Mutational status of *IGHV* is the most reliable prognostic marker in trisomy 12 chronic lymphocytic leukemia

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Supplementary information:

Table S1. CLL cases contributed by each center

Center	n[$]
Amedeo Avogadro University of Eastern Piedmont, Novara, Italy	391
S. Eugenio Hospital and University of Tor Vergata, Rome, Italy	338
Ferrarotto Hospital, Catania, Italy	130
Mayo Clinic, Rochester, MN, U.S.A.	110
Maggiore General Hospital, University of Trieste, Trieste, Italy	58
Azienda Ospedaliera Universitaria S. Maria Misericordia, Udine, Italy	22
Others	27

$ trisomy 12 and control series combined

Table S2. Percentage of nuclei bearing trisomy 12 and del13q in mosaic cases*.

Tris12 prevalent[$]			Equal[§]			Del13 prevalent[#]		
case id	tris12 %	del13 %	case id	tris12 %	del13 %	case id	tris12 %	del13 %
386	54	15	663	52	54	823	8	50
498	49	35	907	28	38	975	13	50
505	54	10	1008	42	48	1058	65	80
858	59	7	1020	7	6	1514	11	50
976	71	15	1206	66	65	1578	71	87
1124	50	29	1219	49	40	1742	7	62
1544	53	11	1222	50	45	1899	14	79
1620	38	16	1230	67	69	2528	60	79
1796	40	8	1253	66	60	2774	77	88
1920	40	11	1260	55	47	2862	64	90
2007	68	20	1323	60	55	1213.m	15	90
2155	62	45	1348	81	88	1442.m	45	58
2741	51	7	1392	56	66	1469.m	21	67
2787	55	15	1795	13	14	1839.m	35	47
1234.m	72	15	1831	42	45	1882.m	72	84
1281.m	50	30	1855	21	29	2069.m	63	90
1461.m	40	25	2010	63	55			
1467.m	47	14	2674	38	40			
1716.m	52	8	2855	72	80			
1775.m	62	22	1238.m	71	64			
2146.m	59	46	1272.m	67	75			
2229.m	68	29	1312.m	69	70			
			1341.m	59	66			
			1347.m	80	75			
			1433.m	34	29			
			2148.m	53	60			
			2170.m	65	69			
			2257.m	62	70			

*Evaluation of the percentage of nuclei bearing trisomy 12 and del13q was evaluable in 66/85 mosaic cases. The random distribution of cases in which tris12 was quantitatively prevalent (22/66 cases) or del13q was prevalent (16/66 cases) or the two lesions were balanced (28/66 cases) is in keeping with the independent occurrence of these lesions (p=0.42, binomial test). Moreover, the observed frequency of mosaic cases in tris12 series was 26%, in the range of the expected frequency, estimated as the product of the frequency of individual abnormality (about 20%-30% of trisomy 12 cases and about 3-4% of all CLL, ref. #1).

$ (tris12 nuclei percentage - del13 nuclei percentage) > +10%
§ (tris12 nuclei percentage - del13 nuclei percentage) ≥ -10% and ≤ +10%
# (tris12 nuclei percentage - del13 nuclei percentage) < -10%

Table S3. Clinical and biological features of the trisomy 12 and control series

	Trisomy 12 (n=322)	Control (n=529)	p
age median, years [range]	66 [30-92]	66 [33-92]	0.91
gender, male %	57	56	0.93
follow up median, years	3.5	7.3	<0.0001
deaths % (n)	17 (54)	14 (76)	0.81
treated % (n)	67 (216)	35 (184)	<0.0001
Rai stage %			0.06
• 0	52	54	
• I-II	41	42	
• III-IV	7	4	
CD49d pos %	85	30	<0.0001
CD38 pos %	61	18	<0.0001
ZAP-70 pos %	58	41	0.16
IGHV unmutated %	53	23	<0.0001
NOTCH1 mutated %	27	8	<0.0001
BIRC3 mutated %	22	1	<0.0001
SF3B1 mutated %	7	7	0.99

Table S4: Mutation features of the *NOTCH1*, *BIRC3* and *SF3B1* genes in the CLL cohort.

