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Identification of a transcriptionally compromised allele of *c-MYC* in a North American family

EDITOR—Chromosomal translocations that target *c-MYC* at 8q24 are found in all Burkitt's lymphomas (BL), AIDS related non-Hodgkin's lymphoma (AIDS-NHL), mouse plasmacytomas (PCTs), in many examples of diffuse large cell lymphoma (DLCL), and in multiple myeloma (MM). Indications are that *c-MYC* is under strict control and when deregulated results in unchecked cellular proliferation and hyperplasia. Non-random chromosomal translocations found such as t(8;14), t(8;22), or t(2;8) in these lymphoid neoplasias places *c-MYC* under the control of strong immunoglobulin enhancers, which leads to overexpression.^{1,2} In addition, *c-MYC* is amplified in many tumours including breast, prostate, gastrointestinal, ovarian, MM, myeloid leukaemia, and melanoma suggesting that the overall transcriptional level is probably a key trans-

forming element associated with *c-MYC*.³ Besides genetic lesions, other epigenetic factors such as activation of growth factor receptors may also lead to constitutive expression of *c-MYC*. Thus, considerable efforts have been made systematically to identify the *c-MYC* transcriptional apparatus (promoters and enhancers) in an effort to control *c-MYC* expression. While *c-MYC* transcription potentially initiates from one of three promoters, P0, P1, and P2 which reside in the exon 1 region, the P2 promoter normally accounts for 75-90% of cytoplasmic *c-MYC* RNAs. To date, more than 20 transcription factors have been found to reside in the proximity of exon 1 of *c-MYC*.¹ Actually, *c-MYC* was one of the first genes to exhibit transcriptional blockage. RNA polymerase II initiation complexes were shown to pause on P2 before activation.⁴⁻⁶ Upon chromosomal translocation, the insertion of IG enhancer elements renders a shift in promoter usage from P2 towards P1 and loss of transcriptional blockage.⁷

In concert with the intensely regulated transcriptional machinery, the sequences surrounding *c-MYC* appear to be strictly conserved across species boundaries and little in the way of sequence variation or allelic polymorphisms has

been identified. In fact, attempts to position *c-MYC* in the mouse by genetic recombination techniques were ultimately achieved only when wild mice were backcrossed to inbred mice.⁸ Recently, we and others⁹ have identified several alleles of human *c-MYC* (S11N, CAA-33) through single nucleotide polymorphism (SNP) analysis of the coding region among a large random panel of normal healthy subjects of African-American and white descent.¹⁰ Comparisons of the S11N and CAA-33 alleles to wild type alleles at the RNA level showed that the CAA-33 allele is transcribed less efficiently in peripheral blood leucocytes. Although the nature of this difference remains to be elucidated, the finding that CAA-33 is transcriptionally compromised and is found almost exclusively in people of African descent underlines the importance of the genetic background in studies on the control of *c-MYC* expression. Thus, studies of allelic differences and transcription of human *c-MYC* will provide useful paradigms in the attempt to control or regulate *c-MYC* expression in normal and disease conditions.

We have considered the possibility that sequence differences that exist in the coding region of *c-MYC* could result in feedback inhibition of transcription. For example, somatic point mutations have been found in both BL^{11,12} and AIDS-NHL^{13,14} to be clustered in *c-MYC* exon 2 in the region responsible for binding of P107 or other factors to the transactivation domain (TAD).^{15,16} This suggests that disruption of binding in this region might lead to a functional inactivation of *c-MYC*. Indeed, a substitution at residue Thr-58 in the TAD of *v-Myc* in the avian retroviruses MC29, MH2, and OK10 is known to contribute to the transformation of fibroblasts.¹⁷ While it is believed that a major consequence of somatic mutation in *c-MYC* could be loss of function, it is not clear which residues are critical.

We wish to report the discovery of a unique sequence (S288K AGC→AAC) in the coding region of *c-MYC* which we have recently found in a North American family (fig 1). The S288K substitution resides just distal to the acidic domain and proximal to the nuclear localisation signal and was detected by PCR amplification and sequencing of the exon 3 region of human *c-MYC*. Subsequently, we developed a single stranded conformational polymorphism (SSCP) assay for S288K which we have used to survey panels of normal, healthy, white (around 200), African-American (around 200), Hispanic (two) and Asian-Pacific (two) subjects. We were unable to find further evidence of the S288K allele among these subjects or among disease

panels of AIDS-NHL (around 200), BL (around 40), MM (around 20), small cell lung carcinoma (around 25), or neuroblastoma/neurocytoma (around 60). Thus, S288K appears to be the lowest frequency *MYC* variant allele identified to date in the North American population. To learn more about the origin of the S288K allele, we obtained peripheral blood samples from the North American family of the proband and we have concluded that the father (No 557) and a daughter (No 554) are heterozygous carriers and present with no apparent phenotypic abnormalities. The family is white with a largely western European background and no apparent predisposition to the development of cancer or other metabolic diseases. We have compared expression of the S288K allele to the wild type allele by SSCP and RT-PCR amplification of RNA made from peripheral blood (fig 1). We find that S288K is expressed at extremely low levels or not at all in either subject and this result has been confirmed by sequencing individual subclones (13 in total) of RT-PCR amplified RNA from No 554 (a ratio of 12:1 subclones for codon 288 K:S).

