

SHORT COMMUNICATION

CORRELATION BETWEEN DOWN SYNDROME AND PROGNOSIS OF ACUTE MEGAKARYOBLASTIC LEUKEMIA

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Down Syndrome (Ds) is one of the most common syndromes among children. This phenomenon has been reported in one child out of 800 children. Children with Ds Suffer from intestine aberration (malformation), respiratory problems, overweight, more prone to infection and they are more likely to get leukemia. Children with Ds are predisposed to developing acute leukemia. The most common leukemia associated with Ds is acute megakaryoblastic leukemia (AMKL), and the incidence is approximately 500-fold higher than in healthy children (Kim *et al.*, 2008). Ds has been recognized as one of the most important leukemia-predisposing syndromes. Patient with Ds and leukemia have unique clinical features but significant differences in treatment response and toxicity profiles compared to patients without Ds (Xavier and Taub, 2010). In trisomy 21, acquired somatic mutation leads to the production of a shorter GATA1 isoform, term GATA1s, associated with TMD and AMKL (Ciovacco *et al.*, 2008). Trisomy 21 may contribute to the development of GATA1 mutations in Ds (Xavier and Taub, 2010).

TMD is an acute megakaryocytic leukemia (AMKL)-related disorder diagnosed in newborn Ds babies based on the detection of megakaryoblasts in the peripheral blood and/or bone marrow. TMD megakaryoblasts have identical morphology and surface antigen expression with AMKL cells. [http://jmd.amjpathol.org/cgi/content/full/11/5/371 - B41](http://jmd.amjpathol.org/cgi/content/full/11/5/371-B41) TMD is restricted to patients harboring trisomy 21 and it has been found in phenotypically normal infants and children who were trisomy 21 mosaics (Xavier *et al.*, 2009). [http://jmd.amjpathol.org/cgi/content/full/11/5/371 - B42](http://jmd.amjpathol.org/cgi/content/full/11/5/371-B42)

GATA1 is a protein encoded by GATA1 gene structure in human. GATA genes are a family of X- linked transcription factors. The GATA family falls into two basic types: the hematopoietic subfamily consisting of GATA1, GATA2 and 3 the non-hematopoietic sub family comprising GATA4-5 and 6. These transcription factors are categorized as a family that they all bind to the DNA consensus sequence .GATA1 is an important member of the GATA family. They play in an integral role in the development of several hematopoietic cell lineages including the erythroid megakaryocyte, eosinophil and mast cell lineages. Other members of the GATA family, which can bind to the same DNA sequence motif, are co-expressed in several hemopoietic lineages, raising the possibility of overlapped function (Pevny *et al.*, 1995). GATA1 is located on the X chromosome at position Xp21-11 (Ferreira *et al.*, 2005). The molecule contains three domains the C-finger, the N-finger, and the activation domain. The activation domain is responsible for GATA1's strong transcriptional activation, (Martin and Orkin, 1990) the gene for GATA1 is on the X-chromosome. Mutation in special region of GATA1 such as N-terminal trans activation and N-finger have been connected to human disease. Majority of the mutations introduce a premature stop codon in the N-terminal trans activation domain of GATA1 but splice site mutation also occurs (Ferreira *et al.*, 2005). Recently, acquired mutations in the *GATA1* gene that have been reported in nearly all cases of TMD and Ds-AMKL have been shown to be specific for Ds-AMKL (Ki *et al.*, 2008).

Leukemogenesis of AMKL in patient with Ds is associated with the presence of somatic mutations involving the GATA1 gene (Xavier and Taub, 2010) but GATA1 mutations have never been observed in cases of Ds ,with ALL .

GATA1 mutations have been found in otherwise healthy Ds neonates at birth that have not yet developed TMD or AMKL .These findings suggest that acquired mutations in *GATA1* and the generation of GATA-1s cooperate frequently with trisomy 21 in initiating megakaryoblastic proliferation, although insufficient for the progression to AMKL. Mutagenesis of *GATA1* is an initiating event in Ds-associated leukemogenesis. *GATA1* mutations have not been found in non-Ds patients with leukemia of any kind, with the following exception. Children without Ds, but with acquired trisomy 21, trisomy 21 mosaicism, or tertasomy 21 in their leukemic cells, might present with AMKL that harbors a *GATA1* mutation (Kim *et al.*, 2008; Sandoval, 2005).