Id	*NOTCH1* MUTATION	*NOTCH1* %	*BIRC3* MUTATION	*BIRC3* %	*SF3B1* MUTATION	*SF3B1* %
375	c.7305_7312dup,p.P2438Lfs*42	38.3	wt	0.0	wt	0.0
395	c.7541_7542delCT,p.P2514Rfs*4	44.2	wt	0.0	c.1997A>C,p.K666T	46.6
442	c.7541_7542delCT,p.P2514Rfs*4	21.7	c.1232G>T,p.R411I	4.3	c.1280C>A,p.P427Q	6.3
481	c.7541_7542delCT,p.P2514Rfs*4	3.5	wt	0.0	wt	0.0
505	c.7541_7542delCT,p.P2514Rfs*4	12.8	wt	0.0	c.1877A>T,p.N626I	7.2
769	c.7541_7542delCT,p.P2514Rfs*4	54.5	c.1656_1659del,p.E553Kfs*14	6.8	wt	0.0
806	c.7541_7542delCT,p.P2514Rfs*4	34.0	wt	0.0	wt	0.0
844	c.7541_7542delCT,p.P2514Rfs*4	2.5	wt	0.0	wt	0.0
889	c.7541_7542delCT,p.P2514Rfs*4	38.6	c.1189_1190delCA p.Q397fs*14	29.0	wt	0.0
931	c.7281_7293del,p.H2428Afs*3	3.3	wt	0.0	wt	0.0
968	wt	0.0	c.1284_1288del,p.E429Gfs*7	21.9	wt	0.0
975	c.7541_7542delCT,p.P2514Rfs*4	1.0[$]	wt	0.0	wt	0.0
976	c.7541_7542delCT,p.P2514Rfs*4	31.1	wt	0.0	c.2339 C>G p.P780R	Sanger
1001	wt	0.0	c.1639del,p.Q547Nfs*21	6.6	wt	0.0
1054	wt	0.0	c.1644dup,p.R549Afs*10	4.5	wt	0.0
1061	wt	0.0	c.1286_1287dup,p.E430Kfs*18	12.6	wt	0.0
1075	c.7541_7542delCT,p.P2514Rfs*4	35.8	c.1644dup,p.R549Afs*10	7.2	wt	0.0
1170	c.7541_7542delCT,p.P2514Rfs*4	37.9	c.1639del,p.Q547Nfs*21	3.5	wt	0.0
1206	c.*7668+371A>G	49.9	c.1285_1286insTA p.E429fs*19	Sanger	wt	0.0
1230	wt	0.0	c.1639delC p.Q547fs*21	Sanger	wt	0.0
1253	wt	0.0	c.1639delC p.Q547fs*21	5.0	wt	0.0
1260	wt	0.0	c.1641delA p.Q547fs*21	Sanger	wt	0.0
1273	c.7541_7542delCT,p.P2514Rfs*4	1.8	wt	0.0	wt	0.0
1317	c.7541_7542delCT,p.P2514Rfs*4	30.5	wt	0.0	wt	0.0
1323	wt	0.0	c.1639del,p.Q547Nfs*21	7.8	wt	0.0
1335	c.7541_7542delCT,p.P2514Rfs*4	32.4	c.1298_1299delAA p.E433fs*4	Sanger	wt	0.0
1368	c.7541_7542delCT,p.P2514Rfs*4	63.0	wt	0.0	wt	0.0

