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Haematologica 2018 [Epub ahead of print]

*Citation: Barbara Mora, Toni Giorgino, Paola Guglielmelli, Elisa Rumi, Margherita Maffioli, Alessandro Rambaldi, Marianna Caramella, Rami Komrokji, Jason Gotlib, Jean-Jacques Kiladjian, Francisco Cervantes, Timothy Devos, Francesca Palandri, Valerio De Stefano, Marco Ruggeri, Richard T. Silver, Giulia Benevolo, Francesco Albano, Chiara Cavalloni, Daniela Barraco, Michele Merli, Daniela Pietra, Rosario Casalone, Tiziano Barbui, Giada Rotunno, Mario Cazzola, Alessandro Maria Vannucchi, and Francesco Passamonti. Value of cytogenetic abnormalities in post-polycythemia vera and post-essential thrombocythemia myelofibrosis: a study of the MYSEC project. Haematologica. 2018; 103:xxx
doi:10.3324/haematol.2017.185751*

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Value of cytogenetic abnormalities in post-polycythemia vera and post-essential thrombocythemia myelofibrosis: a study of the MYSEC project

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Running heads: Cytogenetics of secondary myelofibrosis

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Word count for the main text: 1494

Polycythemia vera (PV) and essential thrombocythemia (ET) are myeloproliferative neoplasms (MPN),¹ that can progress to blast phase² and to post-PV (PPV) myelofibrosis (MF) and post-ET (PET) MF,³ from now on referred to as secondary myelofibrosis (SMF). Progression may depend by many predisposition factors as higher *JAK2* V617F allele burden, abnormal karyotype (AK), *SRSF2* mutation, bone marrow fibrosis grade 1, advanced age, disease duration, leukocytosis, and splenomegaly.⁴⁻⁶ Cytogenetic analysis is performed rarely, making its relevance in SMF unknown.

The MYSEC project (Myelofibrosis Secondary to PV and ET Collaboration) is a retrospective project based on 781 IWGMRT-diagnosed SMF patients, that already disclosed SMF mutation profile⁷ and prognostication.⁸ Here, we analyzed cytogenetic data available at the time of SMF (376 cases: 188 PET MF, 188 PPV MF) in order to study karyotype-genotype-clinical phenotype correlations and the impact on prognosis. G-banding with trypsin was the standard technique for chromosome analysis with at least 20 metaphases described. The study was approved by the Institutional Review Board of each Institution and conducted in accordance with the principles of the Declaration of Helsinki. Continuous baseline values were compared via the Wilcoxon rank sum test and categorical feature counts via the Fisher's exact tests. The Holm correction for multiple testing was used for *post-hoc* analysis. Time-to-event analyses were performed via Kaplan-Meier curves, using log-rank tests for comparisons and semi-parametric Cox models for regression. Tests for differences in normal (NK) *versus* abnormal karyotypes (AK) were conducted first; where a significant departure from the null was found, the individual abnormal karyotypes were compared with respect to the normal one.

Within 376 SMF, AK was found in 128 (34%) patients. Within chromosomal abnormalities, 72 (56%) were sole abnormality, 26 (20%) complex karyotype (of which 11 -8.5%- were MK), 22 (17%) double abnormalities and eight abnormal karyotypes not further specified. List of involved chromosomes, according to single, double and complex chromosomal abnormalities is shown in Table 1S. Among the sole abnormalities, the most prevalent were: 20q- (18 cases, 25%), 13q- (15 cases, 21%), +8 (6 cases, 8%) and +9 (4 cases, 6%). Other individual alterations were present in less than 5% of patients.

