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Editorial

Genetic Mutation Analysis Can Supplement Clinically Confirmed Hereditary Hemorrhagic Telangiectasia Populations

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Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu disease, is a rare vascular disease diagnosed using the Curaçao diagnostic criteria: (1) recurrent nosebleeds (epistaxis), (2) cutaneous or mucosal telangiectasia, (3) visceral arteriovenous malformations (AVMs), and (4) an appropriate family history [1]. The prevalence of HHT is approximately 1 in 5,000–8,000 worldwide [2]. The most common clinical symptom of HHT patients is epistaxis, affecting more than 90% of HHT patients; the average age of onset is 12 years [3]. Large AVMs in the lung, liver, and central nervous system can cause life-threatening complications [2]. Six genetic loci including four identified genes and two genetic loci are reported to be associated with HHT. Mutations in two genes encoding transforming growth factor beta (TGF-β) receptors, endoglin (ENG) and activin A receptor like type 1 (ACVRL1/ALK1), result in clinically indistinguishable HHT1 and HHT2, respectively [4]. More than 80% of HHT patients have heterozygous mutations in these genes [5].

Koenighofer et al. [6] identified three unpublished, five known, and one silent variant in *ENG* and *ACVRL1* from eight unrelated, nonconsanguineous families in Austria. Two novel variants and one known variant were identified in the *ENG* mutation. In the *ACVRL1* mutation, one unpublished and three known variants were identified. The gene mutation study revealed nonsense, frameshift, splice donor, and missense variants [6]. These patterns are similar to those reported in previous studies from other countries.

Several genetic studies have investigated the correlations between genetic mutations and clinical phenotypes outcomes in HHT patients. The overall mutation rate in 14 Chinese Han patients with HHT-associated pulmonary hypertension was 71.4%, including eight ACVRL-1 mutations and two ENG mutations, six of which were novel [7]. The case records of 21 HHT patients indicate that mutations in the *ENG*, *ACVRL1*, and *SMAD4* genes result in different HHT phenotypes. The prevalence of pulmonary AVM is higher in HHT type 1, whereas hepatic AVMs are more common in HHT2 [8]. Seventy-eight patients included 53 HHT1 patients and 25 HHT2 patients. Pulmonary and brain AVMs were predominantly observed in HHT1 whereas hepatic AVMs were detected in HHT2 [9]. Two ENG and one ACVRL1 mutations were identified in three Korean families: a known ENG mutation, a novel ENG mutation, and a novel ACVRL1 mutation [10]. In a national mutation study among Danish patients with HHT, 80% of the patients were diagnosed clinically based on the Curaçao criteria, and the remaining patients were diagnosed by genetic testing [11].

All these studies suggest that ethnicity and regionality play a limited role in the clinical presentation and genetic mutation of HHT. HHT patients are primarily diagnosed by clinical signs according to the Curaçao criteria; however, some patients are diagnosed as possible HHT with only clinical symptoms from the criteria. Genetic analysis is thus recommended to diagnose HHT in these patients. Additional pathogenic mutation studies will further supplement the diagnostic rates in HHT patients.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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