Id	*NOTCH1* MUTATION	*NOTCH1* %	*BIRC3* MUTATION	*BIRC3* %	*SF3B1* MUTATION	*SF3B1* %
1449	c.7318C>T,p.Q2440*	39.2	wt	0.0	wt	0.0
1460	wt	0.0	c.1639del,p.Q547Nfs*21	2.0	wt	0.0
1475	c.7541_7542delCT,p.P2514Rfs*4	1.5	wt	0.0	wt	0.0
1486	c.7541_7542delCT,p.P2514Rfs*4	48.5	wt	0.0	wt	0.0
1490	c.7330C>T,p.Q2444*	30.1	c.1284_1288del,p.E429Gfs*7	15.9	wt	0.0
1507	c.7541_7542delCT,p.P2514Rfs*4	41.7	wt	0.0	wt	0.0
1510	wt	0.0	c.1202G>A,p.R401K	50.7	wt	0.0
1514	c.7541_7542delCT,p.P2514Rfs*4	17.2	wt	0.0	wt	0.0
1542	c.7344delC,p.S2449Afs*28	19.1	c.1639del,p.Q547Nfs*21	2.7	wt	0.0
1544	wt	0.0	c.1639del,p.Q547Nfs*21	1.9	wt	0.0
1569	wt	0.0	c.1664_1665del,p.R555Nfs*3	13.9	wt	0.0
1571	c.7541_7542delCT,p.P2514Rfs*4	32.8	wt	0.0	wt	0.0
1578	wt	0.0	c.1599_1610del,p.Y533*	2.1	wt	0.0
1590	c.7318C>T,p.Q2440*	7.5	wt	0.0	wt	0.0
1631	c.7541_7542delCT,p.P2514Rfs*4	28.6	c.1446dup,p.K483*	13.1	wt	0.0
1670	c.7501C>T,p.Q2501*	3.2	c.1668dup,p.C557Mfs*2	4.0	wt	0.0
1718	c.7541_7542delCT,p.P2514Rfs*4	41.8	wt	0.0	wt	0.0
1723	wt	0.0	wt	0.0	c.1998G>T,p.K666N	1.4
1730	c.*7668+371A>G	45.2	wt	0.0	wt	0.0
1753	wt	0.0	wt	0.0	c.1996A>G,p.K666E	4.7
1754	c.7300delC,p.L2434*	4.6	wt	0.0	wt	0.0
1779	wt	0.0	c.1639del,p.Q547Nfs*21	1.9	wt	0.0
1831	wt	0.0	c.1335A>T,p.L445F	5.5	wt	0.0
1852	c.7180C>T,p.Q2394*	30.0	wt	0.0	wt	0.0
1861	c.*7668+371A>G	45.9	wt	0.0	wt	0.0
1913	c.7541_7542delCT,p.P2514Rfs*4	25.8	wt	0.0	wt	0.0
1988	c.7541_7542delCT,p.P2514Rfs*4	1.2	wt	0.0	wt	0.0
1992	wt	0.0	c.574G>A,p.A192T	49.0	wt	0.0
2010	wt	0.0	c.1643_1644dup,p.R549Cfs*20	3.1	wt	0.0