Table 1 reports demographics of SMF patients according to AK and normal karyotype (NK) status. AK clustered differently according to the type of diagnosis as was found in 76 (40%) patients

within PPV MF and in 52 (28%) with PET MF ($P = .012$). No relationship was found with advanced age, leukocyte count, hemoglobin value, and bone marrow fibrosis grade (2 vs. 3). On the contrary, lower platelet counts were associated with AK ($P = .004$). *Post-hoc* tests of platelets counts versus karyotype found significantly lower platelet counts in monosomal karyotype (MK) (median value, $178 \times 10^9/L$) compared to NK (median value, $365 \times 10^9/L$, $P = .02$) and to sole abnormality (median value, $319 \times 10^9/L$, $P = .04$). We found also a relationship between AK and higher percentage of circulating blast cells ($P < .001$) and larger spleen size ($P = .015$). Sixty-three (51%) with AK and 91 (37%) with NK had constitutional symptoms ($P = .013$). Overall, AK confers a more advanced clinical phenotype.

In 339 patients, we analyzed the correlation between cytogenetic profile and driver mutation. Chromosomal abnormalities were described in 12 (23%) out of 52 *CALR*-mutated patients, in 28 (31%) out of 90 *JAK2*-mutated PET MF, in 73 (41%) out of 178 *JAK2*-mutated PPV MF, in three (23%) out of 13 *MPL*-mutated and in no TN case. *Post hoc* test revealed that AK was differently distributed between *JAK2*-PPV MF (41%) and *CALR* (23%) ($P = .002$). However, this significant association is lost after adjusting for multiple comparisons (minimum $P > .2$).

Thrombotic event after SMF diagnosis occurred in 40 patients and 27 transformed to blast phase (BP). Overall, we did not disclose any relationship between AK and thrombosis ($P = .66$) or blast phase ($P = .4$). However, considering AK types individually, we found that patients with a complex karyotype (CK) had a 3.8-fold (95% CI: 1.3-11.2; $P = .01$) higher risk of developing blast phase than those without.

Median survival was significantly different between NK and AK patients and estimated at 10.1 years (95% CI: 8.1-not reached -NR-) and 6.1 years (95% CI: 4.8-NR), respectively ($P = .012$, Figure 1). The difference retained its statistical significance in Cox regressions adjusted for SMF type ($P = .02$), but when adding MYSEC-PM risk strata in the multivariate analysis, AK *per se* did not disclose any effect on survival ($P = .5$). *Post-hoc* log-rank tests comparing the effect of different cytogenetic abnormalities found that patients with MK, those with CK without MK and those with CK had worse survival with a median estimate of 2.1 years (95% CI: 1-NR), 3.4 years (95% CI: 2.6-NR), and 2.7 years (95% CI: 2-NR), respectively. All groups had inferior survival when compared to NK, sole or double abnormalities ($P < .001$). Of note, MK patients had worse survival (hazard ratio 3.7, 95%

CI: 1.2-10.8) independently of their MYSEC-PM risk group, as shown by stratification by score groups ($P = .018$). Figure 2 illustrates survival estimates according to cytogenetic profile.

Concerning the distribution of cytogenetic status within the MYSEC-PM risk stratification,⁸ a significant association was found between higher MYSEC-PM risk categories and AK ($P = .006$, Supplementary Figure 1S). Chromosomal abnormalities were found in 13 out of 69 low risk (19%), 51 out of 140 intermediate-1 risk (36%), 22 out of 61 intermediate-2 risk (36%) and 17 out of 33 high risk (52%) patients.

Until now, SMF has been managed similarly to PMF; however, differences between the two conditions have been recently identified in terms of clinical presentation as well as of survival estimates or IPSS/DIPSS prognostic model applicability.^{9,10} As a consequence, more detailed information on SMF is indeed necessary.

