**Arterial Events in Vascular Ehlers-Danlos, Loeys-Dietz, and Marfan Syndrome: Findings from the Montalcino Aortic Consortium**

**Brief title: Arterial Events Associated with Aortopathy Genes**

Ernesto Calderon-Martinez, MD\*,a Walter V. Velasco, MD\*,a Dongchuan Guo, PhD\*,a Ellen H. Hostetler, BA,a Zhang Xun, MD, PhD,a Sara Stephens, PhD,b Sherene Shalhub, MD,c Julie De Backer, MD, PhD,d Maral Ouzounian, MD, PhD,e Scott A. LeMaire, MD,f Oiliver Milleron, MD,g Nadine Hanna, MD,h Pauline Arnaud, Pharm D, PhD,h Maria Tchitchinadze, MD,i Siddhart K. Prakash, MD,a Mark Lindsay, MD, PhD,j Julien Marcadier, MD,k Richmond Jeremy, MD, PhD,l Shaine A. Morris, MD, MPH,b Anji T. Yetman, MD,m Catherine Boileau, PhD,n Alan C. Braverman, MD,o Guillaume Jondeau, MD, PhDc ‡, Dianna M. Milewicz, MD, PhDa ‡

**Affiliations:**

aDivision of Medical Genetics, Department of Internal Medicine, McGovern Medical School, The University of Texas Health Science Center at Houston, Houston, TX, USA.

bDivision of Cardiology, Department of Pediatrics, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USA.

cDivision of Vascular and Endovascular Surgery, Department of Surgery, Oregon Health Science University, Portland, OR, USA.

dDepartment of Cardiology and Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium ;Centre National de Reference pour le Syndrome de Marfan et les Syndromes Apparentés, VASCERN HTAD European Reference Centre, AP-HP, Hôpital Bichat-Claude-Bernard, Paris, France.

eDivision of Cardiovascular Surgery, Department of Surgery, University of Toronto, Toronto General Hospital, Toronto, Canada.

fDivision of Cardiothoracic Surgery, Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, TX, USA; Texas Heart Institute, Houston, TX, USA.

g Université de Paris, LVTS, INSERM U1148, Hôpital Bichat-Claude-Bernard, Paris, France; Centre National de Reference pour le Syndrome de Marfan et les Syndromes Apparentés, VASCERN HTAD European Reference Centre, AP-HP, Hôpital Bichat-Claude-Bernard, Paris, France. ;Service de Cardiologie, AP-HP, Hôpital Bichat-Claude-Bernard, Paris, France.

hUniversité de Paris, LVTS, INSERM U1148, Hôpital Bichat-Claude-Bernard, Paris, France; Centre National de Reference pour le Syndrome de Marfan et les Syndromes Apparentés, VASCERN HTAD European Reference Centre, AP-HP, Hôpital Bichat-Claude-Bernard, Paris, France. ;Département de Génétique, AP-HP, Hôpital Bichat-Claude-Bernard, Paris, France.

i Centre National de Reference pour le Syndrome de Marfan et les Syndromes Apparentés, VASCERN HTAD European Reference Centre

jCardiovascular Genetics Program, Massachusetts General Hospital, Boston, MA, USA; Cardiovascular Research Center, Department of Medicine, Massachusetts General Hospital, Boston, MA, USA.

kDepartment of Medical Genetics, Alberta Children's Hospital, Calgary, AB, Canada.

lCentral Clinical School, Faculty of Medicine and Health, University of Sydney, Sydney, New South Wales, Australia; Marfan and Aortic Disease Service, Royal Prince Alfred Hospital, Sydney, New South Wales, Australia.

mDivision of Pediatric Cardiology, Children's Hospital & Medical Center, University of Nebraska Medical Center, Omaha, NE, USA.

nGenetics Department, Hôpital Bichat, Université Paris Cité, Paris, France.

oCardiovascular Division, Department of Medicine, Washington University School of Medicine, St. Louis, MO, USA.

\*These authors share the first authorship.

‡These authors share co-last authorship

**Funding support**

These studies were funded by NIH R01HL109942, NIH K23HL127266, the Genetic Aortic Disorders Association Canada, Ontario, Canada, the Southern Star Medical Research Institute, Houston, Texas, US, the Lauren Ovelgonne Tenney Memorial Fund, Woodlands, Texas, and the John Ritter Foundation, Los Angeles, California, US.

**Author disclosures**

All authors have no relationships relevant to the content of this paper to be disclosed.

**Address for correspondence:**

Dianna M. Milewicz, MD PhD

6431 Fannin Street, MSB 6.100

McGovern Medical School, The University of Texas Health Science Center at Houston

Houston, TX 77030, USA

Phone: 713 500 6727

Email: Dianna.M.Milewicz@uth.tmc.edu

ORCID ID: 0000-0002-7806-0068

**Acknowledgments**

The authors are grateful to the participants and families participating in these studies, along with Josipa Paska and Ludmilla Temertey for their continued support of the Montalcino Aortic Consortium.

**Abstract** (350 words)

**Introduction**: Heritable thoracic aortic disease (**HTAD**) is due to altered genes that confer a highly penetrant risk for thoracic aortic aneurysm and dissection, and a subset of these genes also cause aneurysms and dissections of small and medium-sized arteries. Arterial aneurysms, dissections and ruptures are common in vascular Ehlers-Danlos Syndrome(**vEDS**), due to pathogenic/likely pathogenic variants (**PVs)** in *COL3A1*, but these events are rarer in Marfan syndrome (**MFS**), resulting from in PVs in *FBN1*, or in Loeys-Dietz syndrome (**LDS**), due to PVs in the TGFβ-pathway genes.

**Objectives:** This study sought to define the relative risk of arterial and aortic events in individuals with PVs in *FBN1*, *COL3A1,* and TGFβ-pathway genes.

**Methods**: The Montalcino Aortic Consortium patient registry provided a retrospective cohort of 1825 individuals with PVs in *COL3A1* (n=125), *FBN1* (n=1028) and the TGFβ-pathway genes (*TGFBR1*, n=137; *TGFBR2*, n=168; *SMAD3*, n=196; *TGFB2*, n=126; *TGFB*3, n=45). Arterial events were defined as dissections, ruptures, or aneurysms outside the aorta requiring open or endovascular repair and aortic events were defined by aortic dissections or repair of a proximal thoracic aortic aneurysm.