We present two hypotheses to explain the compromised expression of S288K in comparison to wild type. The conformational change associated with a serine to lysine change at codon 288 could abrogate binding of a transcription factor and lead to repression of *c-MYC*. In fact, the transcription factor YY1 which acts to down regulate *c-MYC* expression through both direct¹⁸ and indirect effects¹⁹ is known to bind in the proximity of this region.²⁰ An alternative hypothesis is that S288K carries additional sequence differences in the 5' untranslated region which affect transcription. We cannot distinguish between these alternatives until more detailed cloning and sequencing is accomplished. Nevertheless, S288K represents the second instance of an allele of *c-MYC* (in addition to CAA-33) in which transcription is less robust in comparison to wild type.

Numerous reports of an *L-MYC* polymorphism have been linked to disease susceptibility in soft tissue sarcomas, oral cancers, colorectal cancers, NHL, breast carcinoma, and non-SCLC, whereas the same alleles seem to be associated with resistance to hepatocellular carcinoma.^{21,22} The reason for this apparent paradox can be attributed to a basic lack of quantitative expression data for *L-MYC* alleles at the RNA or protein level in tumour versus normal tissue.³ Understanding gene expression today has progressed from studies of the 5' untranslated/promoter regions to include large constructs of enhancers, matrix attachment regions, locus control regions, and methylation

Figure 1 Family pedigree for the S288K variant. (Left) Pedigree shows the distribution of the wild type allele (grey) and the S288K allele (black). Subjects 554 (proband) and 557 correspond to the affected daughter and father, respectively. (Right) The SSCP assay of genomic DNA (lane 1, 554, lane 2, 556, and lane 3, 557) and peripheral blood RNA from 554 (lane 4). Arrows depict wild type alleles (grey) and S288K specific alleles (black).

sites. Even through the use of large YAC constructs, we know that not all the components necessary for regulation of transcription have been identified, nor will they be found in proximity to the coding region for the gene of interest. *c-MYC* is no exception in that deregulation can occur in conjunction with chromosomal translocations located as far downstream as the *PVT* locus (260 kb distant to *c-MYC*). Thus, we have attempted to identify alleles of *c-MYC* and to compare rates of transcription in a search for controlling regulatory elements in *c-MYC*. Through the identification of CAA-33, S11N, and S288K alleles, we can begin the process of systematic classification of *c-MYC* expression and predisposition to disease.

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E-cadherin is not frequently mutated in hereditary gastric cancer

EDITOR—Inherited mutations in the *E-cadherin* gene (*CDH1*) were first described in three Maori kindreds with early onset, diffuse, familial gastric cancer.¹ More recently, this finding has been confirmed in other populations²⁻⁷ and this dominantly inherited familial cancer syndrome has been designated a hereditary diffuse gastric cancer (HDGC).⁴ So far, no germline mutations have been identified in site specific intestinal type gastric cancer. Based on the guidelines of the First Workshop of the International Gastric Cancer Linkage Consortium (IGCLC), the

following criteria were introduced: (1) two or more documented cases of diffuse gastric cancer in first/second degree relatives, with at least one diagnosed before the age of 50 or (2) three or more cases of documented diffuse gastric cancer in first/second degree relatives, independently of age of onset. In addition, criteria for familial intestinal gastric cancer (FIGC) were defined.⁸

In the present study, we analysed 11 Finnish gastric cancer patients with a family history of disease and two sporadic cases with germline *E-cadherin* gene mutations (table 1, fig 1). None of these families completely fulfilled the criteria for other inherited cancer syndromes with predisposition to gastric cancer, for example, hereditary non-polyposis colorectal syndrome (HNPCC), familial adenomatous polyposis (FAP), Peutz-Jeghers syndrome, or

Table 1 Features of the families studied

Family	No of gastric cancer cases	Age of onset and histological subtype ('diffuse', 'intestinal', 'unknown')	Other cancer types
1	7	33 ^d , 39 ^u , 40 ^d , 55 ^d , 66 ^d , 68 ^d , 75 ^d	Br*, Bla + Ov, Pro+Bas, Un
2	2	40 ^d , 42 ^d	Ski + Pan, Lu
3	3	37 ^d , 55 ^d , 57 ⁱ	Br, Mel, Sar, Un
4	2	36 ^d , 63 ^u	—
5	2	39 ^d , 67 ^d	Bas, CRC
6	6	41 ^u , 42 ^d , 50 ^u , 71 ^u , 71 ⁱ , 75 ^u	Br, Br, Leu†, Pan, Sar, Liv
7	1	56 ^u	Thy, Pan, Br, CRC
8	1	42 ^d	Lu, Kid
9	2	67 ^d , 68 ^d	Kid, Ut, Bas + Pro, Lu, Ov, Pan+Lu, Leu, Skin, Liv
10	2	27 ^d , 54 ^d	—
11	3	32 ^u , 64 ^d , Un ^u	CRC‡, Lip
12	3	61 ^u , 70 ^u , 76 ^d	CRC, Pan
13	7	45 ⁱ , 53 ⁱ , 53 ⁱ , 55 ⁱ , 56 ^u , 65 ^d , 68 ^u	Bas, Lip§, Lu, Un, Un

*Gastric and breast cancer; †gastric cancer and leukaemia; ‡gastric and colon cancer; §gastric and lip cancer.

Bas, basaloma; Bla, bladder cancer; Br, breast cancer; CRC, colorectal cancer; Kid, kidney cancer; Leu, leukaemia; Lip, lip cancer; Liv, liver cancer; Lu, lung cancer; Mel, melanoma; Ov, ovarian cancer; Pan, pancreatic cancer; Pro, prostate cancer; Sar, sarcoma; Ski, skin cancer; Thy, thyroid cancer; Un, unknown; Ut, uterine cancer.