Mutational Signatures in Cytogenetic Risk Groups of De Novo AML and MDS

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AMP webinar: 10/4/18

Myeloid neoplasms

- Blast count
  - MDS/MPN<20%≤AML
- Genetic features
  - FISH
  - Cytogenetics
  - Sequencing
- Displasia
  - (MDS)

Other myeloproliferative neoplasms (MPN)

- BCR-ABL (Ph+)
  - Chronic Myelogenous Leukemia (CML)
- Ph-
  - Polycythemia vera (PV)
  - Essential thrombocytopenia (AT)
  - Primary myelofibrosis (PMF)

Myeloid neoplasms are heterogeneous

- Cytogenetic abnormalities are associated with prognosis
- Many subtypes exist with multiple overlapping mutations
- Recurrent mutations belong to several distinct pathways
- Pre-leukemic and leukemic cells undergo clonal evolution
  - Heterogeneous cell populations with mutations conferring different functional properties

Genetic basis of myeloid neoplasms

- De novo AML
  - *NPM1, CBF* and *KMT2A* mutations
- MDS
  - Progression to AML assaociated with mutations in *TP53, RUNX1, ETV6, EZH2, ASXL1*
- sAML
  - Spliceosome complex: *SRSF2, SF3B1, U2AF1, ZRSR2*
  - Epigenetic regulators: *ASXL1, EZH2, BCOR*
  - Cohesion Complex: *STAG2*
  - Many mutations from MDS or myelofibrosis and are retained after transformation

AML risk stratification: Medical Research Council (MRC) & Southwest Oncology Group (SWOG)

Table 1 Acute Myeloid Leukemia Cytogenetic Risk Classification

Risk Status	SWOG[1]	CALGB[2][a]	MRC (1998)[3]	MRC (2010)[4]
Favorable	t(15;17), t(8;21), inv(16)/t(16;16)/ del(16q)	(8;21), inv(16)/t(16;16)	t(15;17), t(8;21), inv(16)/t(16;16)/ del(16q)	t(15;17)(q22;q21), t(8;21) (q22;q22), inv(16) (p13q22)/t(16;16)(p13;q22)
Intermediate	Normal, +8, +6, –Y, del(12p)	Normal, –Y, del(5q), t(6;9), t(6;11), –7, loss of 7q, +8 sole, +8 with 1 other abnormality, del(9q), t(9;11), +11, del(11q), t(11;19)(q23;p13.1), +13, del(20q), +21	Normal, 11q23 abn, +8, del(9q), del(7q), +21, +22, all others	Abnormalities not classified as favorable or unfavorable
Unfavorable	abn(3q), del(5q)/ –5, –7/del(7q), t(6;9), t(9;22), 9q, 11q, 20q, 21q, 17p, complex (≥ 3 unrelated abnormalities)	inv(3)/t(3;3), abn(12p), complex (≥ 3 unrelated abnormalities)	abn(3q), del(5q)/ –5, –7, complex (≥ 5 unrelated abnormalities)	abn(3q) [excluding t(3;5) (q21~25;q31~35)], inv(3) (q21q26)/t(3;3)(q21;q26), add(5q), del(5q), –5, add (7q)/del(7q), –7, t(6;11) (q27;q23), t(10;11) (p11~13;q23), t(11q23) [excluding t(9;11) (p21~22;q23) and t(11;19) (q23;p13)],t(9;22)(q34;q11), –17/ abn(17p),complex (≥ 4 unrelated abnormalities)
Unknown	All other abnormalities	Category not recognized	Category not recognized	Category not recognized

[a]Risk for overall survival.
abn = abnormality; CALGB = Cancer and Leukemia Group B; del = deletion; inv = inversion; MRC = Medical Research Council; SWOG = Southwest Oncology Group.

Orozco, et.al., 2012

AML risk stratification: European LeukemiaNet (ELN)

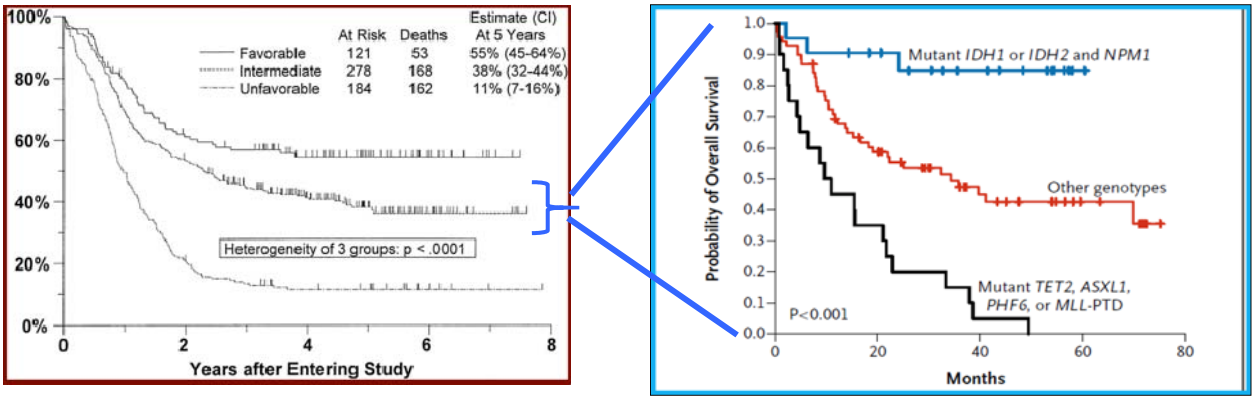
Risk category*	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}†
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}†
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	–5 or del(5q); –7; –17/abn(17p)
	Complex karyotype,§ monosomal karyotype‖
	Wild-type *NPM1* and *FLT3*-ITD^{high}†
	Mutated *RUNX1*¶
	Mutated *ASXL1*¶
	Mutated *TP53*#

Frequencies, response rates, and outcome measures should be reported by risk category, and, if sufficient numbers are available, by specific genetic lesions indicated.

*Prognostic impact of a marker is treatment-dependent and may change with new therapies.
†Low, low allelic ratio (<0.5); high, high allelic ratio (≥0.5); semiquantitative assessment of *FLT3*-ITD allelic ratio (using DNA fragment analysis) is determined as ratio of the area under the curve "*FLT3*-ITD" divided by area under the curve "*FLT3*-wild type"; recent studies indicate that AML with *NPM1* mutation and *FLT3*-ITD low allelic ratio may also have a more favorable prognosis and patients should not routinely be assigned to allogeneic HCT.[57-59,77]
‡The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.
§Three or more unrelated chromosome abnormalities in the absence of 1 of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with *BCR-ABL1*.
‖Defined by the presence of 1 single monosomy (excluding loss of X or Y) in association with at least 1 additional monosomy or structural chromosome abnormality (excluding core-binding factor AML).[116]
¶These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.
#*TP53* mutations are significantly associated with AML with complex and monosomal karyotype.[37,66-69]

Döhner et.al., 2017

AML with intermediate cytogenetic risk can be modified by mutational information



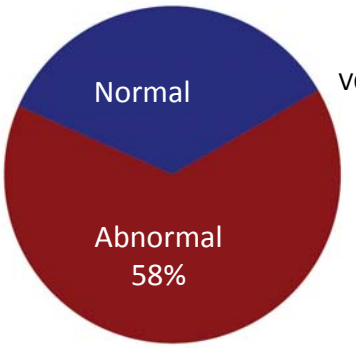
SWOG risk stratification

Patel JP et al.. N Engl J Med, 2012.

