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Gene-expression profiling for discovery of novel markers of minimal disease

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Abstract

Statement of clinical relevance: Disseminated disease is a predictor of poor outcome in children with neuroblastoma, and remains the most difficult challenge for successful patient management and cure. In many children at diagnosis this disease can be detected using current methods. However for a small percentage of children at diagnosis and for those on treatment and during follow up, more sensitive and specific methods for the detection of minimal disease are required. Accurate detection of minimal disease is essential to inform the development of more effective therapies, and for improved disease stratification and monitoring.

To the Editor

As Cheung et al (1) report, accurate assessment of minimal disease (MD) is essential to inform the fight to cure children with neuroblastoma (NB). Cheung et al have exploited gene expression profiling to identify and prioritise targets for the detection of this disease using quantitative reverse transcriptase polymerase chain reaction (QRT-PCR); 8/34 genes are prioritised for investigation.

Using a similar approach we and others have previously identified 3 key mRNA targets (2); one of these targets (Phox2B) has also been prioritised by Cheung et al. Interestingly, the sensitivity and specificity of Phox2B as a target for the detection of MD by QRT-PCR in children with NB has been corroborated (3,4). However, differences in the remaining putative targets for optimal detection of MD may lead to scepticism about the value of genome-wide expression data to inform candidate selection. Unfortunately a direct comparison of data from the two Affymetrix array MD studies in NB (1,2) is limited due to several differences in methodology. Firstly the study of Cheung et al (1) utilised the Affymetrix human U95 platform, in contrast to the U133 Plus 2.0 array used in our study (2). Using the U95 platform, Cheung et al identified MEG3 and MLLT11 as specific sequences, although these probe-sets also match to an additional 5 and 2 potential targets respectively. This reinforces the importance of careful verification of probe-set gene annotation (2). Cheung et al (1) report that they have excluded targets known to be expressed in bone marrow from healthy volunteers, although they do not describe the steps taken to identify such genes. Searching the NCBI EST database for the 34 potential markers of MD identified by Cheung, we found that 6 of these genes have previously been described in bone marrow (CCND1, KIF21A, MLLT11, PFN2, UCHL1 and MAOA) and 11 in peripheral blood (CCND1, KIF21A, MLLT11, PFN2, KIF5C, MEG3, GRIA2, DDC, RGS5, KIF1A, and GABRB3) from healthy volunteers. Not surprisingly then, all but DDC were subsequently detected in normal blood using QRT-PCR (1). The selection of 8 targets for detection of MD by Cheung et al (1) is therefore questionable. The precision of MD

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detection using QRT-PCR will be facilitated by standardised assays for selected candidate genes not expressed in the normal haemopoietic compartments (2,5).

The clinical significance of MD detected by QRT-PCR for individual mRNAs emphasises the importance of this disease and the studies by Cheung et al (1), though it is unfortunate they did not investigate the independent prognostic significance of detecting disease using individual and multiple marker sets (4).

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