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Deciphering Concurrent Tuberous Sclerosis Complex and Bipolar Disorder with a Genetic Approach

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Abstract

Tuberous sclerosis complex (TSC) is a rare genetic disorder that causes benign tumors to form in multiple organs and often begins in early childhood. TSC mainly occurs due to autosomal dominant mutations in the *TSC1* or *TSC2* genes, leading to an aberrant activation of mTOR signaling pathway. TSC is strongly associated with developmental neuropsychiatric disorders such as autism spectrum disorder and intellectual disability. However, only few publications have reported the concurrence of TSC with bipolar disorder (BD) and very little is known regarding the respective underlining mechanism(s). To address such gap in knowledge, we studied an individual who was diagnosed with TSC and BD by using a combination of gross anatomical, magnetic resonance imaging (MRI), and genetic approaches. The study results strongly confirmed a TSC diagnosis in the donor, with less certainty for BD. The genetic screening by whole exome sequencing (WES) on the Illumina next generation sequencing platform (NGS) yielded 77 modified genes with rare (minor allele frequency, MAF ≤ 0.01) and 64 modified genes with low-frequency (0.01 < MAF < 0.05) pathological/deleterious variants. The functional annotation of those genes allowed their grouping into 13 functional categories most relevant to the present case. The most interesting were several genes that participate in PI3K/AKT/mTOR signaling or mediate signaling pathways known to have a cross-talk with mTOR: Sonic hedgehog, Notch, and Wnt. Yet several affected genes were linked to BD/Schizophrenia, pointing toward a possible existence of polygenic components in both the TSC and BD. The strongly modified *AHNAK2* potentially associated with both TSC and BD might indicate the existence of a pleiotropic component in the genetic underlining of the concur-

rent TSC and BD in the present case.

Keywords

Tuberous Sclerosis Complex, Bipolar Disorder, Whole Exome Sequencing, Next Generation Sequencing, *AHNAK2*

1. Introduction

Tuberous sclerosis complex (TSC) is a rare hereditary neurocutaneous disorder which is characterized by benign tumors developing in the nervous system, internal organs, and skin. It is independent from race, ethnicity, or sex and has an incidence of 1:11,000 - 22,000 of live births [1] with the prevalence of 4 - 8 cases per 100,000 people [2]. TSC has an early onset, apparent in infants and early childhood, with skin lesions, seizures, and cellular overgrowth, known as hamartomas, in the heart, brain, and kidneys [3] [4]. Individuals with TSC may experience developmental delays, behavioral challenges, and a range of neurological and systemic complications, which in severe cases could lead to a premature death. There is currently no cure for TSC, and its treatment is mostly symptomatic.

Genetically, TSC is inherited in an autosomal dominant pattern with mutations in either *TSC1* or *TSC2* genes which encode respectively hamartin and tuberin. These mutations lead to the hyperactivation of the mTOR signaling pathway, a critical central regulator of cell growth and proliferation [5]. Additionally, TSC can contribute to a plethora of disabling neurological disorders, including epilepsy, intellectual disability, and autism spectrum disorder [2]. However, there is a paucity of reports in the literature regarding the concurrence of TSC and bipolar disorder (BD). The latter is a chronic, severe neuropsychiatric disorder characterized by recurring manic or hypomanic episodes which may alternate with periods of depression [6]. BD is a significant social burden and one of the leading causes of disability ranking 17th among all diseases worldwide [7]. This could be attributed, at least in part, to a high degree of BD association with other psychiatric conditions such as anxiety (~70%), substance use (~56%), personality disorders (~36%), as well as attention deficit - hyperactivity disorder (10% - 20%) [6]. Yet the suicidal rate among patients with BD is 20 to 30 times higher than in the general population [8]. BD is also characterized by a high prevalence of major chronic diseases including obesity [9] and type 2 diabetes [10]. As a result, BD together with its related comorbidities doubles the risk of death as compared to the general population [6].

Therefore, despite a potentially significant adverse contribution of concurrent BD to the clinical presentation of TSC, this issue has not received proper attention as only six published cases have documented the concurrence of TSC and BD to date [11]. By reporting a novel case of such a concurrence, we aim at gaining additional insights into its molecular underpinnings.