**Results**: Arterial events were identified in 93 individuals, with the highest prevalence in *COL3A1* (24%), followed by *TGFBR1, TGFBR2, SMAD3, TGFB2,* *FBN1,* and *TGFB3*. Kaplan-Meier time-to-arterial event curves identified significant differences among the genes, with *COL3A1* associated with the largest number and earliest events. Males with *COL3A1* had earlier and more events compared to males with TGFβ pathway genes, and these differences were not observed in females. For TGFβ pathway genes and *FBN1*, aortic events were significantly earlier and more penetrant than arterial events, whereas this difference was not present with *COL3A1*. Log-binomial regression demonstrated that smoking was associated with increased arterial events in participants with TGFβ-pathway genes, while hypertension was associated with increased event rate in participants with *FBN1*, and TGFβ-pathway genes.

**Conclusion**: There are significant gene- and sex-specific differences in the prevalence and age of onset of arterial events associated with the HTAD genes for vEDS, LDS and MFS, highlighting the importance of tailored counseling and surveillance based on the causative gene. Furthermore, smoking cessation and hypertension control should be emphasized in these patients to reduce the risk of arterial events.

**Keywords**

Heritable thoracic aortic disease, arterial dissection, arterial aneurysm, Loeys-Dietz syndrome, vascular Ehlers-Danlos syndrome, Marfan syndrome

**Abbreviations**

HTAD Heritable thoracic aortic disease

LDS Loeys-Dietz syndrome

MAC Montalcino Aortic Consortium

PVs Pathogenic/likely pathogenic variants

vEDS vascular Ehlers-Danlos Syndrome

MFS Marfan Syndrome

TGF-β Transforming growth factor-β

IR Incidence Rate

IRR Incidence Rate Ratio

KM Kaplan Meier

**INTRODUCTION**

Pathogenic/likely pathogenic variants (**PV**s) in 11 genes confer a highly penetrant risk for thoracic aortic aneurysm and dissection, termed heritable thoracic aortic disease (**HTAD**).1   
Genes that are associated with HTAD and the function of the corresponding proteins are the following: *FBN1, LOX,* and *COL3A1*, which encode proteins in the extracellular matrix; *TGFBR1, TGFBR2, SMAD3, TGFB2,* and *TGFB3,* which encode proteins involved in canonical TGFβ signaling, which are designated as Loeys-Dietz syndrome (**LDS**) types 1 - 5, respectively; and *ACTA2, MYH11, PRKG1,* and *MYLK*, which encode proteins involved in smooth muscle cell contraction.2,3

The Montalcino Aortic Consortium (**MAC**) is a worldwide patient registry established to define the natural and clinical history associated with PVs in HTAD genes, with a goal of improving outcomes and limiting medical expenditures through gene-specific clinical management. Direct comparison of risks for aortic events, defined as presentation with a type A or B dissection or repair of a thoracic aortic aneurysm, for 7 HTAD genes including *TGFBR1*, *TGFBR2*, *SMAD3*, and *TGFB2*, identified significant differences among these genes as to the age of onset, penetrance, and type of first aortic event.4 Among the TGFβ genes, *TGFBR2* has the earliest onset of aortic events, some occurring in childhood, whereas *SMAD3* has the latest onset with no childhood cases. Thus, these analyses impact aortic surveillance and counseling based on the individual LDS gene involved. 5,6

A subset of genes for HTAD also confer risk for arterial complications, including aneurysm formation, dissections, and ruptures. Individuals with vascular Ehlers-Danlos syndrome (**vEDS**) due to PVs in *COL3A1* are more likely to present with arterial events than an aortic event, whereas MFS participants have fewer reported arterial events that have not been rigorously characterized.7–10 Individuals with LDS or TGFβ gene PVs also have a risk for arterial events but the frequency and onset of these events are not well defined. Previous studies by MAC found a low risk for presentation with arterial events in individuals with *TGFBR1* and *TGFBR2* PVs,11 and only two out of 212 MAC participants with *SMAD3* PVs experienced an arterial event.12 Despite these low rates of arterial events, current guidelines recommend that LDS patients have head-to-pelvis imaging at baseline and repeat imaging annually for cases with aortic aneurysms or dissections or involvement of any arteries.13,14 We sought to more precisely characterize arterial events in individuals with vEDS, LDS and MFS, defined as a dissection, rupture, or open or endovascular repair of an aneurysm, to inform risk and surveillance for these events*.*

**METHODS**

**Study Population**

Institutional Review Boards at institutions participating in MAC obtained informed consent and authorization to use deidentified clinical data from the study participants in this research. Genotype and clinical data from cohorts of participants and their relatives with rare variants in *COL3A1, TGFBR1, TGFBR2, SMAD3, TGFB2, TGFB3,* and *FBN1* were combined for these analyses. Patient recruitment, data collection, and sites were previously described. 11,12 Demographic and clinical data were abstracted from medical records and entered into a Research Electronic Data Capture database. The primary outcome was an arterial event, defined as an arterial dissection, rupture, or aneurysm requiring surgical repair. Aortic events, defined as aortic dissections, ruptures, or aneurysms requiring surgical repair, were also assessed as previously reported.4 Cardiovascular risk factors (e.g., hypertension, smoking) were based on physicians’ notes. Participants with early onset Marfan or infantile MFS were excluded.15–17

Rare variants in genes listed above were curated as to their pathogenicity based on the American College of Medical Genetics- Association for Molecular Pathology guidelines (accessed April 2018),18 and recently modified by the ClinGen General Sequence Variant Curation Process Standard Operating Procedure v3.2 (Supplemental Information 1).19 Functional effects of genetic variants were categorized as missense variant, haploinsufficiency (including leading to premature termination of translation and nonsense mediated decay), in-frame insertion or deletion, and “unknown” (the consequence of protein sequence change is clear, such as start codon alteration or variants that are located at the last introns). In addition, we classified a few splicing region variants as having the same effects on protein sequences as nearby canonical splicing variants.

**Statistical Analysis**

Participants with PVs in *TGFB3* were not included in these analyses due to the rarity of arterial and aortic events in the present cohort. The cohort was stratified by gene, and differences in clinical events were evaluated using Fisher’s exact and chi-square for categorical variables and the Kruskal-Wallis test for continuous variables. The chi-square test was used to examine differences in the frequency of arterial and aortic events by the gene.

