The clinical and biological significance of \textit{HOPX} in \textit{de novo} AML

Chein-Chin Lin$^{1,2}$

$^1$Department of Laboratory medicine, $^2$Division of Hematology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
**HOPX** is an unusual homeobox gene

- HOPX: homeodomain only protein homeobox
- The **smallest** known homeodomain protein
- Composed of a divergent protein incapable of DNA binding
- Important in cardiac development
**HOPX** is an unusual homeobox gene

- **HOPX**: homeodomain only protein homeobox
- The **smallest** known homeodomain protein
- Composed of a divergent protein incapable of DNA binding
- Important in cardiac development

*Cell, 2002*
The role of *HOPX* has been explored in various cancers:

- **Nasopharynx**: Ren, Nat comm, 2017
- **Lung**: Chen, Int J Cancer, 2007
- **Pancreas**: Waraya, BMC Cancer, 2012
- **Stomach**: Ooki, Oncogene, 2010
- **Colon**: Harada, Anticancer Res, 2011
- **Uterus**: Yamaguchi, Int J Cancer, 2009
Reduced $HOPX$ expression is associated with advanced disease status

**Early-stage NPC**

- Normal ($n = 6$)
- LN− ($n = 10$)
- LN+ ($n = 10$)
- DM ($n = 10$)

**Advanced-stage NPC**

- Normal
- NPC

$IHC$ score

- $P = 0.006$
- $P = 0.003$
- $P = 0.002$

$HOPX$ methylation rate (%)

- $P = 0.019$

*Nat Commun.* 2017 Feb 1;8:14053.
HOPX hypermethylation promotes metastasis via activating SNAIL transcription in nasopharyngeal carcinoma
Lung  


Homeobox gene *HOP* has a potential *tumor suppressive* activity in human lung cancer
Cancer specific promoter CpG Islands hypermethylation of *HOP* homeobox (HOPX) gene and its potential tumor suppressive role in pancreatic carcinogenesis

*Pancreas*  
*Waraya, BMC Cancer, 2012*
Potential utility of \textit{HOP} homeobox gene promoter \textit{methylation} as a marker of tumor aggressiveness in gastric cancer

\textbf{Stomach} \textit{Ooki, Oncogene, 2010}
Methylation of the homeobox gene, *HOPX*, is frequently detected in poorly differentiated colorectal cancer.

*Harada, Anticancer Res, 2011*
Homeobox gene *HOPX* is epigenetically silenced in human uterine endometrial cancer and suppresses estrogen-stimulated proliferation of cancer cells by inhibiting serum response factor.

*Yamaguchi, Int J Cancer, 2009*
*HOPX* is a tumor suppressor gene in solid cancers.

*HOPX* expression was lowered by promoter hypermethylation during tumorigenesis.
**HOPX** is a tumor suppressor gene in solid cancers.

**HOPX** expression was lowered by promoter hypermethylation during tumorigenesis.

**Q: What about AML?**
Patients and methods

• 347 de novo AML pts BM samples in NTUH (1995-2011) for mRNA microarray analysis; median f/u
• 227 pts received standard induction chemotherapy
• *Illumina Human HT-12 V4 Expression BeadChip*

347 AML pts

High *HOPX* expression: N=174

Low *HOPX* expression: N=173
**HOPX expression levels and AML patients’ survival**

![Graph showing OS and DFS for HOPX expression levels in NTUH data](image)

- **Lower HOPX**
- **Higher HOPX**

**OS**
- Median 23.7 vs. 116.8
- N = 124
- N = 103
- P < 0.0001

**DFS**
- Median 5.9 vs. NR
- N = 124
- N = 103
- P < 0.0001

*NTUH data*
**HOPX expression levels and AML patients’ survival**

- **Lower HOPX**
- **Higher HOPX**

**NTUH data**

A. Median 23.7 vs. 116.8
   - NTUH: N = 124
   - P < 0.0001

B. Median 5.9 vs. NR
   - NTUH: N = 124
   - P < 0.0001

C. Median 11.1 vs. 19.2
   - TCGA: N = 91
   - P = 0.006

D. Median 7.8 vs. 33.3
   - GSE12417: N = 81
   - P < 0.0001
Validation between array data and qPCR

\[ y = 0.916x - 14.271 \]

\[ R = 0.63 \]

