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The molecular basis of familial chronic lymphocytic leukemia

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It is now well established that inherited genetic predisposition plays an important part in defining individual susceptibility to most common solid tumors. Paradoxically, despite chronic lymphocytic leukemia (CLL) being the most common lymphoid malignancy in Western countries[1] and having a strong familial risk, our understanding of the genetic basis of CLL is only just starting to be recognized and its etiology elucidated.

Familial clustering of chronic lymphocytic leukemia

Over the last seven decades more than 100 families have been reported in the literature in which clustering of CLL has been documented. While not exclusively a consequence of genetic predisposition, familial aggregation provides strong evidence to support the role of inherited genetic factors in disease etiology. In a number of the families reported, CLL cosegregates with other B-cell lymphoproliferative disorders (LPD) such as Hodgkin's lymphoma (HL) suggesting that part of the familial predisposition could be mediated through pleiotropic mechanisms.[2-4] While most of the CLL pedigrees are nuclear families in which less than 4 family members have been affected, some spectacular multigenerational pedigrees have been described.[2,5] In addition to such families providing evidence for a strong familial basis to CLL the pattern of disease transmission in the pedigrees appears compatible with a model of inheritance where dominantly acting mutations confer a substantive risk of CLL.

Familial risks of chronic lymphocytic leukemia

Over the last 34 years, eight epidemiological case-control and cohort studies have systematically enumerated the risk of relatives of CLL patients developing CLL or other LPDs.[4, 6-10] Collectively these data provide evidence for a 2 to 8-fold elevated risk of CLL in case relatives.

In this issue of the journal, Goldin *et al.* have published the most comprehensive study of the risk of CLL and other LPDs in first-degree relatives of CLL cases to date.[11] This study was based on an analysis of 9,717 CLL cases and 38,159 controls ascertained through the Swedish Cancer Registry. Findings underscored CLL being characterized by a high familial relative risk (RR) – the RR of CLL in first-degree relatives of cases in this study was seen to be increased 8.5-fold. Furthermore, the risk of other non-Hodgkin's lymphoma was observed to be increased 1.9-fold. Evaluating NHL subtypes revealed a striking excess of indolent B-cell NHL, specifically lymphoplasmacytic lymphoma/Waldenström macroglobulinemia and hairy cell leukemia. These findings substantiate a relationship between the risk of CLL and other LPDs which has previously been anecdotally noted in case reports of single families and that may reflect the pleiotropic effects of an inherited predisposition.

The general incidence rates for CLL are nearly twice as high in men as in women. With familial CLL, however, the proportion of affected females is higher when

compared to sporadic CLL.[12-14] Females might therefore have more predisposition genes or their genes might be more penetrant than those of males. The relatives of affected females probably share the same predisposition genes, which increase their genetic liability, accounting for the higher proportion of familial cases among females compared to males.

Genetic models of inherited susceptibility

The observation of large families segregating CLL in an apparent Mendelian fashion has provided a strong rationale for searching for moderate-high risk gene mutations through a classical positional cloning strategy. To date, five linkage scans of CLL families have been performed.[5, 15-18] The largest of these so far, certainly in terms of number of families genotyped, was the scan conducted by Sellick *et al.* (2007) which was based on an analysis of 206 CLL pedigrees. The best evidence for a single disease locus in this study was attained at 2q21 under a recessive model in which 68% of families were linked.

Genetic heterogeneity inevitably erodes study power and failure to unambiguously identify a disease locus in this and two other scans may have been a consequence of limited power. To circumvent the issue of heterogeneity, two research groups have performed linkage searches on single, large families. The first was based on the analysis of a family comprising 11 affected members.[5] The second study was based on the analysis of a multigenerational family in which 7 members had been diagnosed with CLL.[18] Neither study provided statistically significant evidence for a single major locus conferring susceptibility to CLL.

Linkage studies are predicated on the assumption that a proportion of familial cases are caused by mutations which confer substantive risks of CLL. The failure to identify a disease-causing gene through linkage has led to a reappraisal of the assumption of Mendelian inheritance of CLL. This made the idea that susceptibility to CLL is, at least in part, a consequence of the coinheritance of low penetrance variants attractive. There may be a large number of such alleles, some of which may be common and individually exert only small effects (i.e. RRs of ~1.1-1.5). However, they could combine in an additive or multiplicative way to confer a range of susceptibilities in the population. Hence, by acting in concert such variants can generate a very high risk of CLL in a subset of the population.

