bjh review

Familial myelodysplasia and acute myeloid leukaemia – a review

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Summary

Familial occurrence of myelodysplasia (MDS) and/or acute myeloid leukaemia (AML) is rare but can provide a useful resource for the investigation of predisposing mutations in these myeloid malignancies. To date, examination of families with MDS/AML has lead to the detection of two culprit genes, *RUNX1* and *CEBPA*. Germline mutations in *RUNX1* result in familial platelet disorder with propensity to myeloid malignancy and inherited mutations of *CEBPA* predispose to AML. Unfortunately, the genetic cause remains obscure in most other reported pedigrees. Further insight into the molecular mechanisms of familial MDS/AML will require awareness by clinicians of new patients with relevant family histories.

Keywords: myelodysplasia, acute myeloid leukaemia, familial, *RUNX1, CEBPA*.

Myelodysplastic syndromes (MDS) and acute myeloid leukaemia (AML) present primarily as sporadic diseases. These myeloid malignancies occur most frequently in older people with a median age at presentation of greater than 65 years and an incidence in adulthood that increases progressively with age (Office for National Statistics 2004). Unfortunately, treatment options are limited and responses to therapy are especially poor for older patients, with less than 5% of patients over 65 years of age surviving 5 years from diagnosis (Menzin *et al*, 2002).

The familial occurrence of MDS and/or AML is very rare but can provide a useful resource for the investigation of predisposing mutations in these diseases. Several groups have examined individual families but these investigations have been difficult due to the rarity of familial MDS/AML. Investigations are also limited by the fact that most pedigrees are small and living-affected family members are few. In addition, familial cases of MDS/AML are heterogeneous with some families inheriting purely AML, and others inheriting purely MDS or both disorders within the same pedigree. As such, there might be several as yet undiscovered genes causing disease in these various families. Alternatively, the possibility of a single gene, which predisposes to both MDS and AML, cannot be excluded.

Patients with familial MDS/AML are younger at presentation than individuals with sporadic disease and are recognized by an unusual family history of more than one first-degree relative with MDS/AML. Most of the families reported in the literature demonstrate a pattern of inheritance consistent with a single gene mutation, inherited in an autosomal dominant manner. These cases have previously been labelled as 'pure familial leukaemia' to discriminate from syndromic cases of MDS and/or AML (Horwitz, 1997). Despite the documentation of several cases of pure familial leukaemia, success in determining culprit gene mutations has been limited. To date, only two genes, *RUNX1* and *CEBPA* have been identified as causative gene mutations in families inheriting pure familial leukaemia (Song *et al*, 1999; Smith *et al*, 2004). Despite these recent discoveries, many reported cases remain unexplained, suggesting that other inherited mutations must predispose to MDS/AML. These exceptionally rare families continue to be investigated in the anticipation that novel insight will be obtained about the genetic basis of these diseases and about the additional steps required for the development of leukaemia in individuals with inherited genetic lesions.

Herein, we review the literature on familial MDS/AML and the molecular mechanisms involved in the development of overt disease.

Syndromic MDS/AML

The most frequent cases of familial MDS/AML arise in those inheriting particular genetic syndromes (Table I). Primary bone marrow failure syndromes, such as Diamond-Blackfan anaemia (Janov *et al*, 1996), severe congenital neutropenia (Donadieu *et al*, 2005), Shwachman-Diamond syndrome (Woods *et al*, 1981) and dyskeratosis congenita (Dokal, 2000) are associated with variable risks of progression to MDS/AML. MDS/AML also occurs in syndromes involving defective DNA repair mechanisms, such as Fanconi anaemia. International registry data report an incidence of MDS/AML of 35–50% by the age of 40 years in patients with Fanconi anaemia (Kutler *et al*, 2003). A similar risk is reported in the

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Table I. Aetiology of familial MDS/AML.

