Published in final edited form as:

Am J Med Genet A. 2010 September ; 152A(9): 2399–2405. doi:10.1002/ajmg.a.33571.

Large Deletions and Uniparental Disomy Detected by SNP Arrays in Adults With Thoracic Aortic Aneurysms and Dissections

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TO THE EDITOR

Oligonucleotide microarrays can detect genomic events that may be missed in metaphase cytogenetic studies [Gondek et al., 2008]. In pediatric and congenital disorders, arrays demonstrate greater sensitivity for small deletions and insertions, low-level mosaicism, loss of heterozygosity, and uniparental disomy (UPD). However, this technology has not been extensively applied to common adult-onset diseases. We used CNV370 Quad SNP arrays (Illumina, Inc., San Diego, CA) to perform genome-wide copy number analysis of 805 Caucasian, non-Hispanic adults with sporadically occurring Thoracic Aortic Aneurysms and Dissections (TAAD).

Aortic aneurysms and aortic dissections cause at least 15,000 deaths in the United States every year [Coady et al., 1999]. Progressive enlargement of the aorta is usually asymptomatic until a potentially catastrophic event such as an aortic dissection or rupture occurs, along with associated complications such as pericardial tamponade, stroke, or acute aortic valvular regurgitation. Once a thoracic aortic aneurysm exceeds 6 cm in diameter, the annual risk of dissection, rupture or death is more than 14% [Elefteriades, 2008]. Timely surgical repair of the aneurysmal aortic segments can prevent death. However, there are few recognized risk factors for the development of TAAD. We hypothesized that rare structural variants contribute to disease risk in TAAD.

Our study included individuals with sporadic ascending aortic aneurysms and/or sporadic aortic dissections who were evaluated at Baylor College of Medicine or the University of Texas Health Science Center at Houston. The research was prospectively reviewed and

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approved by duly constituted ethics committees at both institutions. In all patients, the diagnosis of TAAD was confirmed by echocardiography, computed tomography, magnetic resonance imaging, or aortography. The majority of patients underwent surgical repair of an aortic aneurysm or dissection. Patients who met any of the following criteria were excluded: <31 years of age; TAAD associated with trauma, infection or the Matching package (version 4.7–6) in R (version 2.10.1, R Foundation for Statistical Computing, Vienna, Austria).

In five unrelated patients with sporadic TAAD (0.6% of the cohort), we identified large contiguous regions of mosaicism for loss of heterozygosity (Fig. 1). These include copy-neutral events in 1p, 7q, and 16p, along with 14q in two individuals, characterized by distortion of the ratio of allele-specific signal at heterozygous SNP positions (assessed as B allele frequency or BAF) without significant alteration of the total signal intensity (assessed as log R ratio or LRR), as expected for copy gains or losses (Table I). Because the remainder of the data from those individual samples appears completely normal, the most likely explanation for the abnormal allelic signal ratio is segmental UPD. UPD arises when both alleles of a chromosome are derived exclusively from one parent. Segmental UPD is frequently caused by mitotic recombination in the early embryo and results in mosaicism for normal biparental and abnormal uniparental cell lineages, as in the Beckwith–Weidemann syndrome region on chromosome 11p15 whereas meiotic segregation defects characteristically result in UPD of entire chromosomes [Cooper et al., 2007]. Cell lineages with UPD may be competitively disadvantaged due to functional deficiency of imprinted genes that are expressed from the absent parental allele and are frequently present at variably low levels in adult tissues. We were able to obtain saliva samples from three individuals with the abnormal segmental BAF occurring on 1p, 14q, and 16p. Salivary DNA samples from two of these individuals exhibit evidence of the same segmental aberration, while one had the abnormality in a confirmatory blood sample only. These findings are consistent with somatic mosaicism (Fig. 2).

We also identified two mosaic segmental UPD events in DNA from the peripheral blood of 2,414 age-matched unaffected controls (mean age 63 years) that were >10 Mb in length, involving chromosomes 15q and 16p (Table II). UPD of chromosomes 15 and 16 have been described in individuals without vascular disease [Slater et al., 1994; Bittencourt et al., 1997; Xiao et al., 2006]. The prevalence of large UPD regions in TAAD cases (5 of 805) was significantly higher than in controls (Fisher's exact $P = 0.013$). We did not observe large segmental UPD events involving chromosomes 1 or 7 in a total of 5,725 controls.

