Genotype-Phenotype Correlation in Hemophilia A and Risk of inhibitors of F8 gene mutations

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Objective

Inhibitor development is one of the most serious complications of hemophilia A (HA). It has been suggested that some types of mutations of F8 gene predispose to inhibitor development.
We aimed to investigate the genotype-phenotype correlation in HA and risk of inhibitor development according to the mutation type of *F8* gene.
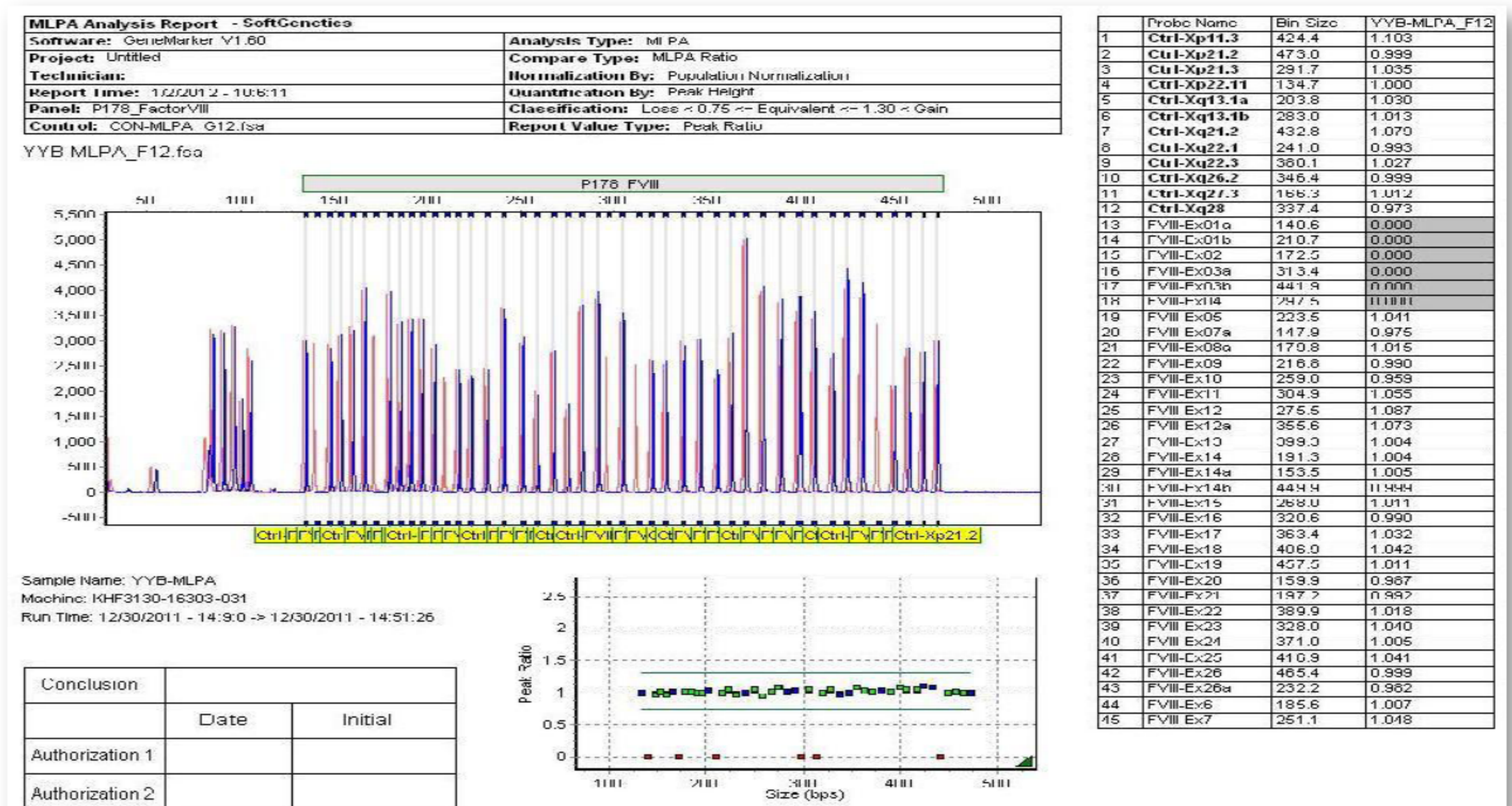
Methods

