

Table S1. Summary of the genetic profile of each subsequent sample.

a) Cases with diagnostic sample (a total of 2 or 3 samples)

Patient ID	Data type	1st sample	2nd sample	3rd sample
1	-	diagnosis	PD1b	PD1
	<u>SNV</u>	<u><i>CREBBP, PABPC1</i></u>	<u><i>CREBBP, PABPC1</i></u>	<u><i>CREBBP</i></u>
	CNV	+5, gain 1q, gain 6p, gain 15q, loss 13q, loss 22q	+19, gain 1q, gain 6p, gain 15q, loss 1p22.1, loss 2q (partial), loss 6q (partial) , loss 13q, loss 20q, loss 22q	+5, +19, gain 1q, gain 6p, gain 15q, loss 1p22.1, loss 2q (partial), loss 6q (partial) , loss 13q, loss 22q
	FISH	No detectable 14q32 translocations	No detectable 14q32 translocations	No detectable 14q32 translocations
2	-	diagnosis	PD1	-
	<u>SNV</u>	<u><i>RET, KRAS, CDKN2C</i></u>	<u><i>RET, KRAS</i></u>	-
	CNV	gain 1q21, +3, +5, +7, +9 (partial), gain 15q, gain 19p, +21 (partial), loss 1p, loss 16q (partial) , loss 18q, loss 22q	gain 1q, gain 1p (partial), +3, +5, gain 6p22.1, +7, +9 (partial), gain 11q24 , gain 15q, gain 19p, +21 (partial), loss 1p12, loss 18q, loss 22q	-
	FISH	No detectable 14q32 translocations	No detectable 14q32 translocations	-
3	-	diagnosis	PD1	-
	<u>SNV</u>	<u><i>BRAF, FANCA, LRP1B</i></u>	<u><i>BRAF, FANCA</i></u>	-
	CNV	gain 1q, +3, gain 5q (partial) , +6 (partial), gain 15q, +19, +21 (partial), loss 6q (partial) , -8, -20, loss 22q	gain 1q, gain 1p (partial) , +3, +6 (partial), gain 15q, +19, +21 (partial), -8, -20	-
	FISH	No detectable 14q32 translocations	No detectable 14q32 translocations	-
4	-	diagnosis	PD1	-
	<u>SNV</u>	<u><i>KRAS, MLH1, APC, PABPC1</i></u>	<u><i>KRAS, MLH1, APC</i></u>	-
	CNV	+5, +11, gain 15q, loss 1p (partial), loss 6q, loss 18q	gain 1q, +5, gain 6p22.1, +11, gain 15q, gain 20q (partial) , loss 1p (partial), -6 (partial) , loss 18q	-
	FISH	No detectable 14q32 translocations	No detectable 14q32 translocations	-
5	-	diagnosis	PD1	-
	<u>SNV</u>	<u><i>DNAH5, KRAS, JAK3, SAMHD1, PABPC1</i></u>	<u><i>DNAH5, KRAS, JAK3, SAMHD1, KMT2C</i></u>	-
	CNV	gain 1q, gain 6p22.1, gain 8q (partial), loss 16q (partial)	+1, gain 6p22.1, gain 8q (partial), gain 20q (partial), loss 13q (partial), loss 20p (partial)	-
	FISH	Translocation 14q32 other than t(4;14) and t(14;16)	Translocation 14q32 other than t(4;14) and t(14;16)	-
6	-	diagnosis	PD1	-
	<u>SNV</u>	<u><i>RYR2, ARID4B, NCOR2</i></u>	<u><i>RYR2, ARID4B, PABPC1, KRAS, LRP1B</i></u>	-
	CNV	+3, +5, gain 6p22.1, +9, +11, gain 15q, +19, loss 1p (partial), loss 16q (partial) , -18	+3, +5, gain 6p22.1, +9, +11, gain 15q, +19, loss 1p (partial)	-
	FISH	No detectable 14q32 translocations	No detectable 14q32 translocations, TP53 deletion	-
7	-	diagnosis	PD1b	PD1
	<u>SNV</u>	<u><i>PABPC1 (c.1223A>T) , KRAS , ARID2, IDH2, BRCA2, KMT2B</i></u>	<u><i>PABPC1 (c.1223A>T) , KRAS , ARID2, BRCA2, KMT2B, PABPC1 (c.1246A>T) , PABPC1 (c.1255C>T) , ZFHX3</i></u>	<u><i>PABPC1 (c.1223A>T) , KRAS, ARID2, BRCA2, KMT2B, PABPC1 (c.1246A>T) , PABPC1 (c.1255C>T) , ZFHX3, FAT4</i></u>
	CNV	+3, +6, +7, +9, +11, gain 15q, +18, +19, +21 (partial)	+3, +6, +7, +9, +11, gain 15q, +18, +19, +21 (partial)	+3, +6, +7, +9, +11, gain 15q, +18, +19, +21 (partial), loss 14q, loss 16q
	FISH	No detectable 14q32 translocations	No detectable 14q32 translocations	No detectable 14q32 translocations
8	-	diagnosis	PD1	-
	<u>SNV</u>	<u><i>NOTCH2, EP300, CDKN1B, TBX3, PABPC1</i></u>	<u><i>NOTCH2, EP300, CDKN1B, TBX3</i></u>	-
	CNV	gain 1q (partial), +7, gain 8q, gain 9q (partial) , gain 19p, loss 6q, loss 8p, -12, loss 13q, -16 , loss 17p (partial), loss 19q (partial), loss 22q	+1, +7, gain 6p22.1, gain 8q, gain 9p, gain 19p, gain 21q, loss 2q, loss 3q26, -4, -6 (partial) , loss 8p, -10 , -12, loss 13q, loss 16q, loss 17p (partial), loss 19q (partial), loss 22q	-
	FISH	Translocation 14q32 other than t(4;14) and t(14;16), TP53 deletion	No data available	-
10	-	diagnosis	PD1	-

