes associated with hypotonia predominated. Several children had round faces as infants. With increasing age, evolving facial changes included lengthening of the face, an increasingly prominent jaw with pointed chin and small mouth. These features combined to form a generally consistent facial gestalt in 8/8 patients with photographs available in Group 2 (Table III). Serial photographs in pt14 of Group 2 document the evolution of the phenotype in the young child (Figure 4). In Group 1, many children had a hypotonic face, but facial characteristics were less distinctive than in Group 2. In Group 3, the five individuals with pictures were not convincingly dysmorphic beyond a hypotonic face seen in younger children.

Medical and surgical complications—The medical problem most frequently reported in all groups was recurrent otitis media (Table VI), documented in 9 of 12 children with normal palates. Most were managed with tympanostomy tubes. Five children had early failure-to-thrive, including two given gastrostomy tubes for several months, and three who had gastroesophageal reflux. None had feeding issues persisting beyond infancy. Indeed, obesity and food foraging were reported in a few older children. Two patients had structural

congenital heart disease, neither requiring surgery. Another two had urinary tract abnormalities, and two had significant spasticity that led to Achilles tendon lengthening procedures. One individual had precocious puberty at 7 years. Scoliosis requiring rod placement occurred in two older individuals in Groups 1 and 2, respectively. One adult in Group 2 had hypertension and depression.

Intellectual disability and neurologic problems—The most common developmental and neurologic problems were intellectual disability (ID) seen in 19 of 29 (66%) individuals, and hypotonia seen in 15 of 17 (88%) patients where this data was available (Table IV). Other health problems included seizures in four patients that were resistant to medical management in two, mild cerebral palsy in two, and a wide based, mildly ataxic gait attributed to hypotonia in several children. Many had mildly hyperextensible joints.

A wide spectrum of developmental and cognitive deficits was found in all three groups, with substantial inter- and intrafamilial variability (Table IV). In general, the size and location of the duplication correlated poorly with the degree of impairment. Combining groups, 14 of 29 had mild ID, and only 5 of 29 had moderate or severe ID, including two who had an affected but less disabled family member. Subjectively, the deficits in Group 3 seemed less severe than in Groups 1 and 2. For example, one Group 3 patient with LD (pt19) had a full scale IQ of 99, but showed significant learning and behavioral abnormalities without autism, while another (pt21a3) completed high school in regular classes. The four probands in Group 3 with centromeric duplication 17p13.3 have a less severe and less specific phenotype with normal brain imaging. The smallest region of overlap contains only three genes (*METTL16*, *LIS1*, *KIAA0664* in Figure 1). While *LIS1* duplication has been proposed as the cause of this phenotype [Bi et al., 2009], little is known about the function of the other two genes.

Across all groups aberrant behavior was frequent, but no consistent behavioral phenotype could be established. Attention deficit hyperactivity disorder, temper tantrums, occasional obsessive-compulsive disorder and food seeking behaviors were noted in all three groups, but we could not define critical regions for these. The presence of significant depression in the oldest proband suggests that psychiatric problems may occur in older individuals with this duplication. Neuropsychological testing was rarely reported in this cohort and would be of interest as there is a suggestion of a possibly distinct neurobehavioral phenotype associated with the duplication.

Autism spectrum disorder—A diagnosis of autism or autism spectrum disorder (ASD) was noted in 7 of 22 medical records of patients in Groups 1–2 (Table IV), but in none from Group 3. This suggests that one or more autism loci (contributory genes) are located in the telomeric portion of 17p13.3. We compared autism between Groups 1+2 and Group 3, but the difference was not statistically significant ($p=0.29$, Fisher's exact test), probably because of small numbers. Among 11 patients with dup 17p13.3 and autism (all from Groups 1–2 as shown in Figure 1), the smallest region of overlap contains only two genes: *MYO1C* and *INPP5K* (Figure 10). Neither is a compelling autism candidate gene based on their known functions. Overexpression of *Inpp5k* in mice affects osmoregulation in kidney collecting ducts [Pernot et al., 2011]. Heterozygous missense mutations in the motor domain of

MYOIC cause hearing loss in humans [Adamek et al., 2011]. However, *MYOIC* is a member of the myosin superfamily that binds phosphatidylinositol-4,5-bisphosphate (PIP2) and links the actin cytoskeleton to cellular membranes to affect mechano-signal transduction and membrane trafficking [Hokanson et al., 2006]. This function potentially links the protein to numerous intracellular signaling pathways including the PI3K-AKT pathway [Wickenden and Watson, 2010], so that further analysis will be important.

The standard critical region mapping approach assumes that a single gene is responsible for the autism phenotype in all individuals with dup 17p13.3. While this is usually valid for rare phenotypes caused by one or a few genes, it could exclude strong candidate genes for more common disorders with known genetic heterogeneity. Prior reports identified *YWHAE* and the adjacent *CRK* as possible candidate genes for the duplication 17p13.3 syndrome. Despite one report [Bruno et al., 2010] that excludes both genes based on autism in a patient with a slightly more centromeric duplication (their Patient 12), we still consider *YWHAE* and *CRK* to be good candidates for autism spectrum disorders seen in this cohort (Figure 10). Two further patients recently evaluated and not included in this report have small duplications involving *YWHAE* and *CRK*, and both have an autism spectrum disorder (CRC, unpublished data).

Brain imaging—We reviewed brain-imaging studies performed for clinical care in 18 patients including 9 in Group 1 (2 affected sibs, both with imaging), 5 in Group 2, and 4 in Group 3 (Figure 9). The most consistent abnormalities involved the corpus callosum, cerebellum, posterior fossa and skull. We found mild hypogenesis of the corpus callosum in 2/9 patients in Group 1 and 1/5 in Group 2. Several others had mild, nonspecific thinning of the corpus callosum. The posterior fossa changes were more interesting, as we found mild but convincing CBVH in 5/5 patients in Group 2, but only 1/9 in Group 1 (Table V). Despite small numbers, the difference is statistically significant ($p=0.003$, Fisher's exact test). If we recalculate after adding the borderline CBVH seen in patient 5, the difference remains significant ($p=0.021$, Fisher's exact test).

Several abnormalities involved the posterior fossa and/or posterior skull including mega-cisterna magna or Dandy-Walker malformation (DWM), sharply angled (downward anterior to posterior) foramen magnum, and flat inferior occiput (Table V). Combining these anomalies, we found mild posterior skull changes in 4/5 patients in Group 2, and in more subtle changes in 5/8 patients in Group 1 (striking in only 1/8). We found none of these changes in the four imaged patients in Group 3.

Among seven patients with definite CBVH or DWM (shown in Figure 9), the smallest region of overlap contains only four genes (*CRK*, *MYOIC*, *INPP5K*, *PITPNA*; Figure 10), none compelling candidate genes for a cerebellar developmental disorder. Further, the frequency of CBVH is higher in Group 2 than Group 1 patients, and the malformations are more severe. The higher penetrance of CBVH in Group 2 patients suggests that the region between *YWHAE* and *LISI* contains an important cerebellar developmental gene, although it may not be the only cerebellar developmental gene in the region.

If we exclude the smallest duplication with CBVH (pt3), the region encompasses a larger genomic region that includes *HIC1* and other genes in our Group 2 (Figure 10). *Hic1* is a tumor suppressor in mice and haploinsufficiency produces gross developmental defects including exencephaly, cleft palate, craniofacial defects and limb abnormalities suggesting an important developmental role [Carter et al., 2000; Grimm et al., 1999]. Also, *Hic1* is expressed in cranial mesenchyme during brain development in mice (Kathleen Millen, PhD, unpublished data). We previously showed that haploinsufficiency of *Foxc1* (and *FOXC1* in humans) results in cerebellar hypoplasia in both mouse and human [Aldinger et al., 2009]. However, this gene is expressed in cranial mesenchyme but not the cerebellum itself, which implicates defects in signaling from the mesenchyme into the developing cerebellum as a cause of cerebellar hypoplasia. Thus, loss of *HIC1* might also affect mesenchymal to cerebellar signaling leading to CBVH.