We analyzed data from mutation data base (Kohemgene) of 251 unrelated Korean HA patients having identified mutation. Mutations were detected as follows. Genomic DNA was extracted from peripheral blood leukocytes. Firstly, we conducted inv(22) test by by long-distance PCR. To identify the causative mutations other than Inv(22), we performed DNA sequencing of F8 by 3130 DNA Analyzer (Applied Biosystems). If no mutation was detected, inv(1) and. gene dosage test using the multiplex ligation-dependent probe amplification Have done sequentially.
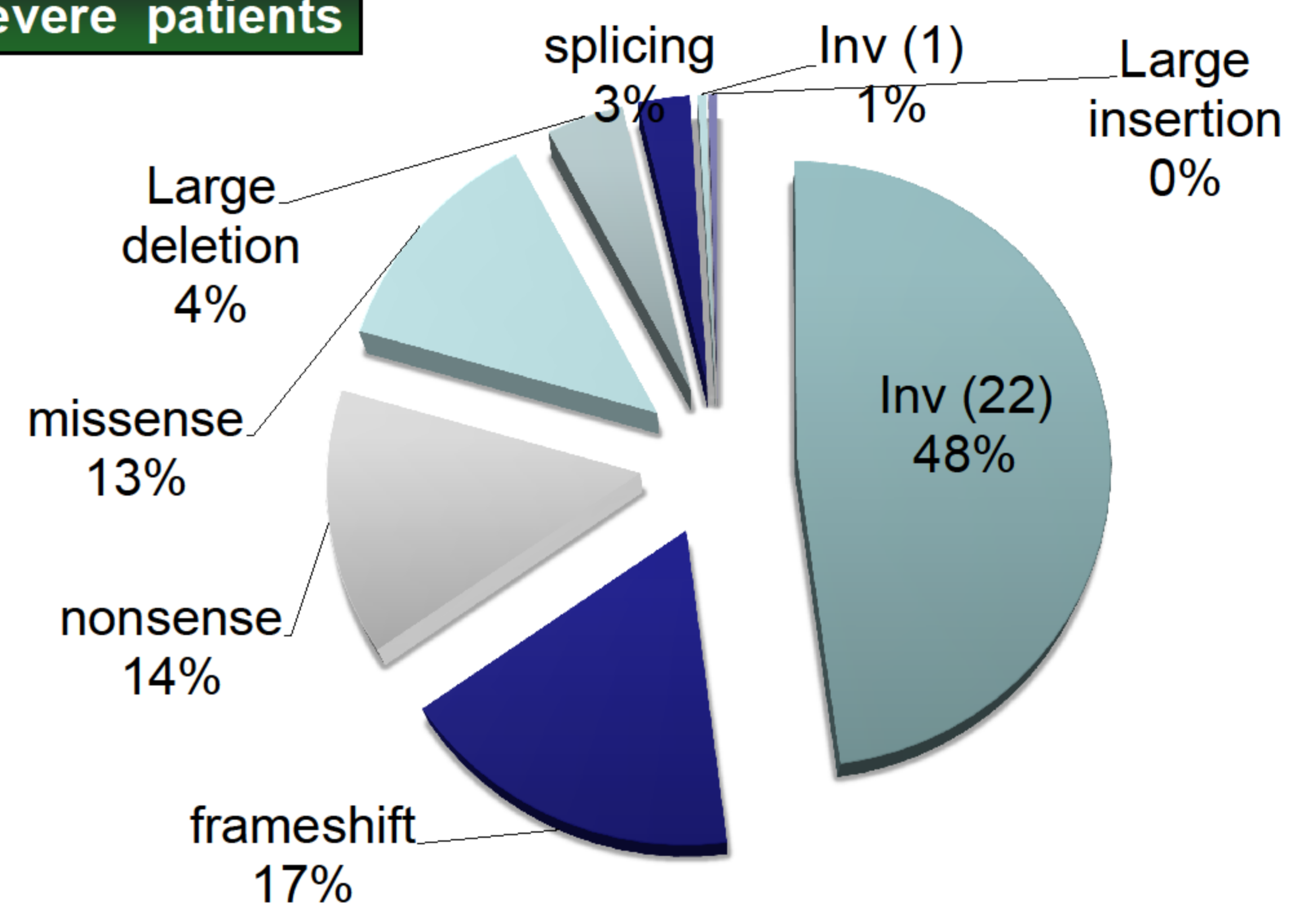
Results

	Total	Serve	Moderate	mild	Inhibitor(%)
Inv(22)	105	105			16 (15)
Inv(1)	1	1			1
Point mutation					
Nonsense	32	31	1		6 (18)
Missense	38	38			11 (28)
Frameshift	58	28	19	11	3 (5)
Splicing	7	6	1		
Large deletion	9	9			
Large insertion	1	1			7 (77)
Total	251	219	21	11	45(17)

