Relationship Between Mutations in *ENG* and *ALK1* Genes and the Affected Organs in Hereditary Hemorrhagic Telangiectasia

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Hereditary hemorrhagic telangiectasia (HHT) is a hereditary disorder that causes refractory nasal bleeding, arteriovenous malformations in the lung (pulmonary arteriovenous fistula: PAVF), central nervous system (CNS-AVF), and liver (hepatic AVF). HHT is caused by genetic abnormalities in endoglin (*ENG*), ACVRL1 (*ALK1*), and other rare genes (e.g., *SMAD4*). The relationship between these gene mutations and the affected organs remains unclear.

We performed genetic analysis from whole blood of 464 suspected HHT patients or HHT carriers from April 2005 to November 2015 in 35 hospitals and found 264

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patients positive for mutation in *ENG, ALK1*, and *SMAD4* genes. Of these 264 positive results, we excluded 68 patients who were sporadic, non-familial cases and performed proband gene analysis. We also excluded 107 non-symptomatic mutation carriers and leaving a total of 89 patients with AVFs.

To clarify the relationship between gene mutations and the affected organs, we assessed the mutations and clinical presentation of these 89 patients. We found 25 mutations in the *ENG* gene from 68 patients and 8 mutations in the *ALK1* gene from 21 patients. We then grouped patient AVF presentation (PAVF, CNS-AVF and hepatic AVF) according to the genetic mutation (Table 26.1).

Among patients with mutations in *ENG*, 19/25 (79%) mutations and 46/68 (69%) of patients presented with the same affected organ pattern. PAVFs were tending to

Table 26.1 Gene mutation and affected organs

Gene	Mutation	*N*	Type	PAVF	CNS-AVF	HAVF
ENG	Met368Thr	4	Missense	All(+)	ALL(−)	NA
ENG	Cly331Ser	6	Missense	All(+)	NA	NA
ENG	IVS3 ds G-C +1	3	Splicing	All(+)	ALL(−)	NA
ENG	Leu162Pro	2	Missense	All(+)	NA	NA
ENG	Skipping of ex.2	2	Splicing	All(+)	NA	NA
ENG	Ala229Profs	2	Frame shift	All(+)	ALL(−)	NA
ENG	Gln505Ter	2	Nonsense	All(+)	ALL(−)	NA
ENG	Leu107Cysfs	2	Frame shift	All(+)	NA	NA
ENG	Gln145Ter	3	Nonsense	All(+)	NA	NA
ENG	Leu194Pro198del5	2	Missense	All(+)	NA	NA
ENG	Glu276IlefsX57	2	Frame shift	All(+)	All(+)	NA
ENG	(Novel1)	2	Frame shift	All(+)	ALL(−)	NA
ENG	(Novel2)	2	Missense	All(+)	ALL(−)	NA
ENG	(Novel3)	2	Splicing	All(+)	NA	NA
ENG	Arg93Ter	2	Nonsense	All(+)	NA	NA
ENG	Arg339GlyfsX22	2	Frame shift	All(+)	ALL(−)	NA
ENG	Glu563Lysfs	2	Frame shift	All(+)	NA	NA
ENG	Leu506Pro	2	Missense	All(+)	NA	NA
ENG	IVS7−1G>A	2	Splicing	All(+)	ALL(−)	NA
ENG	IVS3+1G>A	2	Splicing	Hetero	Hetero	NA
ENG	IVS6 ds T-A +2	4	Splicing	All(+)	Hetero	NA
ENG	Ex.3-8 del	4	Exon del.	All(+)	Hetero	NA
ENG	Cys412Thr	3	Missense	Hetero	All(+)	NA
ENG	IVS8 ds G-A −1	7	Splicing	Hetero	Hetero	Hetero
ENG	(Novel4)	2	Splicing	Hetero	Hetero	NA
ALK1	Arg479Ter	5	Nonsense	All(+)	ALL(−)	All(+)
ALK1	IVS6ds insAA+4_5	3	Splicing	All(+)	NA	NA
ALK1	Pro424Leu	2	Missense	ALL(−)	NA	All(+)
ALK1	Arg200Gly	2	Missense	All(+)	ALL(−)	All(+)
ALK1	Gln118Ter	2	Nonsense	NA	ALL(−)	All(+)
ALK1	IVS5-3C>G	2	Splicing	All(+)	NA	NA
ALK1	Arg484Gln	3	Missense	NA	ALL(−)	Hetero
ALK1	Asp437Gly	2	Missense	ALL(−)	ALL(−)	Hetero

PAVF pulmonary arterio-venous fistula, *CNS-AVF* central nervous system arterio-venous fistula, *HAVF* hepatic arterio-venous fistula, *NA* not assessed
Novel1-Novel4 gene: novel gene mutations

be the same. Hepatic AVFs were rarely described in patient profiles so we were unable to evaluate hepatic AVF presentation patterns in mutated *ENG* patients.

In patients with mutations in *ALK1*, 8/10 (80%) mutations, 16/21 (76%) patients presented with the same affected organ pattern. For example, all five patients with the Arg479X mutation presented with the same affected organ pattern.

Previous reports have suggested that patients with mutations in *ENG* frequently have PAVFs. In contrast, patients with mutations in *ALK1* frequently have hepatic AVFs and gastrointestinal telangiectasias but rarely have CNS-AVFs [1–3]. However, previous reports have not discussed similarity and combination of AVF patterns for each mutation.

In our analysis, approximately 70–80% of HHT patients with a previously detected genetic mutation presented with the same AVF pattern. Our result emphasizes the importance of genetic testing in HHT even if the patient had already been diagnosed according to other clinical findings.

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