Unusual variant phenotypes

Our data demonstrate three distinct rare variant phenotypes associated with duplication 17p13.3, including CLP (or cleft palate alone in one girl), SHFLD, and marfanoid habitus. The first two phenotypes were observed only in individuals with small distal duplications, while data in the third phenotype is difficult to interpret (Figure 11). These findings suggest complex genomic regulation of the region. Alternatively, although less likely, these phenotypes could be unrelated to the duplication.

Cleft lip and palate—Probands in two families had CLP and surgical repair obscuring the usual dup 17p13 facial phenotype (Figure 6). In one family the proband (pt3a1) and his intellectually normal mother both had CLP, while the duplication carrier maternal grandmother did not have CLP or ID. In a second family, the carrier father (Pt5a2) had learning disabilities and CLP. At age 2 years, the affected infant had mild global delay on the Bayley Scales of Infant Development. A third child, described below, had cleft palate and micrognathia consistent with Robin sequence.

Our observation of CLP or cleft palate alone in five patients from three families is novel. All three duplications contained *BHLHA9* and several centromeric genes (*BHLHA9*, *TUSC5*, *YWHAE*, *CRK*, *MYO1C*, *INPP5K*, *PITPNA*), and had at least one breakpoint in the SHFLD region (chr17:853509-1151031). Indeed, all three duplications associated with CLP or cleft palate alone had one breakpoint located within *ABR* (Figure 11), so that CLP or cleft palate could result from haploinsufficiency of *ABR* rather than from duplication of surrounding genes. Cleft palate was reported in 3/8 patients with deletions of distal 17p13.3 that included *ABR* but not *LIS1* [Bruno et al., 2010; Mignon-Ravix et al., 2010; Nagamani et al., 2009], and in 3/27 patients with Miller-Dieker syndrome [Dobyns et al., 1991] using older technology that could not define the molecular breakpoints (but 2/3 had visible chromosome deletions).

Heterozygous and homozygous *Abr* null mouse mutants as well as *Abr*^{-/-};*Bcr*^{-/-} double mutants were reported to have a normal phenotype [Karttinen et al., 2001]. Further, the CLP and cleft palate phenotypes are unlikely to be caused by duplication of *BHLHA9*, as expression in both mouse and human is restricted to the distal limb bud mesenchyme

underlying the apical ectodermal ridge [Klopocki et al., 2012]. Thus, the molecular pathogenesis of CLP associated with dup 17p13.3 is not clear.

SHFLD and cleft palate—This single remarkable child (pt6) has distinctive dysmorphic facial features that include severe blepharophimosis, round cheeks, small jaw and cleft palate (Figure 7), with the latter two consistent with Pierre Robin sequence. Her lower limb defects are consistent with those described in SHFLD. Her left leg has a short tibia that diverges from the fibula at the ankle consistent with a Jones type IV tibial hemimelia, as well as a distally broad fibula distally lacking normal articulation at the ankle. She also has a left equinus deformity, hypoplastic first metatarsal, hypoplastic proximally-placed hallux, and left 2–3 toe syndactyly. Her right foot has a hypoplastic metatarsal with a deep cleft between the first and second toes, greatly enlarged and proximally placed hallux, and intercalary polydactyly attached to the second toe. We initially considered that this girl had a syndrome unrelated to 17p13.3 duplication. However, the publications related to duplication of *BHLHA9* on 17p13.3 describe the SHFLD part of her phenotype [Armour et al., 2011; Klopocki et al., 2012].

These two reports described 58 patients from 20 families with SHFLD associated with small distal dup 17p13.3, and in addition noted incomplete penetrance and highly variable expressivity [Armour et al., 2011; Klopocki et al., 2012]. The critical region derived from Pt6 and the first paper [Armour et al., 2011], and the smaller critical region from the Klopocki et al. paper [2012] are shown in Figure 11. The latter study described SHFLD in 42/80 dup 17p13.3 carriers and attributed the phenotype to duplication of the small *BHLHA9* gene. They also reported higher penetrance in males than females, with 30/42 male duplication carriers affected with SHFLD, but only 12/40 female carriers affected ($P=0.0003$, Fisher's Exact Test). Our calculation of the P value includes probands, as they were not designated in the paper.

The authors attributed the lack of limb anomalies in published patients with dup 17p13.3 as probably due to non-penetrance [Klopocki et al., 2012]. However, the striking SHFLD phenotype was rare in our cohort of individuals with larger duplications (only 1 had SHFLD), even though most had duplications of the same genes. We therefore formally compared penetrance of SHFLD between the two groups. The first group includes individuals ascertained because of SHFLD or a relative with SHFLD; all have 17p13.3 duplications that include *BHLHA9*. We estimated penetrance of the SHFLD phenotype using data from Family 1 in the first paper [Armour et al., 2011] and all 17 families in the second [Klopocki et al., 2012]. After removing one affected individual from each family as a proband, 29/80 duplication carriers had SHFLD.

The second group consists of individuals ascertained because of a developmental disorder or relative with a developmental disorder. We included only individuals from our series and four prior reports [Bi et al., 2009; Bruno et al., 2010; Hyon et al., 2011; Roos et al., 2009] with 17p13.3 duplications that also include *BHLHA9*, as shown in Figure 1. We found that only one of 21 duplication carriers had SHFLD ($P<0.0031$, Fisher's Exact Test), a difference that is statistically significant. We then divided both groups into males and females and repeated the analysis, finding the same statistically significant result for males but not for

females, likely because of fewer females in our cohort and lower penetrance in females in the SHFLD cohorts.

While this analysis is confounded by variable ascertainment and incomplete phenotype data, the results suggest that duplication of *BHLHA9* alone is not enough to cause SHFLD. That is, duplication of the gene may be necessary to cause the SHFLD phenotype, but is not sufficient. We compared the 17p13.3 duplications between the two groups and found two potentially important differences. First, the SHFLD group duplications are smaller (average 244 kb and mean 263 kb) than most developmental disorder group duplications (average 1.55 Mb and mean 1.12 Mb). Second, most SHFLD group duplications have one of the two duplication breakpoints close to *BHLHA9*, with 19/20 located between the start of *ABR* and the end (exon 7) of *TUSC5* (chr17:853509-1151031). In contrast, only 4/17 duplications in our series contained *BHLHA9* and had a breakpoint in this region. This includes Pt6 with SHFLD, cleft palate and additional dysmorphic and ocular features not seen in other subjects. We believe that our data imply a more complex genomic mechanism, and hypothesize that both duplication of *BHLHA9* and disruption or separation from nearby regulatory elements are necessary to cause the SHFLD phenotype.

The data from SHFLD families with dup 17p13.3 showed significantly higher penetrance in males than females [Klopocki et al., 2012]. We asked whether the same phenomenon occurs in patients with larger duplications presenting with developmental phenotypes. Among our 17 probands in Groups 1 and 2, 13 were male and only 4 female. The excess of males in this still relatively small series was not statistically significant, but suggests a trend that bears further observation. Further, Groups 1 and 2 included four instances of mother to son, two instances of father to son, and interestingly no instances of either mother or father to daughter transmission (Table I and Supplementary Table I; we excluded Families 7 and 8 for reasons indicated in the Tables). The sons born to duplication carrier mothers were more severely affected than their mothers, but we have insufficient data to determine whether the sons born to carrier fathers were more severely affected than their fathers. In the entire series, we did not find greater severity among male compared to female probands.

Marfanoid habitus—Two patients in our series and two from the literature have what was termed by their physicians as a “marfanoid habitus”. The first reported patient (Patient 4 in the report) was described as tall, with large hands and long face [Bi et al., 2009]. He had aortic root dilation and mitral valve prolapse treated with Losartan. No molecular studies were performed as he was thought not to meet criteria for either Marfan or Loeys-Dietz syndrome. The second reported patient (Patient 1 in the report) also had severe hypotonia, and muscle biopsy revealed findings suggestive of congenital muscle fiber-type disproportion [Roos et al., 2009]. He was tall (height +3.5 SD) but his parents were also tall. He had long limbs and a long face. Echocardiographic findings and molecular testing were not reported.