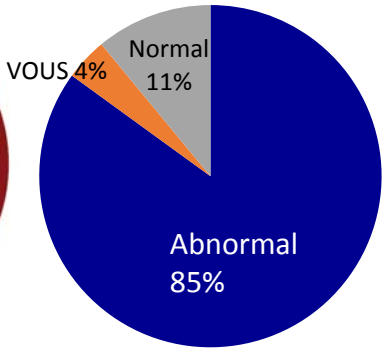
Penn's hematological malignancies NGS panel detects mutations in the majority of AML patients

Heme Version 2: 68 genes

ABL1, ASXL1, ATM, BCOR, BCORL1, BIRC3, BRAF, CALR, CBL, CDH2, CDKN2A, CEBPA, CSF1R, CSF3R, DNMT3A, DDX3X, ETV6, EZH2, FAM5C, FBXW7, FLT3, GATA2, GNAS, HNRNPK, HRAS, IDH1, IDH2, IL7R, JAK2, KLHL6, KIT, KRAS, MAPK1, MPL, MLL2, PHF6, PRPF40B, PTPN11, MAP2K1, miR-142, MYC, MYCN, MYD88, NF1, NOTCH1, NOTCH2, NPM1, NRAS, POT1, PTEN, RAD21, RIT1, RUNX1, SRSF2, SETBP1, SMC1A, SF1, STAG2, SF3A1, SF3B1, TBL1XR1, TET2, TP53, TPMT, U2AF1, U2AF2, WT1, XPO1, ZRSR2, ZMYM3



Chromosome analysis



Sequence analysis

Evolution of the heme panel

Heme Version 1: 33 genes

ASXL1, ATM, BRAF, CBL, CDKN2A, DDX3X, DNMT3A, ETV6, EZH2, FBXW7, FLT3, GNAS, IDH1, IDH2, JAK2, KLHL6, KIT, KRAS, MAPK1, PHF6, PTPN11, MYD88, NOTCH1, NPM1, NRAS, PTEN, RUNX1, SF3B1, TET2, TP53, WT1, XPO1, ZMYM3

Heme Version 2: 68 genes

ABL1, ASXL1, ATM, BCOR, BCORL1, BIRC3, BRAF, CALR, CBL, CDH2, CDKN2A, CEBPA, CSF1R, CSF3R, DNMT3A, DDX3X, ETV6, EZH2, FAM5C, FBXW7, FLT3, GATA2, GNAS, HNRNPK, HRAS, IDH1, IDH2, IL7R, JAK2, KLHL6, KIT, KRAS, MAPK1, MPL, MLL2, PHF6, PRPF40B, PTPN11, MAP2K1, miR-142, MYC, MYCN, MYD88, NF1, NOTCH1, NOTCH2, NPM1, NRAS, POT1, PTEN, RAD21, RIT1, RUNX1, SRSF2, SETBP1, SMC1A, SF1, STAG2, SF3A1, SF3B1, TBL1XR1, TET2, TP53, TPMT, U2AF1, U2AF2, WT1, XPO1, ZRSR2, ZMYM3

Overlapping Risk Stratification with Mutations from CPD

CPD
4500 cases on Heme panel

↓

2190
AML or MDS

Cytogenetics
11,500 karyotypes

↓

1,031
first or second karyotype for a patient

↘ ↙

665 Overlapping patients

- Check chart to confirm AML or MDS
- Check date of karyotype for dnAML
- Check date of NGS for dnAML
- Stratify into risk categories
- No Growth/suboptimal normal karyotypes removed

→

124 dnAMLs
90 MDS patients

AML risk stratification: Medical Research Council (MRC) & Southwest Oncology Group (SWOG)

1 del16q →

1 t(6;9) →

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Intermediate	Normal, +8, +6, –Y, del(12p)	Abnormalities not classified as favorable or unfavorable
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Unknown	All other abnormalities	Category not recognized