NTUH data
Methylation level of HOPX

U937 cell line

Pts samples

Methylation level of HOPX
Hypermethylation of \textit{HOPX} is \textbf{NOT} observed in AML
Clinical manifestations between AML patients with high/low *HOPX* expression

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (n=347)</th>
<th>Higher <em>HOPX</em> Expression (n=174)</th>
<th>Lower <em>HOPX</em> Expression (n=173)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex^1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>196</td>
<td>99</td>
<td>97</td>
<td>0.914</td>
</tr>
<tr>
<td>Female</td>
<td>151</td>
<td>75</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>Age (year)^1</td>
<td>60 (15-91)</td>
<td>53 (18-88)</td>
<td>0.023</td>
<td></td>
</tr>
<tr>
<td>Lab data^1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC (/μL)</td>
<td>14520 (580-34120)</td>
<td>25110 (380-423000)</td>
<td>0.011</td>
<td></td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>8.2 (3.3-13.0)</td>
<td>8.0 (3.7-16.2)</td>
<td>0.911</td>
<td></td>
</tr>
<tr>
<td>Platelet (x1,000 /μL)</td>
<td>55.5 (6-655)</td>
<td>41.0 (2-412)</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Blast (/μL)</td>
<td>6477.8 (0-283213)</td>
<td>10773.5 (0-369070)</td>
<td>0.182</td>
<td></td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>794 (202-7734)</td>
<td>1042 (242-13130)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>FAB^1</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>M0</td>
<td>6</td>
<td>5 (83.3)</td>
<td>1 (16.7)</td>
<td>0.099</td>
</tr>
<tr>
<td>M1</td>
<td>67</td>
<td>42 (62.7)</td>
<td>25 (37.3)</td>
<td>0.021</td>
</tr>
<tr>
<td>M2</td>
<td>109</td>
<td>48 (44.0)</td>
<td>61 (56.0)</td>
<td>0.104</td>
</tr>
<tr>
<td>M3</td>
<td>28</td>
<td>4 (14.3)</td>
<td>24 (85.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>M4</td>
<td>103</td>
<td>58 (56.3)</td>
<td>45 (43.7)</td>
<td>0.126</td>
</tr>
<tr>
<td>M5</td>
<td>20</td>
<td>4 (20.0)</td>
<td>16 (80.0)</td>
<td>0.006</td>
</tr>
<tr>
<td>M6</td>
<td>8</td>
<td>7 (87.5)</td>
<td>1 (12.5)</td>
<td>0.032</td>
</tr>
<tr>
<td>Undetermined</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Induction response^**</td>
<td>227</td>
<td>103</td>
<td>124</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CR</td>
<td>166</td>
<td>60 (58.3) %</td>
<td>106 (85.5) %</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PR+refractory</td>
<td>45</td>
<td>35 (34.0) %</td>
<td>10 (8.1) %</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Induction death</td>
<td>16 (7.0)</td>
<td>8 (7.8)</td>
<td>8 (6.5)</td>
<td>0.702</td>
</tr>
</tbody>
</table>

^1 number of patients.
^2 median (range).
* number of patients (% with higher or lower *HOPX* expression in the AML subtype).
** number of patients (% in the total patients or subgroup of patients with higher or lower *HOPX* expression).

