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EDITORIAL COMMENT

When Genes, More Than Phenotype, Identify Different Diseases

The Case of Nonsyndromic HTAA/D*

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The diagnosis of heritable thoracic aortic aneurysms and dissections (HTAA/D) applies to both families with more affected members and families with a unique affected member who carries a pathological mutation that is causally linked with the TAA (1). HTAA/D manifests as either isolated trait (nonsyndromic) or in syndromes (syndromic) (2). Patients with syndromic HTAA/D demonstrate the involvement of skeletal, ocular, respiratory, neuromuscular, and cutaneous/integumentary systems in variable combinations and characteristics: well-known examples are Marfan syndrome and Ehlers-Danlos syndrome. Specific clinical nosologies (3,4) guide the phenotype-based diagnosis of syndromic HTAA/D; the genetic test plays a confirmatory role and allows preclinical, prenatal, and preimplantation diagnosis when feasible/indicated. Vice versa, nonsyndromic HTAA/Ds encompass phenotypically similar but genetically heterogeneous conditions. Family history and imaging-based family screening provide the evidence of familial versus sporadic disease (2). In nonsyndromic HTAA/D, the genetic test in the proband does not have a diagnostic role for the aneurysm itself, but precisely defines its specific cause that may influence the therapeutic decisions, especially timing of pre-emptive surgery. A gene-based classification is emerging for nonsyndromic HTAA/D (1) that, for instance, can be allelic at the same loci of syndromic HTAA/D. Alternatively, nonsyndromic HTAA/D can be grouped based on the pathways in which disease-genes are involved (transforming growth factor (TGF)-β, vascular smooth muscle cells, collagens, and so on). From a clinical point of view, a nosology orientation is useful, especially when similar phenotypes with different causes demonstrate different levels of risk and call for tailored clinical decisions. Therefore, the clinical diagnosis of familial HTAA requires the echocardiographic family screening while the precise diagnosis of nonsyndromic HTAA/D requires the identification of the genetic cause.

NONSYNDROMIC HTAA/D: DISEASE GENES AND PATHOLOGICAL MUTATIONS

The current fast next-generation sequencing-based tools for gene/genome analysis offer fast strategies for identification of novel disease genes (5). In the last 10 years, the list of candidate and disease genes has been rapidly expanding. In 2015, the National Institutes of Health-funded Clinical Genome Resource (ClinGen) created a new open-access resource to define clinically relevant genes and variants, based on a standardized assessment of the levels of evidence (6). Expert curators have the role of assessing the associations of the disease genes with the phenotype on the basis of pre-defined criteria (7). In this issue of the *Journal*, Renard et al. (8), curators for HTAA/D genes, analyzed 53 candidate genes with variable levels of evidence

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(from strong to no evidence). The levels of evidence of the causative role of mutations in candidate genes are established on the basis of functional data and segregation studies. A clinically oriented

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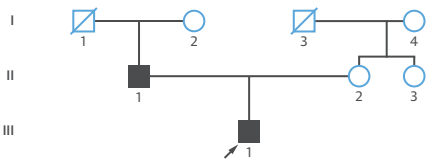
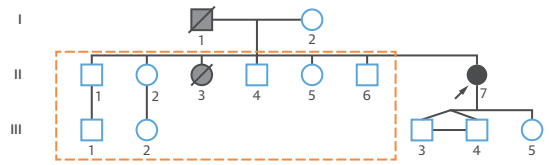
FIGURE 1 Genetics in HTAA/D

A Complex genetics



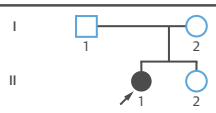
I:1, 65 years; cause of death described as due to "vascular disease"; no autopsy. No genetic test
I:2, 62 years; healthy; *TGFBR2:* negative
I:3, 61 years; DM with vascular complications; no genetic test
I:4, 72 years; Hypertension; no genetic test
II:1, 42 years; Phenotype: TAA, Aortic root Z-score= 2.92; myopia; arterial tortuosity of the neck and brain vessels; craniofacial score=2; *TGFBR2* positive; *COL5A1* negative
II:2 40 years; Clinical screening negative; *TGFBR2* negative; *COL5A1* negative
II:3 38 years; Clinical screening negative
III:1 → 7 years; Z-score= 2.41 - Phenotype: S/H Ratio =1.068; arachnodactyly; wrist and thumb signs: positive; pes planus; mild pectus deformity; prominent joint laxity; light blue sclerae; velvety, translucent skin; craniofacial score=3; arterial tortuosity of the brain vessels. *TGFBR2* p.(His507Arg) + *de novo COL5A1* p.(Gln1825GlufsTer5)

B Pathologic mutation in a definite HTAA/D gene. The mother (1:2) and relatives in the squared area did not undergo clinical screening and genetic testing.



