Supporting Information: Supporting Tables

Babushok et al. Single Nucleotide Polymorphism Array Analysis of Bone Marrow Failure Patients Reveals Characteristic Patterns of Genetic Changes

Corresponding Author: Daria Babushok; Email: daria.babushok@uphs.upenn.edu

Contents:

Supporting Table 1. Breakdown of SNP-A Genotyping by Diagnosis, Number of Arrays and the SNP-A Platform

Diagnostic Group	Number of Patients (n=91)	Patients with One Array	Patients with Two Arrays	Patients with Three Arrays	Patients with Four Arrays	Number of Patients (Quad610)[1]	Number of Patients (Omni1)[2]
Aplastic Anemia	23	16	4	2	1	11	13
Aplastic Anemia with PNH Clone	8	6	2	0	0	3	7
Diamond-Blackfan Anemia	3	2	1	0	0	3	0
Dyskeratosis Congenita	6	6	0	0	0	1	5
Fanconi Anemia	3	2	1	0	0	2	2
Shwachman-Diamond Syndrome	4	1	2	1	0	3	3
Severe Congenital Neutropenia	1	0	1	0	0	1	1
Myelodysplastic Syndrome	4	3	1	0	0	3	1
Anemia NOS	5	4	0	1	0	3	3
Neutropenia NOS	14	9	4	1	0	9	10
Bone Marrow Failure NOS	12	10	1	1	0	6	7
Other	8	7	1	0	0	6	2
Subtotal	91	66	18	6	1	51	54

[1] Number of patients genotyped with Human Quad610 SNP Array**.**

[2] Number of patients genotyped with Human Omni1-Quad SNP Array

Supporting Table 2. Inherited Regions of Extended Homozygosity in BMFS*

Patient Number	Diagnosis	Chr	# of SNPs	Start[1]	End[1]	Length (Mb)	Gene Number	Selected Genes In Region
346.01	NeutropeniaNOS	1	1383	167,642,494	174,605,170	7.0	84	*FASLG, PIGC, TNF* superfamily
344.01	NeutropeniaNOS	5	959	126,938,115	132,673,660	5.7	43	*CSF2, IL3, IL4, IL5, IL13, UQCRQ,RAD50, AFF4*
274.01	AA	8	1115	74,306,675	80,691,801	6.4	23	*IL7, LY96,*
145.01	AAPNH	10	4908	90,053,738	100,189,076	10.1	114	*CYP26C1, CYP2C19, CYP2C9, CYP2C8, CYP26A1, CYP2C18, DNTT, FAS*
328.01	DC	11	5708	54,697,347	69,193,514	14.5	357	*RAD9A, RPS6KB2, MEN1, MAP4K2, MAP3K11, FOSL1*
281.01	AA	13	3097	48,734,519	60,224,565	11.5	66	*RB1, CYSLTR2,LECT1, DHRS12, SETDB2*
049.01	SCN	14	1393	26,403,059	33,625,685	7.2	23	*PRKD1, NUBPL, G2E3*
368.01	BMFNOS	X	943	70,479,791	80,186,893	9.7	73	*ATRX, COX7B, ERCC6L, FGF16, HDAC8, XIST, TAF1, RPS4X*
162.01	MDS	X	371	70,886,761	78,002,855	7.1	58	*FGF16, HDAC8, ERCC6L, XIST*

* Patients with consanguinity are excluded. [1]All chromosome coordinates are based on hg19 (NCBI build 37).