To account for varying follow-up times in the cohort, Kaplan-Meier (**KM**) curves were used to visualize time to first arterial and aortic events stratified by gene and to compare groups using log-rank test. The KM and log-rank analyses were further stratified by sex to assess differences among all genes, with each gene compared to *COL3A1* as the reference and between males and females. Arteries were classified based on their location in five anatomic zones (head and neck, thorax, abdomen/pelvis, upper extremities, and lower extremities). To illustrate the comparative frequency of the artery involved, heatmaps were generated by body region.

Incidence rates (**IR**s) by decade of life were then calculated for arterial events. Additionally IRs of aortic and arterial events per 1000 person-years (equivalent of 100 subjects over a ten-year period) were calculated by gene. These calculations included all arterial and aortic events, encompassing recurrent events, to provide a comprehensive assessment of event rates. To compare the incidence rates of events between groups, incidence rate ratios (**IRR**s) were generated and statistically compared by gene, data from cases with *COL3A1* and *TGFBR2* PVs as the reference for analysis of arterial and aortic events, respectively. Finally, log-binomial analyses were used to examine the risk of the first arterial event by systemic features and cardiovascular risk factors by gene. Risk factors with fewer than six reported features were excluded from the analysis to ensure sufficient sample size and the stability of the estimates. Additionally, risk factors with relative risk (RR) values or confidence intervals (CI) falling outside a predefined range of 0.01 to 100 were excluded from the results to maintain a focus on plausible associations. These thresholds were implemented to minimize the influence of rare events and extreme statistical values, which could reflect data sparsity or overfitting. A two-sided p-value <0.05 was considered statistically significant. Statistical analyses were performed using R studio version 4.3.2.

**RESULTS**

**Study population**

A total of 1825 MAC study participants were identified with PVs in the following genes:  *COL3A1* (n = 125), *TGFBR1* (n = 137), *TGFBR2* (n = 168), *SMAD3* (n = 196), *TGFB2* (n = 126), *FBN1* (n = 1028), and *TGFB3* (n = 45). Those with *TGFB3* PVs were excluded from further analyses due to only one arterial and three aortic events in this group, leaving 1,790 participants for these analyses (Table 1). The majority of patients were recruited in France (66%), followed by the United States (26%), Australia (3.3%), the United Kingdom (1.9%), Canada (1.5%), and Belgium (1.0%). There were no statistical difference as to the number males and females were recruited for each gene. Distribution of ethnicity and race analyses of the non-French cohort found that most participants were white (88%) (Supplemental Table 1); these data were not available for the French cases. The median age at last follow-up varied across the cohort, individuals with ***SMAD3*** had the highest median age (45 years, IQR: 27–58), while those with ***FBN1*** had the youngest (31 years, IQR: 17–45; Table 1).

**Characterization of arterial events**

Ninety-three of the 1,790 participants (5.2%) had one or more arterial events (Table 2). The greatest burden of arterial events was in participants with *COL3A1* PVs (30; 24% of participants), followed by *TGFBR1* (13; 9.5%), *TGFBR2* (13; 7.7%), *SMAD3* (13; 7.1%), *TGFB2* (8; 6.4%), and *FBN1* (16; 1.6%; Table 2 ). Probands were more likely to have an arterial event than relatives (71/916 probands= 7.7% versus 22/864 relatives=2.5%, p<0.01, Supplemental table 2). Dissections were the most common arterial events overall (55.9%), especially for *COL3A1* and *TGFBR1*. Ruptures as first arterial event were rare and observed primarily in *COL3A1* (two in the splenic artery, and a rupture in the renal, brachial, subclavian, common iliac, and external iliac arteries in individual participants), and less common for *SMAD3* (internal mammary artery and common iliac*)* and *TGFB2* (2 cerebral artery ruptures; Table 2). Thirty-one participants had multiple arterial events, with *COL3A1* showing the highest burden of patients with multiple events (12%), followed by *TGFBR2* (2.9%), *TGFBR1* (2.9%), *SMAD3* (2.0%), and *FBN1* (0.3%).

The KM analysis of time to arterial event by gene identified significant differences among the genes, with *COL3A1* demonstrating the earliest arterial events, and *FBN1* the latest (p <0.001; Figure 1A). Compared to patients with PVs in *COL3A1*, those with variants in *TGFBR1* (p=0.009), *TGFBR2* (p=0.003), *SMAD3* (p<0.001), *TGFB2* (p=0.002), and *FBN1* (p<0.001) had significantly longer times to first arterial events (Supplemental Figure 1). For example, by age 40, the KM estimate of patients with *COL3A1* had an arterial event was 22.9%, compared to <8% with an arterial event by age 40 for all other groups (Supplemental Table 3). Time to arterial event among the TGFβ pathway genes did not differ significantly among the genes, but arterial events were significantly earlier for *TGFBR1* (p<0.001), *TGFBR2* (p<0.001), *SMAD3* (p=0.027), *TGFB2* (p=0.003), and TGFβ pathway genes composite (p<0.001) when compared to *FBN1* (Supplemental Figure 2 and 3). Events in childhood (age < 18 years) were rare in our cohort and included participants with *COL3A1* (one male with subclavian artery rupture at 12 years of age).

When KM analyses was stratified by sex, there were significant differences for time to arterial event for the individual genes among males (p<0.001) and females (p<0.001; Figure 1B). Analyses of time-to-event identified sex differences for *FBN1*, with earlier events in males (p=0.006), but sex differences for the composite of TGFβ pathway genes (p= 0.095) and *COL3A1* (p=0.055) were not significant (Figure 1C). When analyzing each gene with *COL3A1* as the reference and stratifying by sex, significantly earlier events occurred in *COL3A1* males when compared with *TGFBR1* (p=0.003), *TGFBR2* (p<0.001), *SMAD3* (p<0.001), *TGFB2* (p<0.001), and *FBN1* males (p<0.001; Supplemental Figure 4). In contrast, females with TGFβ pathway gene PVs showed no significant differences in time to arterial event when compared to *COL3A1*, whereas females with *FBN1* PVs had later onset and fewer events (p<0.001;Supplemental Figure 5). These data support that there are earlier events in males with *COL3A1* PVs than males with TGFβ pathway genes or *FBN1* PVs, whereas femaleswith *COL3A1* PVs have similar arterial event timing as females with TGFβ pathway genes PVs.