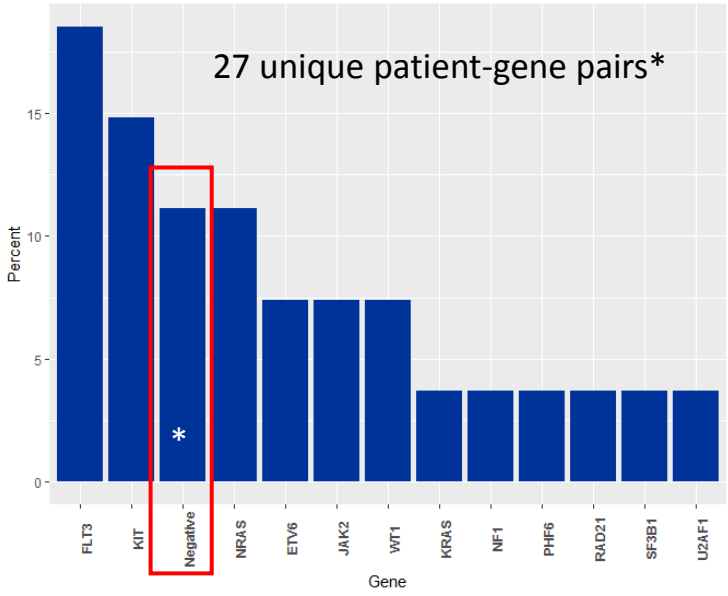
Orozco, et.al., 2012

Mutations were detected in most MRC Favorable AMLs

20 patients

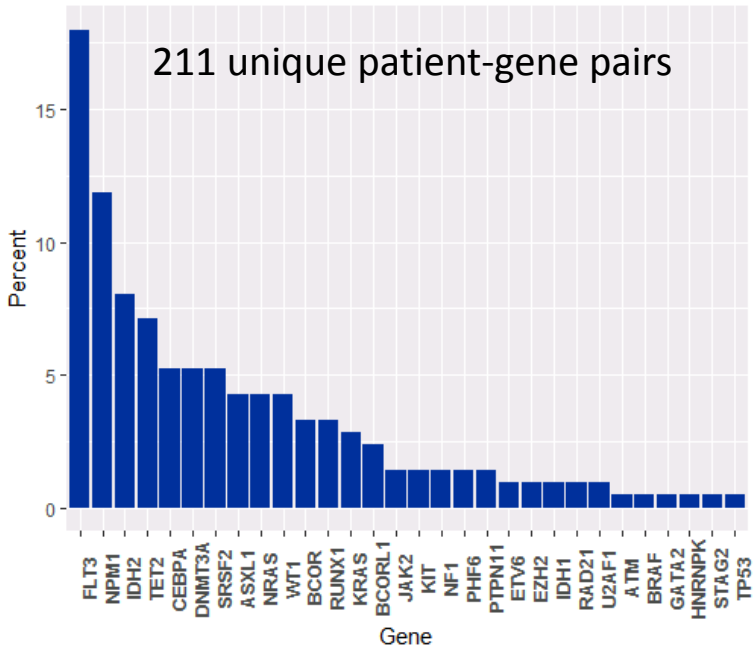
These include:
- t(8;21) (n=10)
- inv(16)/t(16;16) (n= 7)
- t(15;17) (n= 4)

- *FLT3* is the most commonly mutated gene (4/5 of these are ITDs)

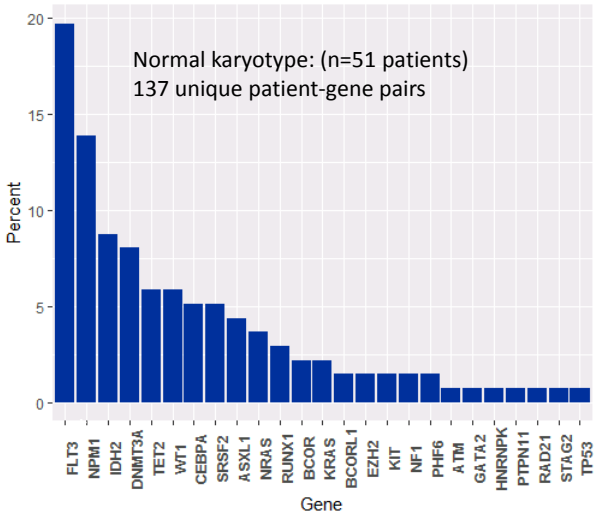


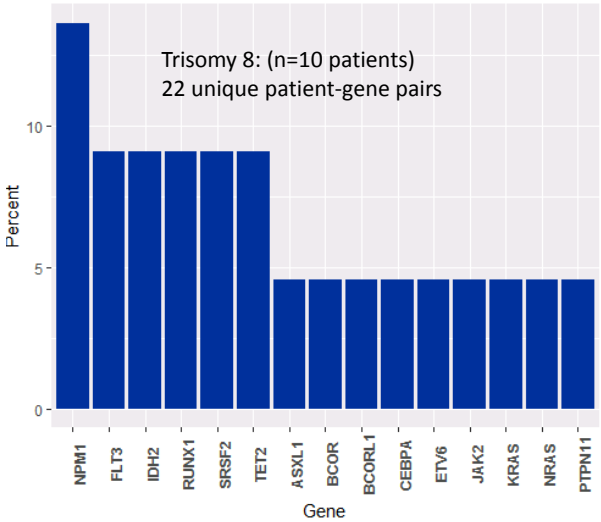
Multiple mutations were detected in most MRC Intermediate AMLs

- 82 patients
- Most common finding: normal karyotype (n=51)
- 24/33 (73%) of *FLT* variants are ITDs
- No negative sequencing studies



Normal karyotypes have more *DNMT3A* and tumor suppressor mutations compared to Trisomy 8s



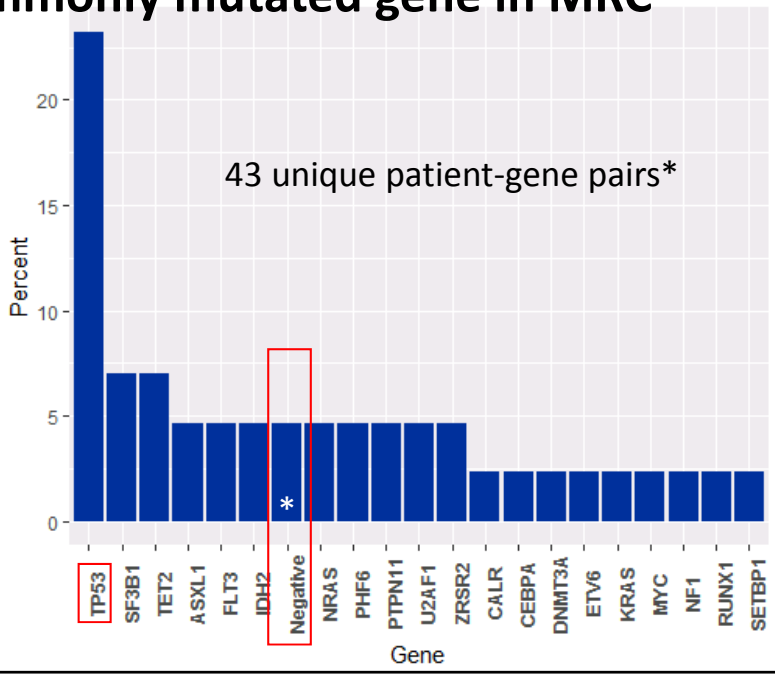


Normal Karyotypes do **not** overlap with negative sequencing studies

TP53 is the most commonly mutated gene in MRC Unfavorable AMLs

29 patients
Complex Karyotypes
(defined as ≥4 abnormalities)

Negative sequencing studies (n=2) overlap with either a complex karyotype or del(5q)



Functional Categorization of Variants

Table 1

FUNCTIONAL CATEGORIZATION OF GENES

CHROMATIN REGULATION	**DNA METHYLATION**	**SIGNALING PATHWAY**		**TRANSCRIPTION FACTOR**
ASXL1	*DNMT3A*	*ABL1*	*ATM*	*CEBPA*
BCOR	*IDH1/IDH2*	*BRAF*	*CALR*	*GATA2*
BCORL1	*TET2*	*CBL*	*CSF1R*	*MYC*
EZH2		*CSF1R*	*FLT3*	*MYCN*
ZMYM3	**SPLICEOSOME COMPLEX**	*GNAS*	*IL7R*	*RUNX1*
MLL2	*PRPF408*	*JAK2*	*KLHL6*	*TBL1XR1*
COHESIN COMPLEX	*SF1*	*KIT*	*KRAS*	**TUMOR SUPPRESSOR**
RAD21	*SF3A1*	*MAP2K1*	*MAPK1*	*ETV6*
SMC1A	*SF3B1*	*MPL*	*MYD88*	*HNRNPK*
STAG2	*SRSF2*	*NF1*	*NOTCH1*	*PTEN*
	U2AF1	*NOTCH2*	*NRAS*	*TP53*
NPM1	*U2AF2*	*PDGFRA*	*PTPN11*	*WT1*
NPM1	*ZRSR2*	*RIT1*	*HRAS*	*PHF6*