In our series, one proband (Pt17a1, Figure 8) has a severe and distinctive connective tissue and craniofacial phenotype that appears more striking than classical Marfan syndrome, although no alternative diagnosis was apparent. His geneticist excluded *MEN2B* and other recognizable syndromes associated with a marfanoid habitus. He presented as a newborn

with a hiatal hernia and bilateral Morgagni hernias that were repaired in infancy, and two ventricular septal defects. He also had a large umbilical hernia, asthenic habitus, kyphosis, arachnodactyly and dilatation of the aortic root, first noted at 13 years. Sequencing and deletion/duplication analysis of *FBN1*, *TGFBR1* and *TGFBR2* were normal. Another patient in our series (Pt1) was described as having a “marfanoid” appearance but no photographs or echocardiographic data were available. He was originally referred for significant hypotonia and had prominent ears, long chest, long lean body and flat feet. No information was available regarding aortic root dilation or molecular testing.

All four of these patients were male and none were described in sufficient detail to allow us to determine their similarity to one another, or the appropriateness of the designation “marfanoid habitus”. Examination of clinical photographs does not suggest a similar craniofacial phenotype for these patients and we are not convinced that they have the same cause for their “marfanoid” appearance. The critical region is large and does not contain an attractive candidate gene (Figure 11). Further reports with clinical and molecular data will be needed to determine if this represents another rare and distinct duplication 17p13.3 phenotype, a coincidence of marfanoid features in families with tall stature, or several different phenotypes with heterogeneous causes. From the data available, it seems reasonable to consider echocardiographic screening of patients with duplication 17p13.3.

Conclusions

In summary, we reviewed 34 individuals from 21 families with duplication 17p13.3 associated with heterogeneous breakpoints, and found several overlapping phenotypes. However, none were pathognomonic or likely to allow recognition of this genomic disorder on clinical grounds alone. Within families we found significant variability of phenotype with parents generally being less severely affected than their child. This suggests that the minimally affected individual with 17p13.3 duplication is unlikely to be ascertained unless a more severely affected child is born.

Our review of 51 patients with duplication 17p13.3 (34 reported here and 16 from the literature) confirms most abnormalities noted in previous reports, and adds information regarding prenatal features, dysmorphic facial features, brain malformations and several less common medical problems. Most importantly, our data demonstrate that incomplete penetrance and highly variable expressivity are characteristic of this duplication syndrome. This suggests that regulation of gene expression in this region must be complex. Further, our data suggest that prior reports linking duplication of specific genes such as *LIS1* with a specific phenotype were premature.

The features associated with telomeric duplications of 17p13.3 (Group 1) include early developmental delay, mild to moderate ID or LD, an increased rate of autism, hypotonia and mildly myopathic facial features in infants and young children, mild but characteristic facial dysmorphic features at older ages, and occasional mild brain malformations involving the corpus callosum, cerebellum and posterior fossa. The features associated with larger duplications of 17p13.3 (Group 2) include the features enumerated above as well as more striking facial dysmorphic findings at older ages consisting of a long face, small mouth, prominent jaw and pointed chin, and malformations of the cerebellum and posterior fossa

that are more consistent and severe than those found with smaller duplications. Several probands of varying ages had persistent hypotonia, hyperextensible joints and mild gait instability irrespective of their group. Most but not all older children and adults were overweight.

The features associated with centromeric duplications (Group 3) were less severe and less specific, consisting of frequent failure-to-thrive in infancy, developmental delay, mild to moderate ID or LD generally less severe than in Groups 1–2, seizures in one, behavioral problems especially temper tantrums and attention deficit disorder, and less distinct dysmorphic facial features. We found no association in Group 3 with autism or brain malformations.

Our analysis of dup 17p13.3-associated phenotypes proved far more challenging than we expected. In retrospect, we attribute this to the lack of any highly penetrant abnormality, the presence of several relatively common and nonspecific features such as failure-to-thrive, obesity, intellectual disability and autism, and to the complex inheritance we found for rare variant phenotypes (CLP, SHFLD and marfanoid habitus). Despite the many CNV-associated syndromes described so far, most genomic regions have not yet been associated with deletion or duplication syndromes. While some are likely to be early lethal, we expect that many more will have non-specific and variable phenotypes, and propose that duplication 17p13.3 may serve as a paradigm for this class of disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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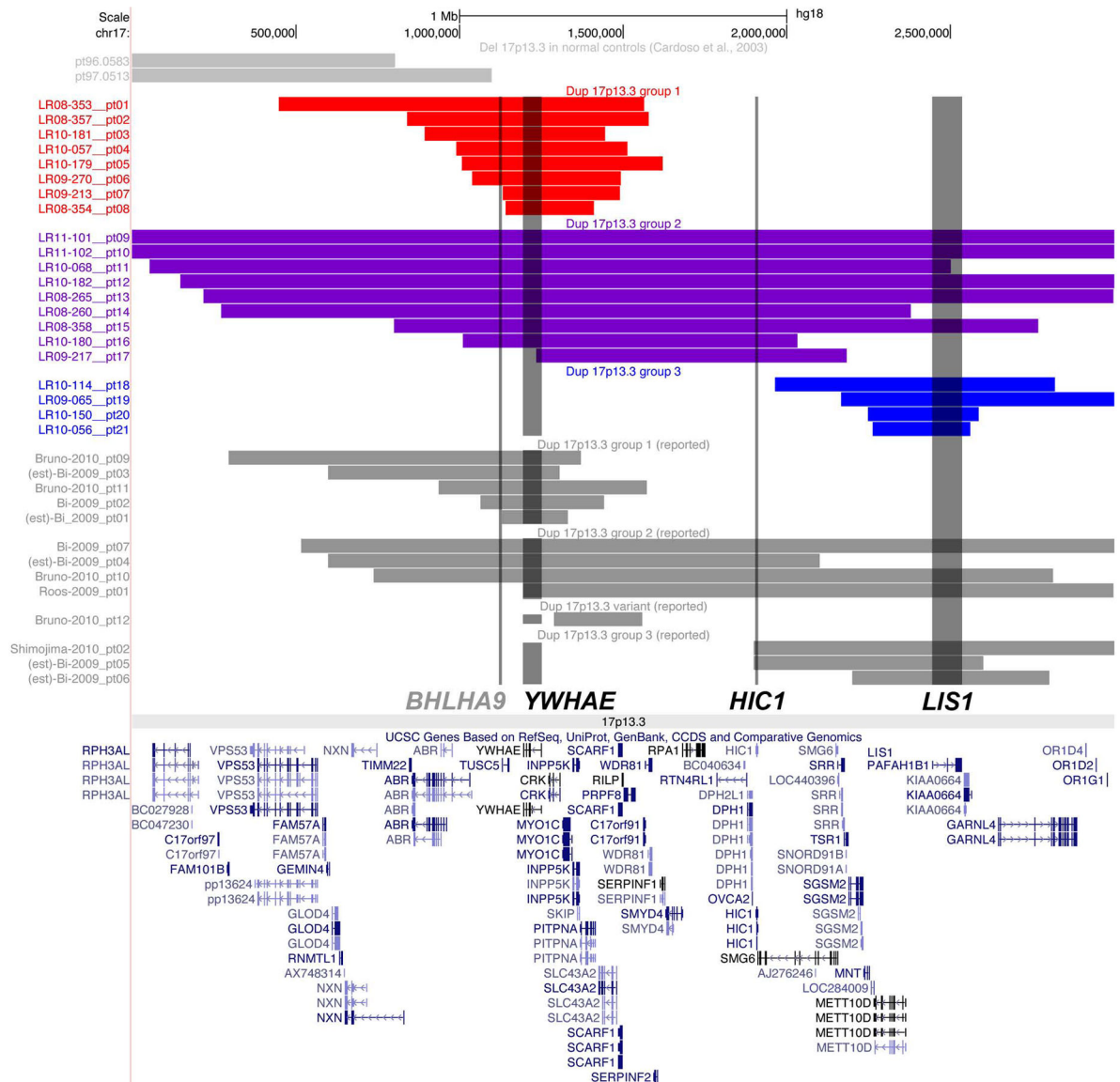


Figure 1. A map of chromosome band 17p13.3 showing the genome location and gene content of duplications in all 21 families in our study as well as 13 additional patients from the literature was made using the Custom Tracks function in the UCSC browser (<http://genome.ucsc.edu>). The map shows Group 1 dups in red, Group 2 dups in purple and Group 3 dups in blue so that the differences in duplication size and position are obvious. The map also shows other reported dups in gray [Bi et al., 2009; Bruno et al., 2010; Roos et al., 2009; Shimojima et al., 2010].

