A literature review and database of how the primary KIT/PDGFRA variant of a gastrointestinal stromal tumour predicts for sensitivity to imatinib

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Table 1

KIT exon 8 variant	*In vitro* / *in silico* sensitivity#	*In vivo* sensitivity %	(CR or PR) + SD / all patients
Deletion p.(Asp419del)	Sensitive [30]	100	1 + 0 / 1 [31]
Deletion/insertion p.(Thr417_Asp419delinsTyr)	ND†	100	1 + 0 / 1 [7]

† ND, no data identified

labelled as (IS) if *in silico* data. Otherwise, all data are *in vitro*-based.

Table 2

KIT exon 9 variant	*In vitro* / *in silico* sensitivity#	*In vivo* sensitivity %	(CR or PR) + SD / all patients
Substitution			
p.(Lys509Ile)*	ND†	100	0 + 1 / 1 [32]
Insertion or duplication			
p.(Ser501_Ala502dup)	Sensitive [20]	100	0 + 1§/ 1 [20]
p.(Ala502_Tyr503dup)	Sensitive [10, 33] Resistant [20, 27]¶	90	7 + 11 / 20 [34-39]

labelled as (IS) if *in silico* data. Otherwise, all data are *in vitro*-based.

† ND, no data identified

* germline variant

¶ Reference 20 described resistance unless higher drug concentrations were used [20].

§ “metastatic foci had been controlled for 40 months” [20]

Table 3

KIT exon 11 variant	*In vitro* / *in silico* sensitivity#	*In vivo* sensitivity %	(CR or PR) + SD / all patients
Substitution			
p.(Pro551Ala)	ND†	100	1 + 0 / 1 [40]
p.(Trp557Arg)	ND	100	1 + 0 / 1 [41]
p.(Trp557Arg)*	ND	100	1 + 0 / 1 [42]
p.(Trp557Gly)	Sensitive (IS) [43]	100	1 + 0 / 1 [44]
p.(Trp557Gly) + p.(Tyr578Cys)‡	Sensitive (IS) [43]	100	1 + 0 / 1 [43]
p.(Lys558Asn)	ND	100	2 + 0 / 2 [34, 45]
p.(Val559Ala)*	ND	100	2 + 0 / 2 [46]
p.(Val559Asp)	Sensitive [47]	100	5 + 1 / 6 [35, 44, 48-50]
p.(Val559Gly)	ND	100	1 + 0 / 1 [34]
p.(Val559Ile)	Resistant [47]	ND	ND
p.(Val560Asp)	Sensitive [27]	100	2 + 0 / 2 [44]
p.(Val560Gly)	Sensitive [10, 11, 51]	100	1 + 0 / 1 [44]
p.(Gly565Arg)	ND	100	0 + 1 / 1 [34]
p.(Leu576Pro)	“Less sensitive” (IS) [52]	100	4 + 1 / 5 [34, 35, 44, 52]
p.(Tyr578Cys)	Sensitive (IS) [43]	ND	ND
Deletion			
p.(Lys550_ Lys558del)	ND	100	3 + 0 / 3 [44, 53]
p.(Lys550_Glu554del)	ND	100	1 + 0 / 1 [48]
p.(Pro551_Tyr553del)	ND	100	1 + 0 / 1 [48]
p.(Pro551_Glu554del)	ND	100	2 + 0 / 2 [44]
p.(Pro551_Val559del)	ND	100	1 + 0 / 1 [48, 54]
p.(Met552_Trp557del)	ND	100	1 + 0 / 1 [44]
p.(Tyr553_ Lys558del)	ND	100	1 + 0 / 1 [44, 55]
p.(Tyr553_ Val559del)	ND	100	1 + 0 / 1 [56]
p.(Glu554_ Lys558del)	ND	100	3 + 0 / 3 [44, 48]
p.(Glu554_Val559del)	ND	100	1 + 0 / 1 [57]
p.(Glu554_ Ile571del)	ND	100	1 + 0 / 1 [44]
p.(Val555_Val559del)	ND	100	2 + 0 / 2 [35, 48]
p.(Gln556_ Pro573del)	ND	100	1 + 0 / 1 [58]
p.(Gln556_Thr574del)	ND	100	1 + 0 / 1 [49]
p.(Trp557_Lys558del)	Sensitive [10, 51]	100	18 + 1 / 19 [34, 35, 37, 44, 45, 48, 58-62]
p.(Trp557_Glu561del)	ND	100	3 + 0 / 3 [41, 44, 58]
p.(Trp557_Tyr570del)	ND	100	1 + 0 / 1 [48]
p.(Lys558_Val559del)	ND	100	1 + 0 / 1 [35]
p.(Lys558_Glu561del)	ND	100	1 + 0 / 1 [34]
p.(Lys558_Glu562del)	ND	100	2 + 1 / 3 [35, 40, 63]
p.(Lys558_Ile563del)	ND	100	0 + 1 / 1 [34]
p.(Lys558_Gly565del)	ND	100	1 + 0 / 1 [64]
p.(Val559del)	ND	100	1 + 0 / 1 [41]
p.(Val559_Val560del)	Sensitive [12]	100	1 + 0 / 1 [44]
p.(Val559_Glu561del)	ND	100	1 + 0 / 1 [41]
p.(Val559_Gly565del)	ND	100	1 + 0 / 1 [48, 65]
p.(Val559_Ile571del)	ND	100	1 + 0 / 1 [66]
p.(Val560del)	ND	100	3 + 0 / 3 [35, 48]
p.(Val560del)*	ND	100	1 + 0 / 1 [67]
p.(Val560_Leu576del)	ND	100	1 + 0 / 1 [34, 68]
p.(Val560_Tyr578del)	Sensitive [69, 70]	ND	ND
p.(Ile563_Leu576del)	ND	100	2 + 0 / 2 [35, 48]
p.(Asn564_Leu576del)	ND	100	1 + 0 / 1 [41]