The location of the artery involved in these events was also analyzed. With *COL3A1*, arterial events occurred predominantly in the abdominopelvic region, accounting for 13.6% of participants and involving the renal artery (4%), common iliac artery (3.2%), external iliac artery (3.2%), splenic artery (1.6%), superior mesenteric (0.8%), internal iliac artery (0.8%). The head and neck zone followed in event burden, with 8.8% of participants affected (Figure 2, Supplemental Figure 6 and 7). Arterial events in the thorax and upper and lower extremities were rare. For TGFβ pathway genes and *FBN1*, the head and neck regions were the most common locations, followed by the abdominopelvic region. When location of arterial events was assessed based on sex, there were no dramatic differences (Supplemental Figure 6 and 7).

**Arterial versus aortic events**

Aortic events, defined as surgical repair of a thoracic aortic aneurysm or presentation with an aortic dissection, were identified in 496 of the 1,790 participants (27.7%, Table 3). Aortic events occurred in 350/916 of probands (38.2%) and 146/864 (16.8%) of relatives (p<0.001; Supplemental Table 2).4 Among all aortic events, aneurysm repair was the most common event overall, followed by type A, then type B dissections. Exceptions include participants with *COL3A1* variants, where type B dissection was the most common event (n=14), and participants with *SMAD3* variants, where type A dissection was most common (n=30; Table 3).

There were significant differences in the KM time to aortic events between individual genes (p<0.001; Supplemental Figure 8), with *TGFBR2* having the earliest onset of aortic events (Table 1, Supplemental Figure 9)*.* For *TGFBR2*, the lifetime risk for an aortic event by age 40 was 48%, which was higher than for *COL3A1* (15%), *TGFBR1* (22%), *SMAD3* (13%), *TGFB2* (21%), and *FBN1* (30%).The onset of aortic events was also significantly earlier for *TGFBR1* (p=0.02) and *FBN1* (p=0.04) compared to *COL3A1* (Supplemental Figure 10).

When time to aortic versus arterial events was analyzed for each gene, the onset of aortic events was significantly earlier than the onset of arterial events (p<0.001) for all genes except *COL3A1* (Figure 3). Events in childhood were rare, except for *TGFBR1, TGFBR2*, and *FBN1,* with the earliest aortic event occurring at 2 years of age (aortic aneurysm repair in *TGFBR2* case). Among males, aortic events occurred earlier than arterial events for all genes except *COL3A1*(p=0.6). For females, aortic events were earlier than arterial events for all genes except *COL3A1* (p=0.9) and *TGFB2* (p=0.3; Supplemental Figure 11 and 12).

*COL3A1* type A aortic dissectionswere associated with the type of variant (p<0.01), with most of the events occurring in the haploinsufficiency participants. The analysis of the association between variant types and aortic aneurysm repair showed a significant overall association between the presence of aneurysm repair events and variant type distribution (p<0.01 for ***FBN1***, p=0.01 for **TGFβ-pathway genes**, and p=0.03 for ***TGFBR2***; Supplemental Table 4-9).

Identifying IRs based on decade of life highlight patterns of arterial events among the genes and allows for all events to be accounted for rather than just the first event. *COL3A1*demonstrated the earliest peak, with an IR of 32.43 events/1000 person-years (100 people over 1 decade) in the 20–29.9 age group, and a second peak of 50.00 events/1000 person-years occurred in the 70–79.9 group (Supplemental Table 10, Supplemental Figure 13A). The rest of the genes showed an overall incremental increase in IR through the decades (Supplemental Table 10). IRRs were calculated to compare overall arterial event rates relative to *COL3A1*, which served as the reference with an IR of 3.05 events per 1,000 person-years (95% CI: 2.37–3.94, Supplemental Table 11). In contrast, *TGFBR1, TGFBR2, SMAD3, TGFB2*, and *FBN1* all showed IRs that did not differ significantly from *COL3A1*.

IRs based on decade of life for aortic events for these genes were calculated, which allows for all events to be accounted for rather than just the first event. *TGFBR2*demonstrated the earliest peak, with an IR of 41.68 events/1000 person-years (100 people over 1 decade) in the 30–39.9 age group (Supplemental Table 12, Supplemental Figure 13B). Incidence rate was calculated for aortic events which identified ***TGFBR2* with the** highest incidence rate of 3.01 events per 1,000 person-years (95% CI: 2.48–3.66, Supplemental Table 13), ***SMAD3*** demonstrated a statistically significant lower event rate compared to ***TGFBR2***, with an incidence rate of 2.12 (95% CI: 1.71–2.64) and an IRR of 0.71 (95% CI: 0.53–0.93; p=0.01). In contrast, the incidence rates for ***COL3A1, TGFB2, TGFBR1***, and ***FBN1*** did not differ significantly from ***TGFBR2***.