Id	*NOTCH1* MUTATION	*NOTCH1* %	*BIRC3* MUTATION	*BIRC3* %	*SF3B1* MUTATION	*SF3B1* %
2155	wt	0.0	c.1639del,p.Q547Nfs*21	5.7	wt	0.0
2630	wt	0.0	wt	0.0	c.1997A>G,p.K666R	6.9
2679	wt	0.0	c.1639del,p.Q547Nfs*21	2.3	wt	0.0
2692	wt	0.0	c.1285_1289del, pE429Gfs*7	3.0	wt	0.0
2698	wt	0.0	c.1680T>A,p.C560*	11.2	c.2292_2294del,p.Y765del	26.3
2840	wt	0.0	c.850G>C,p.V284L	43.3	wt	0.0
2862	wt	0.0	c.1280_1281insC,p.R428Kfs*10	6.6	wt	0.0
10267g	c.*7668+371A>G	22.2	wt	0.0	wt	0.0
1028.m	wt	0.0	c.1656_1659del,p.E553Kfs*14	8.5	wt	0.0
1129.m	c.7330C>T,p.Q2444*	19.0	c.1285dup,p.E429Gfs*9	14.3	wt	0.0
1167.m	wt	0.0	c.1639del,p.Q547Nfs*21	3.8	wt	0.0
11719g	c.7541_7542delCT,p.P2514Rfs*4	8.5	wt	0.0	wt	0.0
11772g	c.7541_7542delCT,p.P2514Rfs*4	1.7	wt	0.0	c.1996A>G,p.K666E	8.4
11799g	c.7541_7542delCT,p.P2514Rfs*4	13.0	wt	0.0	wt	0.0
1183.m	wt	0.0	c.1667del,p.Y556Nfs*12	4.4	wt	0.0
1187.m	wt	0.0	c.1639del,p.Q547Nfs*21	7.0	wt	0.0
1189.m	c.7541_7542delCT,p.P2514Rfs*4	12.3	wt	0.0	c.1986C>A,p.H662Q	9.4
12041g	wt	0.0	wt	0.0	c.2095C>G,p.Q699E	46.5
1206.m	c.7216C>T,p.Q2406*	29.5	wt	0.0	wt	0.0
1213.m	c.7378G>T,p.E2460*	28.5	wt	0.0	wt	0.0
1229.m	wt	0.0	wt	0.0	c.2225G>A,p.G742D	19.6
1233.m	wt	0.0	c.1639del,p.Q547Nfs*21	54.1	wt	0.0
1234.m	c.7541_7542delCT,p.P2514Rfs*4	8.9	wt	0.0	c.2111T>G,p.I704S	1.5
1235.m	c.*7668+371A>G	1.9	wt	0.0	wt	0.0
1238.m	wt	0.0	c.1639del,p.Q547Nfs*21	11.9	wt	0.0
1272.m	wt	0.0	c.1639del,p.Q547Nfs*21	10.2	wt	0.0
1281.m	wt	0.0	c.1318_1319del,p.E440Ifs*3	6.1	wt	0.0
1299.m	wt	0.0	c.272C>T,p.P91L	15.9	wt	0.0
1302.m	wt	0.0	c.1639del,p.Q547Nfs*21	5.0	wt	0.0

Id	*NOTCH1* MUTATION	*NOTCH1* %	*BIRC3* MUTATION	*BIRC3* %	*SF3B1* MUTATION	*SF3B1* %
1312.m	wt	0.0	c.1639del,p.Q547Nfs*21	11.4	wt	0.0
1317.m	wt	0.0	c.1641_1668del,p.Q547Hfs*12	18.4	wt	0.0
1322.m	c.7541_7542delCT,p.P2514Rfs*4	27.4	wt	0.0	wt	0.0
1329.m	c.7541_7542delCT,p.P2514Rfs*4	4.5	c.1291_1309del,p.E431Rfs*10	3.4	wt	0.0
1333.m	wt	0.0	c.1282A>G,p.R428G	5.7	wt	0.0
1335.m	c.7541_7542delCT,p.P2514Rfs*4	20.0	wt	0.0	c.1606C>A,p.L536I	8.2
1341.m	wt	0.0	wt	0.0	c.2219G>A,p.G740E	28.4
1346.m	c.7541_7542delCT,p.P2514Rfs*4	30.2	wt	0.0	wt	0.0
1347.m	wt	0.0	c.1639del,p.Q547Nfs*21	6.6	wt	0.0
13692g	NA	Sanger		0.0		0.0
1387.m	c.7507C>T,p.Q2503*	9.9	wt	0.0	wt	0.0
1392.m	c.7541_7542delCT,p.P2514Rfs*4	50.3	wt	0.0	wt	0.0
1407.m	c.7541_7542delCT,p.P2514Rfs*4	37.3	wt	0.0	wt	0.0
14260g	NA	Sanger		0.0		0.0
14281g	wt	0.0	c.1284_1288del,p.E429Gfs*7	19.1	wt	0.0
1442.m	c.7541_7542delCT,p.P2514Rfs*4	1.3	wt	0.0	wt	0.0
1461.m	wt	0.0	c.1639del,p.Q547Nfs*21	1.7	wt	0.0
1469.m	c.*7668+371A>G	11.0	wt	0.0	wt	0.0
14821g	c.7459C>T,p.Q2487*	1.6	wt	0.0	wt	0.0
1533.m	wt	0.0	wt	0.0	c.2339C>T,p.P780L	2.1
1584.m	wt	0.0	c.1321_1324del,p.S441Mfs*5	5.2	wt	0.0
1595.m	c.7541_7542delCT,p.P2514Rfs*4	11.4	wt	0.0	c.2083_2091del,p.V695_E697del	10.0
1600.m	c.7541_7542delCT,p.P2514Rfs*4	35.1	wt	0.0	wt	0.0
1620.m	c.7386del,p.A2463Pfs*14	47.1	wt	0.0	wt	0.0
1625.m	c.7541_7542delCT,p.P2514Rfs*4	2.9	wt	0.0	wt	0.0
1641.m	wt	0.0	c.1639del,p.Q547Nfs*21	7.2	wt	0.0
1686.m	c.*7668+371A>G	42.3	wt	0.0	wt	0.0
1716.m	c.7541_7542delCT,p.P2514Rfs*4	5.0	wt	0.0	wt	0.0
1775.m	c.6784G>T,p.G2261C	47.9	c.1639del,p.Q547Nfs*21	3.3	wt	0.0