Recent advances

The *common-disease common-variant* hypothesis implies that conducting association analyses based on scans of Single Nucleotide Polymorphisms (SNPs) should be a powerful strategy for identifying low-penetrance genes for CLL. Previous studies aimed at identifying low penetrance alleles for susceptibility to CLL have been based on a candidate gene approach formulated on preconceptions as to the role of specific genes in the development of the disease. Perhaps not surprisingly most studies have to date only evaluated a restricted number of polymorphisms, such as those influencing methylation or carcinogen metabolism. However, without a clear understanding of the biology of predisposition, the definition of suitable genes for the disease is inherently problematic, making an unbiased approach to loci selection highly desirable.

Despite much research, no definitive susceptibility alleles have been unequivocally identified through association studies analyzing only a restricted series of candidate genes. As with many other diseases, positive associations have been reported for various polymorphisms in genes such as *P2X7* and *ARLTS1* from small studies,[19,20] but few of the initial positive results have been replicated in subsequent studies.[21,22] The inherent statistical uncertainty of case-control studies involving just a few hundred cases and controls seriously limits the power of such studies to reliably identify genetic determinants conferring modest but potentially important risks.

Two large-scale association studies of multiple candidate genes have recently been conducted for CLL. In 2007, we analyzed 992 patients and 2,707 healthy controls.[23] To increase the likelihood of identifying disease-causing alleles we genotyped 1,467 coding nonsynonymous single nucleotide polymorphisms (nsSNPs) in 865 candidate cancer genes, biasing nsSNP selection toward those predicted to be deleterious. Preeminent associations were identified in SNPs mapping to genes pivotal in the DNA damage-response and cell-cycle pathways, including *ATM*, *CHEK2*, *BRCA2* and *BUB1B*. These findings provide evidence to implicate variants in the ATM-BRCA2-CHEK2 DNA damage-response axis with risk of CLL.

To identify low-penetrance susceptibility alleles for CLL, Enjuanes *et al.* (2008) analyzed 692 CLL cases and 738 controls genotyped for 768 nsSNPs and tag SNPs in regulatory gene regions of 172 genes implicated in cancer biology.[24] After adjustment for multiple testing, strong associations were identified between CLL risk and genetic variants in *CCNH*, *APAF1*, *IL16*, *CASP8*, *NOS2A*, and *CCR7*. Furthermore, minor alleles for *APAF1* and *IL16* were found to be associated with lower mRNA levels. This study thus presents evidence that common genetic variation in apoptosis- and immunoregulation-related genes is implicated in CLL development.

Because of the large number of polymorphisms in the genome, false-positive associations are inevitably more frequent than true-positive associations even when studies are conducted in a scientifically rigorous fashion. Hence associations need to attain a high level of statistical significance to be established beyond reasonable doubt. Furthermore, positive associations need to be replicated in independent case-control series to further guard against type 1 error. Thus, however biologically plausible findings from these large studies of CLL may be, without independent replication one must be cautious about over-interpreting these data.

Following the sequencing of the human genome, large-scale harvests of SNPs have been conducted and >10 million documented (http://www.dbsnp.org), along with smaller numbers of insertion/deletion and copy number polymorphisms. Patterns of linkage dise-

quilibrium (LD) between SNPs have been characterized allowing subsets of SNPs (tagging SNPs) to be selected that, through LD with other variants, capture a large proportion of the common sequence variation in the human genome. The high resolution LD maps now available (and hence comprehensive sets of tagging SNPs) coupled with the development of highly efficient analytical platforms allow genome wide studies for disease associations to be conducted cost effectively. This approach is unbiased and does not depend upon prior knowledge of function or presumptive involvement of any gene in disease causation. Moreover, it avoids the possibility of missing the identification of important variants in hitherto unstudied genes.

Adopting this approach, we conducted a genome-wide association study of 299,983 tagging SNPs comparing genotypes in 517 cases and 1,438 controls.[25] Fast-tracking the most significant associations from this analysis, we genotyped two additional series comprising a total of 1,529 cases and 3,115 controls to validate associations. Six previously unreported CLL risk loci were identified at 6p25.3 (*IRF4*), 19q13.32 (*PRKD2*), 2q37.1 (*SP140*), 2q13, 11q24.1, and 15q23 for which there was statistically significant evidence for an association on a genome-wide basis (*i.e.* $p<10^{-7}$).

To explore the possibility that the association with *IRF4* might be mediated through differential *IRF4* expression, we investigated the relationship between rs872071 genotype and mRNA expression in EBV-transformed lymphocytes. Expression was significantly associated with genotype in a dose-dependent fashion, with lower expression being associated with risk alleles. This observation is consistent with a model in which the causal variant influences risk by arresting transition of memory B cells through decreased *IRF4* expression.