UPD of chromosomes 1 or 16 is not associated with cardiovascular developmental defects [Field et al., 1998; Kohlhase et al., 2000]. The single TAAD patient with segmental UPD of 16p developed an ascending aortic aneurysm without any other extravascular defects. Chromosome 1p contains one imprinted gene, *TP73* encoding the transcription factor p73 that was shown to be monoallelically expressed in adult brain [Li et al., 2004a]. *TP73* causes apoptosis when overexpressed in vascular smooth muscle cells and is a downstream target of TNF- α , a cytokine associated with aneurysm rupture [Kang et al., 2000; Tang et al., 2005; Xiong et al., 2009]. *TP73* is located within the region of mosaic segmental UPD of a single TAAD patient who also manifested a left posterior diaphragmatic hernia. Congenital diaphragmatic hernias are associated with aortic defects through common molecular and

developmental origins [Jay et al., 2007]. We propose that *TP73* is a candidate gene that may confer predisposition to TAAD and other congenital abnormalities.

In contrast, UPD of chromosomes 7 or 14 is associated with distinctive malformations. Maternal UPD 7 is found in approximately 10% of individuals with Silver–Russell syndrome, a developmental disorder characterized by profound growth restriction, skeletal defects, and characteristic facial features [Hannula et al., 2001]. Cardiovascular abnormalities such as mesocardia or atrial septal defects may be present, but aneurysms have not been described. Of 19 imprinted genes in chromosome 7q, *KLF14*, a transcription factor that represses TGF- β receptor type II expression, is located within a 50 Mb region of mosaic UPD in one individual with TAAD (Fig. 1A) [Truty et al., 2009]. Aberrant TGF- β receptor signaling in vascular smooth muscle cells predisposes to aortic dilation and aneurysm formation in animal models and in patients with Loeys–Dietz syndrome [Loeys et al., 2006; Choudhary et al., 2009; Jones et al., 2009].

UPD 14 (Fig. 1B) causes growth retardation, hypotonia, and obesity (maternal) or a more severe phenotype with delayed ossification, mental retardation, and respiratory failure (paternal) [Ogata et al., 2008]. From the array data it is impossible to determine which parental allele may be present in two TAAD cases with segmental UPD 14. However, *DLK1*, a paternally expressed gene implicated in endothelial differentiation and angiogenesis, is within the isodisomy boundaries of both patients. *DLK1* is one of only two genes on chromosome 14 that are confirmed to be imprinted [Kagami et al., 2008]. Constitutional paternal isodisomy of the entire chromosome has been described in fewer than 20 patients [Kagami et al., 2005]. These findings are not present in controls and have not been reported in individuals without multiple congenital anomalies. After a thorough review of their clinical records, we concluded that none of the individuals with UPD 7 or 14 manifested any detectable extravascular congenital malformations (Table III). We hypothesize that misexpression of genes expressed in the vasculature such as *KLF14*, *TP73*, and *DLK1* in individuals with mosaic segmental UPD predisposes to the development of TAAD.

In one TAAD patient, we identified a 12 Mb deletion of 11q23.3 that overlaps the *FAA1* locus for familial aortic aneurysms (FAA1) [Vaughan et al., 2001]. The *CD146* or *MCAM* gene is located within the 1.2 Mb common interval defined by linkage analysis (Fig. 3A). *CD146* regulates endothelial cell adhesion and integrity, and depletion of *CD146* in mice and zebrafish disrupts vascular development [Bardin et al., 2001; Chan et al., 2005]. In another TAAD patient, we identified a 13 Mb deletion of 20q12–20q13.12 that includes the *MYL9* gene, which encodes the major myosin regulatory light chain in vascular smooth muscle cells (Fig. 3B). Reduced myosin light chain kinase expression and myosin light chain phosphorylation are observed in aortic aneurysms [Tung et al., 2001; Matt et al., 2007]. Pharmacologic or genetic disruption of myosin or myosin phosphorylation reduces aortic contractility and may predispose to aneurysm formation [Li et al., 2004b; Milewicz et al., 2008; Yang et al., 2009]. Both individuals appear to be mosaic with an estimated 40–60% contribution of the deleted alleles in peripheral blood. Tissues from these individuals were not available for confirmation of the deletions by fluorescent in situ hybridization. However, SNP array analysis has consistently proven to be more sensitive than cytogenetic methods to detect mosaic events and provides unequivocal evidence of deletions in both