2. Methods

2.1. Human Cadaveric Body Procurement

The body of a 59-year-old male was received through the Saint Louis University (SLU) Gift Body Program with signed informed consent. The available family reported medical history included TSC, BD, and diabetes (type 1), and the absence of seizures. The donor had one kidney removed due to numerous benign tumors associated with TSC. The donor's family history also included his mother's diagnoses for TSC and BD, whereas his maternal grandfather was diagnosed with BD. His father also had type 1 diabetes. The donor was also nonverbal but had simple receptive understanding. When the donor was a teenager, he was removed from the family and placed into a specialized care institution for developmentally disabled persons because of becoming violent. The cause of death was listed as an end-stage kidney failure.

2.2. Magnetic Resonance Imaging

The cadaver head was imaged at the SSM Health Saint Louis University Hospital by using Siemens Skyra 3T MRI Scanner at a slice thickness of 1 mm. T1 and T2 coronal, axial, and sagittal images were obtained and analyzed using Syngo FastView software to identify location(s) with TSC related pathologies.

2.3. Anatomical Dissection

Removal of the brain, right lung and right kidney followed the dissection procedures in Grant's Dissector, 16th edition [12]. After their removal, the specimens were submerged in a 10% neutrally buffered formalin solution for approximately eight weeks.

2.4. Histochemical Staining

The right lung and right kidney were bisected while the brain was sliced coronally into 10 mm sections. Regions of each specimen were removed, dehydrated, paraffin embedded, sectioned (4 - 5 μm), and stained with hematoxylin and eosin (H&E) according to standard procedures of the Advanced Spatial Biology and Research Histology Facility (Department of Pathology, SLU School of Medicine).

2.5. Light Microscopy

Images were obtained with a Leica Leitz DMRB light microscope equipped with a DFC7000 T camera and controlled by the Neurolucida software (MBF Bioscience, Williston, VT, USA) using the 4×, 10×, 20×, and 63× objectives.

2.6. Genetic Screening

The postmortem genetic screening by WES on the Illumina NGS platform and the respective bioinformatics analysis were performed as previously described [13].

3. Results

3.1. Pathological Examination

External body examination revealed multiple facial angiofibromas that were most prominent on and around the nose (Figure 1(A)). MRI demonstrated the existence of a subependymal nodule in the wall of the lateral ventricle (Figure 1(B)) whereas such nodules were most clearly identified on the coronal section of the dissected brain (Figure 1(C)). The same section was also characterized by the presence of cortical tubers and white matter lesions (Figure 1(C)) with the latter being enriched with large, dysmorphic neuronal cells shown by H&E staining (Figure 1(C), inset).