	<u>SNV</u>	<u>FAT4</u> , KRAS , ARID1A , RYR2 , ATR , KMT2D , EDC4 , <u>MAP3K14</u> , <u>LRP1B</u> (c.3058C>A) , <u>MAN2C1</u> , <u>ZFHX3</u> (c.10523G>C) , HUWE1 , <u>LRP1B</u> (c.3075T>G) , NCOR2 , ZFHX3 (c.10520G>C) , EP300	<u>FAT4</u> , <u>ATM</u> , KRAS, ARID1A , RYR2 , ATR , KMT2D , EDC4 , <u>MAP3K14</u>	-
	CNV	gain 1q, gain 6p22.1, gain 15q	gain 1q, +3 , +5 , gain 6p22.1, +9 , gain 15q, +19 , -4 , loss 14q	-
	FISH	No detectable 14q32 translocations	No detectable 14q32 translocations	-
12	-	diagnosis	PD1	-
	<u>SNV</u>	<u>RYR2</u> , CYLD	<u>RYR2</u> , CYLD , <u>ZFHX3</u>	-
	CNV	+2 , +3 , gain 6p, +8 , +9 (partial) , +11 , gain 15q, +18 , +19 , -4 , loss 6q, -10 , loss 13q, loss 16q	gain 6p, gain 15q, +7 , +18 , +19 , -4 , loss 6q, -10 , -12 , loss 1p, loss 1q (partial), loss 13q, loss 14q, loss 16q, -17 (partial) , -20 , loss 21q	-
	FISH	No detectable 14q32 translocations	No detectable 14q32 translocations	-
13	-	diagnosis	PD1	-
	<u>SNV</u>	KRAS, MPL , GNAS , <u>PABPC1</u>	KRAS , MPL , GNAS , <u>SOX9</u>	-
	CNV	+3 , +5 , gain 6p (partial), +9 , +11 , gain 15q, gain 19q (partial) , loss 1p, -17	+3 , +9 , +11 , gain 15q, loss 1p, loss 17p (partial)	-
	FISH	No detectable 14q32 translocations	No detectable 14q32 translocations, TP53 deletion	-
14	-	diagnosis	PD1	-
	<u>SNV</u>	<u>BCL7A</u> , <u>SP140</u> , <u>TP53</u> (c.818G>A), FUBP1 , NTRK2	<u>BCL7A</u> , <u>SP140</u> , <u>ATR</u> , <u>KDM5A</u> , <u>TP53</u> (c.711G>A), <u>ZNF292</u>	-
	CNV	gain 6p22.1, loss 17p (partial), loss 14q, loss 22q	gain 6p22.1, loss 17p (partial), loss 17q (partial) loss 1p (partial), loss 13q, loss 22q	-
	FISH	No detectable 14q32 translocations, TP53 deletion	No detectable 14q32 translocations, TP53 deletion	-
17		diagnosis	PD3	-
	<u>SNV</u>	ALK , KLHL6 , <u>DNAH5</u>	ALK , KLHL6 , <u>DNAH5</u>	-
	CNV	gain 6p, gain 8q (partial), loss 6q, -8 (partial) , loss 16q	gain 6p, gain 8q (partial), loss 6q, -8 (partial) , loss 16q	-