**Systemic features and cardiovascular risk factors associated with arterial events**

Log-binomial analyses were used to determine if arterial events in the cases are associated with syndromic features or traditional cardiovascular risk factors. For *COL3A1*, arterial events were significantly associated with hypertension in females (RR: 2.95, 95% CI: 1.25–7.00, p = 0.014), wide or atrophic scars (RR: 2.73, 95% CI: 1.54–4.85, p < 0.001), doughy skin texture (RR: 2.99, 95% CI: 1.55–5.76, p = 0.001), and pes planus (RR: 2.86, 95% CI: 1.55–5.28, p = 0.001; Supplemental Table 14). For the TGFβ-pathway genes composite, significant findings included hypertension (RR: 2.44, 95% CI: 1.46–4.07, p = 0.001), smoking (RR: 2.62, 95% CI: 1.54–4.45, p < 0.001), idiopathic cardiomyopathy (RR: 3.19, 95% CI: 1.45–7.03, p = 0.004), hypertelorism (RR: 2.93, 95% CI: 1.65–5.18, p < 0.001), and doughy skin texture (RR: 2.84, 95% CI: 1.59–5.08, p < 0.001; Supplemental Table 15). For *TGFBR1*, arterial events were associated with wide or atrophic scars in females (RR: 3.89, 95% CI: 1.17–12.91, p = 0.026; Supplemental Table 16). In *TGFBR2*significantfindingsincluded hypertension (RR: 2.78, 95% CI: 1.03-7.51, p = 0.044) digital abnormalities (RR: 6.62, 95% CI: 1.88–23.26, p = 0.003), doughy skin texture (RR: 8.64, 95% CI: 1.86–40.07, p = 0.006), and hypertelorism (RR: 5.68, 95% CI: 1.85–17.40, p = 0.002; Supplemental Table 17). For *SMAD3*significantfindingsincluded hypertension (RR: 4.60, 95% CI: 1.89–11.24, p = 0.001), smoking (RR: 4.57, 95% CI: 2.26–13.25, p < 0.001), doughy skin texture (RR: 2.95, 95% CI: 1.09–7.98, p = 0.033), and down slanting palpebral fissures (RR: 3.28, 95% CI: 1.16–9.29, p = 0.025; Supplemental Table 18). For *TGFB2*, kyphosis (RR: 7.67, 95% CI: 1.74–33.78, p = 0.007) and smoking (RR: 3.82, 95% CI: 1.02–14.33, p = 0.047; Supplemental Table 19) were significant. Lastly, for *FBN1*, arterial events were associated with hypertension (RR: 3.30, 95% CI: 1.09–10.03, p = 0.035). Also, arterial events were associated with smoking for males (RR: 3.29, 95% CI: 1.04–10.35, p = 0.042; Supplemental Table 20). Additional positive findings identified for each gene and breakdown by the sex can be found in the supplemental table (Supplemental Tables 14- 20).

**DISCUSSION**

These analyses identify significant variability in the risk, location, and type of arterial events associated with PVsin *COL3A1*, TGFβ pathway genes and *FBN1*. *COL3A1* exhibits earlier onset and higher penetrance of arterial events compared to TGFβ pathway genes and *FBN1*. For all genes except *COL3A1*, aortic events occurred significantly earlier than arterial events and arterial events rarely occurred before aortic events. Events in children were rare for all the genes, with only a few events occurring in *COL3A1*, *TGFBR1, TGFBR2* and *FBN1* participants.

Furthermore, there are significant sex differences that impact arterial events associated with these genes. Males with *FBN1* had earlier events than females, with the largest number of arterial events being arterial repairs. Additionally, males with *COL3A1* PVs exhibit significantly earlier onset of arterial events when compared to TGFβ pathway genes and *FBN1,* whereas females with *COL3A1* show no significant difference in time to arterial events when compared to the TGFβ genes. All TGFβ pathway genes showed earlier onset of arterial events compared to *FBN1*. For females with *TGFB2*, there was no significant difference in time between aortic and arterial events.

Arterial events in *COL3A1* were primarily dissections, followed by aneurysm repairs, and then rare arterial ruptures. Althought not documented in these analyses reported here, these arterial dissections in *COL3A1* cases can occur in arteries that were normal on prior imaging studies. Arterial events in vEDS participants occurred primarily in the head and abdominopelvic zones, which aligns with previous reports for location of these events.21–24 27 Two French cohorts, including 144 participants and 330 with *COL3A1*, reported a prevalence of 29 and 82% of arterial events, respectively, but arterial events were not clearly defined in these studies.25,26 A retrospective study of 86 vEDS patients referred for surgery reported arterial events in 61.6% of the cases, but it is likely the increased arterial events reflect referral bias.28

Similar to *COL3A1*, patients with TGFβ pathway genes have primarily dissections as arterial events, though these occurred later and were less frequent than in *COL3A1*. In contrast, *FBN1* participants had primarily aneurysm repairs, starting in the late 30’s and mostly in males. *TGFBR1*, *TGFBR2,* andTGFβ pathway genes have significantly earlier arterial event rates when compared to *FBN1*. A systematic review of all cases reported in the literature found arterial dissections in only two percent of patients with TGFβ pathway genes but did not specify the locations of these events. 29,30 A cohort study of 53 LDS patients reported that 20 underwent non-aortic interventions, with 30% of these involving endovascular or open vascular repair, but this study did not provide a breakdown by gene and location of interventions.29,30 An Australian cohort of 279 MFS and 28 LDS also concluded that MFS participants are at a lower risk for an arterial event than LDS.31

Previous studies to identify systemic features increasing the risk for arterial events often lack a clear definition for arterial events and do not separate the analyses based on the individual LDS genes.25,26,28 The present analyses identify distinct systemic factors that serve as markers of arterial event risk across specific genetic subgroups. Notably, smoking was significantly associated with an increased incidence of arterial events among individuals harboring TGFβ-pathway **gene variants**. Additionally, hypertension was found to be a significant risk factor for arterial events in individuals with pathogenic variants in ***FBN1*** and TGFβ-pathway **genes**. 32–35

We determined that systemic features, including hypertelorism, kyphosis, atrophic scars, and aortic tortuosity, were significantly associated with an increased risk for arterial events in participants with PVs in TGFβ pathway genes. In another MAC study, univariate analyses in *TGFBR1* and *TGFBR2* participants revealed associations between aortic events and features such as bifid uvula, hypertelorism, craniosynostosis, arched palate, aortic tortuosity, wide scars, and translucent skin. 11  Thus, these systemic features may provide additional clinical indicators for heightened surveillance to optimize patient outcomes. Previous findings from our group highlighted that a history of a hernia was associated with an increased risk of aortic events in *SMAD3* participants. 12 In contrast, we found doughy skin texture, downslating palpebral fissures and wide or atrophic scars were associated with arterial event in *SMAD3* cases. 11

Tailored surveillance protocols based on gene-specific risks are essential to improve outcomes while at the same limit costs. Current AHA/ACC guidelines recommend routine head-to-pelvis imaging for individuals with vEDS and LDS, but not those with MFS, and when to initiate this screening is not specified. 5,36 On the other hand European guidelines recommend imaging only for the initial evaluation.37 Our current findings support early surveillance of the head, neck and thoracoabdominopelvic zones for individuals with *COL3A1*, starting by 12 years of age. In contrast, individuals with *FBN1* need surveillance focused on the aorta initially. Individuals with TGFβ pathway genes should have imaging from head-to-pelvis at baseline, and if normal, imaging for arterial changes based on age, cardiovascular findings, and other risk factors.5,37 Recognizing systemic features, such as hypertelorism and aortic tortuosity, in addition to cardiovascular risk factors, like hypertension and smoking, may further inform surveillance.32,38 Importantlyaddressing these modifiable cardiovascular risk factors can help reduce the patient's overall risk.5

It is important to note that the retrospective nature of the data may introduce biases and limit the ability to establish causality. The centers that participated in this survey are all secondary or tertiary reference centers, so a more severe phenotypes associated with PVs in these genes may be overrepresented. Additionally, the aortic sites are primarily directed at the care of adults, which may result fewer childhood onset participants. Assessment of many of the systemic features is subjective and despite MAC data dictionary with illustrations of these features, the features can vary based on the physician assessing the patient.