We found an abnormal karyotype in one third of patients at SMF diagnosis, similar to the numbers found in PMF by the MD Anderson Cancer Center (35%),⁹ by the Mayo Clinic (37%)¹¹ and by the IPSS (30%) investigators. In MYSEC cases with chromosomal abnormalities, 56% were sole, 20% complex (8.5% MK) and 17% double. The most prevalent single abnormalities were 20q-, 13q-, +8 and +9, accounting for 5%, 4%, 2% and 1% of the whole series ($n=376$), respectively. This figure parallels data on PV and ET. In fact, a recent analysis on 107 PV at diagnosis showed 20q-, +8, and +9 in 3%, 3%, and 5%, respectively. Another study on 196 PV found 20q-, 13q-, +8, and +9 in 3%, 0.5%, 3%, 0.5%,¹² respectively and in ET all are present in less than 1%.¹³ This suggests that these most frequent cytogenetic abnormalities found at the time of SMF are not pathogenic events of SMF, but are a consequence of the PV and ET phase. This seems clear also from recent sequential data on cytogenetics in PV and PPV MF.¹⁴ However, we cannot exclude that small clones at diagnosis can become dominant at progression to SMF, and the clonal dominance may indeed be pathogenic in SMF. In SMF we reported a high rate of double abnormalities (17%) and complex karyotype (20%). This differs from data obtained in the PV and ET phase. Within a cohort of 107 PV patients assessed at diagnosis, double abnormalities were recorded in two, and CK in one,¹⁴ in agreement with other studies: less than 2% in PV¹² and less than 1% in ET.¹³ Hence, finding double abnormalities and complex karyotype seems to be more typical of SMF than of PV and ET. As most double abnormalities found in the MYSEC dataset are in individual patients, it is not possible to

suggest which one is most pathogenetic. In two large cohorts of PMF patients, double abnormalities and complex karyotype are present in 17% and 11%,¹⁵ and in 8% and 5%,⁹ respectively.

Survival of NK patients more closely reflected a benign disease (median value of 10.1 years), while that of AK patients an aggressive one (median value of 6.1 years). Of note, MYSEC-PM still remain the more precise way to stratify survival, as suggested by multivariate analysis including MYSEC-PM strata and abnormal/normal karyotype. Our study identified two SMF cohorts with very short survival: patients with complex karyotype (median value, 2.7 years), and those with monosomal karyotype (median value, 2 years) accounting for 20% and for 8.5% of patients with AK, and for 7% and 3% of the whole SMF population, respectively. The impact of MK on survival resulted independent from the MYSEC-PM stratification and this indicates to consider this abnormality of great relevance for clinical practice.

In conclusion, this study shows that an abnormal karyotype is present in approximately one third of SMF and confers a more advanced clinical phenotype. Patients with monosomal karyotype have a poor survival independently from the MYSEC-PM risk stratification and need to be identified. These findings reinforce the utility of assessing cytogenetics in SMF.

Funding

This work was supported by a grant from the Associazione Italiana per la Ricerca sul Cancro (AIRC; Milano, Italy), Special Program Molecular Clinical Oncology 5x1000 to AIRC-Gruppo Italiano Malattie Mieloproliferative (AGIMM) project #1005. A complete list of AGIMM investigators is available at <http://www.progettoagimm.it>. P.G. also received funding by AIRC IG2014-15967 and by the Ministero della Salute (project code GR-2011-02352109). The Varese group was also supported by grants of the Fondazione Regionale Ricerca Biomedica, Milan, Italy [FRRB project no. 2015-0042, Genomic profiling of rare hematologic malignancies, development of personalized medicine strategies, and their implementation into the Rete Ematologica Lombarda (REL) clinical network], by Fondazione Matarelli (Milano, Italy), Fondazione Rusconi (Varese, Italy) and AIL Varese ONLUS. T.G. acknowledges research funding from the Department of Medicine and Surgery, University of Insubria. R.T.S. was supported in part by the Cancer Research and Treatment Fund, Inc., New York, NY.