SP140 is the lymphoid-restricted homolog of *SP100*, expressed in all mature B cells and plasma cell lines, as well as some T cells. SP100 is a major mediator of EBNA-LP (Epstein- Barr virus (EBV) encoded nuclear antigen leader protein), whose co-activation is important for establishing latent viral infections and EBV-mediated B-cell immortalization. A significant dose relationship between rs13397985 genotype and *SP140* expression in lymphocytes was demonstrable, with risk alleles being associated with reduced levels of mRNA. *SP140* expression has been implicated in innate response to immunodeficiency virus type 1; hence, although speculative, it is possible that genetic variation in *SP140* influences the risk of developing CLL through differing response to antigenic challenge.

While these data provide the strongest evidence to date for the role of common low-risk variants in the etiology of CLL, the SNPs identified are unlikely themselves to be candidates for causality. Identifying the causal variant at each specific locus and its biological impact now poses a significant challenge, contingent on a combination of fine mapping and functional analyses.

Integrating genetics and biology

The recognition that common variants influence the risk of CLL raises the possibility that, while clinically diagnosed CLL may be uncommon in the population, susceptibility may be far more common. Intriguingly this assertion is supported by the observation that CLL-phenotype B cells (CD5+, CD23+, CD20low, sIgMlow) of monoclonal B-cell lymphocytosis (MBL) are detectable in ~ 3% of adults in the general population[26] and that they are essentially indistinguishable from CLL B cells in terms of chromosomal abnormalities and IgVH mutation status. The recent report that MBL develops into CLL at a rate of 1.1% per year provides direct evidence that MBL is a precursor lesion for CLL. These data coupled with the observation that ~10% of relatives of CLL patients have MBL supports the assertion that MBL is a surrogate marker of genetic predisposition.[27]

Evidence suggests that the development of CLL might be influenced by antigenic recognition or selection through the B-cell receptor (BCR). Hence, it is conceivable that familial disease is associated with a more restricted phenotype with respect to immunoglobulin gene usage or ontogenic development, as reflected by the presence or absence of somatic mutation. We recently evaluated this through an analysis of 327 cases with a family history of CLL and 724 apparently sporadic cases.[14] The frequency of mutated CLL was higher in familial CLL, and there was evidence of intrafamilial concordance in mutation status. The repertoire and frequency of IgVH usage was, however, not significantly different between familial and sporadic CLL. Furthermore, IgVH usage was not correlated between affected members of the same family. These observations provide evidence that familial CLL is essentially indistinguishable from sporadic CLL, favoring a multifactorial basis to disease development in general.

Notwithstanding these data, the repertoire of IgVH genes expressed by B cells in CLL patients is, however, biased when compared to that of normal B cells.[28]Asymmetric usage of the immunoglobulin genes have been well characterized in CLL, with notable overrepresentation of various genes, including *IGHV1-69* and *IGHV4-34*.[29] Such preferential usage of certain IgVH genes could indicate selective drive on a B-cell population via a superantigen and lends support to the hypothesis that selection by a common antigen could contribute to disease pathogenesis. Preferential stimulation of B cells expressing the *IGHV4-34* gene occurs in a number of infections, including those caused by Epstein-Barr virus (EBV) and cytomegalovirus (CMV).[30] The first evidence linking latent or persistent infection by EBV and CMV with CLL cases expressing *IGHV4-34* was recently published,[31] signifying the possible involvement of these pathogens in the etiology of CLL. Interestingly, Xu *et al.* (2008) found that EBV transformation of human B cells *in vitro* requires the presence of high levels of *IRF4*,[32] intriguingly the same gene we recently implicated in influencing the risk of CLL.

Conclusions and future directions

Our knowledge of predisposition to CLL is rapidly developing. It is now well established that the disease is characterized by having amongst the highest familial risks of any malignancy. Moreover, the observation

that MBL probably represents a progenitor lesion offers considerable opportunities for understanding the key genetic events in the development of CLL and also other related B-cell LPDs.

As with other tumors, the advent of genome wide association studies is enabling researchers to identify variants that influence an individual's susceptibility to develop CLL. Such studies are at the vanguard of the new technologies which will ultimately offer complete interrogation of genetic variation in the human genome. Defining the sequence changes responsible for causal associations identified should thus provide insight into the biology of CLL and this may lead to the development of etiological hypotheses regarding non-genetic risk factors. Finally, a greater understanding of the biological basis of the disease will hopefully lead to the development of novel therapeutic interventions.

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