	Inheritance	Gene	Locus	Incidence of MDS/AML (%)
Syndrome-associated				
Bone marrow failure syndromes				
Diamond-Blackfan anaemia	AD	*RPS19* (25%)	19q13	0·5–1·0
		RPS24 (2%)	10q22	
	AR	Unknown		
Severe congenital neutropenia	AD	*ELA2* (50%)	19q13	10
		GFI1	1p22	
	AR	*HAX1* (30%)	1q21	
Congenital amegakaryocytic thrombocytopenia	AR	*MPL*	1p34	Unknown
Shwachman-Diamond syndrome	AR	*SBDS*	7q11	10
Dyskeratosis congenita	XL	*DKC1*	Xq28	3–5
	AD	*TERC*	3q26	
DNA repair deficiency syndromes				
Fanconi anaemia	AR	*FANC/BRCA*		50
	XL	pathway		
Bloom syndrome	AR	*BLM*	15q26	25
Tumour suppressor gene syndromes				
Li-Fraumeni	AD	*TP53*	17p13	*c.* 7·5
Neurofibromatosis I	AD	*NF1*	17p11	0·2–0·5
Numerical chromosomal aberration				
Trisomy 21	Sporadic			2·5
Pure familial leukaemia				
Familial platelet disorder with propensity to develop myeloid malignancy	AD	*RUNX1*	21q22	20–60
CEBPA-associated	AD	*CEBPA*	19q13	
Familial monosomy 7	AD	Unknown		Unknown

rarer Bloom syndrome with a 25% lifetime risk of MDS/AML (Aktas *et al*, 2000). Syndromes associated with loss of tumour suppressor genes predispose to multiple malignancies including MDS/AML. Li-Fraumeni syndrome, caused by an inherited germline mutation in the *TP53* tumour suppressor gene, presents with an increased risk of nearly all malignancies, including leukaemia (Imamura *et al*, 1994). Finally, children with trisomy 21 (Down syndrome) have 1·0–1·5% chance of developing either AML or acute lymphoblastic leukaemia (ALL) (Ravindranath, 2005).

Unfortunately, the genetic lesions involved in syndromic cases of MDS/AML have mostly been excluded as aetiologic factors in sporadic disease. Several groups have examined sporadic cases of AML for mutations in the Fanconi anaemia gene pathway (FANC genes) (Condie *et al*, 2002; Tischkowitz *et al*, 2004). Though Fanconi anaemia is a heterogeneous disorder with at least eight different causative genes, *FANCA* mutations account for 65% of cases (Tischkowitz *et al*, 2004). To date, only rare mutations have been detected in *FANCA* in sporadic AML. Similarly, no association has been detected between *GATA1* mutations and MDS/AML, despite the finding of *GATA1* mutations in *c.* 90% of children with trisomy 21 who develop AML or transient myeloproliferative disorder (TMD) (Wechsler *et al*, 2002).

However, syndromic MDS/AML cases may still prove useful in the investigation of the molecular mechanisms of leukaemogenesis. These families may be examined for secondary mutations that trigger the development of overt disease. Additionally, some of the newly discovered mutations in syndromic MDS/AML have yet to be screened as candidate genes for the development of sporadic MDS/AML.

Investigations in Noonan syndrome (NS) have demonstrated the value of syndromic cases of MDS/AML in determining the molecular events involved in leukaemogenesis. NS is an autosomal dominant disorder, characterized by short stature, distinct facial features and congenital cardiac defects. NS is also associated with an increased risk of developing several myeloid disorders including juvenile myelomonocytic leukaemia (JMML), other myelodysplastic syndromes and leukaemias (Gelb & Tartaglia, 2006). Tartaglia *et al* (2001) described the association between NS and mutations in *PTPN11*, which encodes a tyrosine phosphatase involved in the RAS pathway. Subsequently, they and other groups determined that most cases of NS result from one of several

congenital or sporadic heterozygous gain-of-function mutations in genes in the RAS pathway, including *PTPN11*, *SOS1* and *KRAS* (Kratz *et al*, 2007; Roberts *et al*, 2007). *PTPN11* is the most common mutation linked to NS, responsible for at least 50% of cases (Tartaglia *et al*, 2001). The discovery of *PTPN11* mutation as a cause of NS and the association of NS with JMML and MDS prompted Tartaglia *et al* (2003) to investigate children with these myeloid disorders who did not have NS. Mutations in *PTPN11* were detected in 34% of children with JMML, 10% with MDS and 4% with AML (Tartaglia *et al*, 2003). Therefore, the investigation of these patients with NS and syndromic MDS lead to the discovery of a gene involved in the development of sporadic cases of childhood AML/MDS. In contrast, screening of adults with sporadic MDS/AML revealed only a rare occurrence of *PTPN11* mutations (Loh *et al*, 2005; Smith *et al*, 2005).