Abbreviation: LDH, lactate dehydrogenase; CR, complete remission; PR, partial remission.
Association of *HOPX* expression levels with cytogenetic abnormalities

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total</th>
<th>Higher <em>HOPX</em> Expression</th>
<th>Lower <em>HOPX</em> Expression</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Karyotype</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable</td>
<td>58</td>
<td>11</td>
<td>47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>t(8;21)</td>
<td>24</td>
<td>0</td>
<td>24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>t(15;17)</td>
<td>27</td>
<td>4</td>
<td>23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intermediate</td>
<td>196</td>
<td>102</td>
<td>94</td>
<td>0.532</td>
</tr>
<tr>
<td>Normal</td>
<td>166</td>
<td>81</td>
<td>85</td>
<td>0.582</td>
</tr>
<tr>
<td>Unfavorable</td>
<td>71</td>
<td>48</td>
<td>23</td>
<td>0.001</td>
</tr>
</tbody>
</table>

†Favorable, t(15;17), t(8;21), inv (16); unfavorable, -7, del(7q), -5, del(5q), 3q abnormality, complex abnormalities; Intermediate, normal karyotype and other abnormalities.

*NTUH data*
### Association of HOPX expression levels with other genetic alterations

<table>
<thead>
<tr>
<th>Mutation</th>
<th>No. of patients with alteration (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Whole cohort (n=347)</td>
<td>Higher HOPX Expression (n=174)</td>
</tr>
<tr>
<td>FLT3/ITD</td>
<td>84/347 (24.2)</td>
<td>38/174 (21.8)</td>
</tr>
<tr>
<td>FLT3/TKD</td>
<td>32/347 (9.2)</td>
<td>13/174 (7.5)</td>
</tr>
<tr>
<td>N-RAS</td>
<td>59/347 (17.0)</td>
<td>27/174 (15.5)</td>
</tr>
<tr>
<td>K-RAS</td>
<td>15/347 (4.3)</td>
<td>5/174 (2.9)</td>
</tr>
<tr>
<td>PTPN11</td>
<td>22/347 (6.3)</td>
<td>11/174 (6.3)</td>
</tr>
<tr>
<td>KIT</td>
<td>15/347 (4.3)</td>
<td>4/174 (2.3)</td>
</tr>
<tr>
<td>DNMT3A</td>
<td>66/347 (19.0)</td>
<td>41/174 (23.6)</td>
</tr>
<tr>
<td>WTI</td>
<td>26/347 (7.5)</td>
<td>12/174 (6.9)</td>
</tr>
<tr>
<td>NPM1</td>
<td>99/347 (28.5)</td>
<td>41/174 (23.6)</td>
</tr>
<tr>
<td>CEBPA (double mutation)</td>
<td>27/347 (7.8)</td>
<td>5/174 (2.9)</td>
</tr>
<tr>
<td>RUNX1</td>
<td>50/347 (14.4)</td>
<td>39/174 (22.4)</td>
</tr>
<tr>
<td>MLL/PTD</td>
<td>13/346 (3.8)</td>
<td>5/173 (2.9)</td>
</tr>
<tr>
<td>ASXL1</td>
<td>52/347 (15.0)</td>
<td>34/174 (19.5)</td>
</tr>
<tr>
<td>IDH1</td>
<td>20/347 (5.8)</td>
<td>10/174 (5.7)</td>
</tr>
<tr>
<td>IDH2</td>
<td>51/347 (14.7)</td>
<td>37/174 (21.3)</td>
</tr>
<tr>
<td>TP53</td>
<td>16/346 (4.6)</td>
<td>10/173 (5.8)</td>
</tr>
<tr>
<td>TET2</td>
<td>56/347 (16.1)</td>
<td>23/174 (13.2)</td>
</tr>
</tbody>
</table>