All most of all mutations showed severe phenotype except missense mutation. 47.9% (105/219) of severe HA patients had Inv(22) and 15% in Inv(22) have developed inhibitors. Although Inv(22) is the most common mutation in inhibitors of HA, large deletion, frameshift and nonsense were also high risky mutation in inhibitor developments (35.5%<16/45>).
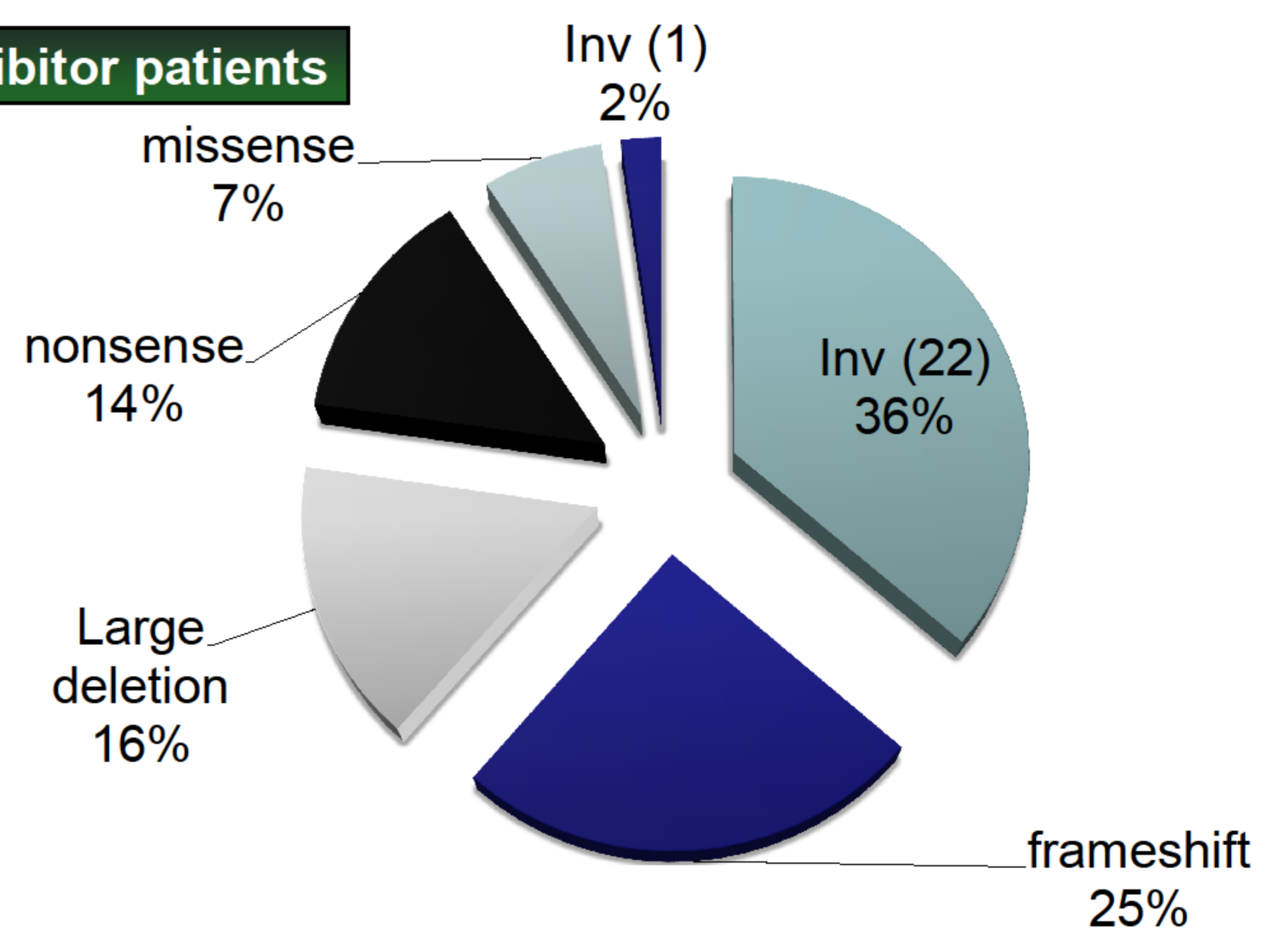
Large deletion patient (analyzed by MLPA)

Severe patients

splicing 3%
Inv (1) 1%
Large insertion 0%
Large deletion 4%
missense 13%
nonsense 14%
frameshift 17%
Inv (22) 48%

Inhibitor patients

Inv (1) 2%
missense 7%
nonsense 14%
Large deletion 16%
Inv (22) 36%
frameshift 25%

Conclusions

Genotype were closely correlated with clinical severity.
Although Inv(22) was wellknown risk factor in inhibitors, it seems to be essential to evaluate the risk of inhibitor development in the HA patients with null mutations such as large deletion, frameshift and nonsense mutations.

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