ASH 2017 Friday Satellite Symposium

INDIVIDUALIZING THERAPEUTIC STRATEGIES FOR PATIENTS WITH MDS

Myeloid Neoplasms with Germline Predisposition

j.fitzgibbon@qmul.ac.uk (PhD)
• Recognition of familial myeloid neoplasia in adults
• Practical considerations for diagnosis and management of patients and carriers
• RUNX1 deficiency (familial platelet disorder with predisposition to myeloid leukemia, FPDMM)
• GATA2 deficiency and related myeloid neoplasms
• Familial CEBPA-mutated acute myeloid leukemia
• DDX41-related myeloid neoplasia
• ETV6 in hematopoiesis and leukemia predisposition
• Classical inherited bone marrow failure syndromes with high risk for myelodysplastic syndrome and acute myelogenous leukemia
• Cancer predisposition syndromes associated with myeloid malignancy
Familial AML/MDS

• > 95% of all AML/MDS cases are sporadic.

• < 5% of the cases where two or more affected individuals are found within the same family.

• New WHO Entity 2016 provisional diagnostic category for heritable myeloid malignancies.
Clinical challenges in Familial AML

- Recognition of inherited forms of these diseases is difficult;
  - Patients may be unaware of their predisposition.
  - Wide variation in the age of onset and disease phenotype.
  - Absence of customized diagnostics.

- Variable penetrance of the disease mutations: symptomatic and asymptomatic carriers.

Roadmap to improve diagnosis, treatment and management

1. Identification of new cases, Individuals at risk
2. Tissue bank, Data collection
3. New genes Functional characterisation
4. Molecular diagnostics, 13 predisposition loci

NOVEL GUIDELINES
IMPROVED MANAGEMENT
All patients with Acute Leukaemia and MDS should be screened at the time of initial diagnosis or referral to rule a familial role

‘Understanding the recognized syndromes is critical for clinicians to have a high index of suspicion’ Lucy Godley.
Familial MDS/AML can be divided into three groups:

- Examples where approved testing exists.
- Emerging from basic research and requiring validation.
- Without an identified genetic basis.

*(Little is known regarding secondary genetic mutations)*
## Current Mutational Landscape

<table>
<thead>
<tr>
<th>GENE</th>
<th>AUTHORS</th>
<th>YEAR</th>
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<tbody>
<tr>
<td>RUNX1</td>
<td>Song <em>et al.</em> Boston, Massachusetts, USA</td>
<td>1999</td>
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<tr>
<td>TERC</td>
<td>Vulliamy <em>et al.</em> London, UK</td>
<td>2001</td>
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<tr>
<td>CEBPA</td>
<td>Smith <em>et al.</em> London, UK</td>
<td>2004</td>
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<tr>
<td>TERT</td>
<td>Hiroki Yamaguchi <em>et al.</em> Atlanta, USA</td>
<td>2005</td>
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<tr>
<td>GATA2</td>
<td>Hahn <em>et al.</em> Adelaide, Australia</td>
<td>2011</td>
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<tr>
<td>ANKRD26</td>
<td>Noris <em>et al.</em> Pavia, Italy</td>
<td>2011</td>
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<tr>
<td>SRP72</td>
<td>Kirwan <em>et al.</em> London, UK</td>
<td>2012</td>
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<tr>
<td>ACD</td>
<td>Guo <em>et al.</em> Philadelphia, USA</td>
<td>2014</td>
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<tr>
<td>ETV6</td>
<td>Zhang <em>et al.</em> Seattle, Washington, USA and Leila Noetzli <em>et al.</em> Colorado USA</td>
<td>2014/2015</td>
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<td>ATG2B/GSKIP</td>
<td>Saliba <em>et al.</em> Villejuif, France</td>
<td>2015</td>
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<td>DDX41</td>
<td>Polprasert <em>et al.</em> Cleveland, USA</td>
<td>2015</td>
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<td>SAMD9</td>
<td>Narumi <em>et al.</em> Tokyo, Japan</td>
<td>2016</td>
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<tr>
<td>SAMD9L</td>
<td>Tesi <em>et al.</em> Stockholm, Sweden</td>
<td>2017</td>
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Current Mutational Landscape – 13 genes and counting

**Myeloid malignancies only**
AML: *CEBPA*
MDS/AML: *DDX41*
MPNs/AML: *ATG2B/GSKIP*

**Cytopenias and/or platelet dysfunction**
FPD/AML: *RUNX1*
*GATA2* deficiency
Thrombocytopenia 2: *ANKRD26*
Thrombocytopenia 5: *ETV6*

**Bone marrow failure syndromes**
Telomere syndromes: *TERT, TERC, ACD*
Aplastic anemia/MDS: *SRP72*

**Other syndromes**
Cytopenia, immunodeficiency, MDS, and neurological symptoms: *SAMD9L*
MIRAGE syndrome: *SAMD9*
Understanding the recognized syndromes is critical for clinicians to have a high index of suspicion

(Taken from Nickels et al., Ther Adv Hematol. 2013)
Mutation of CEBPA in Familial Acute Myeloid Leukemia

Matthew L. Smith, M.B., B.S., Jamie D. Cavenagh, M.D., T. Andrew Lister, M.D., and Jude Fitzgibbon, Ph.D.

