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Clinical Report of a 17q12 Microdeletion with Additional Unreported Clinical Features: Expansion on the Phenotype

BACKGROUND

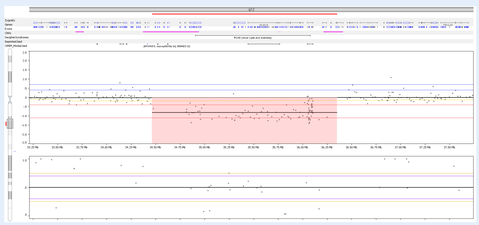
- Copy number variations (CNVs) involving the 17q12 region have been reported in association with unique clinical features such as developmental delay, speech delay, autism, aggression, self-injury, oppositional defiance, biting, hitting, inappropriate language, and auditory hallucinations (Loirat 2010 , Nagamani 2010, and Moreno De-Luca 2010).
- Deletions of 17q12, including the *HNF1B* gene, have been reported to be associated with maturity onset diabetes of the young type 5 (MODY5), cystic renal disease, renal dilations, pancreatic atrophy, and liver abnormalities (Loirat 2010)
- Our proband is a 17-year old male seen in Genetics Clinic at the University of Kansas Medical Center in Kansas City, KS.
- He presented with 46, XY karyotype, normal CPK levels, normal homocysteine levels, normal eye exam, normal MRI, normal EEG, normal liver, and no apparent cardiac abnormalities.
- Abnormal phenotype features included a dysmorphic face, cognitive and developmental delay, abnormal body habitus, joint laxity, and significant psychiatric manifestations (see Table 1).
- Family history was negative for Marfan syndrome, congenital abnormalities, mental retardation, and consanguinity was denied.

METHODS

- A blood sample was collected from the proband and sent to Ambry Genetics (Aliso Viejo, CA) for 400K CGH+ SNP analysis (Agilent Technologies, Santa Clara, CA). Genomic deoxyribonucleic acid (gDNA) was isolated from the patient's specimen using a standardized kit and quantified by agarose gel electrophoresis. The aCGH method is based on the hybridization of fluorescently labeled patient gDNA (Cy-5) with fluorescently labeled reference DNA (Cy-3) to a 400K oligonucleotide array. Genomic patient DNA relative to the reference DNA are represented as fluorescent ratios (Cy5/Cy3) that are further quantified by image analysis software and analytical software.
- Quantified results indicate each targeted-DNA sequence as loss of copy number (deletion), gain of copy number (duplication), or normal copy number. Regions of homozygosity/uniparental disomy (ROH/UPD) are also reported.
- The Ambry CMA 400K CGH+ SNP array contains 400,000 probes (~ 300,000 CGH probes and ~100,000 SNP probes) covering >400 genetic disorders.. The array includes probes for pericentromeric and subtelomeric regions with dense probe coverage spanning 10 Mb at each subtelomere. The backbone spacing of the probes is set at an average of 13 Kb throughout the entire human genome and at 5 Kb on the X chromosome. There is no probe coverage of the pseudoautosomal regions 1 and 2 (PAR1 and PAR2) on the X and Y chromosomes.
- The copy number variation(s) detected through this assay are reported by region and location on the chromosome, and includes the min/max size (Mb) of the span of loss or gain. Deletions less than ~100 Kb and duplications less than ~300 Kb outside known disease loci are not reported. Database of Genomic Variants documented deletion or duplication copy number variations (CNVs) are not reported, unless there is cause to believe the CNV may be correlated with the proband's clinical phenotype, either by uncovering a recessive mutation on the other allele, or due to some other reason.
- The Ambry Marfan, Aneurysm, and Related Disorders Next Generation Panel was also performed for this proband prior to his microarray analysis. This panel is a comprehensive gene sequencing test including the *ACTA2, CBS, FBN1, FBN2, MYH11, COL3A1, SLC2A10, SMAD3, TGFBR1,* and *TGFBR2* genes.

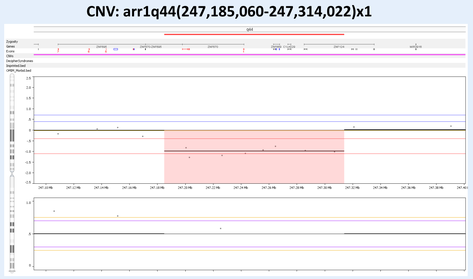
Figure 1. Proband's 400K aCGH+ SNP Array Results