cases [Conlin et al., 2010]. Neither deletion is present in our control Illumina genotypes or in published CNV databases representing an additional 4,519 unaffected individuals [Itsara et al., 2009; Shaikh et al., 2009]. These large aberrations are likely to be pathogenic because they disrupt many genes including previously identified susceptibility loci for TAAD.

In conclusion, we identified unique large genomic deletions or UPD in 7 of 805 (0.8%) TAAD patients with an overall prevalence that is significantly greater than in age-matched controls. With the exception of cancers, in which segmental UPD is highly prevalent, this is the sixth report of UPD that was detected using genome-wide SNP array data [Conlin et al., 2010]. The events on chromosomes 7, 11, 14, and 20 involve genomic loci that have been implicated in cardiovascular disorders or congenital malformations. Segmental UPD of chromosomes 1 and 16 are present in both blood and salivary DNA in keeping with an early embryologic origin. Six of the seven patients had ascending aortic aneurysms and five developed aortic dissections. With the exception of one patient with a diaphragmatic hernia, none manifested significant extravascular defects. Extensive somatic mosaicism, which we observed in all of these individuals, probably mitigates the phenotypic effects of UPD involving developmentally important genes. Individuals with these mosaic events are on average significantly older (73 years) than the study population as a whole (63 years) or the control group (54 years). Accumulation of genomic aberrations with age is postulated to contribute toward tissue-specific and progressive symptoms in other disorders such as myotonic dystrophy and neurofibromatosis, and may also predispose to TAAD [Fortune et al., 2000; Moyhuddin et al., 2003; Watanabe et al., 2008]. Limitations of the study include our inability to determine the contribution of abnormal cell lineages to the aorta in these individuals. We are also unable to rule out subtle clinical abnormalities that were not detected by preoperative imaging, because none of the patients were evaluated by an experienced dysmorphologist. However, our results are remarkable for the burden of rare genomic defects in TAAD patients, supporting our hypothesis that structural variants contribute to the pathogenesis of TAAD.

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FIG. 1. Uniparental disomy of chromosomes 7 (A) and 14 (B) in two TAAD patients output from Genome Studio shows B allele frequencies (BAF, 0 to 1 in increments of 0.1) and log R ratios (LRR, -2 to +2) plotted along the length of each chromosome. Segments of mosaic UPD are visible as deviations of BAF from the median value of 0.5 in heterozygous DNA. The ideogram shows chromosomal bands and positions in base pairs. Arrows mark the boundaries of the UPD segments.

FIG. 2.

Mosaicism for segmental UPD of chromosomes 1 and 14 BAF plots derived from blood (B) are adjacent to BAF and LRR plots derived from saliva (S) from the same individuals for aberrations involving chromosomes 14 (A), 1 (B), and 16 (C). The scale of the plots is the same as in Figure 1. The entire length of each chromosome is shown. Isodisomy regions detected by the CNV partition algorithm in salivary DNA are highlighted in green.

FIG. 3.

Large genomic deletions of chromosome 11 (A) or 20 (B) in two TAAD patients BAF and LRR plots from blood of an individual with a mosaic 12 Mb deletion of chromosome 11 that overlaps the FAA1 locus (A) or a mosaic 13 Mb deletion of chromosome 20 (B). Deviation of BAF values in (A) to 0.65 and 0.35 corresponds with a 40–45% contribution of cells harboring the deletion in peripheral blood. Deviation of BAF values in (B) to 0.70 and 0.30 corresponds with a 55–60% contribution of abnormal cells. Interpretation of mosaic changes follows Conlin et al. [2010]. The critical region defined by linkage analysis of FAA1 is highlighted. The scale of the plots is the same as in Figure 1.