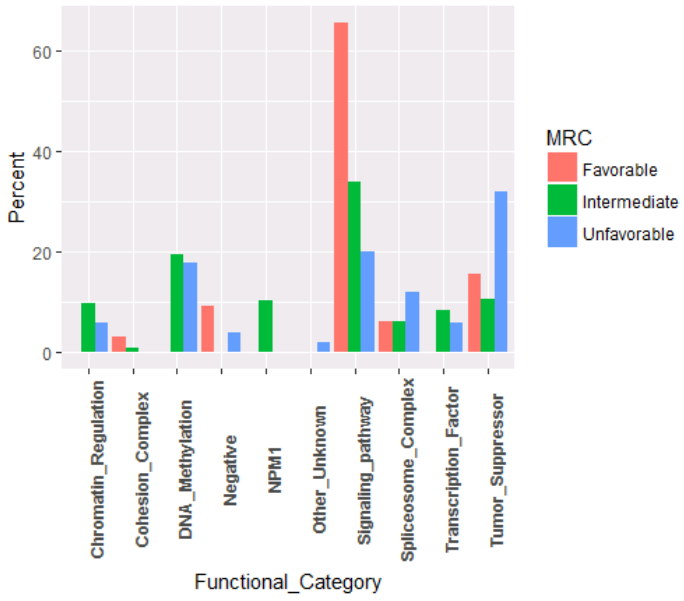
PHARMACO-GENETIC	**OTHER/UNKNOWN**				
TMPT	*BIRC3*	*CDKN2A*	*FAM5C*	*FBXW7*	*MIRI42*
	POT1	*SETBP1*	*CDH2*	*DDX3*	*XPO1*

*WT1 is a tumor suppressor even though mutant WT1 is associated with DNA hypermethylation of PRC1 targets in AML (Sinha et.al. Blood 2015)

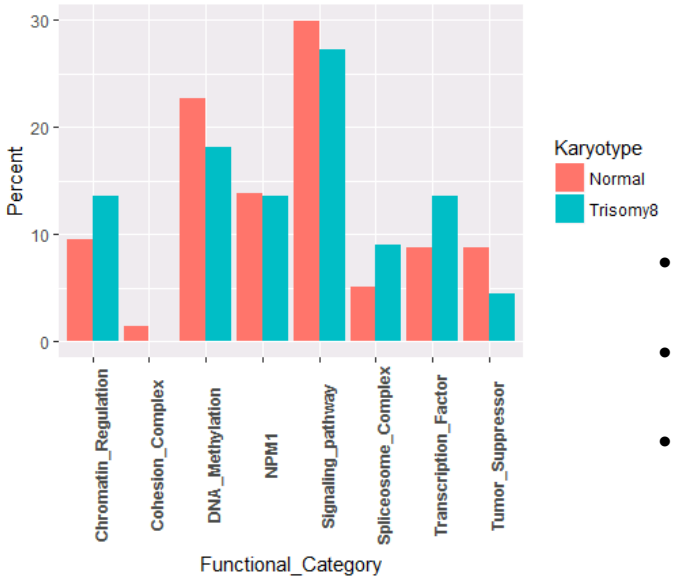
Priya Velu, MD, PhD
Molecular Genetic Pathology Fellow

Functional categorization of mutations by MRC in AML

Increased signaling pathway mutations in favorable and tumor suppressors in unfavorable



Differences between functional categorization of mutations in normal and trisomy 8 karyotypes (Intermediate)



- DNA methylation (*DNMT3A*)
- Tumor suppressors (*WT1*)
- Numbers are low for trisomy 8

Main conclusions from AML (MRC)

- "Negative" sequencing studies exist in both favorable and unfavorable cytogenetic categories. (Limitations of a targeted panel)
- Signaling pathway genes are the most commonly mutated in favorable
  - More variants in favorable than other karyotypes
- No DNA methylation gene mutations in favorable karyotypes
- Tumor Suppressors are mainly mutated in unfavorable karyotypes
  - Almost exclusively *TP53*
- *NPM1* mutations only occur in intermediate karyotypes
- *WT1* mutations are common in favorable and intermediate, do not occur in unfavorable
- Within intermediate karyotypes:
  - Tumor suppressors, signaling pathway and DNA methylation genes mutated in more normal karyotypes than trisomy 8s
  - Chromatin regulatory, spliceosome complex and transcription factor genes mutated more in Trisomy 8 than normal karyotypes.

AML risk stratification: European LeukemiaNet (ELN)

Risk category*	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low†}
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high†}
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low†} (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype,§ monosomal karyotype‖
	Wild-type *NPM1* and *FLT3*-ITD^{high†}
	Mutated *RUNX1*¶
	Mutated *ASXL1*¶
	Mutated *TP53*#

Frequencies, response rates, and outcome measures should be reported by risk category, and, if sufficient numbers are available, by specific genetic lesions indicated.

*Prognostic impact of a marker is treatment-dependent and may change with new therapies.
†Low, low allelic ratio (<0.5); high, high allelic ratio (≥0.5); semiquantitative assessment of *FLT3*-ITD allelic ratio (using DNA fragment analysis) is determined as ratio of the area under the curve "*FLT3*-ITD" divided by area under the curve "*FLT3*-wild type"; recent studies indicate that AML with *NPM1* mutation and *FLT3*-ITD low allelic ratio may also have a more favorable prognosis and patients should not routinely be assigned to allogeneic HCT.[57-59,77]
‡The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.
§Three or more unrelated chromosome abnormalities in the absence of 1 of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with *BCR-ABL1*.
‖Defined by the presence of 1 single monosomy (excluding loss of X or Y) in association with at least 1 additional monosomy or structural chromosome abnormality (excluding core-binding factor AML).[116]
¶These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.
#*TP53* mutations are significantly associated with AML with complex and monosomal karyotype.[37,66-69]

Döhner et.al., 2017

There are significant differences between MRC and ELN categorization schemes

MRC (2010)[4]

t(15;17)(q22;q21), t(8;21)(q22;q22), inv(16)(p13q22)/t(16;16)(p13;q22)
Abnormalities not classified as favorable or unfavorable
abn(3q) [excluding t(3;5)(q21~25;q31~35)], inv(3)(q21q26)/t(3;3)(q21;q26), add(5q), del(5q), −5, add(7q)/del(7q), −7, t(6;11)(q27;q23), t(10;11)(p11~13;q23), t(11q23) [excluding t(9;11)(p21~22;q23) and t(11;19)(q23;p13)],t(9;22)(q34;q11), −17/ abn(17p),complex (≥ 4 unrelated abnormalities)
Category not recognized