Supporting Table 3A. Enrichment Analysis of Copy Number Variants in Neutropenia NOS Patients Compared to Normal Controls (Quad 610 SNP Array, Caucasian)

Gene	Number of Patients With CNV	Number of Controls With CNV	Total Number of Patients	Total Number of Controls	CNV type	OR	p-value*	Bonferroni p-value
GTF2H2	**3**	**12**	**8**	**712**	**del**	**35.7**	**4.00E-04**	**3.80E-02**
NAIP	3	15	8	712	del	28.6	7.00E-04	6.65E-02
TKTL1	4	37	8	712	dup	18.0	5.00E-04	4.75E-02
TEX28	4	37	8	712	dup	18.0	5.00E-04	4.75E-02
OPN1MW2	4	43	8	712	dup	15.4	9.00E-04	8.55E-02
OPN1MW	4	43	8	712	dup	15.4	9.00E-04	8.55E-02
OPN1LW	4	43	8	712	dup	15.4	9.00E-04	8.55E-02
LOC647859	2	10	8	712	del	25.7	0.0068	6.46E-01
CDRT7	1	0	8	712	del	285.0	0.0111	1
MGC12916	1	0	8	712	del	285.0	0.0111	1
COX10	1	0	8	712	del	285.0	0.0111	1
MIR4731	1	0	8	712	del	285.0	0.0111	1
SLC7A9	1	0	8	712	del	285.0	0.0111	1
PMP22	1	0	8	712	del	285.0	0.0111	1
CDRT4	1	0	8	712	del	285.0	0.0111	1
TVP23C	1	0	8	712	del	285.0	0.0111	1
GMDS	1	0	8	712	del	285.0	0.0111	1
CEP89	1	0	8	712	del	285.0	0.0111	1
HS3ST3B1	1	0	8	712	del	285.0	0.0111	1
FAM82A1	1	0	8	712	del	285.0	0.0111	1
TEKT3	1	0	8	712	del	285.0	0.0111	1
CDRT15	1	0	8	712	del	285.0	0.0111	1
TVP23C-CDRT4	1	0	8	712	del	285.0	0.0111	1
FOXC2	1	0	8	712	dup	285.0	0.0111	1
LOC100616530	1	0	8	712	dup	285.0	0.0111	1
MTHFSD	1	0	8	712	dup	285.0	0.0111	1
LOC732275	1	0	8	712	dup	285.0	0.0111	1
FOXF1	1	0	8	712	dup	285.0	0.0111	1
FLJ30679	1	0	8	712	dup	285.0	0.0111	1
LOC146513	1	0	8	712	dup	285.0	0.0111	1
FOXF1-AS1	1	0	8	712	dup	285.0	0.0111	1
MTBP	1	0	8	712	dup	285.0	0.0111	1
FOXL1	1	0	8	712	dup	285.0	0.0111	1
IRF8	1	0	8	712	dup	285.0	0.0111	1
SNTB1	1	0	8	712	dup	285.0	0.0111	1
TFB2M	1	0	8	712	dup	285.0	0.0111	1
CNST	1	0	8	712	dup	285.0	0.0111	1

NEO1	1	1	8	712	del	94.9	0.0221	1
FOXP2	1	1	8	712	del	94.9	0.0221	1
METTL9	1	1	8	712	dup	94.9	0.0221	1
OTOA	1	1	8	712	dup	94.9	0.0221	1
IGSF6	1	1	8	712	dup	94.9	0.0221	1
PKD1L2	1	2	8	712	del	56.8	0.033	1
CNTNAP3B	1	4	8	712	del	31.5	0.0545	1
TXLNB	1	4	8	712	del	31.5	0.0545	1
SSX6	1	4	8	712	del	31.5	0.0545	1
AADAC	1	5	8	712	del	25.7	0.0651	1
MIR548H2	1	5	8	712	del	25.7	0.0651	1
ZNF630	1	5	8	712	del	25.7	0.0651	1

*Only CNVs with unadjusted p-value <0.10 are shown.

Supporting Table 3B. Enrichment Analysis of Copy Number Variants in Acquired Aplastic Anemia Patients Compared to Normal Controls (Quad 610 SNP Array, Caucasian)