CNV: arr17q12(34,464,879-36,352,140)x1



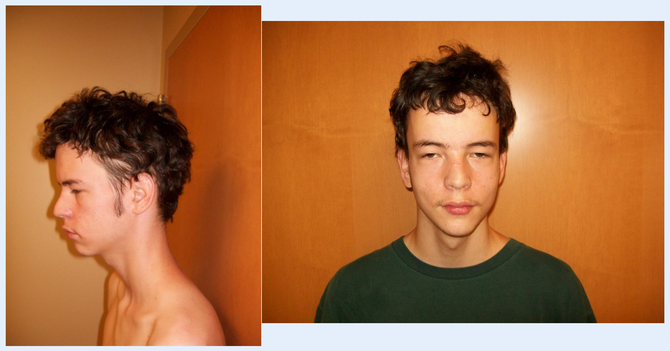
17q12 region genes: ***AATF, ACACA, C17orf78, CCL3L1, CCL3L3****, CCL4L1, CCL4L2,* ***DDX52, DHRS11****,* ***DUSP14****,* ***GGNBP2****,* ***HNF1B, LHX1, LOC284100,*** *LOC440434, MIR2909,* ***MIRM1****,* ***MYO19, PIGW, SYNRG, TADA2A****, TBC1D3, TBC1D3B, TBC1D3C, TBC1D3F,* ***TBC1D3G,*** *TBC1D3H,* ***ZNHIT3***

CNV: arr1q44(247,185,060-247,314,022)x1



1q44 region genes: *C1orf229, ZNF124, ZNF670, ZNF670-ZNF695*

Figure 2. Photos of Proband: Dysmorphic Facial Features



Proband presented with dysmorphic facial features, long and narrow face, prognathia, high and narrow palate. These features expand on the 17q12 deletion phenotype and were not seen in other family members.

Figure 3. Photos of Proband: Habitus and Stature

Proband presented with tall stature (90th percentile), low weight (10-25th percentile), Marfanoid habitus, long fingers, hypermobile joints, pectus abnormalities, and mild splenomegaly. His habitus has not been previously reported in association with the 17q12 microdeletion phenotype.

RESULTS/ DISCUSSION

- Prior to pursuing the Ambry 400K CGH+ SNP microarray, our proband was tested for Marfan syndrome through the Ambry Next Generation panel. His results were negative for mutations or variants of unknown significance (see Methods).
- Results of this patient's 400K CGH+SNP analysis identified two copy number variations of interest: 1q44 encompassing 5 genes, and 17q12 encompassing 28 genes. No regions of homozygosity (ROH) were identified in this array.
- The first CNV identified was a deletion on 1q44 (GRCh 37/hg19:247,185,060-247,314,022) encompassing 5 genes (FIGURE 1). Deletions in this region had not been previously described and none of the genes in that interval were known to be associated with intellectual impairment or congenital abnormalities. Parental FISH analysis revealed this CNV was paternal in origin, and since the proband's father is clinically unaffected, it is likely a benign variant.
- The second identified CNV was a deletion at 17q12 (GRCh 37/hg19:34,464,879-36,352,140) which spanned a minimum size of 1.770 Mb and a maximum size of 2.005 Mb. This deletion encompassed 28 genes, including ***AATF, ACACA, CCL2L1, C17orf78, CCL3L3, DDX52, DHRS11, DUSP14, GGNBP2, HNF1B, LHX1, LOC284100, MIRM1, MY019, PIGW, SYNRG, TADA2A, TBC1D3G,*** *and* ***ZNHIT3*** (see FIGURE 1). Parental FISH analysis revealed this was a *de novo* deletion only found in the proband.
- **Moreno-De-Luca et al. (2010):** identified a 1.4 Mb region deleted in 18 patients (13 males and 5 females) with autism spectrum disorder and schizophrenia encompassing: ***AATF, ACACA, C17orf78, DDX52, DHRS11, DUSP14, GGNBP2, HNF1B, LHX1, MRM1, MYO19, PIGW, SYNRG, TADA2A, ZNHIT3*** genes (see Table 1 for phenotype details)
- **Nagamani et al. (2010):** identified 4 patients with deletions and 5 patients with duplications at 17q12. Patients with deletions showed cognitive impairment, cystic renal disease, seizures, and structural abnormalities of the brain. Patients with duplications presented with cognitive impairment, behavioral abnormalities, but no seizures. Reported 17q12 deletions included genes: ***LHX1, AATF, ACACA, C17orf, ATADA2L, DUSP14, AP1GBP1, DDX52, HNF1B,*** *and* ***LOC284100.*** Reported 17q12 duplication genes included: ***LHX1, AATF, ACACA, C17orf, ATADA2L, DUSP14, AP1GBP1, DDX52, HNF1B,*** *and* ***LOC284100.***
- **Loirat et al. (2010):** identified 17q12 deletions in 3 out of 53 children with cystic or hyperechogenic kidneys. These probands presented with mental retardation, social interaction impairments (autism), verbal and non-verbal communication deficits, and stereotyped behaviors. The reported CNVs ranged from 1.49 Mb to 1.85 Mb and on average encompassed 19 genes including ***HNF1B***.
- **Bernardini et al. (2009) and Hinkes et al. (2012):** identified probands with deletions in ***TCF2, LHX1,*** *and* ***HNF1B*** manifesting Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome and nephropathy.