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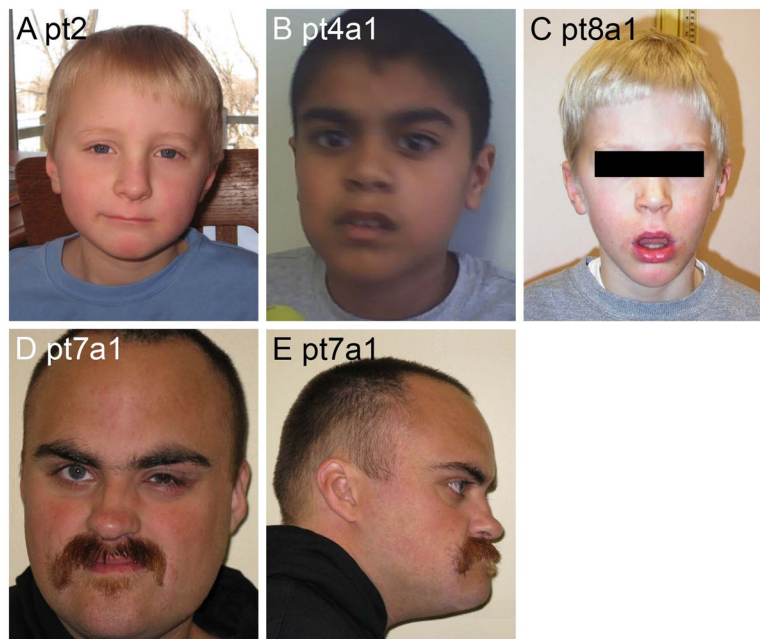


Figure 2.
Facial photos of four patients from Group 1. Note the hypotonic face in Patient 8a1 (D).



Figure 3. Facial photos of eight patients from Group 2. Note the round faces and facial hypotonia in younger Patients 9, 10 and 16 (A–F), and the long faces with prominent jaw and pointed chins in older Patients 11, 12, 13 and 15 (G–L).



Figure 4. Serial photos of Patient 14 from 2.5 to 7 years. Note increasing weight and facial lengthening with increasing age.

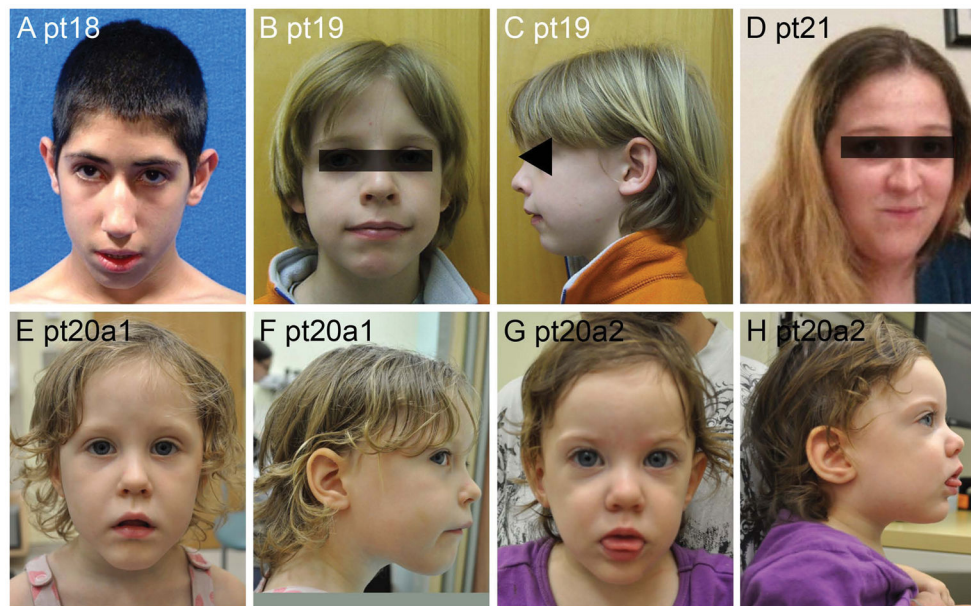


Figure 5. Facial photos of five patients from Group 3. Note an inconsistent phenotype with normal appearance of Patient 19.

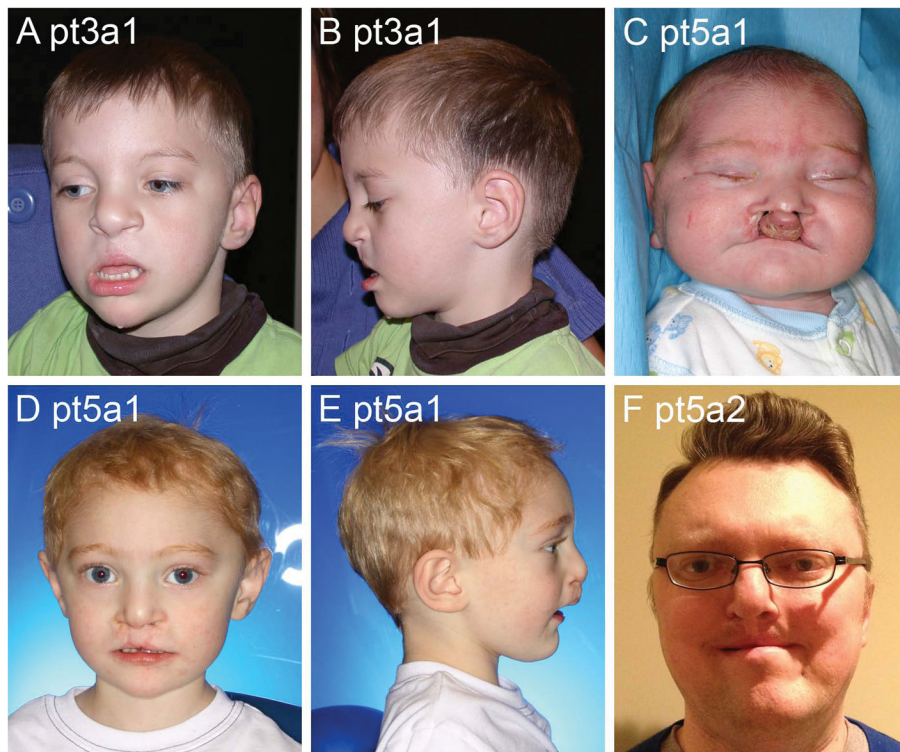


Figure 6. Facial photos of three individuals with cleft lip and palate including one pre-surgical photo (C) and the remainder with repaired cleft lip (A, B and D–F). Also note the typical dup 17p13 adult face in Patient 5a2 (F).