Gene	Number of Patients With CNV	Number of Controls With CNV	Total Number of Patients	Total Number of Controls	CNV type	OR	p-value*	Bonferroni p-value
TKTL1	3	37	8	712	dup	11.5	0.0073	0.5183
TEX28	3	37	8	712	dup	11.5	0.0073	0.5183
OPN1MW2	3	43	8	712	dup	9.8	0.0109	0.7739
OPN1MW	3	43	8	712	dup	9.8	0.0109	0.7739
OPN1LW	3	43	8	712	dup	9.8	0.0109	0.7739
TARP	1	0	8	712	del	285.0	0.0111	0.7881
BAI3	1	0	8	712	dup	285.0	0.0111	0.7881
EXOC4	1	1	8	712	del	94.9	0.0221	1
LOC401134	1	1	8	712	del	94.9	0.0221	1
SNRPN	1	1	8	712	del	94.9	0.0221	1
ANKRD30BP2	1	1	8	712	dup	94.9	0.0221	1
ABCC4	1	1	8	712	dup	94.9	0.0221	1
ERC1	1	2	8	712	del	56.8	0.033	1
OPCML	1	3	8	712	del	40.5	0.0438	1
LRRC37A2	1	3	8	712	dup	40.5	0.0438	1
NSF	1	3	8	712	dup	40.5	0.0438	1
NSFP1	1	3	8	712	dup	40.5	0.0438	1
AADAC	1	5	8	712	del	25.7	0.0651	1
MIR548H2	1	5	8	712	del	25.7	0.0651	1
UGT2B28	1	7	8	712	del	18.8	0.0859	1
NKAIN2	1	7	8	712	dup	18.8	0.0859	1
ARL17B	1	8	8	712	dup	16.6	0.0962	1
ARL17A	1	8	8	712	dup	16.6	0.0962	1

*Only CNVs with unadjusted p-value <0.10 are shown.

Supporting Table 3C. Enrichment Analysis of Copy Number Variants in Neutropenia NOS Patients Compared to Normal Controls (Omni1-Quad SNP Array, Caucasian)

Gene	Number of Patients With CNV	Number of Controls With CNV	Total Number of Patients	Total Number of Controls	CNV type	OR	p-value*	Bonferroni p-value
SBNO2	**10**	**3**	**10**	**89**	**del**	**519.0**	**1.84E-11**	**1.06E-08**
ZNF516	**8**	**8**	**10**	**89**	**del**	**32.6**	**2.87E-06**	**1.65E-03**
MTMR3	3	0	10	89	dup	83.5	8.00E-04	4.60E-01
MSI2	9	30	10	89	del	12.4	9.00E-04	5.18E-01
PCSK5	4	4	10	89	del	13.2	0.0032	1
NXN	3	2	10	89	dup	16.3	0.0068	1
LOC283683	3	2	10	89	del	16.3	0.0068	1
ALDH1A3	2	0	10	89	dup	52.6	0.0093	1
EVI2A	2	0	10	89	del	52.6	0.0093	1
RPS6KA2	2	0	10	89	del	52.6	0.0093	1
NF1	2	0	10	89	del	52.6	0.0093	1
TCF3	5	12	10	89	del	6.2	0.0123	1
HCN1	4	7	10	89	del	7.6	0.0127	1
BCR	4	8	10	89	del	6.6	0.0181	1
SHISA9	3	4	10	89	del	8.9	0.0214	1
ADAP1	2	1	10	89	dup	17.4	0.0263	1
MASP2	2	1	10	89	del	17.4	0.0263	1
FCGR1C	2	1	10	89	del	17.4	0.0263	1
DOCK5	9	48	10	89	del	5.4	0.027	1
KCNMB2	8	38	10	89	del	4.5	0.0271	1
SDK1	6	22	10	89	del	4.3	0.0284	1
TRAK2	4	10	10	89	del	5.2	0.0327	1
DMD	5	16	10	89	del	4.5	0.0332	1
TMTC1	3	6	10	89	del	6.0	0.0457	1
TSC22D1	3	6	10	89	del	6.0	0.0457	1
UGT2B15	2	2	10	89	dup	10.3	0.0497	1
AMY1B	2	2	10	89	dup	10.3	0.0497	1
AMY1A	2	2	10	89	dup	10.3	0.0497	1
AMY1C	2	2	10	89	dup	10.3	0.0497	1
EMR3	5	18	10	89	del	3.9	0.0494	1
VGLL4	5	18	10	89	del	3.9	0.0494	1
STON2	2	2	10	89	del	10.3	0.0497	1
DCDC2	4	12	10	89	del	4.3	0.0532	1
TGFBR3	6	26	10	89	del	3.5	0.0566	1
LOC440970	3	7	10	89	del	5.1	0.0616	1
LOC285441	4	13	10	89	del	3.9	0.0658	1
WNK1	5	20	10	89	del	3.4	0.0702	1