This study highlights the significant gene-specific and sex differences in the prevalence, age of onset, and penetrance of arterial events in participants with *COL3A1*, TGFβ pathway genes, and *FBN1*. The significant associations of traditional cardiovascular risk factors, such as hypertension and smoking, with increased arterial event risk, emphasize the importance of managing these modifiable factors to mitigate overall risk. Our study underscores the importance of personalized medical care in managing participants with a PV in a gene that predisposes to HTAD, guided by the specific gene and variant type, age and sex of the patient, and their individual risk factors. Tailored surveillance and management strategies based on these factors can facilitate early detection and timely intervention, thereby improving patient outcomes.

**REFERENCES**

1. Milewicz DM, Cecchi AC. Heritable Thoracic Aortic Disease Overview. *GeneReviews®*. 2023. Accessed July 10, 2024. https://www.ncbi.nlm.nih.gov/books/NBK1120/.

2. Milewicz DM, Trybus KM, Guo DC, et al. Altered Smooth Muscle Cell Force Generation as a Driver of Thoracic Aortic Aneurysms and Dissections. *Arterioscler Thromb Vasc Biol*. 2017;37:26–34.

3. Pinard A, Jones GT, Milewicz DM. Genetics of Thoracic and Abdominal Aortic Diseases. *Circ Res*. 2019;124:588–606.

4. Regalado ES, Morris SA, Braverman AC, et al. Comparative Risks of Initial Aortic Events Associated With Genetic Thoracic Aortic Disease. *J Am Coll Cardiol*. 2022;80:857–869.

5. Isselbacher EM, Preventza O, Black JH, et al. 2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;146:E334–E482.

6. Lim MS-A, Guo D-C, Velasco Torrez W, et al. Aortic and arterial manifestations and clinical features in TGFB3-related heritable thoracic aortic disease: results from the Montalcino Aortic Consortium. *J Med Genet*. 2024:jmg-2024-110251.

7. Shalhub S, Black JH, Cecchi AC, et al. Molecular diagnosis in vascular Ehlers-Danlos syndrome predicts pattern of arterial involvement and outcomes. *J Vasc Surg*. 2014;60:160–169.

8. Pepin M, Schwarze U, Superti-Furga A, Byers PH. Clinical and genetic features of Ehlers-Danlos syndrome type IV, the vascular type. *N Engl J Med*. 2000;342:673–680.

9. Byers PH, Belmont J, Black J, et al. Diagnosis, natural history, and management in vascular Ehlers-Danlos syndrome. *Am J Med Genet C Semin Med Genet*. 2017;175:40–47.

10. Lopez-Sainz A, Mila L, Rodriguez-Palomares J, et al. Aortic Branch Aneurysms and Vascular Risk in Patients With Marfan Syndrome. *J Am Coll Cardiol*. 2021;77:3005–3012.

11. Jondeau G, Ropers J, Regalado E, et al. International Registry of Patients Carrying TGFBR1 or TGFBR2 Mutations: Results of the Montalcino Aortic Consortium. *Circ Cardiovasc Genet*. 2016;9:548.

12. Hostetler EM, Regalado ES, Guo DC, et al. SMAD3 pathogenic variants: risk for thoracic aortic disease and associated complications from the Montalcino Aortic Consortium. *J Med Genet*. 2019;56:252–260.

13. MacCarrick G, Black JH, Bowdin S, et al. Loeys-Dietz syndrome: a primer for diagnosis and management. *Genet Med*. 2014;16:576–587.

14. Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the Diagnosis and Management of Patients With Thoracic Aortic Disease. *Circulation*. 2010;121:266–369.

15. Soma K, Kitagawa Y, Toki T, et al. Early-onset Marfan syndrome with a novel missense mutation: A case report. *J Cardiol Cases*. 2023;27:283–286.

16. Ozyurt A, Baykan A, Argun M, et al. Early onset marfan syndrome: Atypical clinical presentation of two cases. *Balkan J Med Genet*. 2015;18:71.

17. Ardhanari M, Barbouth D, Swaminathan S. Early-Onset Marfan Syndrome: A Case Series. *J Pediatr Genet*. 2019;8:86.

18. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17:405–424.

19. ClinGen Variant Curation SOP Committee. ClinGen General Sequence Variant Curation Process Standard Operating Procedure v3.2. *https://clinicalgenome.org/site/assets/files/7438/variant\_curation\_sop\_v3\_2\_oct\_2022.pdf*. 2022.

20. Tran-Fadulu V, Pannu H, Kim DH, et al. Analysis of multigenerational families with thoracic aortic aneurysms and dissections due to TGFBR1 or TGFBR2 mutations. *J Med Genet*. 2009;46:607–613.

21. Buso G, Paini A, Agabiti-Rosei C, et al. Despite celiprolol therapy, patients with vascular Ehlers-Danlos syndrome remain at risk of vascular events: A 12-year experience in an Italian referral center. *Vasc Med*. 2024;29:265–273.

22. Akutsu K, Watanabe A, Yamada T, Sahara T, Hiraoka S, Shimizu W. Vascular Involvements Are Common in the Branch Arteries of the Abdominal Aorta Rather Than in the Aorta in Vascular Ehlers-Danlos Syndrome. *CJC Open*. 2023;5:72–76.

23. Frank M, Adham S, Seigle S, et al. Vascular Ehlers-Danlos Syndrome: Long-Term Observational Study. *J Am Coll Cardiol*. 2019;73:1948–1957.