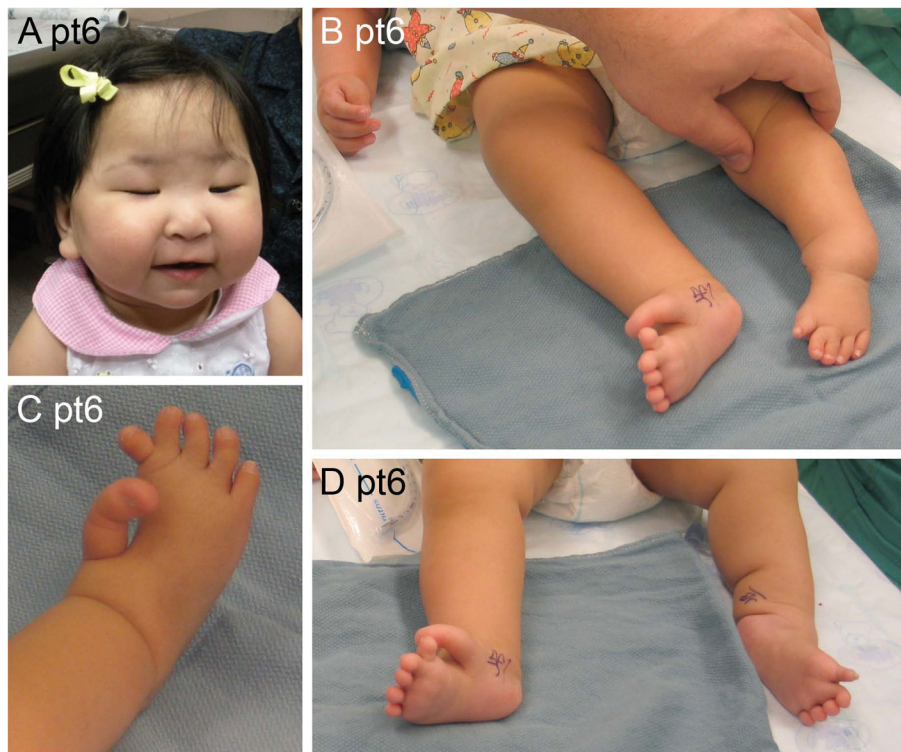


Figure 7. Facial and limb photos of a girl with split hand/foot with long bone deficiency show blepharophimosis, full cheeks and Robin sequence (A). She also has tibial deficiency with intercalary polydactyly and syndactyly (B–D).

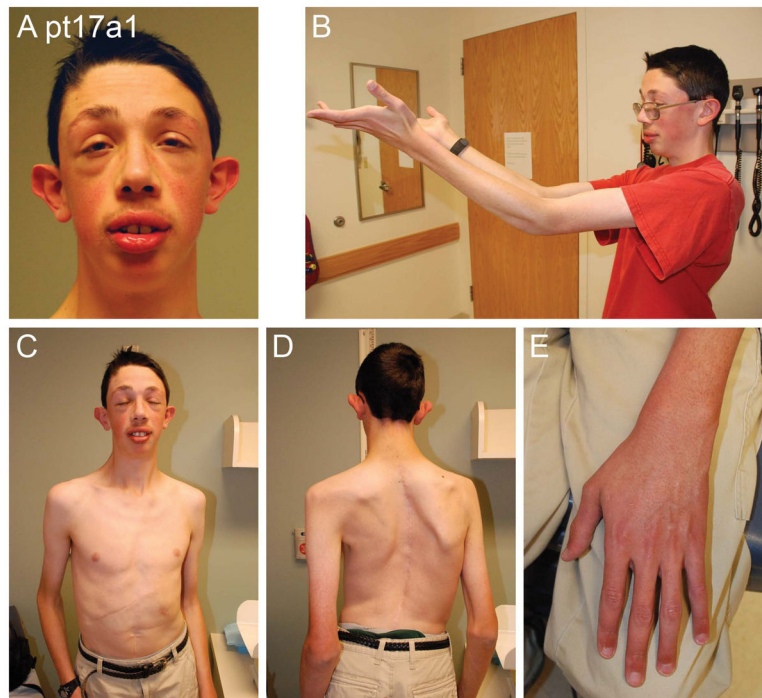


Figure 8. Facial and body photos of Patient 11 show dysmorphic facial features (A, C), and an unusual marfanoid habitus with scoliosis (D) and long limbs and fingers (B–E). He also has a dilated aortic root.

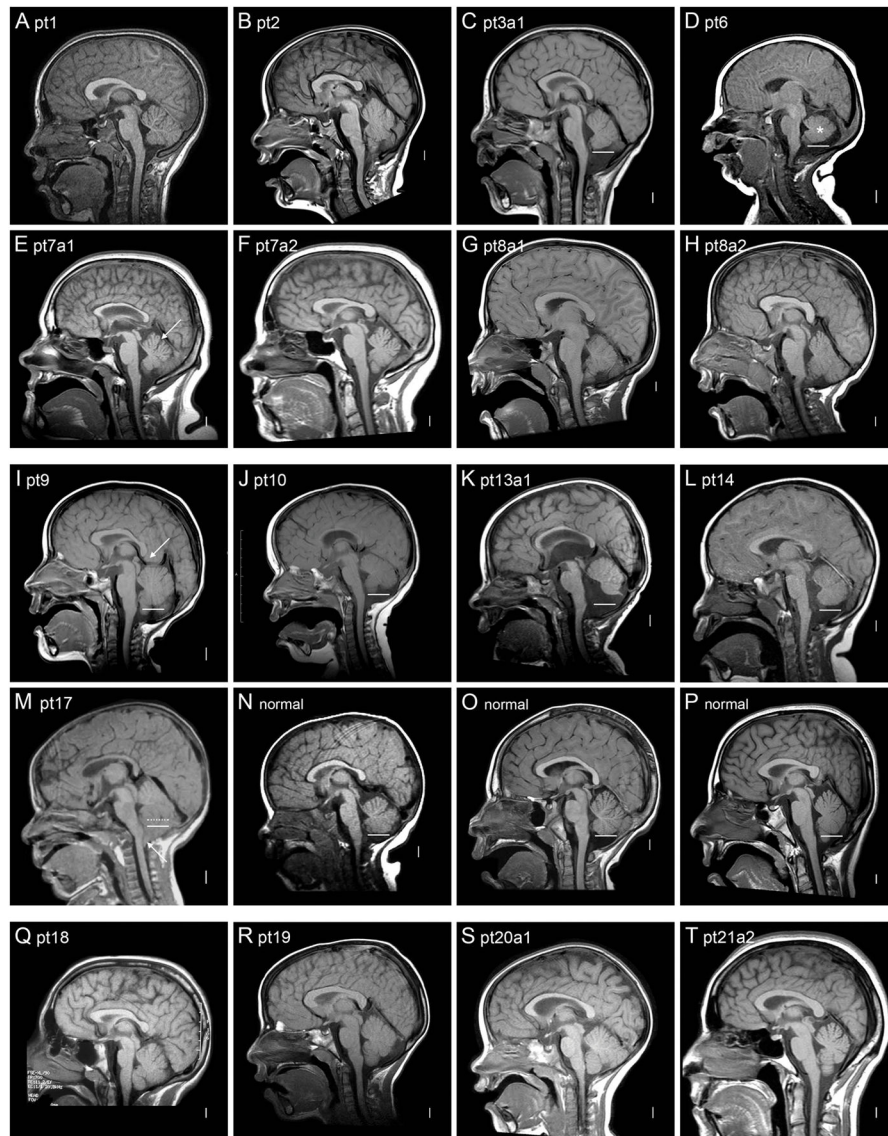


Figure 9.

Brain imaging. T1-weighted midline sagittal brain magnetic resonance images are shown from individuals from Group 1 (A–H), Group 2 (I–M), and Group 3 (Q–T), as well as from three normal individuals (N–P). The solid white bars seen in multiple images show the level of the obex, which typically marks the level of the most inferior portion of the vermis as seen in the normal controls (N–P). The dotted white bar in M marks the lower limit of the vermis, which is difficult to see because of Chiari malformation in this patient. These images show a mildly small cerebellar vermis in two of eight patients in Group 1 (C and D), and in all five patients in Group 2 (I–M). The arrow in E points to a mildly prominent primary fissure, which suggests mild atrophy. The asterisk in D marks the smallest vermis, with normal vermian anatomy not well seen, probably because the image is just off midline. The arrow in image I points to mild protrusion or ectopia of the mesial parietal lobes into the tentorial notch between the corpus callosum and superior vermis. The vermis appears normal in all patients in Group 3 (Q–T). The images also show steeply angled foramen

magnum (B, C, G, H, I, K, L) and flat inferior occiput (D, G, H, I, M) in most patients in Groups 1 and 2.