NTUH data
Multivariate analysis (Cox regression) on overall survival

<table>
<thead>
<tr>
<th>Variables</th>
<th>HR</th>
<th>Lower</th>
<th>Upper</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cohort (n=227)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.017</td>
<td>1.002</td>
<td>1.031</td>
<td>0.021</td>
</tr>
<tr>
<td>WBC/1000</td>
<td>1.004</td>
<td>1.001</td>
<td>1.006</td>
<td>0.012</td>
</tr>
<tr>
<td>Karyotype</td>
<td>3.725</td>
<td>2.273</td>
<td>6.105</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FLT3-ITD</td>
<td>1.522</td>
<td>0.968</td>
<td>2.391</td>
<td>0.069</td>
</tr>
<tr>
<td>CEBPA&lt;sup&gt;double mutation&lt;/sup&gt;</td>
<td>0.299</td>
<td>0.114</td>
<td>0.785</td>
<td>0.014</td>
</tr>
<tr>
<td>RUNX1</td>
<td>1.542</td>
<td>0.849</td>
<td>2.800</td>
<td>0.155</td>
</tr>
<tr>
<td>MLL-PTD</td>
<td>3.150</td>
<td>1.438</td>
<td>6.902</td>
<td>0.004</td>
</tr>
<tr>
<td>WT1</td>
<td>1.804</td>
<td>0.993</td>
<td>3.278</td>
<td>0.053</td>
</tr>
<tr>
<td>TP53</td>
<td>3.085</td>
<td>1.151</td>
<td>8.267</td>
<td>0.025</td>
</tr>
<tr>
<td><strong>HOPX</strong></td>
<td>1.172</td>
<td>1.050</td>
<td>1.307</td>
<td>0.005</td>
</tr>
<tr>
<td>HOXA9</td>
<td>1.142</td>
<td>0.815</td>
<td>1.600</td>
<td>0.441</td>
</tr>
</tbody>
</table>

*The model was generated from a stepwise Cox regression model that included age, WBC, karyotype (unfavorable cytogenetics versus others), gene mutations of FLT3, WT1, CEBPA, RUNX1, MLL, TP53 and expression level of HOXA9 and HOPX.

Abbreviations: HR, hazard ratio; CI, confidence interval; WBC, white blood cell count

NTUH data
Gene expression signature for prognostication in AML

• A three-gene expression-based risk score can refine the European LeukemiaNet AML classification. *(J hema oncol, 2016)*

• Epigenetics meets genetics in acute myeloid leukemia: clinical impact of a novel seven-gene score. *(JCO, 2014)*

• An mRNA expression signature (11-gene) for prognostication in de novo acute myeloid leukemia patients with normal karyotype. *(Oncotarget, 2016)*

• Identification of a 24-gene prognostic signature that improves the European LeukemiaNet risk classification of acute myeloid leukemia: an international collaborative study. *(JCO, 2013)*
### Comparisons of HOPX to published prognostic gene signatures

<table>
<thead>
<tr>
<th>Predictor</th>
<th>NTUH (n=227)</th>
<th>TCGA (n=186)</th>
<th>GSE12417 (n=162)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HOPX</strong></td>
<td>0.001</td>
<td>0.003</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>(1.46;1.17-1.82)</td>
<td>(1.34;1.11-1.61)</td>
<td>(1.52;1.22-1.89)</td>
</tr>
<tr>
<td><strong>HOPX</strong></td>
<td>0.039</td>
<td>0.015</td>
<td>0.002</td>
</tr>
<tr>
<td>3-gene score (Wilop et al.)</td>
<td>(1.29;1.01-1.65)</td>
<td>(1.31;1.05-1.63)</td>
<td>(1.43;1.15-1.78)</td>
</tr>
<tr>
<td><strong>HOPX</strong></td>
<td>0.125</td>
<td>0.014</td>
<td>0.009</td>
</tr>
<tr>
<td>7-gene score (Marcucci et al.)</td>
<td>(1.22;0.95-1.58)</td>
<td>(1.33;1.06-1.68)</td>
<td>(1.35;1.08-1.68)</td>
</tr>
<tr>
<td><strong>HOPX</strong></td>
<td>0.004</td>
<td>0.597</td>
<td>0.010</td>
</tr>
<tr>
<td>11-gene score (Chuang et al.)</td>
<td>(1.07;1.02-1.11)</td>
<td>(1.01;0.96-1.07)</td>
<td>(1.05;1.01-1.10)</td>
</tr>
<tr>
<td><strong>HOPX</strong></td>
<td>0.030</td>
<td>0.070</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-gene score (Li et al.)</td>
<td>(1.30;1.03-1.64)</td>
<td>(1.19;0.99-1.44)</td>
<td>(1.47;1.20-1.79)</td>
</tr>
</tbody>
</table>