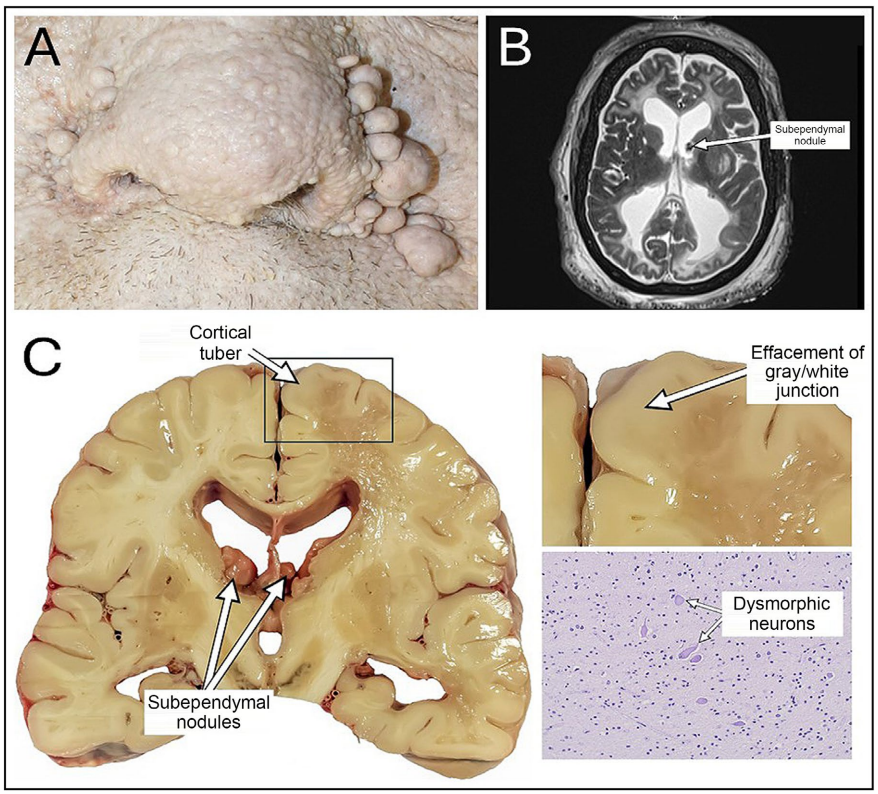

Figure 1. Cutaneous and neurologic pathological features in the present case. (A): Multiple facial angiofibromas on and around the nose. (B): A subependymal nodule in the wall of the lateral ventricle as demonstrated by MRI. (C): Multiple subependymal nodules present in the lateral ventricles and a cortical tuber. Upper right panel: Effacement of the gray/matter junction characteristic of cortical tubers. Lower right panel: Loss of normal cortical cytoarchitecture and collection of large, dysmorphic neuronal cells as shown by H&E staining.

Besides the brain, the other internal organs mostly affected in the donor were the lungs and the remaining right kidney (the other was surgically removed), while examination of the other internal organs did not reveal any gross abnormalities. The kidney had multiple, bilateral, relatively well-circumscribed nodular lesions in the renal parenchyma. The nodules show a variegated appearance without hemorrhage or necrosis. Additionally, cysts were present in the kidney (Figure

2(A)). Histopathological examination of the kidney nodules revealed a triphasic lesion composed of disorganized mature adipose tissue, associated with bundles of smooth muscle and thick-walled blood vessels (Figure 2(B)). Histological analysis of the cysts characterized them as simple cysts lined by unremarkable flat epithelium (Figure 2(C)).

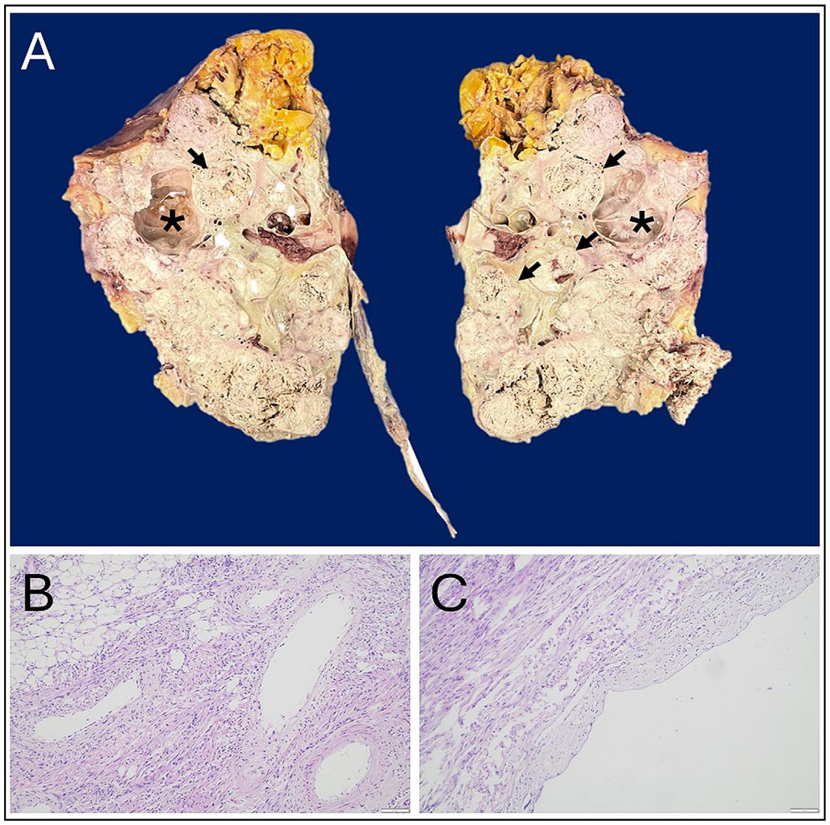

Figure 2. Gross and microscopic kidney findings. (A): The bisected right kidney showed well-circumscribed, unencapsulated nodular masses in the renal parenchyma (black arrows). Simple cysts were also identified (asterisks). (B): A section of the nodules show admixed mature adipose tissue, smooth muscle, and thick-walled blood vessels, consistent with classic angiomyolipomas. (C): Histological examination of the cysts shows a simple cyst lined by unremarkable flat epithelium. (H&E, 100×).