PTPRD	9	55	10	89	del	3.9	0.0716	1
CFH	2	3	10	89	dup	7.3	0.0783	1
FAM211A	2	3	10	89	dup	7.3	0.0783	1
AMY2A	2	3	10	89	dup	7.3	0.0783	1
LRRC27	2	3	10	89	del	7.3	0.0783	1
LOC388692	2	3	10	89	del	7.3	0.0783	1
CROCC	2	3	10	89	del	7.3	0.0783	1
AGRN	3	8	10	89	del	4.5	0.0799	1
SEMA3E	4	14	10	89	del	3.6	0.08	1

*Only CNVs with unadjusted p-value <0.10 are shown.

Supporting Table 3D. Enrichment Analysis of Copy Number Variants in Acquired Aplastic Anemia Patients Compared to Normal Controls (Omni1-Quad SNP Array, Caucasian)

Gene	Number of Patients With CNV	Number of Controls With CNV	Total Number of Patients	Total Number of Controls	CNV type	OR	p-value*	Bonferroni p-value
SBNO2	**8**	**3**	**12**	**89**	**del**	**46.7**	**3.59E-07**	**0.000243137**
B4GALNT3	4	0	12	89	del	94.8	1.00E-04	0.0677
EXT1	8	13	12	89	del	10.7	3.00E-04	0.2031
MYO16	10	25	12	89	del	10.6	4.00E-04	0.2708
KRT16P1	5	4	12	89	del	13.9	0.001	0.677
LOC339240	5	4	12	89	del	13.9	0.001	0.677
MTMR3	3	0	12	89	dup	65.9	0.0013	0.8801
JARID2	3	0	12	89	del	65.9	0.0013	0.8801
SEMA4D	3	0	12	89	del	65.9	0.0013	0.8801
LOC283683	4	2	12	89	del	18.5	0.0016	1
SEMA3E	7	14	12	89	del	7.1	0.0026	1
CFH	4	3	12	89	dup	13.1	0.0035	1
MAD1L1	5	7	12	89	del	8.1	0.0051	1
EEF1DP3	4	4	12	89	del	10.1	0.0064	1
ZNF516	5	8	12	89	del	7.0	0.0077	1
KCNMB2	10	38	12	89	del	5.6	0.0086	1
LINC00616	6	13	12	89	del	5.7	0.0092	1
TJP2	10	39	12	89	del	5.4	0.0105	1
NXN	3	2	12	89	dup	12.9	0.0114	1
LOC649352	3	2	12	89	dup	12.9	0.0114	1
FAM66A	3	2	12	89	dup	12.9	0.0114	1
ZFHX4-AS1	2	0	12	89	del	42.6	0.0131	1
RUNDC3B	2	0	12	89	del	42.6	0.0131	1
MDGA2	2	0	12	89	del	42.6	0.0131	1
DLGAP2	2	0	12	89	del	42.6	0.0131	1
SERINC2	2	0	12	89	del	42.6	0.0131	1
ABCB1	2	0	12	89	del	42.6	0.0131	1
NDUFA12	2	0	12	89	del	42.6	0.0131	1
ZNF554	2	0	12	89	del	42.6	0.0131	1
TRPM2	2	0	12	89	del	42.6	0.0131	1
LOC727849	2	0	12	89	del	42.6	0.0131	1
LOC440297	2	0	12	89	del	42.6	0.0131	1
TGFBR3	8	26	12	89	del	4.5	0.014	1
SMAD1	10	42	12	89	del	4.7	0.0183	1
FGF12	6	16	12	89	del	4.5	0.0211	1
GALNT9	3	3	12	89	del	9.1	0.0213	1
MGAM	8	29	12	89	del	3.9	0.0256	1
LGALS9C	5	12	12	89	del	4.5	0.0283	1