Cases of NS have also been useful in investigating the mechanisms of overt leukaemia development from a single predisposing mutation. Karow *et al* (2007) recently described the acquisition of uniparental disomy (UPD) in leukaemic blasts from a patient with NS. The observation of UPD provided evidence that loss of the wild-type copy of *PTPN11* with duplication of the mutant copy was an important 'second hit' that may have been the trigger for the development of leukaemia (Karow *et al*, 2007). Acquisition of UPD has previously been demonstrated to result in homozygosity of disease-associated mutations in AML (Fitzgibbon *et al*, 2005; Raghavan *et al*, 2005). A similar sequence of events has been reported in cases of Neurofibromatosis 1 in which UPD of the mutated *NF1* tumour suppressor gene is associated with the development of AML in children inheriting heterozygous *NF1* mutations (Stephens *et al*, 2006).

Therefore, though syndromic cases of MDS/AML are interesting, analyses of families in which a predisposition to MDS/AML is the only inherited trait have a better chance of detecting new causative gene mutations. To date, only two individual genes, *RUNX1* and *CEBPA* have been detected as germline mutations in pure familial leukaemia pedigrees.

Familial platelet disorder with propensity to develop myeloid malignancy (FPD/AML) [Familial RUNX1 mutation]

Individual pedigrees of familial MDS/AML have been reported in the literature for many decades (Anderson, 1951; Heath & Moloney, 1965; Le Marec *et al*, 1985; Horwitz *et al*, 1996; Olopade *et al*, 1996). These cases are of particular interest because they were reported in families without congenital syndromes that were known to predispose to haematological malignancy.

Familial platelet disorder with propensity to develop myeloid malignancy (FPD/AML) is an autosomal dominant disorder characterized by abnormalities in platelet number and function and a propensity to develop MDS/AML. First reported by Dowton *et al* (1985) in a large French-Canadian family, there have now been more than a dozen confirmed cases reported in the literature (Song *et al*, 1999; Michaud *et al*, 2002; Heller *et al*, 2005; Kirito *et al*, 2006). Genetic linkage to chromosome 21q22 was reported by Ho *et al* (1996) and subsequently, the same group later detected a germline heterozygous mutation in *RUNX1* (also known as *AML1* or *CBFA2*) (Song *et al*, 1999). *RUNX1* is also commonly involved in sporadic cases of MDS and AML, by translocations in AML (Perry *et al*, 2002) and by point mutations in MDS (Harada *et al*, 2004).

RUNX1 encodes a subunit of the core binding factor (CBF) transcription factor, which regulates expression of several haematopoietic genes. The RUNX1 protein contains a DNA-binding domain (termed runt homology domain – RHD) and a domain that enables it to dimerize with its partner, CBFB. A variety of mutations in *RUNX1* have been described in individual families with FPD/AML, most in the RHD (Song *et al*, 1999). Individual mutations are thought to result in different degrees of functional loss of the RUNX1 protein and variable phenotypes of the FPD/AML disease between families.

The clinical phenotype of FPD/AML is heterogeneous with fewer than 50% of individuals who inherit a *RUNX1* mutation developing MDS/AML. The most consistent clinical feature is that of a mild to moderate bleeding tendency. No dysmorphic features are reported and there is no increased risk of non-myeloid cancers. Patients present with normal or mildly reduced platelet counts, normal platelet morphology and variable levels of platelet dysfunction. Most patients exhibit impaired platelet aggregation with collagen and epinephrine, similar to abnormalities caused by aspirin, as well as a dense-granule storage pool deficiency (Walker *et al*, 2002; Ganly *et al*, 2004). The clinical bleeding history is variable and usually evident from childhood. Ganly *et al* (2004) reviewed the published cases until 2004 and reported an incidence of MDS/AML in affected family members varying from 20 to 60% in different families, with a median of 35%. The median age of onset was much younger than in sporadic MDS/AML at 33 years. No clear association was noted with the subtype of AML or with additional cytogenetic abnormalities noted at the time of myeloid malignancy. Long-term data on the outcomes of patients treated for FPD/AML-associated leukaemias is limited, making a determination of prognosis in these patients difficult (Ganly *et al*, 2004).