Risk category*	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
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	Complex karyotype,§ monosomal karyotype‖
	Wild-type *NPM1* and *FLT3*-ITD^{high}†
	Mutated *RUNX1*¶
	Mutated *ASXL1*¶
	Mutated *TP53*#

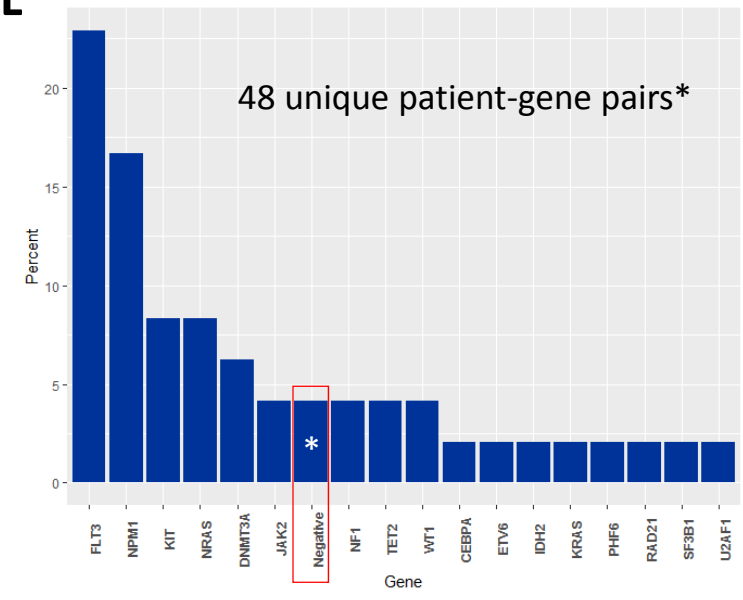
§Three or more unrelated chromosome abnormalities in the absence of 1 of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with *BCR-ABL1*.

ELN Favorable AML

25 patients

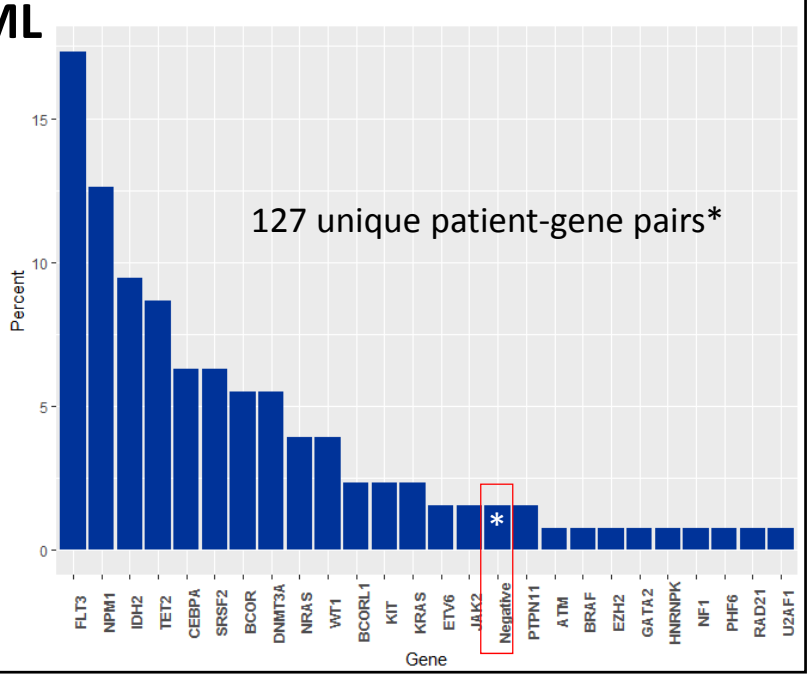
These include:

- t(8;21) (n=10)
- inv(16)/t(16;16) (n= 7)
- *NPM1* mutant with *FLT3* ITD VAF <50%
- No t(15;17)



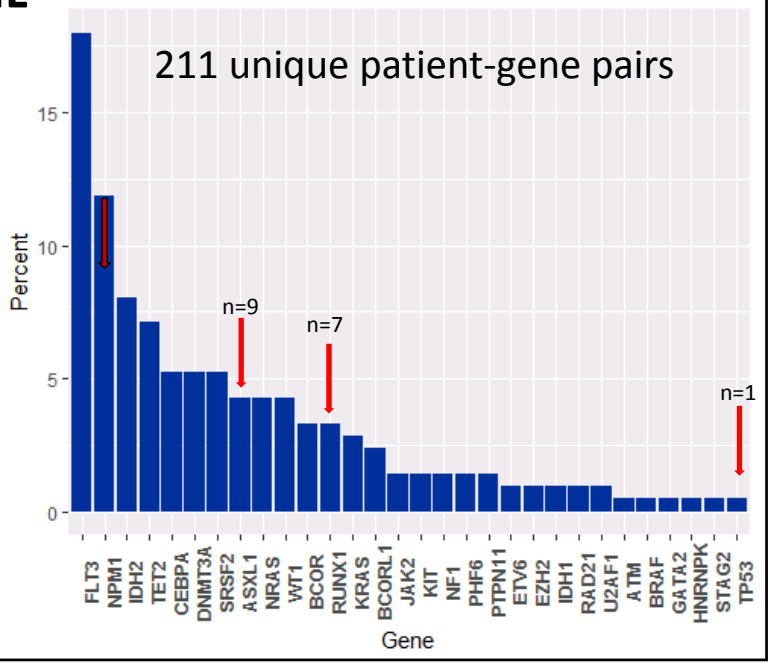
ELN Intermediate AML

- 56 patients
- 4 added with t(15;17)
- 35 removed
  - 3 v. 4 abnormalities
  - *NPM1* wild type with *FLT3* ITD high VAF
  - *NPM1* mutant with *FLT3* ITD low VAF or no *FLT3*
  - *RUNX1*
  - *ASXL1*
  - *TP53*