ACTG1P4	3	4	12	89	dup	7.0	0.0347	1
CXADRP2	3	4	12	89	dup	7.0	0.0347	1
LOC646214	3	4	12	89	dup	7.0	0.0347	1
AMY2B	3	4	12	89	dup	7.0	0.0347	1
BOK	4	8	12	89	del	5.1	0.0344	1
CTNNA3	3	4	12	89	del	7.0	0.0347	1
SLC24A2	3	4	12	89	del	7.0	0.0347	1
GALNTL2	5	13	12	89	del	4.2	0.0366	1
SERF1A	2	1	12	89	del	14.0	0.0366	1
SERF1B	2	1	12	89	del	14.0	0.0366	1
PKHD1	9	39	12	89	del	3.5	0.0416	1
ACOT11	8	32	12	89	del	3.3	0.0433	1
CRCP	4	9	12	89	del	4.5	0.0462	1
LOC646762	4	9	12	89	del	4.5	0.0462	1
FAM35B2	3	5	12	89	dup	5.7	0.0516	1
FLJ43860	3	5	12	89	del	5.7	0.0516	1
AK8	3	5	12	89	del	5.7	0.0516	1
TRAK2	4	10	12	89	del	4.0	0.0603	1
LOC439994	2	2	12	89	dup	8.3	0.0682	1
RNF212	2	2	12	89	dup	8.3	0.0682	1
BMS1P1	3	6	12	89	dup	4.7	0.072	1
BMS1P5	3	6	12	89	dup	4.7	0.072	1
POTEB	3	6	12	89	dup	4.7	0.072	1
NF1P2	3	6	12	89	dup	4.7	0.072	1
GLUD1P7	3	6	12	89	dup	4.7	0.072	1
PPFIA2	7	28	12	89	del	2.9	0.0677	1
LINGO2	7	28	12	89	del	2.9	0.0677	1
POU4F1-AS1	2	2	12	89	del	8.3	0.0682	1
MIR1233-2	2	2	12	89	del	8.3	0.0682	1
LOC401164	2	2	12	89	del	8.3	0.0682	1
DACT2	2	2	12	89	del	8.3	0.0682	1
SMN2	2	2	12	89	del	8.3	0.0682	1
SMN1	2	2	12	89	del	8.3	0.0682	1
MIR1233-1	2	2	12	89	del	8.3	0.0682	1
EDARADD	2	2	12	89	del	8.3	0.0682	1
TCERG1L	8	35	12	89	del	2.9	0.0692	1
PDGFD	5	16	12	89	del	3.3	0.0705	1
TSC22D1	3	6	12	89	del	4.7	0.072	1
MOB2	3	6	12	89	del	4.7	0.072	1
GRID2	4	11	12	89	del	3.6	0.0765	1
MSI2	7	30	12	89	del	2.7	0.0914	1

*Only CNVs with unadjusted p-value <0.10 are shown.

Supporting Table 4. Targeted Analysis of Genes Implicated in BMFS and Hematologic Malignancies.