Authorship

Contribution: F.P., B.M., A.M.V., M.M. contributed to the conception of the work; F.P., B.M., T.G. contributed to the design of the work; T.G. performed the statistical analysis; B.M., F.P., P.G., M.C., M.M., A.R., M.C., R.K., J.G., J.J.K., F.C., T.D., F.P., V.D.S., M.R., R.T.S., G.B., F.A., D.B., E.R., M.Me., D.P., T.B., A.B., G.R., A.M.V. contributed to the acquisition, analysis, or interpretation of data for the work; B.M., F.P., T.G., P.G., M.C., M.M., A.R., M.C., R.K., J.G., J.J.K., F.C., T.D., F.P., V.D.S., M.R., R.T.S., G.B., F.A., A.S., E.R., M.Me., D.P., T.B., A.B., G.R., A.M.V. contributed to revising the manuscript critically for important intellectual content and approved the final version of the manuscript.

Conflict-of-interest disclosure: No conflict of interest to disclose for this study by all Authors.

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Table 1. Demographics of the 376 patients with post polycythemia vera and post essential thrombocythemia myelofibrosis according to karyotype.

	Abnormal (N = 128)	Normal (N = 248)	P value
Male gender, n. (%)	66 (52)	134 (54)	.62
Age at SMF, median (range), years	66 (33-96)	64 (25-86)	.41
SMF type: PPV MF, n. (%)	76 (40)	112 (60)	.009
SMF type: PET MF, n. (%)	52 (28)	136 (72)	
WBC, median (range), x 10 ⁹ /L	11.7 (1.7-54.1)	10.4 (1.7-97.3)	.47
Hb, median (range), g/dL	11.1 (6.0-15.7)	11.5 (6.3-15.6)	.13
PLT, median (range), x 10 ⁹ /L	293 (25-959)	365 (20-1420)	.004
Blasts >1%, n. (%)	55 (46)	65 (28)	< .001
Spleen size, median (range), cm	9 (0-29)	6 (0-34)	.015
Constitutional symptoms, n. (%)	63 (51)	91 (37)	.013
Bone marrow fibrosis grade 2, n. (%)	78 (67)	156 (68)	.91
Bone marrow fibrosis grade 3, n. (%)	38 (33)	74 (32)	
<i>Driver mutation type:</i>			
<i>CALR</i> , n. (%)	12 (10)	40 (18)	minimum >.2
<i>JAK2</i> -PET MF, n. (%)	28 (24)	62 (28)	
<i>JAK2</i> -PPV MF, n. (%)	73 (63)	105 (47)	
<i>MPL</i> , n. (%)	3 (3)	10 (4)	
TN, n. (%)	0 (0)	6 (3)	
<i>MYSEC-PM risk category:</i>			
Low, n. (%)	13 (13)	56 (28)	.006
Intermediate-1, n. (%)	51 (50)	89 (44)	
Intermediate-2, n. (%)	22 (21)	39 (20)	
High, n. (%)	17 (16)	16 (8)	

% was calculated on available data.

Legend to Figures

Figure 1: Survival estimates of 376 patients with post polycythemia vera and post essential thrombocythemia myelofibrosis according to karyotype (normal versus abnormal). Median survival was 10.1 years (95% CI: 8.1-NR) in patients with NK and 6.1 years (95% CI 4.8-NR) in those with AK ($P = .012$). Survival curves not overlapping the shaded region are a significantly different at the 95% level.

Figure 2: Survival estimates of 376 patients with post polycythemia vera and post essential thrombocythemia myelofibrosis according to different cytogenetic abnormalities. Median survival was 10.1 years (95% CI: 8.1-NA) for NK, 9.3 years (95% CI: 5.7-NA) for sole abnormality, 7.4 years (95% CI: 2.5-NA) for double abnormalities, 3.4 years (95% CI: 2.6-NA) for complex karyotype without MK, and 2.1 years (95% CI: 1-NA) for MK.