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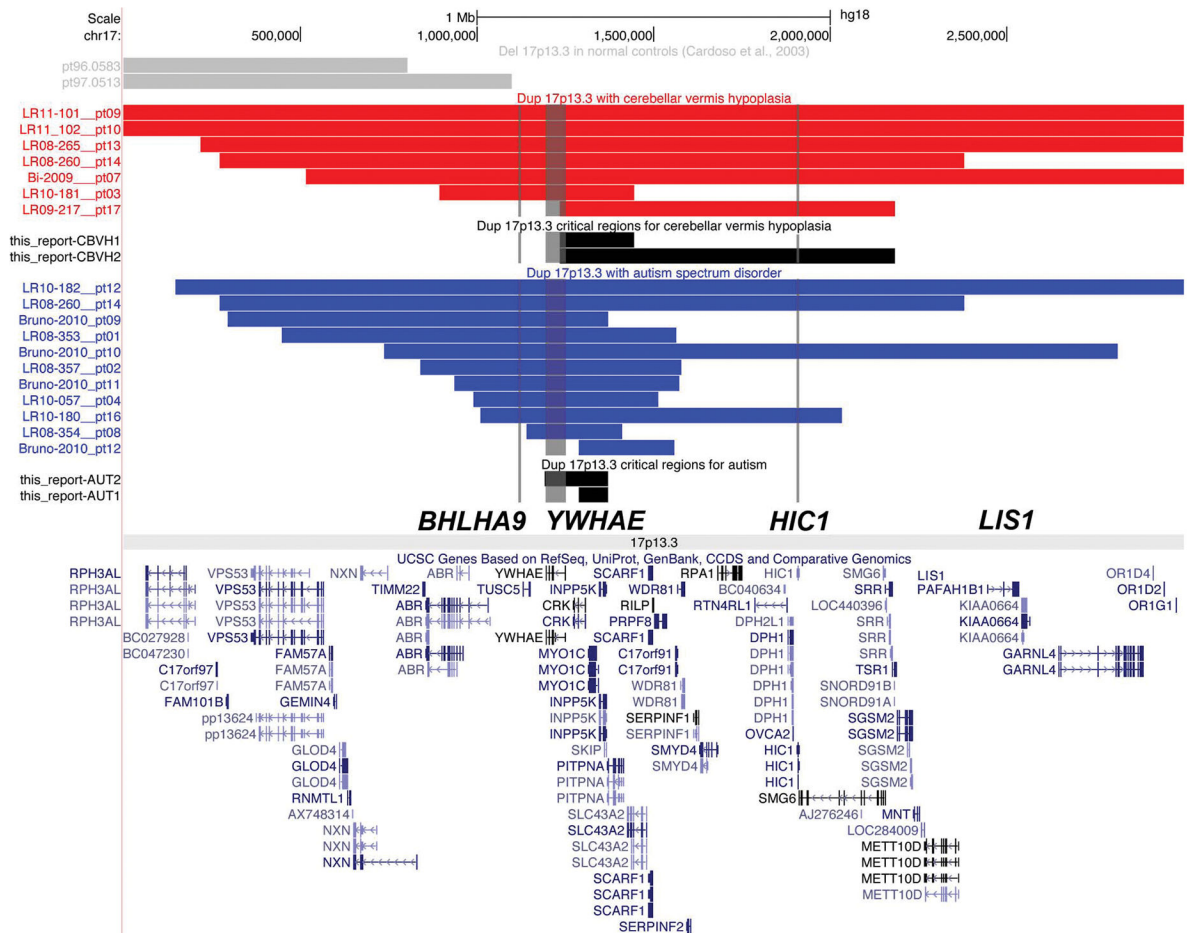


Figure 10.

Map of chromosome 17p13.3 shows possible critical regions for cerebellar vermis hypoplasia in red and autism in blue. The smaller critical regions were determined assuming a single locus for each disorder, while the larger regions allow for limited causal heterogeneity by removing the patient with the smallest duplication.

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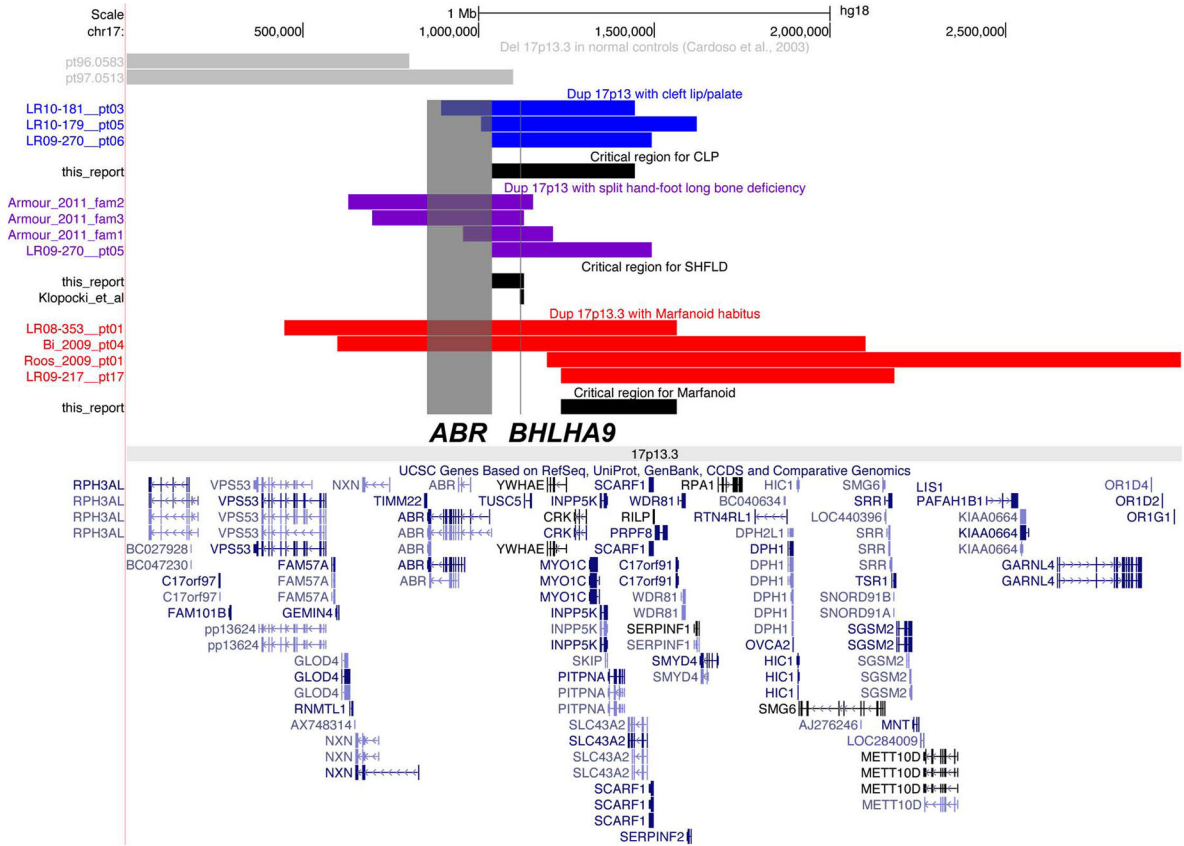


Figure 11.

Map of chromosome 17p13.3 shows possible critical regions for rare abnormalities including cleft lip and palate (CLP) in blue, split hand/foot with long bone deficiency (SHFLD) in purple, and marfanoid habitus in red. The rearrangements associated with CLP and SHFLD suggest a more complex mechanism than simple duplication, as explained in the text. All three dups associated with CLP have one breakpoint located within the ABR gene. All 4 dups associated with SHFLD shown here as well as 16/17 additional dups associated with SHFLD from another recent report [Klopocki et al., 2012] have one breakpoint located within or between the ABR and TUSC5 genes, suggesting disruption of regulatory elements.