The initial report of *RUNX1* mutations in FPD/AML by Song *et al* (1999) described mutations in six pedigrees with no two families inheriting the same mutation. The first pedigree was observed to transmit an intragenic deletion of *RUNX1*, suggesting that haploinsufficiency of RUNX1 was sufficient to cause the disease phenotype in this family. The other pedigrees transmitted point mutations, which resulted in frameshift, nonsense and missense mutations. All mutations were within or included the RHD. Interestingly, no difference in disease phenotype could be detected between these pedigrees, despite the variable mutations (Song *et al*, 1999).

The accumulation of information from subsequent families with FPD/AML has suggested that the phenotype of disease varies between families depending on the type of mutation inherited (Ganly *et al*, 2004). Michaud *et al* (2002) described several pedigrees and reported the first mutations outside the RHD domain. Through several *in vitro* studies, they demonstrated that some mutant proteins exert dominant-negative effects and that the pedigree with the highest incidence of leukaemia had the highest predicted dominant-negative activity (Michaud *et al*, 2002; Ganly *et al*, 2004). They also noted that a rarer C-terminal mutant [with only two reported cases to date (Michaud *et al*, 2002; Heller *et al*, 2005)] demonstrated normal DNA binding but repressed wild-type RUNX1, producing a higher incidence of leukaemia than was observed in the families inheriting mutant RUNX1 proteins that act by haploinsufficiency (Michaud *et al*, 2002). Evidence of dominant-negative activity was recently confirmed by Matheny *et al* (2007), when they examined the effects of different RHD mutations on RUNX1 function.

More recently, a novel mutation was described in the 5′ untranslated region of the *RUNX1* gene in a family presenting with a FPD/AML phenotype, indicating for the first time that non-coding mutations may also be important in FPD/AML (Kirito *et al*, 2006). Finally, the genetics of FPD/AML may be yet more complicated. Minelli *et al* (2004) reported a single pedigree with a clinical history consistent with FPD/AML in which no mutation was detected in *RUNX1* and in which linkage to chromosome 21 was excluded, implying that other genetic lesions, outside this region, may also cause an FPD/AML-like phenotype (Minelli *et al*, 2004).

Pure familial leukaemia with CEBPA mutation

Mutations in *CEBPA*, a gene encoding the CCAAT enhancer binding protein α, transcription factor (C/EBPα) have also been noted to segregate with pure familial leukaemia in an autosomal dominant pattern. The first family was reported by Smith *et al* (2004) with three members, over two generations affected with AML. Unlike in FPD/AML, the clinical and pathological phenotypes of patients with germline *CEBPA* mutations are very consistent (Table II). The morphological features of the disease are distinctive, with most patients having FAB M1 or M2 subtypes, many Auer rods, aberrant CD7 expression and normal karyotypes. These features are similar to those reviewed by Leroy *et al* (2005) in sporadic cases of AML with *CEBPA* mutations in which there is a predominance of M1 and M2 subtypes and 70% of patients have a normal karyotype. These individuals also have a good prognosis, even following relapse. The first individual in the family reported by Smith *et al* (2004) achieved a complete remission and long-term survival after receiving much less intensive therapy than would be today's standard. The individuals within the subsequent reported families have also had lasting remissions, some despite several relapses (Sellick

Table II. Germline *CEBPA* mutation in pure familial leukaemia.

Pedigree	Age at diagnosis (years)	FAB subtype	Cytogenetics	Clinical history
Smith *et al* (2004)	Father – 10	M1	N/A	Relapsed × 2 with persistent remission after prednisone + cyclophosphamide (40 years)
	Son – 30	M2Eo + Auer rods	46 XY	Intensive chemotherapy × 4 cycles, CR after cycle 1 Arthralgias + neutrophilia after treatment, persistent remission (3 years)
	Daughter – 18	M2Eo + Auer rods	46 XY	Intensive chemotherapy × 4 cycles, CR after cycle 1 Arthralgias + neutrophilia after treatment, persistent remission (3 years)
Sellick *et al* (2005)	Father – 34	Not specified	N/A	Received intensive chemotherapy died 1 year postdiagnosis of uncertain cause
	Son (1) – 25	M4Eo	46XYdel[6]q[21] in 5/16 cells examined	Treated with intensive chemotherapy, 2 relapses, 2 × autologous BMT followed by persistent remission (8 years)
	Son of Son (1) – 4	M1	46 XY	Intensive chemotherapy to partial remission followed by high dose therapy with autologous BMT to a persistent remission (6 years)
	Son (2) – 24	M1	46 XY	Intensive chemotherapy with autologous BMT to a persistent remission (13 years)
Nanri *et al* (2006)	Father – 39	M2 + Auer rods	46 XY	Single relapse 7 years after initial treatment, followed by autologous SCT and persistent remission (12 years)
	Son (1) – 26	M2Eo + Auer rods	N/A	Intensive chemotherapy followed by persistent remission (2 years)
	Son (2) – unaffected	None		Normal bone marrow but presence of *CEBPA* germline mutation on screening

FAB, French–American–British classification; Eo, eosinophils; BMT, bone marrow transplantation; SCT, stem cell transplantation; N/A, not available.