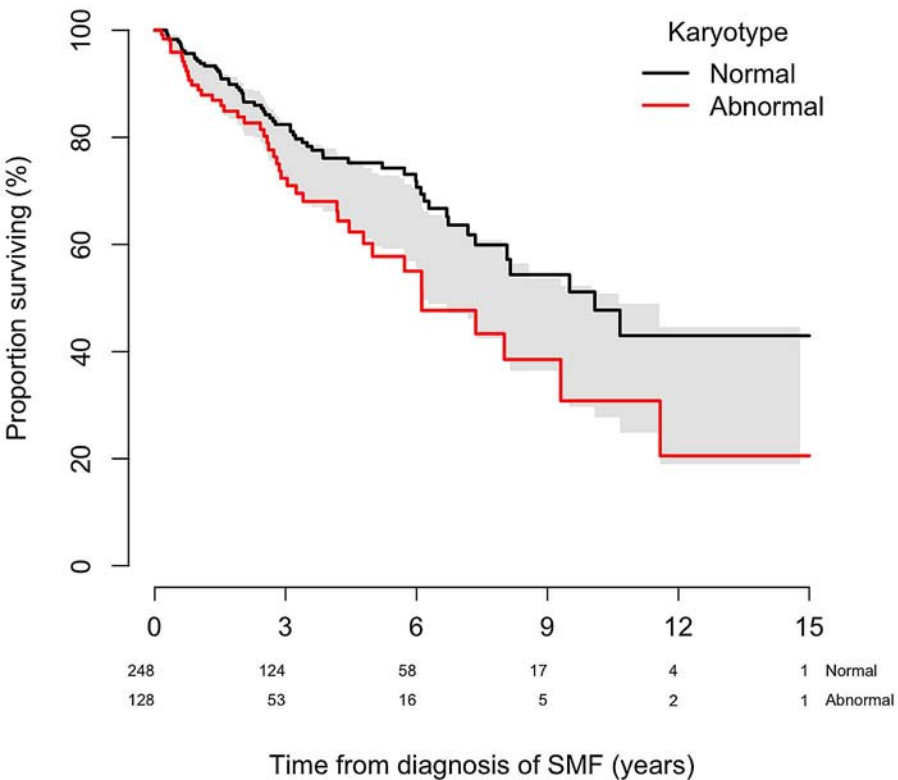


Figure 1

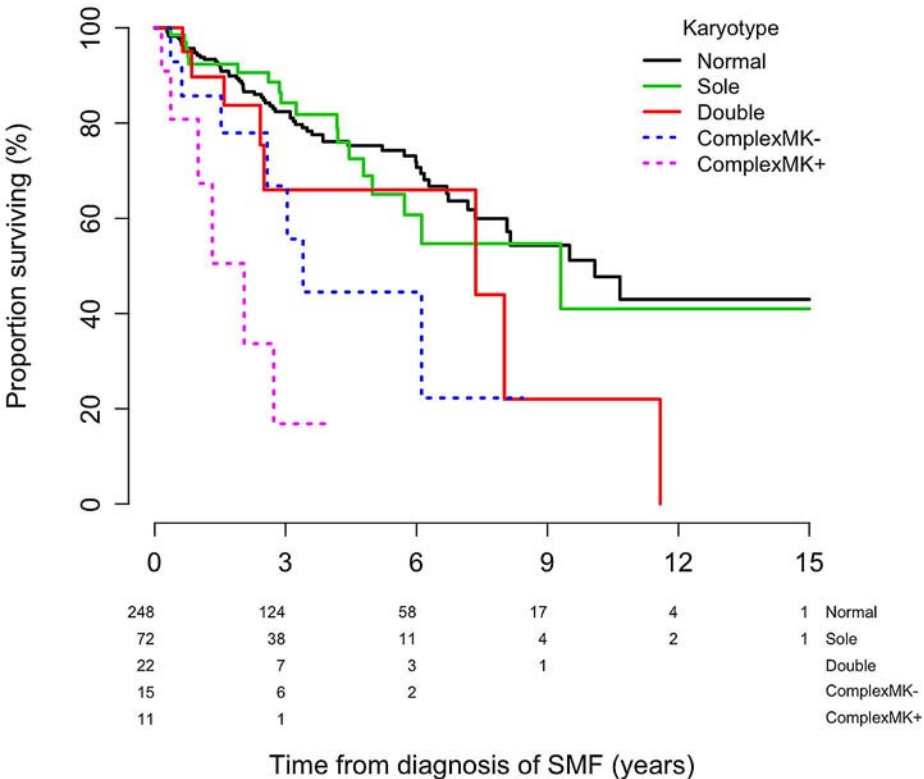


Figure 2

Value of cytogenetic abnormalities in in post-polycythemia vera and post-essential thrombocythemia myelofibrosis: data from the MYSEC-project