24. Frank M, Albuisson J, Ranque B, et al. The type of variants at the COL3A1 gene associates with the phenotype and severity of vascular Ehlers-Danlos syndrome. *Eur J Hum Genet*. 2015;23:1657–1664.

25. Adham S, Legrand A, Bruno RM, et al. Assessment of arterial damage in vascular Ehlers-Danlos syndrome: A retrospective multicentric cohort. *Front Cardiovasc Med*. 2022;9.

26. Frank M, Adham S, Seigle S, et al. Vascular Ehlers-Danlos Syndrome: Long-Term Observational Study. *J Am Coll Cardiol*. 2019;73:1948–1957.

27. Shalhub S, Byers PH, Hicks KL, et al. A multi-institutional experience in the aortic and arterial pathology in individuals with genetically confirmed vascular Ehlers-Danlos syndrome. *J Vasc Surg*. 2019;70:1543–1554.

28. Shabani M, Abdollahi A, Brar BK, et al. Vascular aneurysms in Ehlers-Danlos syndrome subtypes: A systematic review. *Clin Genet*. 2023;103:261–267.

29. Gouda P, Kay R, Habib M, Aziz A, Aziza E, Welsh R. Clinical features and complications of Loeys-Dietz syndrome: A systematic review. *Int J Cardiol*. 2022;362:158–167.

30. Aftab M, Cikach FS, Zhu Y, et al. Loeys-Dietz syndrome: Intermediate-term outcomes of medically and surgically managed patients. *J Thorac Cardiovasc Surg*. 2019;157:439-450.e5.

31. Robertson EN, Bannon PG, Jeremy RW. Long-term outcomes in heritable thoracic aortic disease. *Front Cardiovasc Med*. 2022;9:1009947.

32. Huguenard AL, Johnson GW, Desai RR, Osbun JW, Dacey RG, Braverman AC. Relationship between phenotypic features in Loeys-Dietz syndrome and the presence of intracranial aneurysms. *J Neurosurg*. 2022;138:1385–1392.

33. Loeys BL, Schwarze U, Holm T, et al. Aneurysm syndromes caused by mutations in the TGF-beta receptor. *N Engl J Med*. 2006;355:788–798.

34. Chmielewski P, Ponińska JK, Michalak E, et al. Cardiovascular involvement and prognosis in Loeys-Dietz syndrome. *Kardiol Pol*. 2023;81:1096–1102.

35. Maghsoudi D, Nixon TRW, Snead MP. Retinal detachment in Loeys-Dietz syndrome. *Am J Med Genet A*. 2023;191:846–849.

36. Morris SA, Flyer JN, Yetman AT, et al. Cardiovascular Management of Aortopathy in Children: A Scientific Statement From the American Heart Association. *Circulation*. 2024;150:e228–e254.

37. Mazzolai L, Teixido-Tura G, Lanzi S, et al. 2024 ESC Guidelines for the management of peripheral arterial and aortic diseases. *Eur Heart J*. 2024;45.

38. Perez-Vega C, Domingo RA, Tripathi S, et al. Intracranial Aneurysms in Loeys-Dietz Syndrome: A Multicenter Propensity-Matched Analysis. *Neurosurgery*. 2022;91:541–546.

Table 1: Study population and pathogenic and likely pathogenic variants in genes.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **TOTAL**  **(n=1825)** | ***COL3A1***  **(n = 125)** | ***TGFBR1***  **(n=137)** | ***TGFBR2***  **(n=168)** | ***SMAD3***  **(n= 196)** | ***TGFB2***  **(n=126)** | ***TGFB3***  **(n=45)** | ***FBN1***  **(n=1028)** |
| No of Probands | 916  (50.2%) | 101  (80.8%) | 74  (54.0%) | 74  (44.0%) | 79  (40.3%) | 54  (42.9%) | 25  (55.5%) | 534  (51.9%) |
| <18 years | 417  (22.8%) | 21  (16.8%) | 28  (20.4%) | 39  (23.2%) | 20  (10.2%) | 30  (23.8%) | 13  (28.8%) | 266  (25.9%) |
| **Type of variant** | | | | | | | | |
| Missense | 1131  (62.0%) | 80  (64.0%) | 121  (88.3%) | 148  (88.1%) | 112  (57.1%) | 57  (45.2%) | 17  (37.8%) | 596  (57.9%) |
| Haploinsufficency | 469  (25.7%) | 16  (12.8%) | 10  (7.3%) | 1  (0.6%) | 52  (26.5%) | 69  (54.8%) | 28  (62.2%) | 293  (28.5%) |
| Inframe Indel | 173  (9.4%) | 25  (20.0%) | 6  (4.4%) | 2  (1.2%) | 12  (6.1%) | 0  (0.0%) | 0  (0.0%) | 128  (12.5%) |
| PTC non NMD | 40  (2.2) | 2  (1.6%) | 0  (0.0%) | 12  (7.1%) | 15  (7.7%) | 0  (0.0%) | 0  (0.0%) | 11 (1.1%) |
| Other | 12  (0.7%) | 2  (1.6%) | 0  (0.0%) | 5  (3.0%) | 5  (2.6%) | 0  (0.0%) | 0  (0.0%) | 0  (0.0%) |
| Age | | | | | | | | |
| Overall Median (IQR) | 33.7  (19-48.7) | 42  (27-52) | 34.6  (20-55) | 36  (18.9-47) | 45  (27-58.2) | 36  (18.2-50.8) | 35  (16-47.2) | 30.7  (17.5-45.2) |
| Female Median (IQR) | 36  (21.1-50.4) | 43.5  (29.5-52) | 35.2  (23.9-57) | 39  (21.1–49.1) | 42  (27-58.1) | 39  (20.3-2) | 41  (40-54) | 33.2  (19.2-48.1) |
| Male Median (IQR) | 31  (17.2-46.4) | 41  (24.5-47.5) | 33  (16.1-49.1) | 34.5  (18.5–46.1) | 45.5  (26.7-58.2) | 32  (17-48) | 20.5  (15-32.8) | 29.2  (24.5-47.5) |
| **Sex** | | | | | | | | |
| Male | 935  (51.2%) | 55  (44%) | 63  (46.0%) | 84  (50.0%) | 99  (50.5%) | 69  (54.8%) | 21  (46.7%) | 496  (48.2%) |
| Female | 890  (48.8%) | 70  (56%) | 74  (54.0%) | 84  (50.0%) | 97  (49.5%) | 57  (45.2%) | 24  (53.3%) | 532  (51.8%) |
| **Location of recruitment** | | | | | | | | |
| Australia | 60  (3.3%) | 7  (5.6%) | 14  (10.2%) | 9  (5.4%) | 27  (13.8%) | 1  (0.8%) | 1  (2.2%) | 1  (0.1%) |
| Belgium | 18  (1.0%) | 1  (0.8%) | 2  (1.5%) | 5  (3.0%) | 5  (2.5%) | 2  (1.6%) | 3  (6.7%) | 0  (0.0%) |
| Canada | 28  (1.5%) | 5  (4.0%) | 5  (3.6%) | 4  (2.4%) | 8  (4.1%) | 0  (0.0%) | 4  (8.9%) | 2  (0.1)% |
| France | 1209  (66.2%) | 1  (0.8%) | 55  (40.9%) | 59  (35.1%) | 79  (40.3%) | 23  (18.3%) | 15  (33,3%) | 976  (94.9%) |
| United Kindom | 34  (1.9%) | 8  (6.4%) | 6  (4.4%) | 10  (5.9%) | 7  (3.6%) | 2  (1.6%) | 1  (2.2%) | 0  (0.0%) |
| United States | 476  (26.1%) | 103  (82.4%) | 54  (39.4%) | 81  (48.2%) | 70  (35.7%) | 98  (77.7%) | 21  (46.7%) | 49  (4.9%) |