The gross examination of the lungs showed several parenchymal, round to oval, thin-walled cysts of varying size (Figure 3(A)). Histopathological analysis of H&E-stained lung tissue sections showed simple cysts (Figure 3(B)) focally surrounded by smooth-muscle-like cells, consistent with lymphangiomatosis (Figure 3(C)).

3.2. Genetic Analysis

The pathogenic heterozygous splicing *TSC2* mutation (rs45443096, ClinVar) was identified in the WES dataset and supported the donor's TSC diagnosis. The second TSC causative gene, *TSC1* [5], was not pathologically affected. The very stringent, five-step analytical process which included sequential filtering through three independent databases, SIFT, PolyPhen_2-HDIV, and PROVEAN [13], was ap-

plied to the sequencing data and yielded 77 genes with rare (MAF ≤ 0.01) and 64 genes with low-frequency (0.01 < MAF < 0.05) pathological/deleterious variants. These genes were then annotated by searching GeneCards, Google Scholar, and PubMed databases and grouped into 13 categories most relevant to the present case (Table 1, Table 2). These categories were chosen based on the medical history of the donor with the TSC diagnosis and the respective clinical presentation, its associated comorbidities as well as on biological/signaling pathways known to drive a variety of developmental programs in humans.

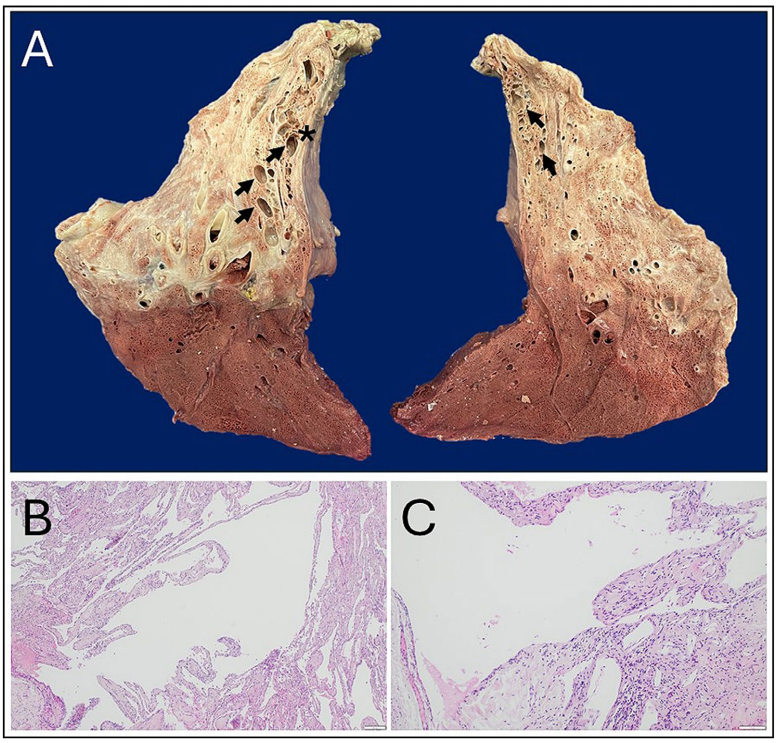

Figure 3. Gross and microscopic lung findings. (A): Photograph of the bisected right lung showing several cysts (black arrows), some of them subpleural (asterisk). (B): Micrscopic low power view of the simple cysts (H&E, 40×). (C): High power view of simple cyst with a foci of lymphangioleiomyomatosis cells (H&E, 100×).

Table 1. Genes with rare pathological/deleterious variants most relevant to the present case.