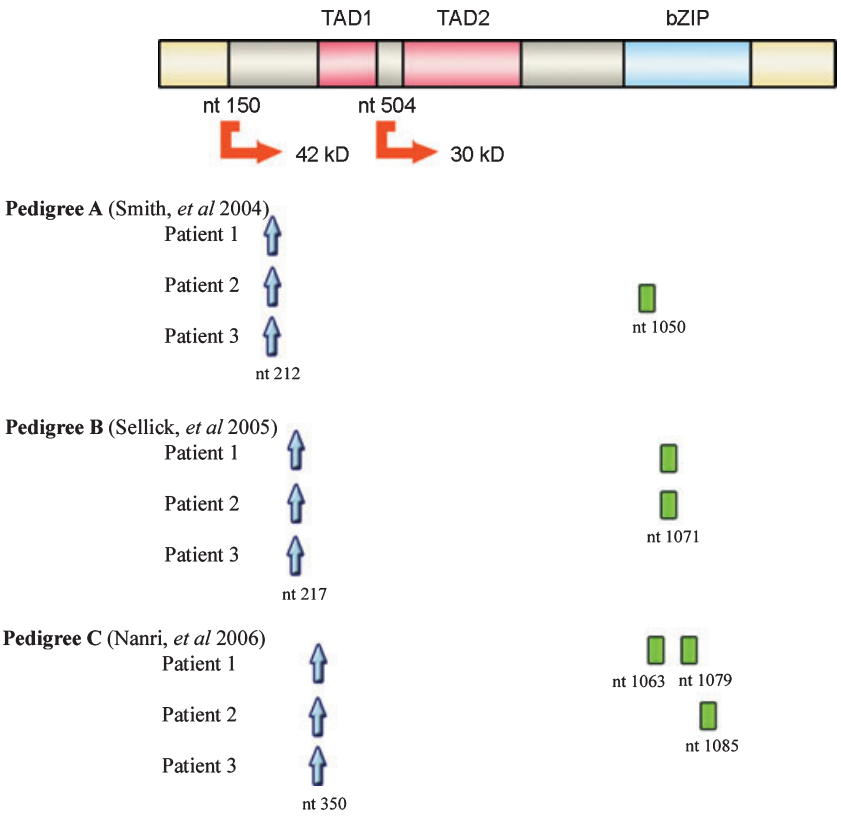

Fig 1. Demonstrates the position of mutations detected in the three pedigrees with Familial AML with *CEBPA* mutation. Transactivating domains 1 and 2 [TAD1 and TAD2 (pink)], the basic region and leucine zipper [bZIP (blue)] and untranslated regions (gold) are indicated. Start codons, located at nucleotides (nt) 150 and 504 are indicated by red arrows. Blue arrows represent the N-terminal germline mutations, with *Pedigree A* inheriting a single nt deletion at position 212, *Pedigree B* inheriting a single nt insertion at position 217 and *Pedigree C* inheriting a 4 base pair (bp) insertion at position 350. Somatic mutations are represented by green bars and are all observed in the C-terminal region. One individual in *Pedigree A* acquired a 35-bp duplication at position 1050; one individual in *Pedigree B* acquired a 7-bp deletion and 10-bp insertion at position 1071, and his brother acquired a 3-bp insertion at position 1071; one individual in *Pedigree C* acquired a 18-bp insertion at position 1063 at diagnosis and a distinct 3-bp insertion at position 1079 at relapse, and his son acquired a 3-bp insertion at position 1085 (Diagram not to scale).

et al, 2005; Nanri *et al*, 2006). The familial cases confirm findings in sporadic AML in which *CEBPA* mutations are also noted to confer a favourable prognosis (Preudhomme *et al*, 2002; Leroy *et al*, 2005).