MRC Intermediate AML

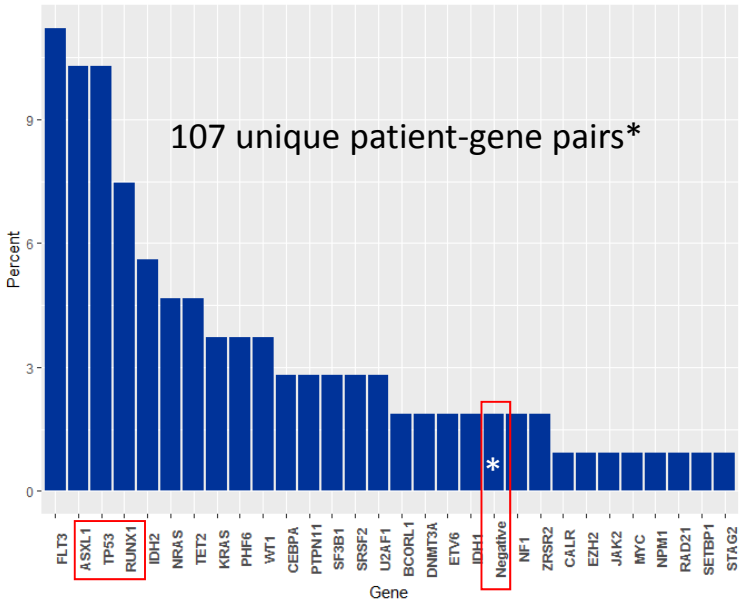
- 82 patients
- Most common finding: normal karyotype (n=51)
- 24/33 (73%) of *FLT* variants are ITDs
- 8 of these have VAF <50% with NPM1 mutations (ELN favorable)
- *ASXL1, RUNX1* and *TP53* mutant AMLs are all ELN unfavorable (n=17 from this group)
- *NPM1* wild type with *FLT3* ITD high (>50%) ELN unfavorable (n=7)
  - 2 with t(6;9)



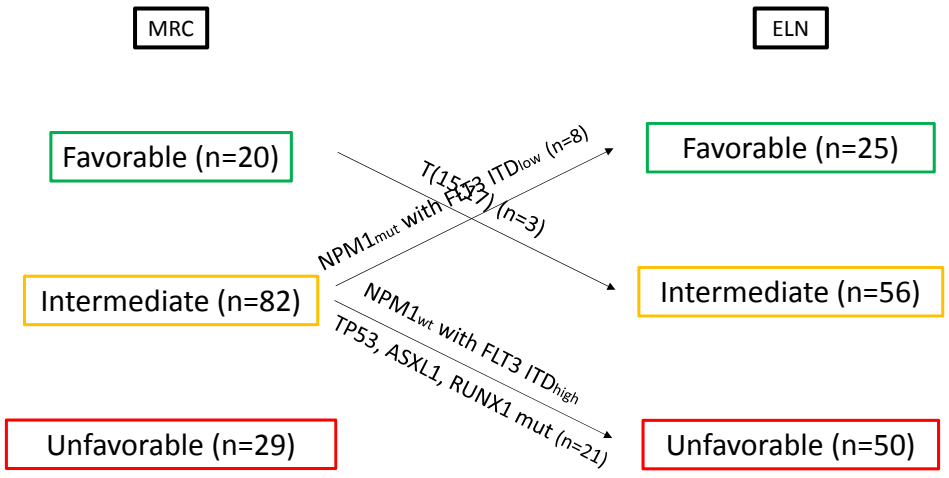
ELN unfavorable AML

50 patients

- Complex Karyotypes (≥3 abnormalities)
- *NPM1* wild type with FLT3 ITD high
- *RUNX1*
- *ASXL1*
- *TP53*
- t(6;9)



Shift of patients from MRC vs ELN



Functional Categorization of Variants

Table 1

FUNCTIONAL CATEGORIZATION OF GENES

CHROMATIN REGULATION	**DNA METHYLATION**	**SIGNALING PATHWAY**		**TRANSCRIPTION FACTOR**
ASXL1	*DNMT3A*	*ABL1*	*ATM*	*CEBPA*
BCOR	*IDH1/IDH2*	*BRAF*	*CALR*	*GATA2*
BCORL1	*TET2*	*CBL*	*CSF1R*	*MYC*
EZH2		*CSF1R*	*FLT3*	*MYCN*
ZMYM3	**SPLICEOSOME COMPLEX**	*GNAS*	*IL7R*	*RUNX1*
MLL2	*PRPF408*	*JAK2*	*KLHL6*	*TBL1XR1*
COHESIN COMPLEX	*SF1*	*KIT*	*KRAS*	**TUMOR SUPPRESSOR**
RAD21	*SF3A1*	*MAP2K1*	*MAPK1*	*ETV6*
SMC1A	*SF3B1*	*MPL*	*MYD88*	*HNRNPK*
STAG2	*SRSF2*	*NF1*	*NOTCH1*	*PTEN*
NPM1	*U2AF1*	*NOTCH2*	*NRAS*	*TP53*
NPM1	*U2AF2*	*PDGFRA*	*PTPN11*	*WT1*
	ZRSR2	*RIT1*	*HRAS*	*PHF6*

PHARMACO-GENETIC	**OTHER/UNKNOWN**				
TMPT	*BIRC3*	*CDKN2A*	*FAM5C*	*FBXW7*	*MIRI42*
	POT1	*SETBP1*	*CDH2*	*DDX3*	*XPO1*

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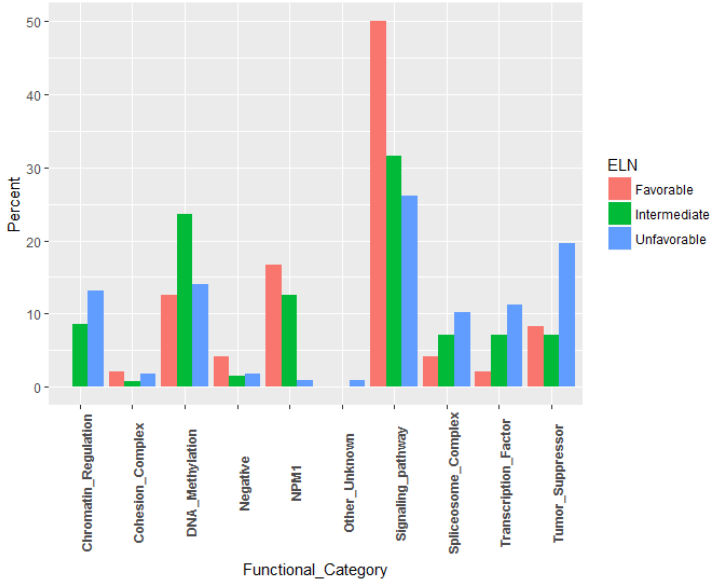
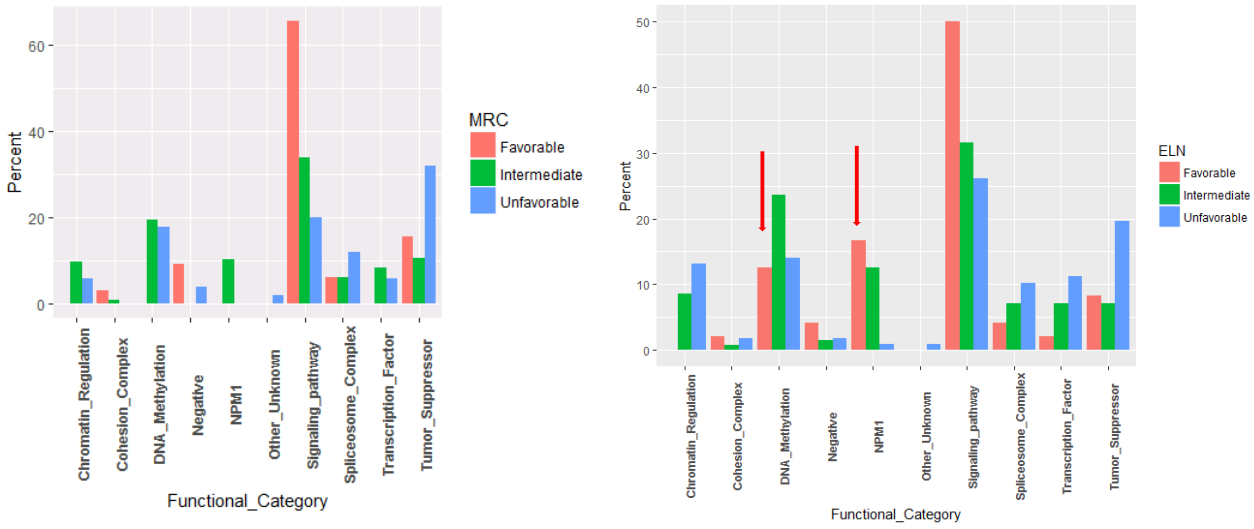
Molecular Genetic Pathology Fellow