	FISH	t(11;14)	t(11;14)	-
18	-	diagnosis	PD2	-
	<u>SNV</u>	KRAS	KRAS , <u>PABPC1</u> (c.1240C>T) , <u>PABPC1</u> (c.1223A>T)	-
	CNV	gain 6 p (partial)	-	-
	FISH	Translocation 14q32 other than t(4;14) and t(14;16)	Translocation 14q32 other than t(4;14) and t(14;16)	-
19	-	diagnosis	PD3	-
	<u>SNV</u>	<u>CSMD3</u> , <u>EGR1</u>	<u>CSMD3</u> , <u>EGR1</u> , <u>KRAS</u>	-
	CNV	gain 1q , +3 , +5 , +7 , +9 , gain 15q, +18 , +19 , loss 1p (partial), loss 13q	gain 1q, +3 , +7 , gain 6p , gain 6q (partial) gain 15q, +18 , +19 , loss 10p, loss 13q	-
	FISH	No detectable 14q32 translocations	No detectable 14q32 translocations	-
20		diagnosis	PD3	-
	<u>SNV</u>	EGR1 , LRRK2 , <u>KRAS</u> , DIS3	EGR1, LRRK2, <u>CD79A</u> , PBRM1	-
	CNV	+11 , loss 14q (partial)	loss 14q (partial), loss 1 p (partial), loss 2q (partial), loss 6q, loss 10q (partial), loss 12q (partial), loss 13q, -17 , gain 6p, gain 11q, gain 15q	-
	FISH	Translocation 14q32 other than t(4;14) and t(14;16)	Translocation 14q32 other than t(4;14) and t(14;16), <u>TP53</u> deletion	-
21		diagnosis	PD3	-
	<u>SNV</u>	ARID1A (c.2397G>T) , ARID1A (c.2390G>C) , KRAS , <u>MAP3K14</u> , RYR2, TET2 , ABCF1 , ZFHX3 (c.8780G>C) , ZFHX3 (c.2556C>G) , DICER1 , <u>PABPC1</u>	ARID1A (c.2397G>T), ARID1A (c.2390G>C), KRAS , <u>MAP3K14</u> , RYR2 , TET2 , ABCF1 , ZFHX3 (c.8780G>C) , ZFHX3 (c.2556C>G) , DICER1 , <u>ALK</u> , EIF4G2 , NFKB2 , NOTCH3 , KMT2B , KDMSC , ARID1A (c.4208T>G) , DNMT3A , FAT4, PRDM9 , KMT2D , TP53 (c.814G>A) , TP53 (c.550G>C) , RYR1 , RUNX1 , HUWE1 , SOX9 , STAT6 , UBR5	-
	CNV	gain 1q, gain 2p , +3 , gain 4p , +5 , +6 , +7 , +9 , +11 , gain 15q , +19 , +21 (partial) , loss 1p, loss 2q, loss 4q, -8 , -10 , -12 , loss 13q, loss 14q, -16 , -17 , -18 , -20 , loss 22q	gain 1q, +5 , loss 1p, loss 4q, -8 , -10 , -12 , loss 13q, loss 14q, loss 16q (partial), -17 , -18 , -20	-
	FISH	Translocation 14q32 other than t(4;14) and t(14;16)	Translocation 14q32 other than t(4;14) and t(14;16)	-