Despite these consistencies, the age of presentation of disease is extremely variable in familial AML with *CEBPA* mutation, ranging from 4 to 39 years. Clearly, a latency period is required for the development of secondary mutations, which occur at different times in different individuals. The disease also appears to have near complete penetrance, as all healthy individuals who were tested within the pedigree of Smith *et al* (2004) were free from mutation. Only one individual aged 21 years was reported by Nanri *et al* (2006) with a germline mutation in *CEBPA* and no evidence of AML to date.

In keeping with the clinical similarities in these three families, the molecular lesions in the *CEBPA* gene are also remarkably constant in these unrelated families (Fig 1). C/EBPα is a transcription factor, which regulates genes involved in myeloid differentiation, particularly by inducing granulocytic development of bipotential myeloid progenitors. The protein consists of N-terminal transactivating domains, a DNA-binding domain and a C-terminal leucine-zipper region (bZIP), necessary for dimerization. The transactivating domain is important in binding of C/EBPα to the specific promoter regions of the genes it regulates. The gene contains two translational start sites, yielding a 42-kD product and a smaller 30-kD isoform. The function of the wild-type 30-kD isoform has not been well described. All three pedigrees were noted to exhibit a germline N-terminal, out-of-frame *CEBPA* mutation, which abolished the production of the full-length 42 kD protein with potential upregulation of the truncated 30-kD isoform. The 30-kD C/EBPα isoform lacks the first transactivating domain but retains the bZIP region required for dimerization and is thus able to dimerize with the wild-type 42-kD protein, potentially inhibiting its function in a dominant-negative manner (Pabst *et al*, 2001).

The nature and timing of *CEBPA* mutations in familial AML has also provided an insight into the sequence of molecular events in the development of leukaemia (Fig 1). This insight comes particularly from second or biallelic mutations, which are commonly observed in familial and sporadic *CEBPA*-associated AML. Somatic *CEBPA* mutations are reported in

sporadic cases of AML and are similar to those described in familial cases. These mutations are noted in *c.* 9% of sporadic AML cases (Preudhomme *et al*, 2002; Frohling *et al*, 2004; Leroy *et al*, 2005). Second mutations are usually C-terminal mutations and are in-frame insertions or deletions, which result in interference with dimerization and subsequent loss of C/EBPα function (Leroy *et al*, 2005). The family described by Smith *et al* (2004) was noted to have one individual who acquired a somatic C-terminal mutation in addition to her germline N-terminal mutation. The pedigree reported by Sellick *et al* (2005) were noted to have remarkably similar mutations to those of the first family with a similar N-terminal germline mutation and two individuals with additional (yet distinct) C-terminal somatic mutations. Finally, Nanri *et al* (2006) reported a family with two affected individuals demonstrating distinct somatic C-terminal mutations. Interestingly, one individual was noted to have two separate C-terminal mutations, one acquired at diagnosis and another at relapse, suggesting the occurrence of two independent episodes of AML in this patient.

The presence of germline N-terminal mutations and somatic C-terminal mutations in these familial cases suggests that C-terminal mutations are later events in leukaemogenesis. The clinical similarity between somatic and inherited *CEBPA* mutations and AML is striking (Frohling *et al*, 2004; Leroy *et al*, 2005) and this concordance is very encouraging for the extrapolation of findings in familial MDS/AML to other sporadic cases.

Additional Loci

The success in discovering *RUNX1* and *CEBPA* mutations in families with MDS/AML contrasts with an inability to explain the occurrence of disease in several other pedigrees. The potential remains for future discoveries in these families that will provide insight into other molecular events, which may also occur in sporadic disease. New molecular techniques are being investigated and these will hopefully begin to answer the remaining questions.

Monosomy 7

Monosomy 7 in association with pure familial MDS/AML has been reported in 12 pedigrees (Kwong *et al*, 2000; Minelli *et al*, 2001) (atlasgeneticsoncology.org /Kprones/FamilMono7ID10059.html). This cytogenetic abnormality is frequently observed as a sign of progressive disease in congenital syndromes and has been linked to the development of MDS/AML in many of these syndromes (Hasle, 1994; Luna-Fineman *et al*, 1995). However, several cases of familial monosomy 7 have been described in families without evidence of congenital syndromes.