Barbara Mora,^{1*} Toni Giorgino,^{2*} Paola Guglielmelli,³ Elisa Rumi,⁴ Margherita Maffioli,¹ Alessandro Rambaldi,⁵ Marianna Caramella,⁶ Rami Komrokji,⁷ Jason Gotlib,⁸ Jean Jacques Kiladjian,⁹ Francisco Cervantes,¹⁰ Timothy Devos,¹¹ Francesca Palandri,¹² Valerio De Stefano,¹³ Marco Ruggeri,¹⁴ Richard T. Silver,¹⁵ Giulia Benevolo,¹⁶ Francesco Albano,¹⁷ Daniela Barraco,¹ Michele Merli,¹ Daniela Pietra,⁴ Adelaide Bussini,¹⁸ Tiziano Barbui,¹⁹ Giada Rotunno,³ Mario Cazzola,^{4§} Alessandro Maria Vannucchi^{3§} and Francesco Passamonti.^{1*}

Table 1S. List of involved chromosomes according to single, double and complex chromosomal abnormalities in 376 patients with post-polycythemia vera and post-essential thrombocythemia myelofibrosis.

Chromosomal Abnormalities	PET-MF	PPV-MF	Total
<i>Sole abnormality</i>			
abnormality chromosome n. 1	1	1	2
abnormality chromosome n. 20	0	1	1
del(9p)	0	1	1
del(11q)	1	1	2
del(13q)	8	7	15
del(20q)	4	14	18
del(7q)	1	1	2
del(9q)	1	0	1
der(15) t(1;15)	0	2	2
der(5) t(1;5)	1	0	1
der(6) t(1;6)	1	0	1
der(13)	0	1	1
der(19)	1	1	2
der(7)	0	1	1
der(9) t(1;9)	0	1	1
inv(10)	1	0	1
loss of Y	1	0	1
rearrangement 1q	1	0	1
t(11;12)	0	1	1
t(5;12)	1	1	2
t(6;15)	0	1	1
t(8;20)	1	0	1
t(9;22)	0	1	1
t(X;20)	1	0	1
trisomy 1q	0	1	1
trisomy 8	3	3	6
trisomy 9	2	2	4

<i>Double abnormality</i>			
der(15) t(1;5)	0	1	1
trisomy 1q, trisomy 9p	0	1	1
del(5q), t(3;12)	1	0	1
del(13q), trisomy 8	0	1	1
del(20), monosomy 8	0	1	1
del(20q), t(6;15)	0	1	1
del(7),+mar	1	0	1
del(7q), del(20q)	1	0	1
del(9), del(15)	1	0	1
del(9q), der(17) t(1;17)	0	1	1
dup(1q), t(7;12)	0	1	1
iso(17q), del(7q)	1	0	1
loss of Y, t(8;22)	1	0	1
t(9;11), t(6;20)	1	0	1
t(X;12), t(3;12)	1	0	1
trisomy 1, der(1;13)	1	0	1
trisomy 8, del(13q)	0	1	1
trisomy 8, trisomy 9	1	2	3
trisomy 9, der(1)	0	1	1
trisomy 9, trisomy 1	0	1	1
<i>Complex, not monosomal</i>			
del(3p), +8, +9, +13	0	1	1
+6, +7, +8, +9, +15	0	1	1
dup(1), del(6p), del(11q)	0	1	1
invdup(1p), der(6) t(6;?), der(9) t(9;20), der(14) t(9;14)	0	1	1
t(10;5;11;9)	0	1	1
t(2;7;8;12;18)	0	1	1
der(13), +14, +15	0	1	1
+9, +8, t(12;14)	1	0	1
t(3;14;17)	0	1	1