p.(Asn564_Tyr578del)	ND	100	1 + 0 / 1 [35]
p.(Val569_Thr574del)	ND	100	1 + 0 / 1 [61]
p.(Val569_Leu576del)	ND	100	6 + 1 / 7 [34, 35, 45, 48]
p.(Pro577_Tyr578del)	ND	0	0 + 0 / 1¶ [35]
p.(Asp579del)	Sensitive [10]	100	1 + 0 / 1 [71]
p.(Asp579del)*	ND	100	1 + 0 / 1 [72]
Insertion or duplication			
p.(Pro573_Thr574dup)	ND	100	0 + 1 / 1 [34]
p.(Pro573_Asp579dup)	ND	100	1 + 0 / 1 [73]
p.(Pro573_Asn587dup)	ND	100	0 + 1 / 1 [48]
p.(Thr574_Asp579dup)	ND	100	1 + 0 / 1 [35]
p.(Asp579_His580insLeuTyr)	ND	100	1 + 0 / 1 [74]
p.(Phe591_Gly592ins(15))	ND	100	1 + 0 / 1 [75]
Deletion/insertion			
p.(Lys550_Trp557delinsPheLeu)	ND	100	0 + 1 / 1 [44]
p.(Lys550_ Lys558delinsGln)	ND	100	1 + 0 / 1 [34]
p.(Pro551_Met552delinsLeu)	ND	100	1 + 0 / 1 [41]
p.(Pro551_ Glu554delinsHisMetTyr)	ND	100	2 + 0 / 2 [35, 48]
p.(Met552_Val559delinsIle)	ND	100	1 + 0 / 1 [76]
p.(Gln556_Val559delinsHis)	ND	100	1 + 0 / 1 [48]
p.(Trp557_Lys558delinsCysPro)	ND	100	1 + 0 / 1 [77]
p.(Trp557_Lys558delinsGlu)	ND	100	1 + 0 / 1 [78]
p.(Trp557_Val559delinsPhe)	ND	100	1 + 0 / 1 [79, 80]
p.(Trp557_Val560delinsCys)	ND	100	1 + 0 / 1 [44]
p.(Trp557_Val560delinsPhe)	ND	100	1 + 0 / 1 [44]
p.(Lys558delinsAsnGln)	ND	100	2 + 0 / 2 [35, 48]
p.(Lys558delinsAsnPro)	Sensitive [81]	100	2 + 0 / 2 [35, 44]
p.(Lys558_Val559delinsAsn)	ND	100	1 + 0 / 1 [44]
p.(Lys558_Val559delinsSer)	ND	100	1 + 0 / 1 [41]
p.(Lys558_Val560delinsIle)	ND	100	1 + 0 / 1 [41]
p.(Gly565_Asp579delinsVal)	ND	100	1 + 0 / 1 [34]
p.(Gln575_Pro577delinsHis)*	ND	100	1 + 1 / 2 [82]

labelled as (IS) if *in silico* data. Otherwise, all data are *in vitro*-based.

* germline variant

† ND, no data identified

‡ Double primary mutation

¶ Reported as “primary resistance” [35].

Table 4

KIT exon 13 variant	*In vitro* / *in silico* sensitivity#	*In vivo* sensitivity %	(CR or PR) + SD / all patients
Substitution			
p.(Lys642Glu)	Sensitive [10, 12, 81, 83]	100	8 + 1 / 9 [8, 35, 44, 48]§
p.(Lys642Glu)*	ND†	100	2 + 0 / 2 [84, 85]¶
p.(Asn655Lys)*	"lower sensitivity" [86] ‡	0	0 + 0 / 1 [86]‡

labelled as (IS) if *in silico* data. Otherwise, all data are *in vitro*-based.

† ND, no data identified

* germline variant

§ Reference 8 described six exon 13 variants [five as p.(Lys642Glu) and one as p.(Glu635Lys)] and reported four cases to show PR and two cases to show SD. However, because the published results did not match the genotypes to the responses, it can only be assumed that at least three cases of p.(Lys642Glu) showed PR and at least one case to show SD [8].