Id	*NOTCH1* MUTATION	*NOTCH1* %	*BIRC3* MUTATION	*BIRC3* %	*SF3B1* MUTATION	*SF3B1* %
1820.m	wt	0.0	c.1299_1300del,p.R434Sfs*3	3.6	wt	0.0
1828.m	c.7541_7542delCT,p.P2514Rfs*4	27.4	wt	0.0	c.2225G>A,p.G742D	47.4
1843.m	c.7541_7542delCT,p.P2514Rfs*4	1.7	wt	0.0	wt	0.0
1859.m	wt	0.0	c.1639del,p.Q547Nfs*21	8.4	wt	0.0
1882.m	wt	0.0	c.1639del,p.Q547Nfs*21	15.2	wt	0.0
1887.m	c.7541_7542delCT,p.P2514Rfs*4	42.7	wt	0.0	wt	0.0
1948.m	wt	0.0	c.1639del,p.Q547Nfs*21	18.8	wt	0.0
2065.m	c.7541_7542delCT,p.P2514Rfs*4	20.8	wt	0.0	wt	0.0
2069.m	wt	0.0	c.1639del,p.Q547Nfs*21	12.5	wt	0.0
2148.m	wt	0.0	c.1639del,p.Q547Nfs*21	3.4	wt	0.0
2170.m	wt	0.0	c.1639del,p.Q547Nfs*21	3.3	wt	0.0
2175.m	wt	0.0	c.1639del,p.Q547Nfs*21	2.6	wt	0.0
2194.m	c.7541_7542delCT,p.P2514Rfs*4	46.4	c.1331del,p.L444Yfs*3	38.0	wt	0.0
2229.m	wt	0.0	c.1639del,p.Q547Nfs*21	2.8	wt	0.0
2240.m	c.7541_7542delCT,p.P2514Rfs*4	1.7	wt	0.0	wt	0.0
2257.m	wt	0.0	c.1639del,p.Q547Nfs*21	1.8	wt	0.0
3121g	c.6509G>A,p.S2170N	48.0	wt	0.0	wt	0.0
3392g	NA	Sanger		0.0		0.0
3703g	wt	0.0	c.1295dup,p.E433Rfs*5	2.8	wt	0.0
3706g	c.7541_7542delCT,p.P2514Rfs*4	29.3	wt	0.0	c.2231C>A,p.A744D	2.9
3714g	wt	0.0	c.1638dup,p.Q547Yfs*12	24.8	wt	0.0
3717g	c.7541_7542delCT,p.P2514Rfs*4	1.3	wt	0.0	wt	0.0
3878g	c.7390del,p.L2464Cfs*13	44.0	c.1279dup,p.I427Nfs*11	9.3	wt	0.0
4190g	wt	0.0	wt	0.0	c.1603A>T,p.I535F	14.2
4261g	c.7541_7542delCT,p.P2514Rfs*4	56.5	wt	0.0	wt	0.0
4341g	NA	Sanger		0.0		0.0
4718g	c.*7668+371A>G	45.7	wt	0.0	wt	0.0
4938g	c.7448C>T,p.T2483M	2.1	wt	0.0	c.2111T>A,p.I704N	38.4
5076g	c.7541_7542delCT,p.P2514Rfs*4	7.9	wt	0.0	wt	0.0

