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CORRECTION
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Corrigendum: Candidate Gene Resequencing in a Large Bicuspid Aortic Valve-Associated Thoracic Aortic Aneurysm Cohort: *SMAD6* as an Important Contributor

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A corrigendum on

Candidate Gene Resequencing in a Large Bicuspid Aortic Valve-Associated Thoracic Aortic Aneurysm Cohort: *SMAD6* as an Important Contributor

by Gillis, E., Kumar, A. A., Luyckx, I., Preuss, C., Cannaerts, E., van de Beek, G., et al. (2017). Front. Physiol. 8:400. doi: 10.3389/fphys.2017.00400

In the original article, we noted two mutation annotation errors. The correction of these two mistakes does not change the scientific conclusions in any way. The authors apologize for these nomenclature errors. Please find below the corrected annotations of those two mutations:

(1) The correct RNA and protein annotations of the *SMAD6* variant in P99 are c.455_461del and p.Pro152Profs*27, and not c.454_461del and p.Gly166Valfs*23.

(2) The correct RNA and protein annotations of the *SMAD6* variant in P128 are c.74_79del and p.Ser27_Gly28del, and not c.73_79del and p.Gly26_Ser27del.

As a consequence, a correction has been made to RESULTS, Paragraphs 5 and 6:

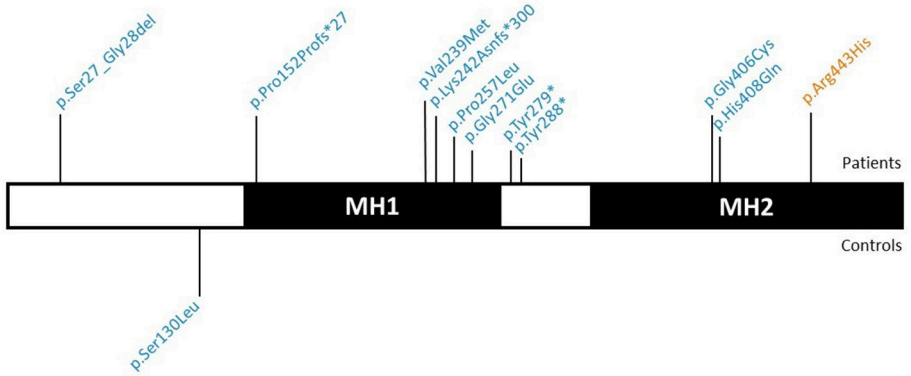

FIGURE 2 | Graphical representation of the identified *SMAD6* variants. SMAD6 has two major protein domains, a DNA-binding MH1 domain and a MH2 domain that interacts with components of the TGF-β and BMP signaling pathways. Variants above the protein have been found in patients, while those below the protein occurred in control individuals. Variants in blue are absent from the ExAC database, variants in orange have an ExAC MAF below 0.01%. TGF-β, Transforming growth factor-β; BMP, Bone morphogenetic protein; ExAC, Exome Aggregation Consortium; MAF, Minor Allele frequency.

The *SMAD6* c.726del variant leads to a frameshift (p.Lys242Asnfs*300) and a predicted protein with a C-terminal extension due to loss of the intended stop codon. The c.455_461del frameshift variant (p.Pro152Profs*27) causes the introduction of a premature stop codon, most likely resulting in haploinsufficiency due to nonsense-mediated mRNA decay (NMD). Also the two nonsense variants (p.Tyr279* and p.Tyr288*) are predicted to lead to NMD. All of the missense variants cluster in the functionally important MH1 and MH2 domains (Makkar et al., 2009) (amino acids 148–275 and 331–496, respectively), which is not the case for the sole missense variant (p.Ser130Leu) found in a control individual (**Figure 2**). All but one (p.Arg443His) of the identified variants were absent in the ExAC control cohort (v0.3.1; Supplementary Table 2). Moreover, the missense variants in the patient cohort (7/7) are enriched in the MH1 and MH2 domains when compared to ExAC controls ($n = 228/430$; $p = 0.02$).

For two SMAD6 mutation carriers (P89, p.Gly271Glu; P99, p.Pro152Profs*27), gDNA of family members was available for segregation analysis (Supplementary Figure 1). Although neither of these probands had a documented family history of BAV/TAA, a brother of P89 has been diagnosed with a sinus of Valsalva aneurysm (45 mm) and carried the SMAD6 mutation. The mutation was also observed in an unaffected daughter (age 28) of the proband (Supplementary Figure 1). Three unaffected siblings at ages 54, 58, and 64 did not carry the mutation. No gDNA was available from a sister of P99 with unspecified aortic valve problems. The p.Pro152Profs*27 mutation was found in an unaffected daughter (age 39) of P99 but was absent in his 37 year-old unaffected son (Supplementary Figure 1).

We also provide a corrected **Figure 2** and Supplementary Table 2.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fphys.2017.00730/full#supplementary-material

REFERENCES

Makkar, P., Metpally, R. P., Sangadala, S., and Reddy, B. V. (2009). Modeling and analysis of MH1 domain of Smads and their interaction with promoter DNA sequence motif. *J. Mol. Graph. Model.* 27, 803–812. doi: 10.1016/j.jmgm.2008.12.003

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.