SPECIAL FOCUS REVIEW

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Sequence based identification of RNA editing sites

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RNA editing diversifies the human transcriptome beyond the genomic repertoire. Recent years have proven a strategy based on genomics and computational sequence analysis as a powerful tool for identification and characterization of RNA editing. In particular, analysis of the human transcriptome has resulted in the identification of thousands of A-to-I editing sites within genomic repeats, as well as a few hundred sites located outside repeats. We review these recent advancements, emphasizing the principles underlying the various methods used. Possible directions for extending these methods are discussed.

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Adenosine-to-inosine (A-to-I) RNA editing is a post-transcriptional modification of RNA, resulting in RNA sequences different than their genomic blueprint. Enzymes of the ADARs (adenosine deaminases that act on RNA) protein family bind to double-stranded RNA structures within the newly formed RNA molecules and deaminate targeted adenosines (A) within these structures into inosines (I). Downstream RNA processing enzymes, such as the ribosome and the splicing apparatus, recognize the inosine as guanosine (G), thus allowing for different fates for the edited RNA molecules.

The first mammalian A-to-I RNA editing was discovered almost two decades ago.[1] However, despite much effort, only a limited number of editing targets were found in the human genome till recently, mostly due to discoveries by chance. Accumulating evidence suggested that editing is of high importance: mice lacking ADARs die in-utero or shortly after birth.[2-4] In addition, a number of neurological diseases were associated with altered editing patterns.[5-8] Later on, it was found that editing activity of ADAR1 is essential for hematopoiesis.[9,10] These phenotypes were not all explained by the few editing targets identified. Moreover, pioneering experimental work found that inosine exists in mRNA in large amounts[11], much larger than could be accounted for by the handful of targets known at that time. Accordingly, the search for more targets continued and several experimental methods to find additional editing events and their levels were developed[12-21] with various levels of success.

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Bioinformatic screens

Computational detection of editing sites should be simple, in principle. Like the endogenous enzymes, most sequencing reactions also read an edited adenosine "A" site within cDNA as a guanosine "G". Therefore, naively, one has only to align the millions of publicly available ESTs and full length RNAs to the genome and search for such A-to-G mismatches (**Fig. 1**). However, this straight-forward approach fails in reality due to the extremely low signal-to-noise ratio. The total fraction of mismatches between the genome and the expressed sequences amounts to 1-2 percent.[22] The main contributors for these discrepancies are random sequencing errors in the expressed sequences and genomic polymorphisms that result in genomic differences between the different individuals contributing to the expressed sequences and the reference genome. Additional causes of variance between RNA and the genome include mutations and erroneous alignment of duplicate RNA sequences to the genome.

The first editing sites to be discovered reside all within the coding regions of mRNAs. These editing sites were shown to be functional - their editing results in an amino-acid substitution and affects the protein function. Looking at these sites carefully, one observes a unique feature – the genomic sequence surrounding these sites is highly conserved among species.[23] This can be easily understood in terms of the additional evolutionary constraint: in order to keep the editing event conserved, not only has the sequence to be conserved against changes in the amino-acid coding information, but also the double-stranded RNA structure must be left intact. This constraint leads to higher conservation at the DNA level, and has proven to be a very useful signature of editing sites, to be employed in bioinformatic searches.[23-25] Unlike editing sites, sequencing errors and genomic polymorphisms are not often shared between species. The additional filter of conservation thus allows one to find the few editing recoding sites among tens of millions of mismatches between ESTs/RNAs and the genome. This strategy was demonstrated by a number of groups: looking for such conserved mismatches located in the exact same position in human and mouse resulted in a few additional A-to-I editing substrates.[24,26,27] The newly discovered sites are now under investigation in order to determine their biological function and regulation potential[28-31]. We note that using