Smith et al., NEJM 2004
International collaboration on Familial CEBPA-AML: 25 patients – 11 pedigrees

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Year</th>
<th>Country</th>
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<tr>
<td>Smith</td>
<td>NEJM</td>
<td>2004</td>
<td>UK</td>
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<td>Sellick</td>
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<td>Pabst et al.</td>
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<td>Stelljes</td>
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<td>Germany</td>
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<td>Taskesen</td>
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<td>Germany</td>
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<tr>
<td>Savic A</td>
<td>unpublished</td>
<td></td>
<td>Serbia</td>
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<tr>
<td>Debeljak</td>
<td>Haematologica</td>
<td>2013</td>
<td>Slovenia</td>
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Distribution of *CEBPA* mutations

Key:
- In-frame insertion or deletion
- Frameshift mutation
- Missense mutation

Germline mutations

Acquired mutations

**In-frame insertion or deletion**
- Frameshift mutation
- Missense mutation
Timeline of clinical events in all 25 Familial CEBPA AMLs
Comparison Familial versus MRC *CEBPA* series - Familial Cases

A) Overall survival

B) Post-relapse survival

Tawana et al., Blood 2015
Patients are cured of initial disease but are predisposed to new leukaemic episodes

New *CEBPA* C-terminal mutations at relapse

![Diagram showing new CEBPA C-terminal mutations at relapse with corresponding pedigrees, diagnosis, and relapse timelines.](image)

- **B/II.1**
  - Diagnosis: p.R306ins3bp
  - Relapse: Wild type
  - Time: 13 mths

- **B/II.2**
  - Diagnosis: p.N281fs
  - Relapse: p.K313del
  - Time: 14 yrs

- **E/II.1**
  - Diagnosis: p.Q305ins18bp
  - Relapse: p.Q312dup
  - Time: 6.6 yrs

New examples in our practice – FLT3-ve/ NPM-ve/CEBPA

Tawana *et al.*, Blood 2015
Collective experience

- **Chemotherapy alone** can be used to treat patients without adverse disease features.

- High frequency of **late ‘chemosensitive’ relapses**, where intensive consolidation, preferably with allogeneic transplantation, may well prove beneficial in preventing further disease events.

- Perform **germ-line testing in sporadic CEBPA AML of <40 yrs at diagnosis**.

- **Counselling** of affected individuals and asymptomatic carriers requires full knowledge and understanding of the implications of inherited CEBPA mutations and, above all, recognition and consideration for an individual’s choice.

- Where possible, we advocate **screening of all potential sibling donors**, preparing for both treatment escalation in affected cases and identifying asymptomatic mutation carriers for counselling and surveillance.
Lessons from familial leukaemia?

Questions unique to familial leukaemia

- Disease Latency and penetrance - **Protection factor**
- The order by which mutations arise - **Modelling leukaemia**
- Genes not mutated in sporadic AML - **Novel mechanisms**
Disease Latency and penetrance

**RUNX1** – JAK pathway, same secondary mutation

Tawana et al. Eu J Hum Genet 2017
Reduced penetrance in GATA2-mutated MDS/AML - p.T354M mutations

Bödör et al., Haematologica 2012
**GATA2** monoallelic expression discriminates between symptomatic and asymptomatic carriers

*Al Seraihi et al., Unpublished*
Epigenetic reprogramming regulates monoallelic GATA2 expression

1. DNA methylation as a partial mechanism of silencing the WT allele.

2. Enhanced H3K4me3 promoter deposition on the mutant allele.

Al Seraihi et al., Unpublished
Our cohort of MDS/AML families

- 82 MDS/AML families
  - KNOWN GENES SEQUENCING PANEL PLUS
    - West Midlands Regional Genetics Laboratories
    - Birmingham Women's NHS Foundation Trust
  - 46 uncharacterised families
  - 41 characterised families

<table>
<thead>
<tr>
<th>^ Mutated Gene</th>
<th>Number of Families</th>
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<tr>
<td>CEBPA</td>
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<td>DDX41</td>
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<td>GATA2</td>
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<td>TERT</td>
<td>4</td>
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<tr>
<td>ETV6</td>
<td>1</td>
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Rio-Machin et al., Unpublished
Challenges in identifying a familial MDS/AML loci

(Primary Assumption: inherited mutation is a coding variant)
Challenges in identifying a familial MDS/AML loci – no obvious candidates

Low hanging gene fruit have all been identified – A Global Strategy Required

Pedigree 2

- Variant frequency < 0.0001 (ExAC)
- Predicted to be damaging (Polyphen and MutationTester scores)
- In at least 2, 3, 4……. Families?
Challenges in Familial AML

• Awareness of and Recognition of inherited forms is difficult.
• Paucity of clinical guidelines (e.g. progress on *CEBPA*).
• 13 recognised genes: 3-4 go beyond a few families.
• 41 uncharacterised families: list of new GL candidate mutations however no obvious functional link.
• Penetrance, Host genetics, latency.....all interesting biological areas.
Acknowledgements

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Joanne Mason

Csaba Bodor

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(Germany)
Lucy Godley (USA)

Semmelweiss - Hungary

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Beating blood cancer since 1960

Children with Cancer

Cancer Research UK