Unlike *RUNX1* and *CEBPA* germline mutations, in which individuals usually present with disease in adulthood, familial MDS in association with monosomy 7 develops at a young age, with most patients less than 18 years of age at diagnosis. Typically, individuals are first-degree relatives with males and females equally affected, suggesting an autosomal dominant mode of transmission. One group reported different parental origins of the remaining chromosome 7 in individuals within the same monosomy 7 family (Shannon *et al*, 1992; Savage *et al*, 1994) and this was subsequently confirmed by Minelli *et al* (2001). This random or non-preferential deletion of parental chromosomes suggests that the predisposing locus does not reside on chromosome 7. Despite these findings, more than a decade later, little more has been determined about the pathogenesis of familial monosomy 7.

Monosomy 7 is not a germline mutation but represents a recurring secondary event in leukaemogenesis and confers an adverse prognosis. This chromosomal abnormality is the most commonly acquired abnormality in children with syndromes that predispose to MDS/AML, such as Fanconi anaemia. The development of a monosomy 7 in these children is often a harbinger of progression to MDS/AML. Epidemiological studies suggest that many children with familial monosomy 7 and MDS may harbour otherwise-silent congenital mutations associated with known constitutional disorders such as *NF1*, mosaic trisomy 21 or Fanconi anaemia, despite lacking other features of the syndromes (Hasle *et al*, 1999).

Given the uncertainty of the mechanism of MDS/AML development in children with monosomy 7, further investigation of these families will be important in determining molecular triggers for the development of overt disease. Minelli *et al* (2001) have postulated that these families harbour a mutated gene which predisposes to the development of subsequent genetic abnormalities, including monosomy 7. This same 'mutator' gene may be involved in sporadic cases of both MDS and AML. As monosomy 7 is a poor prognostic factor in sporadic MDS/AML (Greenberg *et al*, 1997), a determination of the molecular cause of this condition could have significant clinical impact and represents the best example of how investigation of familial MDS/AML could have impact on patients with sporadic disease.

Approach to the investigation of familial MDS/AML

The most important step in the investigation of familial MDS/AML is the identification of affected families. MDS and AML are uncommon disorders such that it is unusual for more than one member of a family to be affected. When two or more family members present with MDS/AML, a consideration arises about the possibility of an inherited predisposition or a shared environmental exposure. Several epidemiological studies have investigated the possibility of inherited genetic polymorphisms that increase the susceptibility to environmental carcinogens, thereby predisposing to MDS/AML. The glutathione S-transferase system (GST) enzymes are thought to be the most interesting candidates, because of their importance in detoxifying numerous carcinogens. Unfortunately, there has not been consistent evidence to support a link between *GST*

mu 1 and/or *GST theta 1* null genotypes and a predisposition to myeloid malignancy (Crump *et al*, 2000; Arruda *et al*, 2001). An inactivating polymorphism of the NAD(P)H: quinone oxidoreductase (NQO1) gene (*NQO1*) has also been linked to increased risks of therapy-associated AML and AML involving abnormalities of chromosomes 5 and/or 7 (Larson *et al*, 1999). However, the absolute risks reported from these polymorphisms are small. Therefore, if these enzyme deficiencies are involved in increasing an individual's risk of MDS/AML, they cannot fully explain the existence of disease in multiple family members.

Traditional linkage analysis techniques have proven difficult because of small families and insufficient samples. However, Horwitz's group accumulated several pedigrees that have supported linkage of familial MDS/AML to a locus on chromosome 16q22 (Horwitz *et al*, 1997; Gao *et al*, 2000). This hypothesis was initially proposed based on the finding of a fragile site at the 16q22 region in a family where the father developed AML and a daughter died of ALL (Ferro *et al*, 1994). Focussed linkage analysis of the 16q22 region was performed on a large pedigree and the results suggested linkage to 16q22 with a LOD (logarithm of the odds) score of 2·82, just below the generally accepted linkage criterion of a LOD score ≥3·0 (Horwitz *et al*, 1997). Several candidate genes on chromosome 16 were subsequently excluded including *RUNX1*'s partner gene *CBFB* (Escher *et al*, 2004a,b). Investigations of a second pedigree also suggested a possible linkage to 16q22 with a LOD score of 1·19 (Gao *et al*, 2000). Though a single gene causing familial MDS/AML is likely in these pedigrees, the underlying gene mutations remain elusive.