Table 1

Genome data for duplication 17p13.3 patients

LisIb#	Pt#	Genome coordinates [hg18]	Size	Sentinel genes	Inheritance	Microarray
Group 1						
LR08-353	1	(chr17:447,066-1,563,813)×3	1.12 Mb	YWHAE	paternal na*	SGL OS 135K
LR08-357	2	(chr17:840,149-1,578,598)×3	738.4 kb	YWHAE	de novo	SGL OS 135K
LR10-181a1	3a1	(chr17:894,983-1,443,730)×3	548.7 kb	YWHAE	maternal	OGT 105K
LR10-181a2	3a2	same as 3a1	"	YWHAE	maternal	OGT 105K
LR10-057a1	4a1	(chr17:991,473-1,513,936)×3	522.5 kb	YWHAE	germline	Genzyme Clarisure
LR10-057a2	4a2	same as 4a1	"	YWHAE	mosaic	SGL OS 135K
LR10-179a1	5a1	(chr17:1,007,000-1,619,962)×3	613.0 kb	YWHAE	paternal	SGL OS 135K
LR10-179a2	5a2	same as 5a1	"	YWHAE	na	SGL OS 135K
LR09-270	6	(chr17:1,039,126-1,491,785)×3	452.7 kb	YWHAE	de novo	SGL OS 105K
LR09-213a1	7a1	(chr17:1,131,224-1,448,997)×3	317.8 kb	YWHAE	maternal	SGL OS 105K
LR09-213a2	7a2	same as 7a1	"	YWHAE	na	SGL OS 105K
LR08-354a1	8a1	(chr17:1,140,796-1,410,997)×3	270.2 kb	YWHAE	mat/pat	SGL OS 135K
LR08-354a2	8a2	same as 8a1	"	YWHAE	mat/pat	SGL BAC
LR08-354a3	8a3	na	na	na	na	
Group 2						
LR11-101	9	(chr17:1-3,012,800)×3 and (chr17:1,448,942-1,503,503)×4	3.0 Mb	YWHAE-HIC1-LIS1	de novo	Agilent 244K
LR11-102	10	(chr17:1-4,052,847)×3	4 Mb	YWHAE-HIC1-LIS1	de novo	Agilent 244K
LR10-068a1	11a1	(chr17:52,934-2,501,198)×3	2.45 Mb	YWHAE-HIC1-LIS1	maternal	SGL OS 135K
LR10-068a2	11a2	dup confirmed by FISH	"	YWHAE-HIC1-LIS1	mosaic 72%	FISH
LR10-182	12	(chr17:148,091-3,505,143)×3	3.4 Mb	YWHAE-HIC1-LIS1	de novo	UNC SGLSelect 105K
LR08-265a1	13a1	(chr17:219,072-2,996,360)×3	2.78 Mb	YWHAE-HIC1-LIS1	paternal	Agilent 660K-quad
LR08-265a2	13a2	same as 13a1	"	YWHAE-HIC1-LIS1	na	Agilent 660K-quad
LR08-260	14	(chr17:271,999-2,277,555)×3	2.01 Mb	YWHAE-HIC1	de novo	Genome Dx 105K
LR08-358	15	(chr17:800,495-2,767,054)×3	2.16 Mb	YWHAE-HIC1-LIS1	de novo	Agilent 105 K
LR10-180	16	(chr17:1,010,661-2,032,333)×3	1.02 Mb	YWHAE-HIC1	de novo	OGT 105K
LR09-217a1	17a1	dup 17p13.3; dup 16p13.11	948.5 kb; 1.24 Mb	YWHAE-HIC1	17p maternal	SGL OS 135K

Lisdb#	Pt#	Genome coordinates [hg18]	Size	Sentinel genes	Inheritance	Microarray
		(chr17:1,235,314-2,183,796)×3 (chr16:14,957,300-16,195,404)×3			16p de novo	
LR09-217a2	17a2	17p same as 17a1.no 16p dup	**	YWHAE-HICI	na	SGL OS 135K
Group 3						
LR10-114	18	(chr17:1,963,450-2,816,939)×3	853.5 kb	LIS1	de novo	Agilent 105K
LR09-065	19	dup 17p13.3, dup 17p13.2 (chr17:2,165,727-4,237,227)×3 (chr17:4,014,003-4,468,074)×3	2.27 Mb, 454.0 kb	LIS1	de novo	Genome Dx 105K
LR10-150a1	20a1	(chr17:2,249,109-2,586,017)×3	336.9 kb	LIS1	paternal	SGL OS 105K
LR10-150a2	20a2	same as 20a1	336.9 kb	LIS1	paternal	SGL OS 105K
LR10-150a3	20a3	same as 20a1	336.9 kb	LIS1	na	SGL OS 105K
LR10-056a1	21a1	dup 17p13.3, dup 17p13.2 (chr17:2,260,944-2,560,922)×3 (chr17:4,028,199-4,436,327)×3	300.0 kb 408.1 kb	LIS1	maternal	SGL OS 135K
LR10-056a2	21a2	same as 21a1	**	LIS1	maternal	SGL OS 135K
LR10-056a3	21a3	same as 21a1	**	LIS1	na	SGL OS 135K

Abbreviations: mat/pat, inherited but parent-of-origin unknown; mosaic, mosaicism implying de novo inheritance; na, not available; Pt#, patient #; *, maternal array normal. Chromosome microarrays: Agilent 105K; Agilent Human Genome CGH 105K; Agilent 244K, Agilent Human Genome CGH 244K (Agilent Technologies, Santa Clara, CA); Illumina 660K; Illumina HD Human660W-Quad BeadChip SNP array (Illumina, San Diego CA); SGL OS 105K and SGL OS135K, Signature Genomics Laboratories oligonucleotide arrays; OGT; Oxford Gene Technology; UNC University North Carolina.

Table 2

Prenatal findings in isolated 17p13.3 duplications

Patient #	Indication	Prenatal US	CVS/AMNIO	Inheritance	Comments
6	Routine	dilated renal pelves	Not done	Not tested	Diagnosis in infancy
4a1	Recurrence dup 17p13, MA	Not available	CVS microarray dup 17p13.3	Both parents normal; two affected sibs	Germline mosaicism in one parent; fetus terminated
10	Routine	Probable ACC; VMEG; oligo at 33 weeks	Amnio karyotype 46, XY	Not tested	Diagnosis in infancy
11a1	Routine	SUA; renal anomalies	Amnio karyotype 46, XY; microarray dup 17p13.3	Maternal mosaicism 72%	Unilateral multi-cystic dysplastic kidney
14	MA, abnormal AFP	None	Amnio karyotype 46, XX	Not tested	Diagnosis at 2.5 years
16	Routine 1st trimester	Nuchal trans-lucency 7.5 mm	Not done	Not tested	Diagnosis at 2 years
20a1	Routine	Probable IVH, resolved before birth	Not done	Not tested	Diagnosis at 4 years
21a1	Routine 2nd trimester	VMEG, CP cysts, endocardial fibroelastosis	Amnio microarray 17p13.3 dup	Maternal	Terminated with no autopsy; previous SB with hydrops

Abbreviations: ACC, agenesis of the corpus callosum; AFP, alpha-fetoprotein; Amnio, amniocentesis; CP, choroid plexus; CVS, chorionic villus sample; dup, duplication; IVH, intraventricular hemorrhage; MA, maternal age; oligo, oligohydramnios; SB, stillbirth; SUA, single umbilical artery; US, ultrasound; VMEG, ventriculomegaly.