I:1, 50 years; sudden death, vascular (?)
I:2, 65 years; II:1, 51 years; II:2, 50 years; II:4, 47 years; II:5, 45 years; II:6, 43 years → all described as healthy
II:3, 37 years; unexplained cause of death
II:7,→ proband, age at the event (Type B dissection): 41 years; height 169 cm; weight 82 kg; myopia, no iris flocculi; *ACTA2*, p.(Arg149Cys)
III:1, 22 years and III:2, 25 years: both described as healthy
III:3 and III:4, 7 years; clinically healthy, 2DTTE negative
III:5, 3 years, clinically healthy, 2DTTE negative

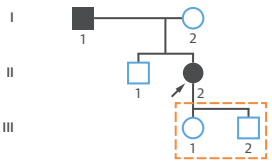
C De novo mutations support the pathogenicity of the mutation identified in the proband



I:1, 54 years and 1:2, 49 years: clinical and genetic screening negative
II:1, → 18 years;
- TAA aortic root (Z-score = 4,24) and mitral valve disease with moderate regurgitation: flat feet; myopia; short stature.
- Genetic testing: *de novo TGFB2* p.(Arg330Cys)

II:2, 16 years; clinical and genetic screening negative

D Novel variants of uncertain/unknown significance in HTAA/D definite genes



I:1 67 years; acute type A dissection at 48 years; three aortic surgeries: Bentall, arch and descending thoracic aorta; flat feet; astigmatism. Carrier of the variant identified in the proband (II:2)
I:2, 65 years; clinically healthy
II:1, 40 years; clinically and genetically healthy
II:2 → 36 years; TAA (Z-score 3.62), bicuspid aortic valve, flat feet, astigmatism, arched palate. Carrier of the *MYH11* variant c.748-5G>A
III:1, 7 years and III: 2, 4 years. Both are clinically healthy; genetic testing not performed because of the uncertain role of the maternal variant

(A) Complex genetics. The proband (III:1) was addressed to clinical attention for aortic root dilation, incidentally identified in the context of a multidisciplinary evaluation for severe joint laxity. Family screening demonstrated mild aortic root dilation in both father and son. Genetic testing in III:1 identified 2 novel variants/mutations: *TGFBR2* p.(His507Arg) and *COL5A1* p.(Gln1825GlufsTer5). The former was inherited from the father; the latter was de novo. The boy inherited the *TGFBR2* variant from the father, who showed aortic root dilation and arterial tortuosity of the neck and brain arteries. The *COL5A1* truncation predicting mutation was de novo in the proband and likely explains the severe joint laxity. **(B)** Validated pathological mutations in definite genes. Pedigree and summary data of a Nigerian family in which the proband (II:7) experienced acute post-isthmic thoracic aorta dissection (type B) at the seventh month of her second pregnancy. Clinical family screening could not be performed. The pedigree was generated on the narrative of the proband. 2DTTE performed in the 3 children was negative; the genetic test has not yet been performed. Although missing the study of segregation in the family, a pathogenic role is assigned to the mutation because *ACTA2* is a definite HTAA/D gene and the mutation (p.(Arg149Cys)) is confirmed as pathogenic. **(C)** De novo mutations in definite disease genes support their pathological role. The young proband (II:1) demonstrated both aortic and valve involvement and minor, nonspecific, noncardiovascular traits. The parents tested negative. The sister had a genetic test aimed at excluding germinal mosaic (requested by parents). **(D)** VUS and interpretation. The identification of a VUS in the proband, the small size of the family, and the uncertain role of the variant suggest caution before testing the children of the proband. Both are very young and their 2DTTE showed negative findings. 2DTTE = 2-dimensional transthoracic echocardiography; DM = diabetes mellitus; S/H Ratio = span/height ratio.

selection of patients to be addressed to testing of pre-specified genes is easy in syndromic but is difficult in nonsyndromic HTAA/D. In some probands, the association of HTAA/D with extravascular traits (e.g., *ACTA2*-HTAA/D and iris flocculi [9]; *MYH11*-HTAA/D and patent ductus arteriosus [10]) may suggest specific disease genes; however, these traits can be absent. The demonstration of familial aggregation, although increasing the probability of identifying the genetic cause, does not inform about the disease gene in the given family. The pattern of inheritance may further help; however, most nonsyndromic HTAA/Ds are autosomal dominant diseases (2). Therefore, the search for the genetic cause of nonsyndromic HTAA/D remains based on the screening of unselected known disease