Genotype-phenotype correlations in a series of patients with von Hippel-Lindau disease in one single tertiary centre

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Background

- von Hippel-Lindau (VHL) disease is an autosomal dominant inherited tumour syndrome with an important phenotypic variability.
- Genetic testing for VHL is simple and accurate.

Objectives

- In this study we investigated the relationships between genotype and phenotype in a series of patients with different VHL gene mutations.

Methods

- This was a retrospective analysis of the clinical and molecular characteristics of 15 VHL patients followed between 1965 and 2014 at the Cliniques Universitaires Saint-Luc.
- Patients were divided into two groups in order to investigate possible differences in tumour risk and age of onset : Group 1 included 6 patients with missense mutations, while Group 2 included 9 patients with nonsense mutations (n=7), gene deletion (n=1) or gene insertion (n=1).

Results

Table 1. Clinical characteristics of all subjects:

	Number of subjects	Values
Age of onset of symptoms (years)	15	20.6 ± 9.1 (11-37)
• Men	7	17,7 ± 7,9 (12-33)
• Women	8	23,1± 9,9 (11-37)
Sex ratio (M/F)	7/8	0,9
Family history +	9/15	60%

Table 2. Molecular characteristics of all subjects:

Patients	Exon	DNA change	Protein change/Codon	Mutation type
1	3	c.481C>G	p.Arg161Gly	Missense
2	2	c.394C>T	p.Gln132X	Nonsense
3	1	c.256C>T	p.Pro86Ser	Missense
4	1	c.336C>G	p.Tyr112X	Nonsense
5	1	c.233A>G	p.Asp78Ser	Missense
6	2	c.343C>T	p.His115Tyr	Missense
7	2	c.343C>T	p.His115Tyr	Missense
8	3	c.599C>T	Arg- Leu	Missense
9	3	c.583C>T	p.Q195X	Nonsense
10	3	c.583C>T	p.Q195X	Nonsense
11	3	c.583C>T	p.Q195X	Nonsense
12	3	c.583C>T	p.Q195X	Nonsense
13	3	c.583C>T	p.Q195X	Nonsense
14	2	/	/	Deletion
15	3	c.738insA	p.A525X	Insertion

Table 3. Initial manifestation of VHL in our series of patients:

CNS haemangioblastoma	27,0%
Retinal haemangioblastoma	27,0%
Phaeochromocytoma	20,0%
Multiple pancreatic cysts	13,3%
Renal cancer	6,6%
Endolymphatic sac tumour	6,6 %

Table 4. Frequency of the different VHL gene mutations in our series of patients:

	Mutation type	Frequency (%)
Group 1 (n=6)	Missense	40,0
Group 2 (n=9)	Nonsense Deletion Insertion	46,7 6,7 6,7

Table 5. Age of onset and tumour risk in our series of patients:

VHL manifestation	Group 1 (n=6)		Group 2 (n=9)	
	Average age of onset (years)	Frequency (%)	Average age of onset (years)	Frequency (%)
Cerebellar haemangiomas	30,2 ± 13,3	5/6 (83,3%)	27,9 ± 9,4	9/9 (100%)
Spinal cord haemangiomas	26,8 ± 6,8	5/6(83,3%)	33,0 ± 9,3	8/9 (88,9%)
Retinal haemangiomas	28,7 ± 6,4	3/6 (50%)	26,6 ± 12,4	7/9 (77,8%)
Renal cancer	39,0 ± 14,0	3/6(50%)	39,0 ± 13,6	4/9(44,4%)
Pheomochromocytoma	26,5 ± 7,0	*4/6 (66,7%)*	27,8 ± 11,0	*2/9 (44,4%)*
Multiple pancreatic cysts	35,0 ± 17,1	3/6 (50%)	29,8 ± 13,3	5/9(55,5%)
Pancreatic neuroendocrine T.	37,3 ± 14,0	3/6 (50%)	31,0 ± 8,5	2/9(44,4%)
Endolymphatic sac tumour	/	*0/6*	25,7 ± 13,5	*3/9(33,3%)*

Conclusions

- In our study there was no significant difference in the phenotype of patients with missense vs. nonsense gene alterations.
- Patients from group 1 tended to have more frequently a pheochromocytoma (4/6, 66,7%) than patients from group 2 (4/9, 44,4%).
- Patients from group 2 tended to have more frequently a endolymphatic sac tumour (3/9, 33,3%) than patients from group 1 (0/6).

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