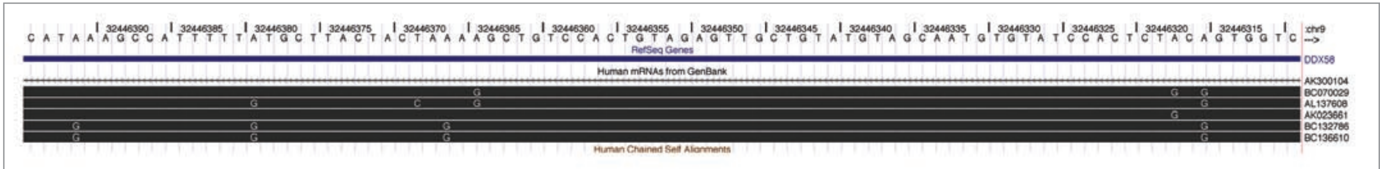

Figure 1. Exemplary RNA editing cluster. Evidence for editing cluster in the DEAD (Asp-Glu-Ala-Asp) box polypeptide 58 (DDX58) gene as found by alignment of mRNAs and ESTs to the reference genome observed in the UCSC genome browser. The mismatches are highlighted; 15 of 16 mismatches are A-to-G changes.

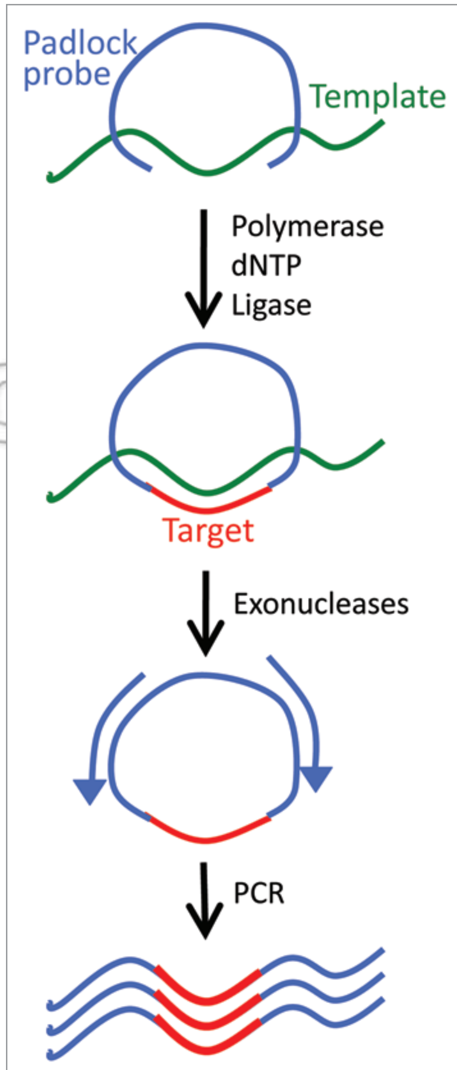

Figure 2. Padlock capture technology. To specifically capture and amplify targets of interest in the template, multiple padlock probes simultaneously hybridize the template. Shown in the diagram is a single padlock probe for a single target. Each of the probes comprises two target-specific capturing arms, which anchor the target and are linked by a common sequence shared by all probes. After the polymerase and dNTP are added, the target gaps are filled simultaneously. The ligase then seals all gaps, thus circularizing the padlock probes with the targets captured. Exonucleases are then added to digest linear DNA away. The remaining circles are then amplified by a single pair of primers annealing the common sequence of all probes.

this approach one seems to be better off not implementing the requirement for a dsRNA structure, as the typical dsRNA structures of the few known targets are rather weak and hard to predict computationally.[32] Another point to note is that most of the novel editing sites appear in the SNP database (dbSNP), due to an erroneous interpretation of the variability among expressed sequences in these sites as a sign for a single-nucleotide polymorphism (SNP).[33] A careful analysis of dbSNP could result in more editing sites hidden as mis-annotated SNPs.[34]