b) Cases with diagnostic sample (a total of 4 samples)

Patient ID	Data type	1st sample	2nd sample	3rd sample	4th sample
16	-	<u>diagnosis</u>	PD1	PD2	PD3
	SN V	<u>BRCA2</u> , DIS3 , RYR2 , ATRX, DNAH11 , SPEN , FAT4, SOX9 , ZFHX3 , RUNX1 , LRP1B , EDC4	<u>BRCA2</u> , DIS3 , RYR2 , ATRX DNAH11	<u>BRCA2</u> , DIS3 , RYR2 , ATRX , DNAH11 , LRP1B , EDC4 , CYLD (c.2065C>T)	<u>BRCA2</u> , DIS3 , RYR2 , ATRX , LRP1B , EDC4 , CYLD (c.2065C>T) , CYLD (c.2465A>G) , FAT4, SOX9 , ZFHX3 , SPEN
	CN V	gain 6p22.1, +9, gain 16p, gain 17q, loss 16q, loss 17p (partial)	gain 6p22.1, +7, +9, gain 17q, loss 16q, loss 17p (partial), loss 6q (partial), loss 18q,	gain 6p22.1, +7, +9, gain 17q, loss 16q, loss 17p (partial), loss 6q (partial)	+7, +9, gain 17q, loss 16q, loss 17p (partial), loss 6q (partial)
	FISH	t(11;14) plus TP53 deletion	t(11;14) plus TP53 deletion	t(11;14) plus TP53 deletion	No data available
22	-	<u>diagnosis</u>	PD2	PD3	PD4
	SN V	PABPC1 , BRCA2	PABPC1 , BRCA2 , BRAF , XBP1	PABPC1 , BRCA2 , BRAF , XBP1	PABPC1 , BRCA2 , BRAF , XBP1
	CN V	gain 1q, +3, loss 1p, gain 6p22.1, loss 7p (partial), loss 13q, -18	gain 1q, +3, gain 6p22.1, gain 9q, loss 1p, loss 7p (partial), loss 13q	gain 1q, +3, gain 6p22.1, loss 1p, loss 7p (partial), loss 13q,	gain 1q, +3, gain 6p22.1, loss 1p, loss 7p (partial), loss 13q, loss 14q, -18
	FISH	t(4;14)	No data available	t(4;14)	No data available

c) Cases with only relapsed samples

Patient ID	Data type	1st sample	2nd sample	3rd sample
23	-	PD3	PD4	PD5
	SN V	<u>KRAS</u> , PABPC1 , HIST1H1E	<u>KRAS</u> , PABPC1 , HIST1H1E , SF3B1	<u>KRAS</u> , PABPC1 , HIST1H1E , SF3B1
	CN V	+1, loss 13q, loss 22q (partial)	+1, loss 3p26, loss 13q, loss 22q (partial)	+1, gain 6p22.1, gain 19q14, loss 13q, loss 22q (partial)