Categories	Genes
Development	*ABCA7*, *BRICD5*, *CFAP206*, *DIS3L*, *FAM53A*, *GLI2*, *GRIP1*, *GSC2*, *KIAA1217*, *KRIT1*, *OR2T3*, *PCNX1*, *PKHD1*, *PTH1R*, *VWA8*, *WDR90*, *ZNF699*
Neurodevelopment	*AHNAK2**, *ATRN*, *BRICD5*, *CCDC88A*, *CCSER2*, *CGNL1*, *CHD1*, *FOXC1*, *GFAP*, *GLI2*, *KRIT1*, *KRT12*, *MOK*, *NRCAM*, *ODF1*, *OR2T3*, *PCTP*, *PLEKHG3*, *PTH1R*, *RBSN*, *SLC9C1*, *SMO*
Cancer/Tumorigenesis	*ATRN*, *BRICD5*, *C17ORF64*, *CCDC88A*, *CD276*, *DIS3L*, *ESYT2*, *FAM53A*, *FFAR3*, *FOXC1*, *GALNT8*, *GBGT1*, *GLI2*, *KIAA1217*, *KRT39*, *LCN1*, *METAP1D*, *MOK*, *NRCAM*, *ODF1*, *OSMR*, *PCNX1*, *PFKL*, *PKHD1*, *PTH1R*, *RAD1*, *RAI14*, *RBSN*, *RFX2*, *SLC39A11*, *SLC47A2*, *TBC1D9*, *TJP1*, *TMPRSS4*

Continued

Bipolar disorder/Schizophrenia	*AHNAK2**, *ATRN*, *C17ORF64*, *CGNL1*, *CHD1*, *HLA-DQB1*, *HLA-DRB5*, *MOK*
Intellectual disability	*CHD1*, *DOCK8*, *GFAP*, *GSC2*, *NRCAM*, *OR2T3*, *PLEKHG3*, *RBSN*
Cognitive impairment	*CHAT*, *DCLK3*, *DNAJB2*, *FFAR3*, *GFAP*, *METAP1D*
Autism spectrum disorder	*DOCK8*, *FAM53A*, *HLA-DRB5*, *NRCAM*, *PLEKHG3*
Diabetes	*FFAR3*, *PTGR2*, *RFX2*, *SLC47A2*, *STEAP4*
PI3K/AKT/mTOR signaling	*AHNAK2**, *RAI14*
Sonic Hedgehog signaling	*GLI2*, *SMO*
Notch signaling	*PCNX1*
Wnt signaling	*KRIT1*
Cilia biogenesis/Function	*CFAP206*, *MOK*, *PDZD7*, *PKHD1*, *RFX2*, *RSPH1*, *SLC9C1*, *WDR90*

*Homozygous variant.

Table 2. Genes with low-frequency pathological/deleterious variants most relevant to the present case.

Categories	Genes
Development	*ACOT4*, *AGBL2*, *DCP1B*, *ELOA2*, *F2RL2*, *KDM4E*, *KRTAP4-8*, *MYO18B*, *PABPN1L*, *PACS2*
Neurodevelopment	*AHNAK2**, *AGBL2*, *DYRK4*, *LSS*, *MICALL2*, *MYADML2*, *NDUFA9*, *NSRP1*, *PACS2*, *RASA4B*, *SCN8A*
Cancer/Tumorigenesis	*ACOT4*, *ADRA1A*, *AGBL2*, *APLF*, *ARMC2**, *BTN2A1*, *C1ORF194*, *CALCA*, *CARD14*, *CCDC191*, *COL6A6*, *CYP4F2*, *DCAKD*, *DCP1B*, *DNASE1L3*, *DYRK4*, *EGFL6**, *F2RL2*, *FNDC3A*, *GJB4*, *GPA33*, *HLA-B*, *IER5*, *KDM4E*, *KLK1*, *KRT37*, *KRT8*, *LSS*, *MICALL2*, *MRPL1*, *MYADML2*, *MYO18B*, *NSRP1*, *OR4F15*, *OR51L1*, *OR5I1*, *OR7A17*, *PPP1R26*, *SFSWAP*, *SLC22A16*, *STARD3*, *TEKT5*
Bipolar disorder/Schizophrenia	*AHNAK2**, *DCAKD*
Intellectual disability	*KCNJ10*, *KRTAP4-8*, *LRP2*, *PACS2*
Cognitive impairment	*N/A*
Autism spectrum disorder	*BMP3*, *ELOA2*, *FNDC3A*, *ZNF763*
Diabetes	*ACOT4*, *ANK1*, *F2RL2*, *GJB4*, *PACS2*
PI3K/AKT/mTOR signaling	*ACOT4*, *ADRA1A*, *AHNAK2**, *MYO18B*
Sonic hedgehog signaling	*LRP2*
Notch signaling	*IER5*
Wnt signaling	*EGFL6**, *GJB4*
Cilia biogenesis/Function	*AGBL2*, *ARMC2**, *KRTAP4-8*, *TEKT5*

*Homozygous variant.