¶ The patient of the reference 84 case report showed PR of gastric disease and SD of oesophageal disease [84].

‡ Reference 86 reported this exon 13 variant to be less sensitive *in vitro* than p.(Trp557_Lys558del) and the patient's multifocal abdominal disease to "progress slowly" despite imatinib therapy [86].

Table 5

KIT exon 17 variant	*In vitro* / *in silico* sensitivity#	*In vivo* sensitivity %	(CR or PR) + SD / all patients
Substitution			
p.(Asp816Val)	Resistant [10, 11]	ND†	ND
p.(Asp820Tyr)	Resistant [12]	ND	ND
p.(Asn822His)	Sensitive [10]	ND	ND
p.(Asn822Lys)	Sensitive [10]	0	0 + 0 / 2 [44, 87]

labelled as (IS) if *in silico* data. Otherwise, all data are *in vitro*-based.

† ND, no data identified

Table 6

PDGFRA exon 5 variant	*In vitro* / *in silico* sensitivity#	*In vivo* sensitivity %	(CR or PR) + SD / all patients
Substitution			
p.(Leu221Phe)	ND†	100	1 + 0 / 1 [4]

labelled as (IS) if *in silico* data. Otherwise, all data are *in vitro*-based.

† ND, no data identified

Table 7

PDGFRA exon 12 variant	*In vitro* / *in silico* sensitivity#	*In vivo* sensitivity %	(CR or PR) + SD / all patients
Substitution			
p.(Val561Asp)	Sensitive [10, 27, 88-90] / Sensitive (IS) [91]	100	2 + 0 / 2 [44, 91]
p.(Pro581Ser)	ND	100	1 + 0 / 1 [4]
Deletion			
p.(Trp559_Arg560del)	ND	100	1 + 0 / 1 [92]
Insertion or duplication			
p.(Val561_Ile562insGluArg)	Sensitive [88]	ND	ND

labelled as (IS) if *in silico* data. Otherwise, all data are *in vitro*-based.

† ND, no data identified

Table 8

PDGFRA exon 14 variant	*In vitro* / *in silico* sensitivity#	*In vivo* sensitivity %	(CR or PR) + SD / all patients
Substitution p.(Asn659Lys)	Sensitive [88]	ND†	ND

labelled as (IS) if *in silico* data. Otherwise, all data are *in vitro*-based.

† ND, no data identified

Table 9

PDGFRA exon 18 variant	*In vitro* / *in silico* sensitivity#	*In vivo* sensitivity %	(CR or PR) + SD / all patients
Substitution			
p.(Asp842Val)	Resistant [10, 27, 51, 88-90, 93]	33	2 + 18 / 60 [4, 8, 10, 35, 44, 71, 94, 95]
p.(Asp842Tyr)	Sensitive [88]	100	1 + 0 / 1 [95]
p.(Asp846Tyr)	Sensitive [88]	100	0 + 1 / 1 [4]
p.(Asp846Val)	ND	0	0 + 0 / 2 [4, 8]
p.(Asn848Lys)	Sensitive [88]	ND†	ND
p.(Tyr849Cys)	Sensitive [88]	ND	ND
p.(Tyr849His)	ND	100	1 + 0 / 1 [95]
Deletion			
p.(Asp842del)	ND	67	2 + 0 / 3 [4, 94]
p.(Asp842_Met844del)	Sensitive [93]	100	2 + 2 / 4 [4, 96, 97]§
p.(Asp842_His845del)	Sensitive [10] / Sensitive (IS) [91]	100	3 + 2 / 5 [4, 91, 95]
p.(Asp842_Asn848del)	ND	100	1 + 0 / 1 [95]
p.(Ile843del)	Sensitive [10]	100	1 + 0 / 1 [94]
p.(Ile843_His845del)	ND	100	1 + 0 / 1 [4]
p.(Ile843_Asp846del)	ND	86	4 + 2 / 7 [4, 94, 95, 98]
p.(Ile843_Ser847del)	ND	100	1 + 0 / 1 [4]
Deletion/insertion			
p.(Arg841_Asp842delinsLysIle)	Resistant [88]	ND	ND
p.(Asp842_Ile843delinsIleMet)	Resistant [88]	ND	ND
p.(Asp842_Asp846delinsGlu)	ND	0	0 + 0 / 1 [99]
p.(Asp842_Asp846delinsGly)	ND	100	0 + 1 / 1 [95]
p.(Asp842_Ser847delinsValLeu)	ND	100	0 + 2 / 2 [4]
p.(Ile843_Ser847delinsThr)	ND	100	0 + 2 / 2 [4, 95]
p.(His845_Asn848delinsPro)	Sensitive [88] / Sensitive (IS) [100]	100	1 + 0 / 1 [100]

labelled as (IS) if *in silico* data. Otherwise, all data are *in vitro*-based.

† ND, no data identified

§ In Reference 97, genotyping was performed on blood derived, cell-free DNA [97].