	FIS H	Translocation 14q32 other than t(4;14) and t(14;16)	Translocation 14q32 other than t(4;14) and t(14;16)	Translocation 14q32 other than t(4;14) and t(14;16)
24	-	PD1	PD2	
	SN V	HIST1H1C, DNAH11 , <u>EGFR</u> , DUSP2 (c.662G>C), CCND1 (c.28G>A), CCND1 (c.131A>C), ATM , DUSP2 (c.720A>G), CYLD, <u>ZFHX3 (c.10523G>C)</u> ,	HIST1H1C , DNAH11 , <u>EGFR</u> , DUSP2 (c.662G>C) , <u>CCND1 (c.28G>A)</u> , CCND1 (c.131A>C) , ATM , DUSP2 (c.720A>G) , CYLD , <u>PAK2</u>	-
	CN V	gain 1q, gain 3q (partial), <u>gain 6p (partial)</u> , +7, gain 8q, +18, loss 16q, loss 8p	gain 1q, gain 3q (partial), +7, +18, loss 16q	-
	FIS H	Translocation 14q32 other than t(4;14) and t(14;16)	No data available	
25	-	PD1	PD2	
	SN V	<u>FANCA</u> , <u>ATM</u>	<u>FANCA</u> , <u>ATM</u> , <u>PABPC1</u>	-
	CN V	gain 1q (partial), <u>gain 6p (partial)</u> , gain 9p, <u>gain 16p</u> , gain 17q, loss 1p (partial), loss 2q, loss 4q (partial), loss 5q, loss 11q (partial), -12, loss 13q, loss 16q (partial), loss 20p, loss 22q	gain 1q (partial), <u>gain 5p</u> , gain 9p, gain 17q, loss 1p (partial), loss 2q, loss 4q (partial), loss 5q, loss 11q (partial), -12, loss 13q, loss 16q (partial), <u>loss 17p (partial)</u> , loss 20p, loss 22q	-
	FIS H	t(4;14)	t(4;14) + delTP53	
26	-	PD2	PD3	
	SN V	<u>RET</u> , KRAS , BRIP1, TET2 , TP53 , <u>HIST1H1C</u> , ETV6	<u>RET</u> , KRAS, BRIP1 , TET2 , TP53 , <u>HIST1H1C</u> , ETV6	-
	CN V	+1, +6, +9, gain 15q, +19, loss 13q, loss 14q, loss 17p (partial), <u>loss 18q</u>	gain 1q (partial) +6, +9, gain 15q, <u>gain 18p</u> , +19, loss 13q, loss 14q, loss 17p partial,	-
	FIS H	No detectable 14q32 translocations, TP53 deletion	No detectable 14q32 translocations, TP53 deletion	
27	-	PD4	PD5	
	SN V	KMT2C, ERN1	KMT2C, ERN1, <u>TP53</u>	-
	CN V	gain 1q, <u>gain 6p22.1</u> , loss 13q, gain 15q, gain 17q (partial), loss 17q (partial), <u>loss 18q</u> , +19	gain 1q (partial), gain 15q, gain 17q (partial), loss 13q, <u>loss 17p</u> , loss 17q (partial), +19	-
	FIS H	t(4;14), TP53 deletion	t(4;14), TP53 deletion	
28	-	PD1	PD2	
	SN V	<u>RET</u> , <u>BRCA2</u> , FGFR3	<u>RET</u> , <u>BRCA2</u> , FGFR3	-
	CN V	gain 1q	gain 1q, <u>gain 15q</u> , <u>gain 17q (partial)</u> , loss 3p (partial), loss 8p (partial), loss 13q, loss 16q (partial), loss 18q	-
	FIS H	t(4;14)	t(4;14)	
29	-	PD5	PD6	
	SN V	SETD2 , TET2 , KMT2C (c.6368C>G), KMT2C (c.5013G>T) , KMT2B , SPEN , ID3, ATR , <u>FAT4</u> , <u>SYNE1</u> , <u>POT1</u> , <u>BRAF</u> , EDC4 , HMCN1 , ATM (c.6745G>T) , HUWE1 , DNAH11 , DICER1 , SOX9 , <u>ZFHX3 (c.8440G>A)</u> , ZFHX3 (c.2556C>G) , <u>RBX1</u> , <u>USP9X</u> , HMCN1 , PIK3CA (c.42C>G) , ZNF292 , <u>Ryr2</u> , ABCF1 , ATM (c.6739A>C) , PIK3CA (c.40C>A) , PIK3CA (c.44T>G) , NCOR2	SETD2 , TET2 , KMT2C (c.6368C>G), KMT2C (c.5013G>T), KMT2B , SPEN , ID3, ATR , <u>FAT4</u> , <u>SYNE1</u> , <u>POT1</u> , <u>BRAF</u> , KMT2C, EDC4 , HMCN1 , ATM (c.6745G>T) , HUWE1 , DNAH11 , DICER1 , SOX9 , <u>ZFHX3 (c.8440G>A)</u> , ZFHX3 (c.2556C>G) , <u>RBX1</u> , <u>USP9X</u> , HMCN1 , PIK3CA (c.42C>G) , ZNF292 , <u>TP53</u>	-
	CN V	gain 1q, gain 6p22.1, loss 1p (partial), loss 13q, loss 17p (partial)	gain 1q, loss 1p (partial), gain 6p22.1, loss 13q, loss 17p, <u>+18</u>	
	FIS H	Translocation 14q32 not specified, TP53 deletion	Translocation 14q32 not specified, TP53 deletion	
30	-	PD5	PD6	PD7