At present, several inherited and one somatic mutation in GATA1 have been functionally linked to a number of syndromes inherited missense. Mutations in GATA1 make a group of blood disorder characterized by various

cytopenias while somatic mutations seem to be exclusively associated with cases of trisomy 21 and lead to AMKL in affected patient (Ciovacco *et al.*, 2008).

Reduction in the GATA1 function is an early stage in the pathogenesis of Ds –AMKL which prevents differentiation of the precursor cells but allows their survival (Ferreira *et al.*, 2005).

A study in mice showed that the chromosomal abnormality causing Ds might harbor a genetic aberration that protects them against colon cancer (Seppa, 2008).

Ds children have a unique genetic susceptibility to develop leukemia in particular, acute megakaryoblastic leukemia (AMKL) associated with somatic GATA1 mutation (Cabelof *et al.*, 2009).

They have a 10-20fold elevated risk of developing leukemia, particularly acute megakaryoblastic leukemia (AMKL) (Wechsler *et al.*, 2002).

Chromosome 21 carries 231 genes, including some that may well suppressed cancer (Seppa, 2009). Children with Ds and AMKL have been shown to have increased sensitivity to cytarabine based chemotherapy (Ariffin *et al.*, 2009).

Previous studies, have demonstrated that the high event-free survival rates of Ds patients with AMKL are related to increased in vitro sensitivity of Ds megakaryoblasts to cytarabine (ara-C), and daunorubicin due, in part, to the presence of GATA1 mutation (Xavier and Taub, 2010). The increased ara-C sensitivity of Ds myeloblasts may reflect the altered expression of multiple genes encoding enzymes involved in ara-C metabolism (Ge *et al.*, 2004). Cell with normal GATA1 protein are 8-17 times less sensitive against chemotherapy. Children with Ds respond more favorably to leukemia treatment than other children and it is likely due to a genetic mutation found only in Ds, characterized by constitutional trisomy 21. The increased in vitro sensitivity to chemotherapy observed in Ds patients with AML does not extend to those with ALL (Xavier and Taub, 2010). Although in most cases the leukemic cells disappear spontaneously after the first months of life, irreversible acute megakaryoblastic leukemia develops in 20% of these individuals within 4 years (Hitzler and Zipursky, 2005). Since an initial report in 1992, studies of the pediatric oncology group, children's cancer group, and other pediatric oncology cooperative groups have consistently reported that after treatment with cytosine arabinoside (ara-C) based protocol Ds children with AML have substantially higher event-free survival rates (80%-100%), and lower relapse rates (<15%) than non Ds AML patients (Ge *et al.*, 2005).

Mutations in the gene encoding the transcription factor GATA1 contributes to a specific type of leukemia in people with Ds. This finding suggested a multistep pathway of leukemia development that involves GATA1 and one or more genes on chromosome 21 (Look, 2002).

The comparison between complexes identified with wild-type and mutant GATA1 proteins may reveal specific functions of a particular posttranscriptional modification because there are many more elusive aspects of GATA1 biology (Ferreira *et al.*, 2005).

By answering the following questions, first of all the mechanisms of GATA1 mutation and its role in treatment of leukemia would be revealed.

Making disease and its treatment is related to other parts, meaning that whether it is uni or multi factorial?

To what extent mutated GATA1 function might be effective in treating leukemia?

Can we create the same sensitivity in ordinary people that GATA1 does in children with Ds?

Suppose a method was created by GATA1 performance, in attention to genetically and mutant of the protein how would be the success probability, fail probability and regurgitate (relapse)?

What is the relationship between trisomy 21 and AMKL?

Would it be possible to treat leukemic patients by means of GATA1 function?

Why mutated GATA1 has better performance in AMKL but not in other type of leukemia?

Are the role of GATA2 and GATA3 similar to GATA1 in cancer?

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(Accepted for publication October 2011)