Id	*NOTCH1* MUTATION	*NOTCH1* %	*BIRC3* MUTATION	*BIRC3* %	*SF3B1* MUTATION	*SF3B1* %
5825g	c.7541_7542delCT,p.P2514Rfs*4	10.8	c.1802C>A,p.T601K	10.6	wt	0.0
5842g	c.7541_7542delCT,p.P2514Rfs*4	2.5	wt	0.0	wt	0.0
5984g	c.7541_7542delCT,p.P2514Rfs*4	40.7	wt	0.0	wt	0.0
6624g	NA	Sanger		0.0		0.0
7398g	c.7017_7020del,p.S2341Cfs*6	21.9	wt	0.0	wt	0.0

$ mutations ≤ 2% have been reported only if confirmed in public datasets (cancer.sanger.ac.uk/cosmic)

Table S5. Cox regression analysis using optimal cut-point for CD49d, CD38 and ZAP-70

	Trisomy 12 series			
	UV		MV[§]	
	HR	**p**	**HR**	**p**
OS				
*CD49d pos	7.3	0.05	-	-
*CD38 pos	1.62	0.44	-	-
*ZAP-70 pos	1.48	0.22	-	-
IGHV unmutated	2.13	0.0112	2.13	0.0112
NOTCH1 mutated	1.54	0.17	-	-
SF3B1 mutated	2.18	0.07	ns	ns
BIRC3 mutated	1.46	0.23	-	-
TTFT				
*CD49d pos	2.59	0.0004	2.20	0.0008
*CD38 pos	2.18	0.0039	-	-
*ZAP-70 pos	1.65	0.0077	-	-
IGHV unmutated	1.67	0.0003	1.58	0.0014
NOTCH1 mutated	1.53	0.0046	ns	ns
SF3B1 mutated	1.56	0.09	ns	ns
BIRC3 mutated	1.10	0.55	-	-