	SN V	LRP1B , <u>HOXA10-HOXA9</u> , <u>NCOR2</u> , <u>FGFR3</u> , <u>PTPRT</u> , EDC4 , PTPRT, ZFHX3 (c.8780G>C) , ZFHX3 (c.2556C>G) , BRAF , PABPC1	LRP1B , <u>HOXA10-HOXA9</u> , <u>NCOR2</u> , <u>FGFR3</u> , <u>PTPRT</u> , EDC4 , PTPRT, ZFHX3 (c.8780G>C) , ZFHX3 (c.2556C>G) , <u>BRAF</u> , <u>PABPC1</u> , SPEN , LRRK2	LRP1B , <u>HOXA10-HOXA9</u> , <u>NCOR2</u> , <u>FGFR3</u> , <u>PTPRT</u> , EDC4 , PTPRT, ZFHX3 (c.8780G>C) , ZFHX3 (c.2556C>G) , SPEN , LRRK2 , ARID1A (c.3091A>C) , ARID1A (c.3094G>C) , KMT2D (c.9370G>A) , KMT2D (c.5875G>A) , DICER1 , SETD2 , LRRK2 , ARID1A (c.3098A>T) , HACE1 (c.49C>A) , HACE1 (c.40T>G) , HACE1 (c.28C>G) , KMT2A
	CN V	gain 1q, +3, gain 4q, +5, gain 6p, +7, gain 9p, gain 15q, gain 17q (partial), +19, +21 (partial), loss 4p, loss 13q, loss 14q, -18	gain 1q, +3 , gain 4q, +5 , gain 6p, +7 , gain 9p, gain 15q, gain 17q (partial) , +19 , +21 (partial) , loss 4p, loss 13q, loss 14q, -18	gain 1q, gain 6p (partial), gain 16p
	FISH	t(4;14)	No data available	t(4;14)
31		PD4	PD5	PD6
		LRP1B , IRF4 , SYNE1 , FAT4 , CDKN2A , LRRK2 , CYLD ,	LRP1B , IRF4 , SYNE1 , FAT4 , CDKN2A , LRRK2 , CYLD, <u>DNAH11</u>	LRP1B , IRF4 , SYNE1 , FAT4 , CDKN2A , LRRK2 , CYLD , <u>DNAH11</u>
		gain 1q, gain 2p (partial), gain 6p, gain 6q (partial) , gain 8q, loss 6q (partial), loss 14q, loss 18q	gain 2p (partial), gain 6p, gain 8q, gain 15q , loss 6q (partial), loss 8p , loss 13q , loss 14q	gain 1q, gain 6p, gain 6q (partial) , gain 8q, gain 9q , loss 6q (partial), loss 13q , loss 14q
		No detectable 14q32 translocations	No detectable 14q32 translocations	No data available
32		PD7	PD8	-
		PRDM9 , PABPC1 , ARID2 , <u>RYR1</u> , CSMD3	PRDM9 , PABPC1 , ARID2 , <u>RYR1</u> , CSMD3	-
		gain 1q 21 , +6, +7, gain 15q, +19, loss 13q	+3 , +5 , +6, +7, +11 , gain 15q, +19, loss 13q, loss 22q	-
		No detectable 14q32 translocations	No detectable 14q32 translocations	-
33		PD1	PD3	-
		KRAS , ZFHX3 , TCF3 , SHANK2 , LRP1B (c.3075T>G) , MAST4 , <u>DNAH5</u>	KRAS , ZFHX3 , TCF3 , SHANK2 , LRP1B (c.3075T>G) , MAST4 , <u>DNAH5</u> , ATR , RYR2 , EDC4 , LRP1B (c.3058C>A) , SOX9 , ARID1A , NCOR2	-
		+5 (partial), gain 6p22.1, gain 9q, +11, gain 15q, +19, gain 21q, loss 1p , loss 13q	gain 1q21 , gain 2p (partial), +5, gain 6p22.1, +9 , +11, gain 15q, +19, +21 (partial) , loss 2p (partial), loss 17q (partial)	-
		No detectable 14q32 translocations	No detectable 14q32 translocations	-

Description: In orange, blue and white are SNVs/CNVs acquired, lost and unchanged over time, respectively.

SNVs present in at least two samples with variant allele frequency of at least 40% are underlined. Abbreviations:

b, biochemical progression; CNV, copy number variants; FISH; fluorescence in-situ hybridization; PDn, nth disease progression; SNV, single nucleotide variants.