TABLE I

Large Copy-Neutral Events in TAAD Cases

Chr	Begin	End	LRR(S)	SD	LRR(G)	Diff	Type	Age	Gender
1	1	48842491	0.0217	0.1046	-0.0071	0.0288	CN	75	M
7	103097058	158812247	0.0028	0.1084	-0.0188	0.0216	CN	69	M
14	62921929	104339273	0.0266	0.1745	0.0048	0.0218	CN	79	M
14	21312486	104766491	0.0076	0.1005	-0.0222	0.0298	CN	74	M
16	1	30888403	-0.0278	0.1432	-0.0306	0.0028	CN	82	F
2	116098366	118024517	0.2373	0.1636	-0.0097	0.247	G	64	M
16	14667268	16693507	0.1665	0.2248	0.0079	0.1586	G	60	M
11	106633223	117868079	-0.1876	0.1699	-0.0663	-0.1213	ML	76	F
20	30469393	44484622	-0.1651	0.0992	-0.0051	-0.16	ML	56	F
4	163163784	174197337	-0.5928	0.4909	-0.0715	-0.5213	L	72	F

Chr, chromosome; Begin/End, positions in build 36.1 sequence; LRR(S), average of log R ratios across segment; SD, standard deviation of log R ratios; LRR(G), average of log R ratios across genome, excluding the involved chromosome; Diff, difference between segmental and genome-wide average; LRR, negative for copy losses and positive for copy gains; CN, copy-neutral; G, copy gain, ML, mosaic copy loss and L, copy loss are provided for comparison.

TABLE II

Large Copy-Neutral Events in Controls

Chr	Begin	End	LRR(S)	SD	LRR(G)	Diff	Type	Age	Gender
15	18285782	100320863	0.0085	0.1739	0.00855	-5.00E-05	CN	74	F
16	1	27973037	-0.0232	0.218	-0.0342	0.01978	CN	69	F
5	105058906	180837061	0.1676	0.2265	0.00575	0.16185	G	46	F
8	72627419	146264218	0.2208	0.1332	-0.0428	0.2636	G	49	F
11	1	49483921	0.1063	0.2521	-0.0416	0.1479	MG	72	M

Chr, chromosome; Begin/End, positions in build 36.1 sequence; LRR(S), average of log R ratios across segment; SD, standard deviation of log R ratios across genome, excluding the involved chromosome; Diff, difference between segmental and genome-wide average; LRR, negative for copy losses and positive for copy gains; CN, copy-neutral; G, copy gain; ML, mosaic copy loss; L, copy loss. There were two large copy-neutral events in a total of 2,414 age-matched control individuals, for an age-adjusted rate that is significantly lower than in TAAAD cases (Fisher's exact $P = 0.013$).

TABLE III

Clinical Features of Individuals With Large Genomic Events

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Demographics							
Gender	M	M	M	M	F	F	F
Age (years)	75	69	79	74	82	76	56
Smoking	Y	N	Y	N	N	Y	N
BMI	20.8	25.7	31.5	28.6	26.7	NA	29.7
Aneurysm							
Involves root	Y	N	N	Y	N	N	N
Dissection	B	B	N	A	N	A	A
Bicuspid valve	N	N	N	N	N	Y	N
Aortic diameter (cm)	8.3	NA	5.5	6.4	4.9	NA	4.5
Other conditions	Diaphragmatic hernia	None	Polymyalgia Rheumatica ^a	None	Cataracts ^a	None	None
CNV							
Chromosome	1p33-pter	7q31.1-qter	14q23.2-qter	14q11.1-qter	16p11.2-pter	11q23.3	20q12-20q13.2
Size (bp)	42335514	55715190	41417344	83454006	30784737	12516437	14015229
Type	Mosaic UPD	Mosaic UPD	Mosaic UPD	Mosaic UPD	Mosaic UPD	Mosaic deletion	Mosaic deletion
Candidate genes	<i>P73</i>	<i>KLF14</i>	<i>DLK1</i>	<i>DLK1</i>	<i>SOX8</i>	<i>CD146</i>	<i>MYL9</i>

M, male; F, female; BMI, body mass index (kg/m²); Involves root, Annuloaortic ectasia or root repair; Dissection, Stanford Type A (ascending aorta) or B (descending aorta) or N (none); UPD: segmental uniparental disomy; NA, not available.

^a Age of onset could not be determined from the available data.