IQR: Quartil

PTC non NMD: Premature Termination Codon non-Nonsense-Mediated Decay

Table 2. First arterial event by gene and variant type

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **TOTAL**  **(n=1790)** | ***COL3A1***  **(n = 125)** | ***TGFBR1***  **(n=137)** | ***TGFBR2***  **(n=168)** | | ***SMAD3***  **(n= 196)** | ***TGFB2***  **(n=126)** | ***FBN1***  **(n=1028)** |
| Arterial events | **93 (5.2%)** | **30 (24%)** | **13 (9.5%)** | **13 (7.7%)** | | **13 (7.1%)** | **8 (6.4%)** | **16 (1.6%)** |
| Variant Type | | | | | | | | |
| Missense | 63  (67.7%) | 17  (56.7%) | 13  (100.0%) | | 12  (93.3%) | 7  (53.8%) | 6  (75%) | 8  (50.0%) |
| Happloinssuficence | 18  (19.4%) | 6  (20%) | 0  (0.0%) | | 0  (0.0%) | 4  (30.8%) | 2  (25.0%) | 6  (37.5%) |
| Inframe Indels | 10  (10.8%) | 7  (23.3%) | 0  (0.0%) | | 1  (7.7%) | 0  (0.0%) | 0  (0.0%) | 2  (12.5%) |
| PTC nonNMD | 2  (2.1%) | 0  (0.0%) | 0  (0.0%) | | 0s  (0.0%) | 2  (15.4%) | 0  (0.0%) | 0  (0.0%) |
| Type of arterial event | | | | | | | | |
| Dissections | 52  (55.9%) | 19  (63.4%) | 10  (76.9%) | | 6  (46.1%) | 8  (61.5%) | 3  (37.5%) | 6  (45.4%) |
| Ruptures | 11  (11.8%) | 7  (23.3%) | 0  (0.0%) | | 0  (0.0%) | 2  (15.4%) | 2  (25.0%) | 0  (0.0%) |
| Aneurysm Repairs | 30  (32.3%) | 4  (13.3%) | 3  (23.1%) | | 7  (53.9%) | 3  (23.1%) | 3  (37.5%) | 10  (54.6%) |

NA= Not available

All values are listed as n, n (%) or median (25%,75%)

PTC nonNMD: Premature Termination Codon non-Nonsense-Mediated Decay

Table 3. First aortic event by gene and variant type

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **TOTAL**  **(n=1790)** | ***COL3A1***  **(n = 125)** | ***TGFBR1***  **(n=137)** | ***TGFBR2***  **(n=168)** | ***SMAD3***  **(n= 196)** | ***TGFB2***  **(n=126)** | ***FBN1***  **(n=1028)** |
| Aortic events | **496 (27.7%)** | **32 (25.6%)** | **52 (37.9%)** | **72 (42.9%)** | **66 (33.7%)** | **38 (30.1%)** | **236 (22.9%)** |
| Variant type | | | | | | | |
| Missense | 296  (59.7%) | 21  (65.6%) | 49  (94.2 %) | 62  (86.1%) | 33  (50.0%) | 24  (63.2%) | 107  (45.3%) |
| Happloinssuficence | 135  (27.2%) | 7  (21.9%) | 2  (3.8%) | 1  (1.4%) | 16  (24.2%) | 14  (36.8%) | 95  (40.3%) |
| Inframe Indels | 42  (8.5%) | 3  (9.4%) | 1  (2.0%) | 2  (2.8%) | 6  (9.1%) | 0  (0.0%) | 30  (12.7%) |
| PTC nonNMD | 19  (3.8%) | 0  (0.0%) | 0  (0.0%) | 6  (8.3%) | 9  (13.7%) | 0  (0.0%) | 4  (1.7%) |
| Others | 4  (0.8%) | 1  (3.1%) | 0  (0.0%) | 1  (1.4%) | 2  (3.0%) | 0  (0.0%) | 0  (0.0%) |
| Type of aortic event | | | | | | | |
| Type A | 116  (23.4%) | 8  (25.0%) | 16  (30.8%) | 24  (33.3%) | 30  (45.5%) | 11  (28.9%) | 27  (11.4%) |
| Type B | 54  (10.9%) | 14  (43.8%) | 1  (1.9%) | 3  (4.2%) | 7  (10.6%) | 2  (5.3%) | 27  (11.4%) |
| Aneurysm Repair | 326  (65.7%) | 10  (31.2%) | 35  (67.3%) | 45  (62.5%) | 29  (43.9%) | 25  (65.8%) | 182  (77.2%) |

NA= Not available

All values are listed as n, n (%) or median (25%,75%)

PTC nonNMD: Premature Termination Codon non-Nonsense-Mediated Decay