# CORRESPONDENCE

## VARIABLE BREAKPOINTS ON Ph¹-CHROMOSOME

*To the Editor:*

We are pleased to see the recent articles by Bartram and his colleagues that show the position of the Ph¹-chromosome breakpoint is variable in patients with chronic myelogenous leukemia (CML).[1,2] Their findings have clearly documented at the molecular level what we have demonstrated earlier at the cytologic level.[3] In our report we suggested that based on the relative size of the Ph¹-chromosome, four types of Ph¹s were proposed. We further speculated that there is reason to expect that even "larger" or "smaller" Ph¹-chromosomes may be found as more cases are studied by the appropriate techniques. Bartram and his colleagues have further suggested that the *c-abl* gene is located on the long arm of chromosome 9 (band 9q34 → qter) and is translocated to the long arm of chromosome 22 and the translocation of the *c-abl* gene is responsible for the genesis of CML. However, the recent observations of Groffen et al[4] have localized another oncogene called *c-sis* on the long arm of chromosome 22 (22q) and have suggested that the translocation of *c-sis* to 9q could be a possible mechanism in the genesis of CML. In another publication, two patients with variant translocations have been studied by the same group.[5] In both cases, chromosome 9 was involved in the complex translocations. To our knowledge, no one has studied at the molecular level patients who are Ph¹-positive where 9q is apparently not involved. Such cases will determine the importance of the *c-sis* oncogene.

The *exact* position of the *c-sis* oncogene on 22q has not yet been mapped. However, patients with a "very large" or "large" Ph¹-chromosome, where the material translocated from 22q is minimal, suggest that if *c-sis* is the important oncogene, it is located near the telomeric region of chromosome 22q (bands 13.3).[3] This has been shown recently at the molecular level.[1] However, patients with CML having variant translocations not involving chromosome 9 and varying sizes of the Ph¹-chromosome will provide a definite clue to the location of *c-sis* and whether *c-sis* or *c-abl* oncogene(s) are responsible for the genesis of CML. Nevertheless, the identification of the oncogenes and the definition of their regulation and function in the leukemic cells are the most fascinating aspects of the field. How does an acquired balanced q9/22q translocation in stem cell lines contribute to CML? Though such translocations may be important in those patients, they do not explain the remaining 5%–8% CML cases without any translocation.

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### REFERENCES

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*To the Editor:*

Drs Verma and Dosik refer to their paper in which they state that at the cytologic level in CML patients "the break on the long arm of chromosome 22 is not point specific and can happen anywhere."[1] This fully contrasts to our recent observations.

1. We demonstrated that the breakpoints in Ph¹-positive CML patients are, indeed, individual, but cluster in a limited region of 5 Kb, called bcr (breakpoint cluster region) on chromosome 22.[2,3] In our opinion this bcr region is probably an important part of the genetic rearrangement occurring in Ph¹ (+) CML.

2. The cellular oncogene *abl* is translocated from chromosome 9 in *all* cytogenetic types of Ph¹ studied so far. Recent studies with in situ hybridization of *c-abl* sequences demonstrated the presence of *c-abl* on the Ph¹ in three Ph¹ variants resulting from apparently simple translocations between 22 and 4, 7, or 12, and in one case of masked "Ph¹."[4,5,6]

3. It is a question of general agreement and it is our experience that in Ph¹(+) CML, the cytogenetic breakpoint is restricted to 22q11, far away from the *c-sis* locus on chromosome 22q12.3-q13.1.[7] We agree with Verma and Dosik that the study of the *c-sis* localization in rare variants of the Ph¹ chromosome can be useful, particularly when cytogenetic study alone, even with high resolution banding, is unable to fully resolve the complex rearrangement leading to some unusual Ph¹ chromosomes. However, at present, there is no evidence that *c-sis* plays an essential role in the genesis of CML.

The observations of Verma and Dosik[1] were made in 1980. The supporting documentation shows only partial karyotypes of very short chromosomes, which furthermore were qualitatively diminished by photographic reproduction (as stated by the authors). We have no doubt that the authors observed large and very large Ph¹s. But this finding is not incompatible with a breakpoint on 22q11; the amount of material translocated to the Ph¹s may also vary. Re-evaluation of these cases using high resolution banding techniques could very well show that these larger Ph¹s are a form of masked Ph¹ as found by us and others; these Ph¹s originate from more complex rearrangements than suspected at first (unpublished results).