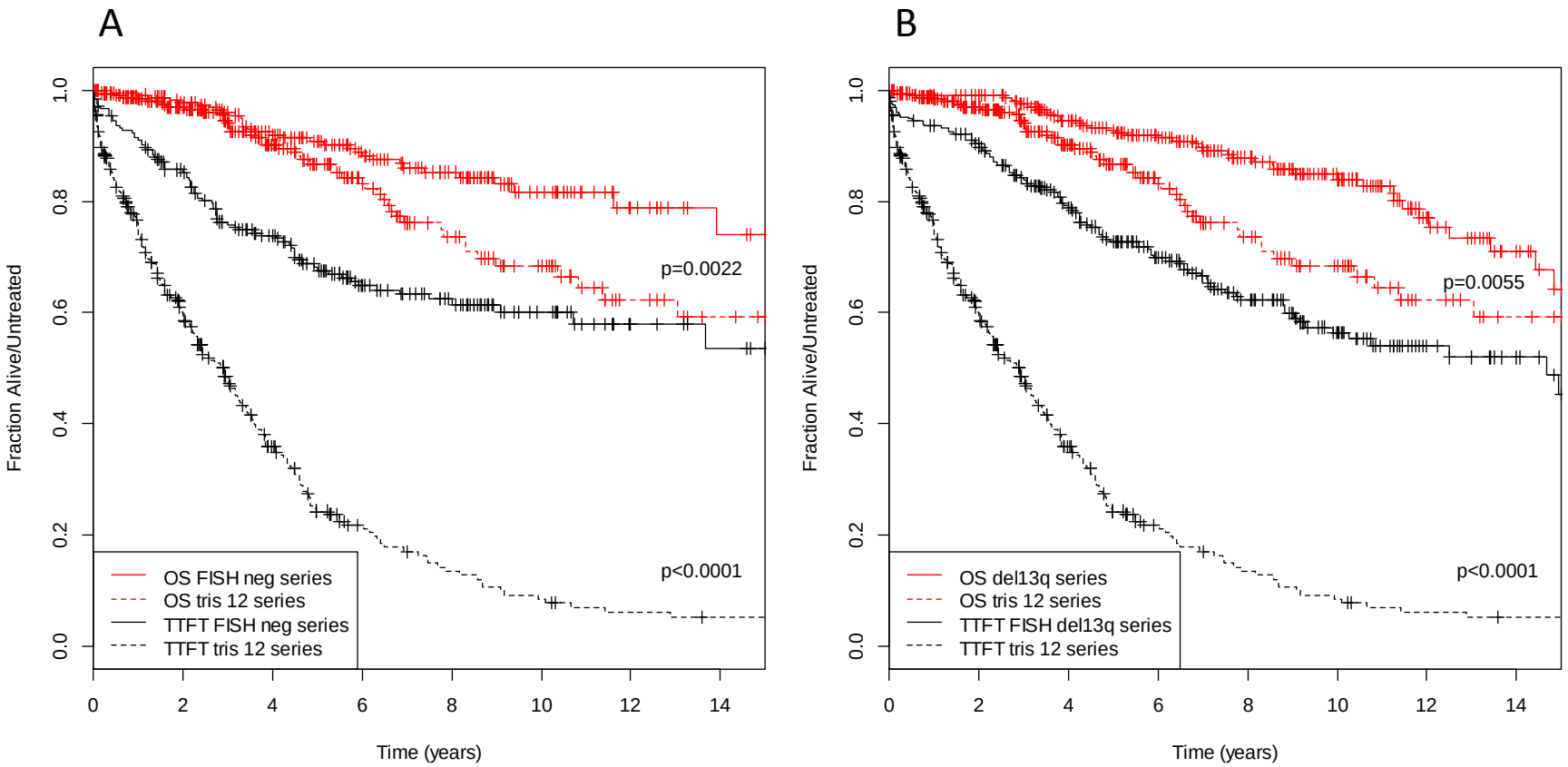
UV: univariate analysis; MV: multivariate analysis; HR: hazard ratio; p: logrank test,
§: factors with $p \leq 0.10$ were entered in MV analysis, ns: not significant factors after stepwise selection.
*: optimal cut-point by recursive partitioning: CD49d 43% (OS) and 34% (TTT); CD38 4% (OS) and 5% (TTT); ZAP-70 20% (OS) and 49% (TTT)