Pathogenic Variants				
Gene	Diagnostic Group	Patients Affected/Total	Abnormality	Significance
FANCA	Fanconi Anemia	2/4	CN-LOH	Unmasked recessive *FANCA* mutation
SBDS	Shwachman Diamond Syndrome	1/4	CN-LOH	Gene conversion selecting for a hypomorphic *SBDS* allele
CBL	Other	1/7	CN-LOH	Known oncogenic mutation in *CBL* underlying 11q CN-LOH acquisition
RUNX1	BMFNOS	1/13	Het del	*RUNX1* haploinsufficiency associated with congenital thrombocytopenia, AML/MDS.
FLT3	Other (AML)	1/7	Acquired CN-LOH	Known oncogenic mutation *FLT3* ITD underlying 13q CN-LOH acquisition
Variants of Unknown Significance				
RTEL1	Dyskeratosis Congenita	3/6	Dup (ex 30-35)	Unknown significance.
ATM	Other	1/7	Acquired CNLOH	Unknown significance; within a region of acquired 11q CN-LOH.
	Fanconi Anemia	1/4	29 MB CNLOH	Within a larger region of homozygosity by descent.
BRAF	MDS	1/4	Acquired dup	Within isochromosome 7; significance unknown.
	MDS	1/4	Acquired del	Within monosomy 7; significance unknown.
ETV6	AA	4/13	Intronic deletion	Unknown significance.
	AAPNH	2/5		
	BMFNOS	4/8		
	SDS	3/3		
EZH2	MDS	1/4	Acquired dup	Within isochromosome 7; significance unknown.
	MDS	1/4	Acquired del	Within monosomy 7; significance unknown.
GATA2	Fanconi Anemia	1/4	16.1 MB CNLOH	Within a larger region of homozygosity by descent.
GNAS	Other	1/7	7.4 MB CNLOH	Within a larger region of homozygosity by descent.
KLHL6	Fanconi Anemia	1/4	9.1 MB CNLOH	Within a larger region of homozygosity by descent.
SF3B1	Other	1/7	15.4 MB CNLOH	Within a larger region of homozygosity by descent.
TERT	Fanconi Anemia	1/4	7.2 MB CNLOH	Within a larger region of homozygosity by descent.

Supporting Table 5. Comparison of Clinical Information Provided by SNP Array and Metaphase Cytogenetics

Cytogenetics (% of Total)	610 Quad, n (%)	Omni1, n (%)	Overall, n (%)
Normal Cytogenetics (87.9%)	57	52	109
Normal Array	14 (24.6)	1 (1.9)	15 (13.8)
Abnormal Array	43 (75.4)	51 (98.1)	94 (86.2)
Abnormal Cytogenetics (8.9%)	9	2	11
Normal Array	0 (0)	0 (0)	0 (0)
Abnormal Array	9 (100)	2 (100)	11 (100)
No Cytogenetics (3.2 %)	1	3	4
Normal Array	1 (100)	0 (0)	1 (0.25)
Abnormal Array	0 (0)	3 (100)	3 (0.75)
Total	67	57	124

Supporting Table 6. Comparison of Acquired CN-LOH Frequencies in aAA Versus non-aAA BMFS in Published Studies of SNP-A Genotyping in BMFS

Publication	Patients with acquired CN-LOH (aAA)	Patients With No CN-LOH (aAA)	Patients with acquired CN-LOH (Non-aAA BMFS)	Patients with No CN-LOH (Non-aAA BMFS)	Description of Non-AA BMFS Population
Katagiri *et al.*[1]	34	272	n/a	n/a	n/a
Afable *et al.* [2]	7	86	0	24	Hypoplastic MDS
Quentin *et al*.[3]	n/a	n/a	1	31	FA patients genotyped using SNP-A (11 with myelodysplasia, 16 with aplastic marrow, 5 with normal marrow; patients who transformed to leukemia were excluded from this analysis)
Current Study Babushok *et al.*	6	25	1	51	See Table 1, "Other" category excluded
Total	47	383	2	106	

Comparison of acquired CN-LOH in patients with aAA versus non-aAA BMFS: Odds Ratio 6.504, 95% CI: 1.653-56.053, p=0.0022.

Supporting References

1. Katagiri T, Sato-Otsubo A, Kashiwase K, et al. Frequent loss of HLA alleles associated with copy number-neutral 6pLOH in acquired aplastic anemia. Blood 2011;118:6601-9.
2. Afable MG, 2nd, Wlodarski M, Makishima H, et al. SNP array-based karyotyping: differences and similarities between aplastic anemia and hypocellular myelodysplastic syndromes. Blood 2011;117:6876-84.
3. Quentin S, Cuccuini W, Ceccaldi R, et al. Myelodysplasia and leukemia of Fanconi anemia are associated with a specific pattern of genomic abnormalities that includes cryptic RUNX1/AML1 lesions. Blood 2011;117:e161-70.