*J hema oncol, 2016*

*JCO, 2014*

*Oncotarget, 2016*

*JCO, 2013*
### Comparisons of \textit{HOPX} to published prognostic gene signatures

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<td>&lt;0.001 (1.52;1.22-1.89)</td>
</tr>
<tr>
<td>3-gene score</td>
<td>0.103 (1.24;0.96-1.60)</td>
<td>0.005 (1.34;1.10-1.65)</td>
<td>0.601 (1.06;0.85-1.33)</td>
</tr>
<tr>
<td>\textit{HOPX}</td>
<td>0.039 (1.29;1.01-1.65)</td>
<td>0.015 (1.31;1.05-1.63)</td>
<td>0.002 (1.43;1.15-1.78)</td>
</tr>
<tr>
<td>7-gene score</td>
<td>0.014 (1.20;1.04-1.39)</td>
<td>0.356 (1.06;0.94-1.20)</td>
<td>0.117 (1.13;0.97-1.32)</td>
</tr>
<tr>
<td>\textit{HOPX}</td>
<td>0.125 (1.22;0.95-1.58)</td>
<td>0.014 (1.01;0.96-1.07)</td>
<td>0.009 (1.05;1.01-1.10)</td>
</tr>
<tr>
<td>11-gene score</td>
<td>0.004 (1.07;1.02-1.11)</td>
<td>0.597 (1.01;0.96-1.07)</td>
<td>0.010 (1.05;1.01-1.10)</td>
</tr>
<tr>
<td>\textit{HOPX}</td>
<td>0.030 (1.30;1.03-1.64)</td>
<td>0.070 (1.19;0.99-1.44)</td>
<td>&lt;0.001 (1.47;1.20-1.79)</td>
</tr>
<tr>
<td>24-gene score</td>
<td>0.005 (1.13;1.04-1.24)</td>
<td>&lt;0.001 (1.11;1.05-1.17)</td>
<td>0.041 (1.07;1.00-1.14)</td>
</tr>
</tbody>
</table>

* \textit{J hema oncol, 2016} \hspace{1cm} \textit{JCO, 2014} \hspace{1cm} \textit{Oncotarget, 2016} \hspace{1cm} \textit{JCO, 2013}
High *HOPX* expression is an independent poor prognostic factor in AML
High *HOPX* expression is an independent poor prognostic factor in AML

**Q:** Why poor prognosis?
Hopx expression defines a subset of multipotent hair follicle stem cells and a progenitor population primed to give rise to K6⁺ niche cells

Norifumi Takeda¹,²,³,*, Rajan Jain¹,²,³,*, Matthew R. LeBoeuf¹,⁴, Arun Padmanabhan¹,²,³, Qiaohong Wang¹,²,³, Li Li², Min Min Lu², Sarah E. Millar¹,⁴ and Jonathan A. Epstein¹,²,³,‡
Inter-conversion between intestinal stem cell populations in distinct niches

Norifumi Takeda¹,²,³, *, Rajan Jain¹,²,³, *, Matthew R. LeBoeuf¹,⁴, Qiaohong Wang¹,²,³, Min Min Lu², and Jonathan A. Epstein¹,²,³, #
Small intestine crypt

(Crypt base columnar stem cells)

Q: Is *HOPX* a marker of leukemia stem cell (LSC)?