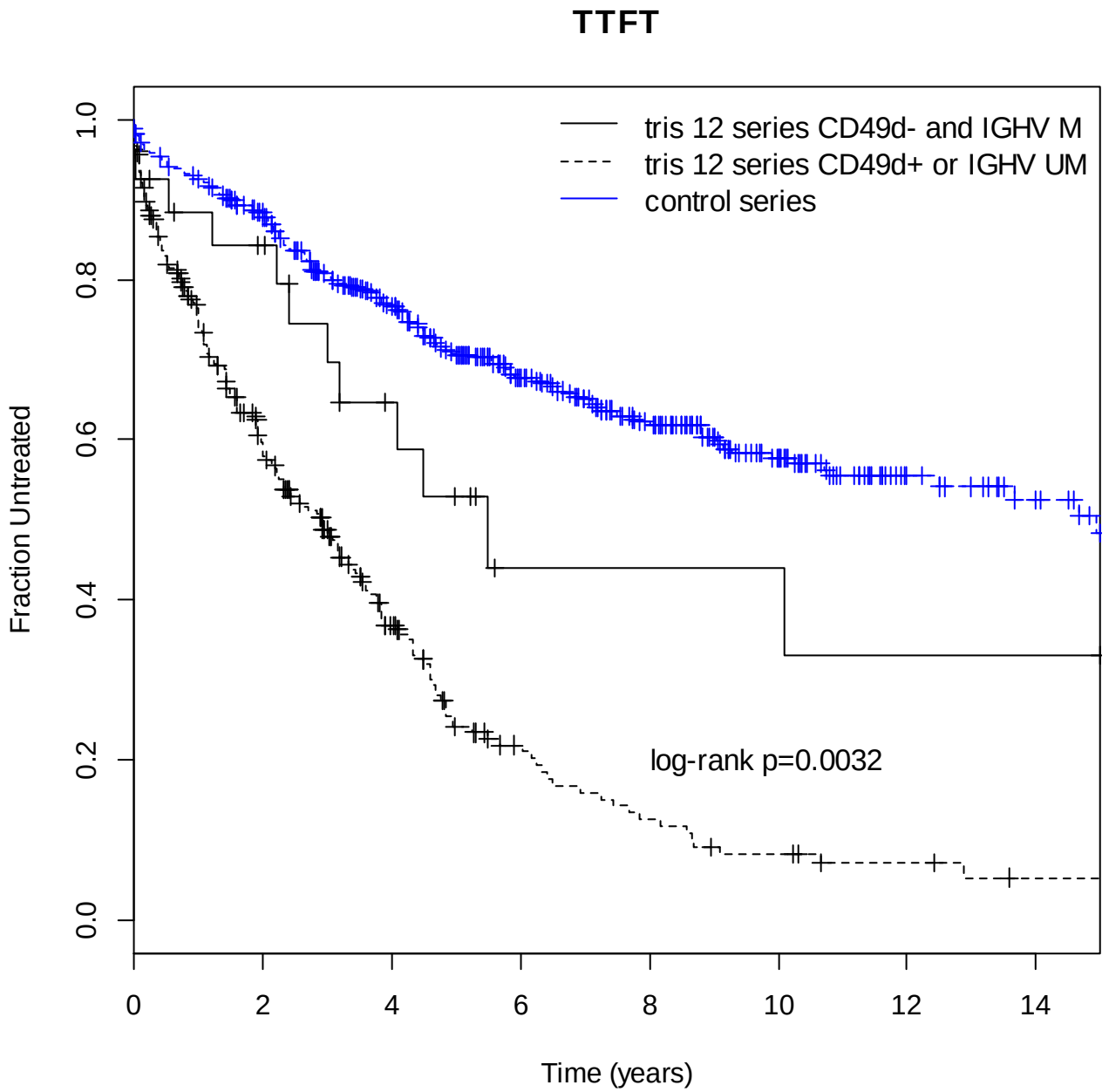
Supplementary figure legend

Figure S1. OS and TTFT Kaplan Meier curves and log-rank statistics in trisomy 12 and FISH negative series or 13q deleted series; **A)** OS (red lines) and TTFT (black lines) in trisomy 12 (dotted lines) and FISH negative series (continuous lines); **B)** OS (red lines) and TTFT (black lines) in trisomy 12 (dotted lines) and 13q deleted series (continuous lines).

Figure S2. TTFT Kaplan Meier curves and stratification of tris12 series by IGHV and CD49d

FIG. S1


A
Fraction Alive/Untreated
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
12
14
Time (years)
p=0.0022
p<0.0001
OS FISH neg series
OS tris 12 series
TTFT FISH neg series
TTFT tris 12 series
B
Fraction Alive/Untreated
Time (years)
p=0.0055
p<0.0001
OS del13q series
OS tris 12 series
TTFT FISH del13q series
TTFT tris 12 series


TTFT
tris 12 series CD49d- and IGHV M
tris 12 series CD49d+ or IGHV UM
control series
log-rank p=0.0032
Fraction Untreated
0.0
0.2
0.4
0.6
0.8
1.0
0
2
4
6
8
10
12
14
Time (years)