Table 1: Proband's Phenotype in Comparison to Previously Described Features Associated with 17q12 Deletions: Expansion on the Reported Phenotype

Our Proband's Phenotype	Reported 17q12 Deletion Phenotype
Physical Examination Findings	**Physical Examination Findings**
Weight: 48.6 kg (10-25th percentile @ age 15)	(not reported)
Height: 181cm (90th percentile @ age 15)	(not reported)
Marfanoid habitus	(not reported)
Mild facial dysmorphism	Mild facial dysmorphic features (Moreno De-Luca et al., 2010)
Long, narrow face (Marfan-like)	(not reported)
Prognathism with high, narrow (intact) palate	(not reported)
Mildly abnormal pectus	(not reported)
Mild scoliosis	Scoliosis (Moreno De-Luca et al., 2010 and Nagamani et al., 2010)
Hypermobile joints	Hypermobility of elbows, knees, and hips (Hinkes et al., 2012)
Long fingers with joint laxity	(not reported)
Developmental delay	Coordination and motor skill disabilities (Moreno De-Luca et al., 2010)
First words/language at age 4 years	Delays affecting speech (Moreno De-Luca et al., 2010); Speech problems (Nagamani et al, 2010)
Intellectual disability/MR (IQ= 66)	Intellectual disability (Moreno De-Luca et al., 2010); Mental retardation (Nagamani et al., 2010)
High blood glucose levels	Diabetes (Moreno De-Luca et al., 2010 and Loirat et al., 2010)
Small pancreas	Pancreatic atrophy (Nagamani et al., 2010)
Normal kidneys	Kidney cysts (Moreno De-Luca et al., 2010); renal disease (Nagamani et al., 2010)
Mild splenomegaly with 1.3 cm accessory spenule	(not reported)
Normal EEG	Seizures (Nagamani et al., 2010)
Behavioral/Psychiatric Findings	**Behavioral/Psychiatric Findings**
Autism spectrum disorder/Asperger syndrome	Autism spectrum disorders/Asperger syndrome (Moreno De-Luca et al., 2010 and Loirat et al., 2010)
Significant physical and verbal aggression	Self-injurious behavior/aggression (Moreno De-Luca et al., 2010)
Remarkably high pain tolerance (abnormal)	Minimal response to pain (Moreno De-Luca et al., 2010)
Obsessive-compulsive behavior	Obsessive-compulsive behavior (Moreno De-Luca et al., 2010)
Oppositional-defiance/ anxiety	Prominent anxiety (Moreno De-Luca et al., 2010)
Hyperactivity	Hyperactivity (Moreno De-Luca et al., 2010)
	Depression and migraines (Moreno De-Luca et al., 2010)
	Pica (Moreno De-Luca et al., 2010)
	Hallucinations (Moreno De-Luca et al., 2010)

CONCLUSIONS

- 400K aCGH+ SNP array analysis revealed a 17q12 pathogenic deletion previously described in the literature with phenotypic overlap with our proband.
- Our proband presents with developmental and cognitive delay, mild scoliosis, dysmorphic facial features, delayed speech, high blood glucose levels, autism spectrum disorder, physical and verbal aggression, high pain tolerance, obsessive-compulsive behavior, oppositional defiance, and hyperactivity which has been reported in other cases of 17q12 microdeletion.
- Our proband's remarkable habitus, long and narrow face, prognathia, pectus abnormalities, hypermobile joints, and long fingers with joint laxity expand upon the reported 17q12 microdeletion phenotype.
- Based on case reports, a critical region involving ***AATF, ACACA, CCL3L, C17orf78, DDX52, DUSP14, DHRS11, GGNBP2, HNF1B, LHX1, LOC284100, TBC1D3G, MRM1, MYO19, PIGW, SYNRG, TADA2A,*** and ***ZNHIT3*** genes exists in association with a 17q12 rearrangement phenotype.
- We encourage continued reporting of other individuals with involvement of this chromosome region to further delineate the clinical presentation and features.

References

1) Bernardini L, *et al.* (2009) *Orph J Rare Dis* 4:25.
2) Hinkes B *et al.* (2012) *BMC Neph* 13:27.
3) Loirat C, *et al.* (2010) *Nephrol Dial Transplant* 25:3430-3433.
4) Moreno-De-Luca D, *et al.* (2010) *Am J Hum Genet* 87:618-630.
5) Nagamani S, *et al.* (2010) *Eur J Hum Genet* 18:278-284.