*HOPX* is a stem cell marker in hair follicle and small intestine.
HOPX and HOX family expression in normal hematopoietic populations

GSE24759

HSC  ERY  MEGA  GMP  DC  B  NK  NKT  T

-2.0  +2.0

HOPX
HOXB2
HOXA3
HOXA7
HOXA6
HOXB3
HOXA4
HOXA5
HOXB5
HOXA9
HOXA10
MEIS1
Stem cell gene expression programs influence clinical outcome in human leukemia

A 17-gene stemness score for rapid determination of risk in acute leukaemia

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Molecular Signatures of Proliferation and Quiescence in Hematopoietic Stem Cells

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A. [Graph showing marrow cellularity and HSC in cycle over days after SFU treatment]

B. [Diagram showing quiescence group TOMs 0, 1, 10, 30, genes changing over time course, and proliferation group TOM 2, 3, 6]

C. [Flowchart showing up-regulated genes in adult HSC, up-regulated in FL-HSC, and genes changing over time course]

D. [Diagram showing P-sig with 94% up-regulated in adult HSC, up-regulated in FL-HSC, and genes changing over time course]

E. [Diagram showing Q-sig with 96% up-regulated in adult HSC, up-regulated in FL-HSC, and genes changing over time course]

F. [Circle diagram showing P-sig with cP-sig at 73%, ST-HSC sig.]

G. [Circle diagram showing Q-sig with cQ-sig at 58%, LT-HSC sig.]

Adult HSC

Fetal liver HSC
Higher *HOPX* expression is associated with quiescent stem cell signature

**Proliferation signature**

![Box plot for Proliferation signature](image1)

**Quiescence signature**

![Box plot for Quiescence signature](image2)

- **Higher HOPX**: T-test P-value: 3.69e-03
  
P = 0.0036

- **Lower HOPX**: T-test P-value: 5.17e-04
  
P = 0.0005
High $HOPX$ expression is associated with quiescent stem cell character in AML
ABC transporters contribute to chemoresistance

ABC (ATP-binding cassette) transporter

ABC transporters upregulated in chemoresistant AML

- ABC A2
- ABC B1
- ABC B5
- ABC B6
- ABC C13
- ABC G1
- ABC G2

Haematologica, 2011
ABC transporters upregulated in chemoresistant AML

Independently poor prognostic

- ABC A2
- ABC B1
- ABC B5
- ABC B6
- ABC C13
- ABC G1
- ABC G2

Haematologica, 2011
Higher $HOPX$ expression is associated with chemoresistant-ABC transporters

**NTUH data**
Correlation between *HOPX* level and prognostic ABC transporters

<table>
<thead>
<tr>
<th>Probe</th>
<th>Higher <em>HOPX</em></th>
<th>Lower <em>HOPX</em></th>
<th><em>P</em> value</th>
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<tbody>
<tr>
<td><em>ABCB1</em></td>
<td>5.879</td>
<td>5.455</td>
<td>&lt; 0.001</td>
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<tr>
<td><em>ABCB1</em></td>
<td>6.557</td>
<td>5.946</td>
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<td><em>ABCG1</em></td>
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<tr>
<td><em>ABCG1</em></td>
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<tr>
<td><em>ABCG1</em></td>
<td>5.931</td>
<td>5.864</td>
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<tr>
<td><em>ABCG2</em></td>
<td>5.330</td>
<td>5.274</td>
<td>0.001</td>
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</table>

*NTUH data*
High *HOPX* expression is associated with chemoresistance in AML
Hypermethylation of *HOPX* is NOT observed in AML

High *HOPX* expression is an independent poor prognostic factor in AML

High *HOPX* expression is associated with quiescent stem cell character in AML

High *HOPX* expression is associated with chemoresistance in AML
Generation of \textit{HOPX} gene-editing mouse model
Generation of \textit{HOPX} gene-editing mouse model

\textit{HOPX} Knockout mice \hspace{1cm} \textit{HOPX} transgenic mice
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