Interestingly, *AHNAK2* was present in both gene sets with two rare homozygous mutations and one low-frequency homozygous and one low-frequency heterozygous mutations (Table 3).

Table 3. Pathological/deleterious variants of *AHNAK2* (encodes AHNAK Nucleoprotein 2) associated with the present case.

Gene	Variant	MAF	Type*
AHNAK2	NM_001350929:p.P3071L; NM_138420:p.P3171L	0.0001	HOMO
	NM_001350929:p.V3055A; NM_138420:p.V3155A	0.0004	HOMO
	NM_001350929:p.P1941L; NM_138420:p.P2041L	0.0160	HOMO
	NM_138420:p.R51W	0.0342	HET

*HOMO—homozygous variant; HET—heterozygous variant.

4. Discussion

The results of the gross anatomical and pathological examination provided two major criteria for the definite TSC diagnosis in the donor: multiple facial angiofibromas and subependymal nodules (n ≥ 2) [14]. The pathogenic splicing *TSC2* mutation (rs45443096, ClinVar) in the donor is the most likely driver of TSC development in the present case and could also serve as a sufficient criterion for the above diagnosis [14].

Unfortunately, because of the postmortem nature of the current study as well as a lack of specific BD histopathological identifiers the donor's BD diagnosis cannot be independently confirmed. However, the family history of BD spanning three generations and the well-known high BD heritability (60% - 85%) [15]-[17] raises no serious doubts in the validity of the donor's BD diagnosis. This notion is also consistent with the results of neuropathologic examination indicating severely impaired white matter development in the donor's brain which could be associated with BD [18] [19].

One of the important features of the present case is its complex genetic underlining. Indeed, multiple genes with both rare and low-frequency mutations were present in the categories whose impairment or aberrant activation might have a significant bearing on the TSC development and manifestation in the donor. Such categories include Development, Neurodevelopment, Cancer/Tumorigenesis, Bipolar Disorder/Schizophrenia, Intellectual Disability, Cognitive Impairment, Autism Spectrum Disorder, Diabetes, and Cilia Biogenesis/Function. Yet even the core TSC signaling pathway, mTOR, that is pathologically activated by either *TSC1* or *TSC2* mutations [5], could be additionally affected in the present case by rare mutations in *AHNAK2* [20] and *RAI14* [21] as well as by low-frequency mutations in *ACOT4* [22], *ADRA1A* [23], *AHNAK2* [20], and *MYO18B* [24]. The

cross-talk between mTOR and other signaling pathways known to regulate human development such as Sonic hedgehog (Shh) [25], Notch [26], and Wnt [27] should be also taken into account.

Notable was the presence of a heavily modified *AHNAK2* with two rare homozygous and two low-frequency (one homozygous, one heterozygous) pathological/deleterious variants in two of the functional categories, BD and PI3/AKT/mTOR signaling. This overlap positions *AHNAK2* as a potential molecular bridge between BD and the PI3K/AKT/mTOR pathway, highlighting its possible role in shared pathogenic mechanisms.

5. Conclusions

The TSC disorder in the present case could be driven by the pathogenic splicing mutation in *TSC2* with a potential contribution from the heavily modified *AHNAK2*.

A possible contribution to TSC from other affected genes in signaling pathways, such as Shh, Notch, and Wnt, which interact with the mTOR pathway, cannot be excluded as contributors to TSC development and its clinical presentation.

The BD component in the present case could be underpinned by several affected genes, including *AHNAK2*. A possible link of modified *AHNAK2* to both TSC and BD could be indicative of the existence of a pleiotropic component in the genetic underlining of concurrent TSC and BD in the present case.

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Limitations

The study was performed postmortem with one participant and as such should be viewed as an essential step for the follow-up studies using a large cohort of patients and/or the respective clinical database(s).

Authors' Contribution

All authors have read and approved the final version of the manuscript.

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Ethics Statement

Throughout the study no living human subjects were used. The cadaveric body

used in the study was received through the SLU Gift Body Program with the signed informed consent from an immediate member of the donor's family. The SLU Gift Body Program abides by all rules set forth by the Uniform Anatomical Gift Act (UAGA). All work with the cadavers as well as with any material procured from the deceased bodies are exempt from the Institutional Review Board approval as long as the identity of the deceased individual is not revealed.

Conflicts of Interest

The authors declare that they have no competing interests.

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