Functional Categories by ELN in AML



- 1 unfavorable with NPM1 because this patient also had an ASXL1 mutation
- Negative in all 3
- Signaling pathway mutations common in favorable
- Tumor suppressor mutations common in unfavorable

Trends in functional categories are unchanged



Differences between MRC, ELN and SWOG

- MRC and SWOG are very similar. Two intermediate cases would be changed (1 to SWOG favorable, 1 to SWOG unfavorable)
  - Therefore no additional analysis with SWOG
- ELN incorporated t(6;9) into unfavorable which moved two cases from intermediate to unfavorable (also had unfavorable mutations)
- ELN favorable does not include t(15;17) in criteria
- ELN includes mutation detection: all *ASXL1*, *RUNX1* and *TP53* mutant AMLs are unfavorable
  - *NPM1* wild type or mutant with *FLT3* ITD
    - *FLT3* ITD high = >50% VAF. Need to consider % blasts in the sample
- ELN has more unfavorable AMLs from our cohort

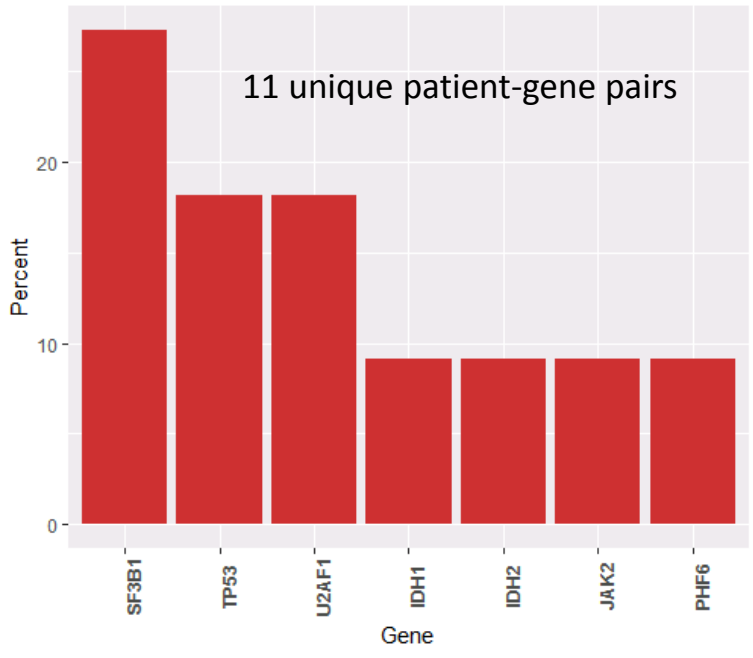
MDS risk stratification by International Prognostic Scoring System (IPSS-R)

Cytogenetic prognostic subgroups	Cytogenetic abnormalities
Very good	-Y, del(11q)
Good	Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), Complex: 3 abnormalities
Very poor	Complex: >3 abnormalities