Following these investigations, more recent techniques have been directed at specific candidate gene exclusions or work based on unique features of the disease, such as 'anticipation'. Anticipation is the observation of increasing severity or earlier age of onset of disease with each passing generation in autosomal dominant disorders (Horwitz, 1997). Anticipation was first reported in Huntington disease and other neurodegenerative disorders and was eventually mechanistically explained by the intergenerational expansion of unstable trinucleotide repeats (Schalling *et al*, 1993). Many familial MDS/AML pedigrees have been reported to demonstrate anticipation. The observation of anticipation in familial MDS/AML thus triggered genomewide and candidate region screening for repetitive sequence elements in several pedigrees. Unfortunately, no clear association could be determined as with chronic lymphocytic leukaemia (CLL) which has been similarly investigated (Horwitz *et al*, 1997; Auer *et al*, 2007). As with the early reports of anticipation in Huntington disease, there has been concern that anticipation is not a real phenomenon but is caused by ascertainment bias. Horwitz (1997) reviewed the literature prior to 1997 and detected a significant intergenerational age drop in nearly every parent-child pair, in the reported MDS/AML pedigrees. While ascertainment bias cannot completely be excluded in such a rare disease, it seems evident that anticipation does occur in familial MDS/AML and this occurrence may help direct future studies. Investigations of telomere length and/or telomerase deficiencies may be useful, given the finding of telomerase mutations causing autosomal dominant dyskeratosis congenita (AD-DC), an inherited bone marrow failure syndrome that frequently progresses to MDS/AML. AD-DC also displays anticipation, caused by proceeding generations inheriting progressively shorter telomeres (Vulliamy *et al*, 2006).

New molecular approaches

Clearly, novel techniques will need to be applied in order to further investigate these rare families. New techniques, such as genomewide single nucleotide polymorphism (SNP) analysis, gene expression profiling and global methylation studies, are increasingly being used in the investigation of cancer and cancer development. These techniques may also be useful in the future to detect germline or secondary events in familial MDS/AML. Recently, Pradhan *et al* (2004) reported their findings of differentially expressed genes in an adult familial MDS pedigree. Our current strategy is to employ systematic mutation screening of known loci including *RUNX1* and *CEBPA* and to apply large-scale genotyping analysis in germline and affected samples from families with MDS/AML. Molecular discoveries in MDS/AML continue to provide candidates for mutation screening including *PTPN11*, other RAS pathway genes and the recent description of a polymorphism in the granulocyte colony-stimulating factor receptor associated with high-risk MDS (Wolfler *et al*, 2005). Cases of *PTPN11* and *NF1* germline mutations which become homozygous suggest that studies to detect loss of heterozygosity along with copy-number analysis, such as SNP profiling, may provide the means to restrict analysis to regions harbouring new tumour suppressor genes or 'mutator' genes that contribute to leukaemogenesis.

Conclusions

The recent discoveries of *RUNX1* mutations in FPD/AML and *CEBPA* mutations in familial AML have greatly advanced the field and have provided significant insight into both the predisposing mutations and the potential secondary events in leukaemogenesis. However, most case reports describe families in which no genetic cause can be identified (Mandla *et al*, 1998; Kumar *et al*, 2000; Cameron *et al*, 2002; Lynch *et al*, 2002; Wrobel *et al*, 2006). Investigations are often limited by small sample size and a lack of DNA from deceased family members. Additionally, modern small families make it difficult to distinguish between two sporadic cases arising within a pedigree *versus* a true familial inheritance pattern. Only in the case of *RUNX1*, has the use of linkage analysis proven worthwhile. Mutations in *CEBPA* were detected by a systematic mutation analysis but a similar approach has not yet been successful in several other cases including familial monosomy 7. In the absence of large

familial cases, the molecular options open to the researcher are limited.

Careful screening by clinicians of new patients with MDS or AML for family history is crucial for detecting these rare pedigrees. Subsequent investigation of such pedigrees with both established and newer techniques may lead to the identification of novel gene mutations. Though familial MDS/AML presents at a younger age than sporadic disease, most overt cases present in adulthood, suggesting that a long latency period is required for the development of leukaemia. This latency allows for the development of necessary secondary mutations but is also clinically important when considering issues such as choice of donor for haematopoietic stem cell transplantation. Therefore, ongoing investigation of familial MDS/AML pedigrees has immense value in clarifying the clinical-molecular course of the disease, which should translate into a better understanding of sporadic MDS and AML.

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