Table 3

Facial features in duplication 17p13.3 patients

Pt#	Age	OFC (centile)	Dysmorphic facial features									
			Gestalt	Hypo-tonic	Long	Malar hypo	Prom jaw	Pointed chin	Small mouth	Other		
Group 1												
2	4y	50	-	+/-	-	-	+	+	-	-	-	-
3a1	4y	NL	-	+	+/-	-	+	+	+	+	-	CLP, hypertelorism
4a1	8y	<5	-	-	-	-	+	+	-	-	-	-
5a1	3y	NA	-	-	-	-	-	-	+	+	+	CLP
5a2	adult	NA	+	-	+	+	+	+	+	+	+	CLP
6	14mo	NA	-	-	-	-	-	-	-	-	-	Blepharophimosis, CP
7a1	27y	<3	±	-	+	-	-	+	+	+	+	Midface hypoplasia
8a1	4y	75-90	±	+	+	-	-	+/-	+	+	+	
Group 2												
9	12mo	-1.5 SD	+	+	-	-	+	+	+	+	+	Short nose
10	13mo	NA	+	+	+	-	+	+	+	+	+	
11a2	24y	NA	++	?	+	-	-	+	+	+	-	
12	28y	50-75	++	+	+	-	-	+	+	+	+	
13a1	13mo	25	+	+	+	-	-	+	+	+	+	
13a2	adult	NA	++	NA	+	-	-	-	+	+	+	
14	6y	25-50	+	+	+	-	-	-	+	+	+	Midface hypoplasia
15	14y	25-50	++	NA	+	-	-	+	+	+	+	
16	2y	NA	-	+	-	-	-	-	+	+	-	Short nose; smooth philtrum
Group 3												
18	15y	<3	-	+	+	+	+	-	-	-	-	
19	5.5y	50	-	-	-	+	+	-	-	-	-	
20a1	3.9y	50	±	+	+	+	+	-	+	+	+	
20a2	18mo	10	±	+	+	+	+	-	+	+	+	
21a2	27y	NA	+	-	+	-	-	+	+	+	+	

Abbreviations: CLP, cleft lip and palate; CP, cleft palate; hypo, hypoplasia; mo, months; NA, not available; prom, prominent; rd, round; SD, standard deviations; y, years.

Table 4

Developmental and neurologic status in duplication 17p13.3 patients

Pt#	Hypotonia	Seizures	Cognition	ASD	Other
Group 1					
1	+	-	Mild ID	+	Poor balance
2	+	-	Mild ID	+	
3a1	+	-	Mild ID	-	
3a2	na	-	Normal	-	
4a1	na	-	Mild ID	+	
5a1	+	-	Mild ID	-	
5a2	na	+	LD	-	ADD, unusual affect
6	+	-	Mod ID	-	
7a1	-	+	Severe ID	-	Mild spasticity, ataxia
7a2	na	-	LD	-	
8a1	+	-	Mild ID	-	
8a2	+	-	Mod ID	-	
8a3	na	-	Mild ID	+	Both parents have ASD
Group 2					
9	+	-	Mild ID	-	
10	+	-	Mod ID	-	
11a2	na	-	LD	-	
12	na	+	LD	+	ADD, mild spasticity, ataxia, depression
13a1	-	-	Mild ID	-	
13a2	na	-	LD	-	
14	+	-	Mild ID	+	Poor balance, temper tantrums
15	+	-	Mild ID	-	Poor balance
16	+	-	Mild ID	+	Temper tantrums
17a1	+	-	Mild ID	-	
Group 3					
18	na	-	Mod ID	-	ADHD

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Pt#	Hypotonia	Seizures	Cognition	ASD	Other
19	+	-	LD	-	ADHD, behavior problems
20a1	+	-	Mild ID	-	Temper tantrums
20a2	+	+	Mild ID	-	Temper tantrums
20a3	na	-	LD	-	
21a2	na	-	Normal	-	
21a3	na	-	Normal	-	

Abbreviations: ADHD, attention deficit hyperactivity disorder; ASD, autistic spectrum disorder; ID, intellectual disability; LD, learning disability; Mod, moderate ID; na, not available; Pt#, patient number.

Table 5

Brain imaging abnormalities in duplication 17p13.3 patients

Pt#	Cerebral hemispheres	Corpus callosum	Lateral ventricles	Brainstem	Cerebellum	Posterior fossa, skull
Group 1						
1	N	N	N	N	N	N
2	N	Short	N	N	N	±BOM
3a1	N	N	N	N	CBVH	MCM-BOM
4a1	N	N	N	N	N	N
6	N	Short	N	N	±CBVH	±BOM
7a1	Atrophy	Thin	VMEG	N	Atrophy	N
7a2	N	N	N	N	N	N
8a1	N	N	N	N	N	±BOM
8a2	N	N	N	N	N	±BOM
Group 2						
9	N	N	N	N	CBVH	BOM
10	N	Short	Fetal	N	CBVH	N
13a1	N	Thin	VMEG	N	DWM/CBVH	MCM-BOM
14	N	N	N	N	CBVH	MCM-BOM
17a1	N	Thin	VMEG	N	±CBVH	CBTE, ±BOM
Group 3						
18	Atrophy	N	VMEG	N	N	N
19	N	N	N	N	N	N
20a1	N	N	VMEG	N	N	N
21a2	N	N	N	N	N	N

Abbreviations: ±BOM, normal except for subtle basi-occipital changes such as downsloanted foramen magnum or flat inferior occiput; CBTE, cerebellar tonsillar ectopia with Chiari 1 malformation; CBVH, cerebellar vermis hypoplasia; ±CBVH, probable or mild CBVH; DWM, Dandy-Walker malformation; MCM-BOM, mega-cisterna magna with associated basi-occipital skull anomalies; Pt#, patient number; Short, short and thin corpus callosum consistent with mild partial agenesis; VMEG, ventriculomegaly. Fetal, fetal VMEG described as normal on postnatal imaging.

Table 6

Rare phenotypes and other health problems in duplication 17p13.3 patients

Pt#	MARF	SHFLD	CL/P	Other health problems
Group 1				
1	+	-	-	Flat feet, leg cramps, constipation
2	-	-	-	BOM
3a1	-	-	+	Pectus excavatum, hydrocele, pneumonia, BOM
3a2	-	-	+	BOM
4a1	-	-	-	
5a1	-	-	+	BOM
5a2	-	-	+	BOM
6	-	+	(+)	Cleft palate only, micrognathia, blepharophimosis, GER, bicuspid AoV, gastrostomy tube, orthopedic surgeries, BOM
7a1	-	-	-	Achilles lengthening
8a1	-	-	-	BOM
8a2	-	-	-	BOM
Group 2				
9	-	-	-	FTT, BOM
10	-	-	-	Dislocated hip, inguinal hernia, recurrent URI, micropenis
11a1	-	-	-	Multicystic dysplastic kidney (unilateral)
11a2	-	-	-	
12	-	-	-	depression; hypertension; scoliosis with rods; incontinence, hydronephrosis; breast reduction, abdominoplasty, jaw reconstruction; Achilles lengthening
13a1	-	-	-	FTT, GER, gastrostomy tube, eczema
13a2	-	-	-	
14	-	-	-	FTT, GER; later overweight; precocious puberty
15	-	-	-	Hearing loss; UTI, ureteral reimplantation; sleep apnea; scoliosis; BOM
16	-	-	-	
17a1	+	-	-	Hiatal hernia; umbilical hernia; Morgagni hernia, VSD, hemivertebrae; GER, GT, BOM
Group 3				
18	-	-	-	FTT
19	-	-	-	FTT, GER; gastrostomy tube; pneumonia; BOM
20a1	-	-	-	BOM
20a2	-	-	-	FTT
21a1	-	-	-	endocardial fibroelastosis
21a2	-	-	-	

Abbreviations: AoV, aortic valve; CLP, cleft lip and palate; FTT, failure-to-thrive; F/U, follow-up; GER, gastroesophageal reflux; MARF, Marfanoid habitus; BOM, recurrent bilateral otitis media; Pt#, patient number; SHFLD, split hand-foot limb deficiency; URI, upper respiratory infections; UTI, serial urinary tract infections, VSD, ventricular septal defects.