+8, +9, der(19) t(1;19), del(4), der(13) t(4;13)	0	1	1
+8, +9, +16	1	0	1
t(5;9), del(12), del(13)	1	0	1
del(5q), del(13q), der(20) t(20;?)	1	0	1
t(1;7), trisomy 9; tetrasomy 21	1	0	1
abnormality chromosome n. 5, n. 6, n. 10, n. 12	0	1	1
<i>Complex, monosomal</i>			
del(5q), -18, der(16), t(6;7;18)	0	1	1
-18, der(18) t(1;18), -22, der(22) t(1;22)	0	1	1
der(2) t(2;17), del(5q), dic(5;18), add(13p), add(15p), -17	1	0	1
-1, del(7), del(8), add(11), del(13), -14, -18, add(20), +2mar	0	1	1
+8, +16, -22, +der(9) t(1;9)	1	0	1
del(7q), add(17p), add(18q), -21	1	0	1
del(5q), -6, del(7q), t(12;14), +mar	1	0	1
del(13q), add(1p), -6, -X, +2, del(4q)	0	1	1
del(9p), -18, -20	0	1	1
del(6q), -16, +mar	0	1	1
+mar1, +mar2, -19	0	1	1

Legend to Figure

Figure 1S. Distribution of karyotype (normal and abnormal) among the MYSEC-PM risk categories.

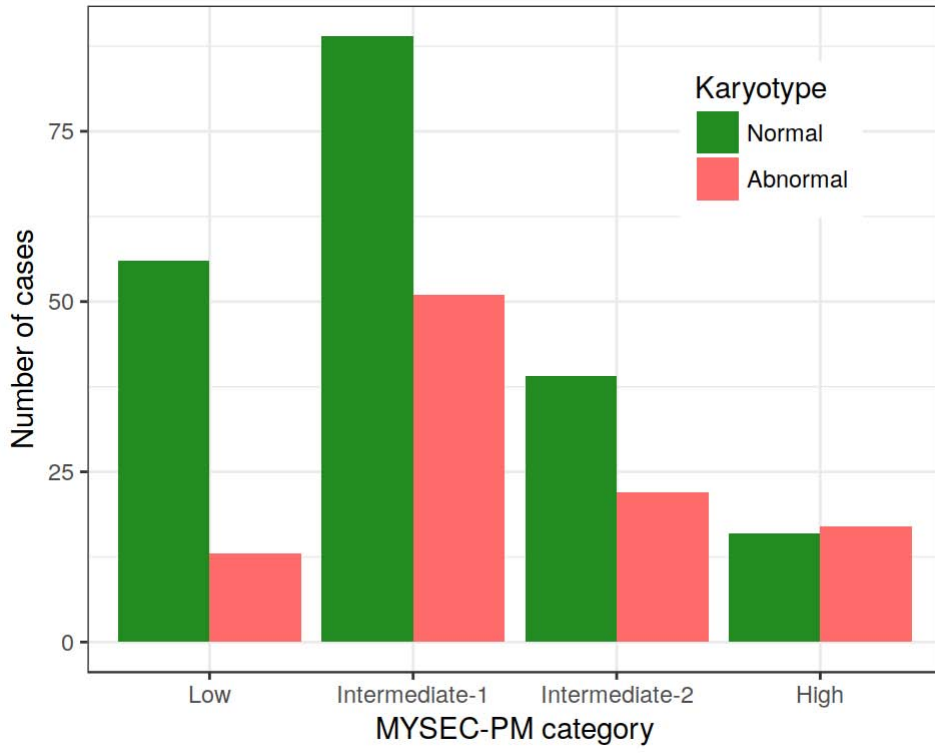


Figure 1S