No Cases with matching sequencing

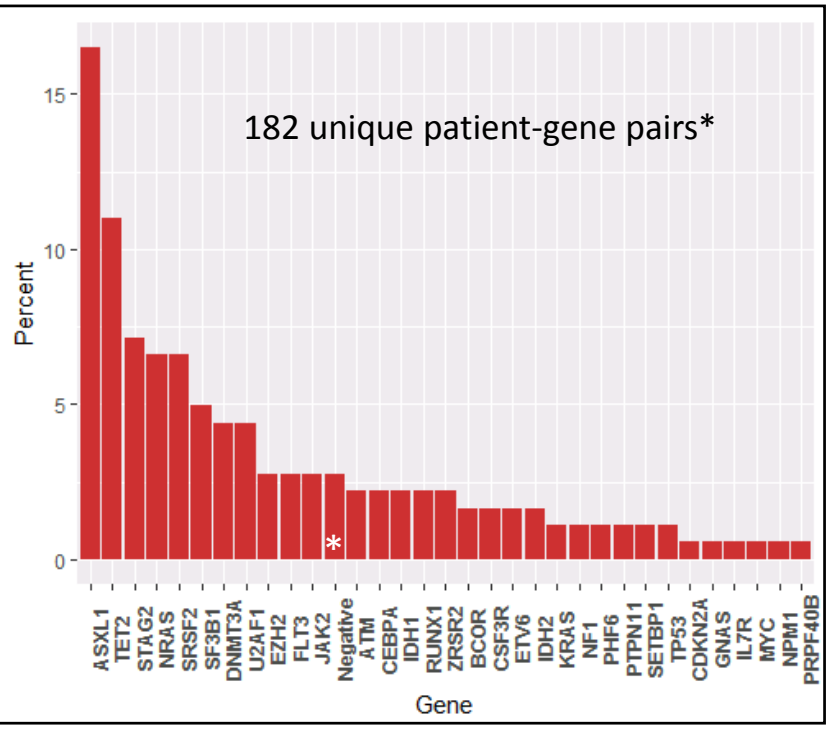
Good MDS

7 patients



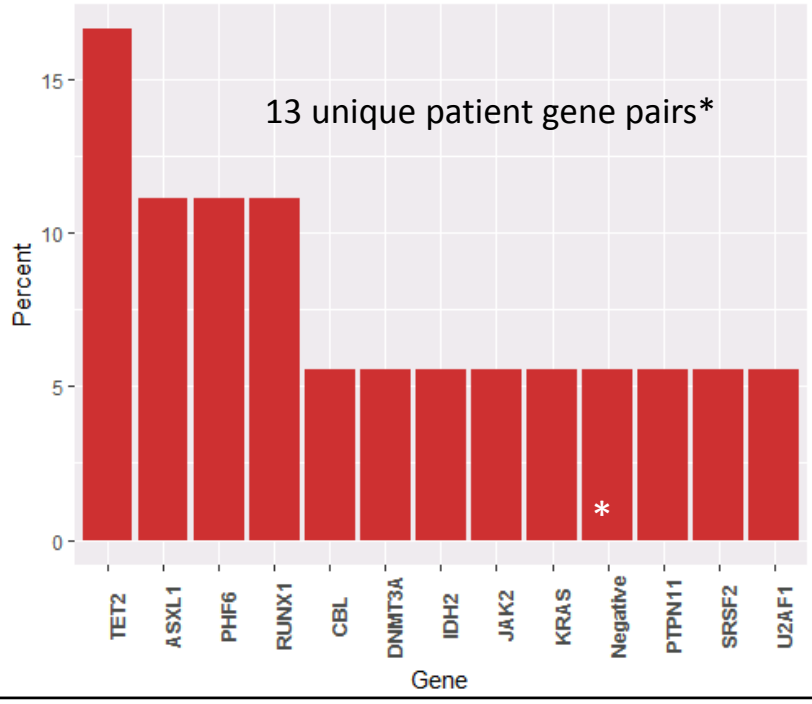
Intermediate MDS

63 patients



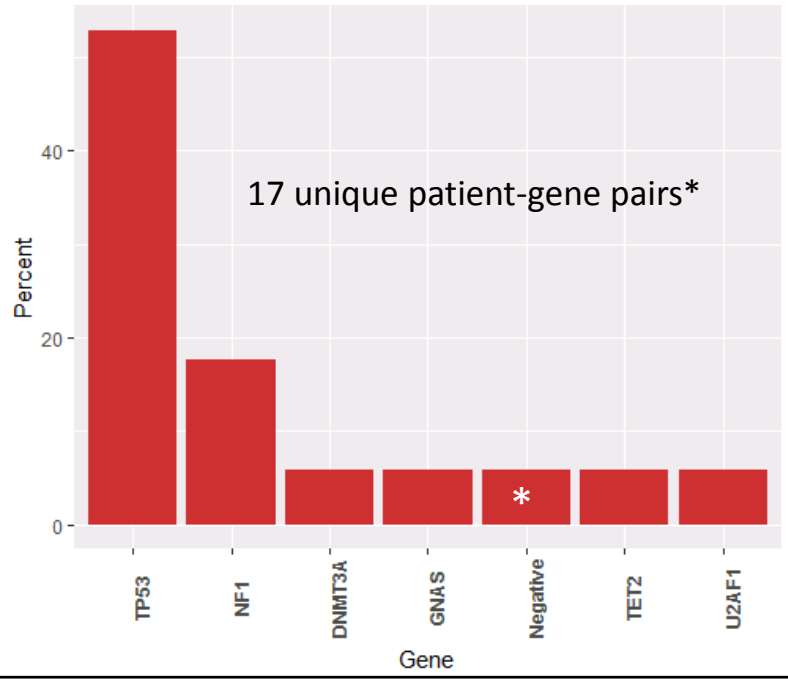
Poor MDS

7 patients

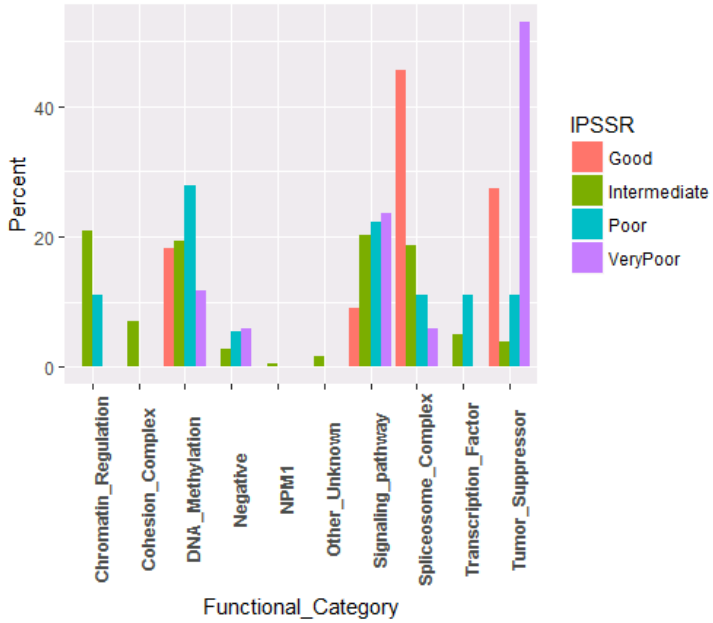


Very Poor MDS

13 patients



Functional Categories by IPSS-R in MDS



Main conclusions from MDS

- "Negative" sequencing studies exist in 3/4 cytogenetic categories. (Limitations of a targeted panel)
- Spliceosome complex genes are the most commonly mutated in good MDS
  - More variants in good than other karyotypes
- Cohesion complex gene mutations are exclusive to intermediate MDS
- Tumor suppressors are mainly mutated in very poor karyotypes
  - Almost exclusively TP53
- Very few NPM1 mutations in MDS
- The n is low for all risk categories except intermediate

Overall considerations for study design

- Clean data set with dnAML and new MDS.
  - Could include sAMLs
  - Older MDS
    - For both, karyotypes could be different than the current data set but you could still link risk/prognosis from karyotype to mutational signatures
- WT1 is a tumor suppressor
  - Mutant WT1 can cause a hyper-methylated phenotype in AML
  - This is causal and not a direct function by WT1
- Mutations by functional category trends do not differ between MRC and ELN AML
  - Survival data may show one to be superior to the other
- Use type of alteration as a way to stratify cytogenetics
  - Trisomys, monosomys, translocations, deletions, etc.

Thank you key players

- Priya Velu, Penn MGP fellow
- Jennifer Morrissette, Director of Cytogenetics and Clinical Director of CPD
- Dan Ackerman, Staff Scientist
- Ashkan Bigdeli, Bioinformatics Specialist

- Beckman Coulter Life Sciences (Genomic Reagents)
  - We have transitioned the majority of our extractions onto FormaPure Total for FFPE, cytology, fresh tissue and are validating for bone cores