Deep Sequencing approach

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With recent advancement in massively parallel sequencing technologies, one could start sequencing whole transcriptomes in order to determine the full scope of RNA editing. However, observing a consistent discrepancy between the RNA sequence and the reference genome does not prove the site to be an editing site. One must exclude the possibility of genomic diversity between the reference genome and the genome of the RNA source tissue. Thus, identifying RNA editing sites requires sequencing of both genomic DNA and cDNA from the same source. Second, editing levels vary among tissues, and therefore one would need to repeat the experiment for a wide variety of tissues. Even with the massively parallel DNA sequencing technologies, this kind of experiment is still prohibitively expensive. A combination of a computational approach together with a novel targeted sequencing technique was recently shown to meet this challenge, expanding the A-to-I RNA "editome" from <20 to hundreds of sites residing out of the repetitive elements.[35] First, a bioinformatic search was conducted by aligning eight million human ESTs against the human reference genome. After the known genomic polymorphisms were removed, there remained ~60,000 potentially edited sites in the non-repetitive portion of the human genome. A targeted capture and sequencing approach was taken to specifically sequence the predicted sites in parallel. For each of the predicted editing sites, a padlock probe (also known as molecular inversion probe) was designed for specific anchoring and amplification (**Fig. 2**).[36] All sites were simultaneously captured, amplified, and sequenced. To identify true RNA editing sites, genomic DNA and cDNA from several different tissues (mainly brain) were used, all derived from a single donor so as to rule out polymorphisms among populations. The pool of probes was hybridized to the DNA and cDNA in separate amplification reactions. The amplicons were sequenced, and the resulting sequences were scanned in order to identify sites where an "A" allele was observed in genomic DNA, whereas at least a fraction of the reads in the cDNA samples show

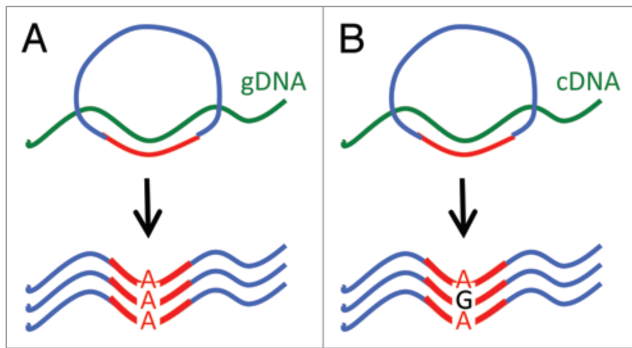

Figure 3. Schematic diagram to identify RNA editing sites using the padlock capture technology. Padlock probes are designed to capture the predicted RNA editing sites in separate reactions of both genomic DNA (gDNA) (A) and cDNA (B) from the same source. All sites are captured, amplified, and sequenced in parallel. The indication to call a site A-to-I RNA editing site is that all genomic reads bear an "A", while at least a fraction of the cDNA reads have a "G" at the site.

"G" (**Fig. 3**). This method allows for parallel sequencing of tens of thousands of suspected sites in a single reaction.

Editing within repetitive elements

The growth in the number of known editing sites within the coding sequence (editing of which might modify the encoded protein) could not meet the challenge posed by the large amount of inosine observed in total mRNA. However, a large number of clusters of editing events were found in non-coding regions, suggesting many more editing events could be found in the non-conserved and non-coding part of the transcriptome. Three groups have devised computational methods for identifying such clusters, based on analysis of mismatches in otherwise almost perfect alignments of RNA.[37-40] The methods differ by the clustering criteria used and the statistical analysis employed. Remarkably, the three independent procedures resulted in highly similar results: A-to-G substitutions, which could arise from A-to-I editing events, account for more than 80% of the 12 possible types of mismatches in the selected set of transcripts. As this disparity in mismatches distribution is unlikely to occur for genomic polymorphisms and sequencing errors, it provides a clear signature of editing in tens of thousands of sites within the human transcriptome.

Virtually all of these clusters are harbored within *Alu* repetitive elements. *Alu* elements are short interspersed elements (SINEs), roughly 300bp long each. Humans have about a million copies of Alu, accounting for ~10% of its genome.[41] Since these repeats are so common, especially in gene-rich regions, pairing of two oppositely oriented *Alus* located in the same pre-mRNA structure is likely. Such pairing produces a long and stable dsRNA structure, an ideal target for the ADARs.

Editing events couple with splicing, thus they may occur in introns as well. However, computational approaches based on expressed sequences are obviously limited in their ability to detect editing within introns. Therefore, it is anticipated that the actual number of editing sites in the human genome is even much higher than the tens of thousands sites reported in the above works. Indeed, direct sequencing of human brain total RNA has revealed that up to 1 in 1000 bp of the expressed regions are being edited.[42]

Implications and future directions

The large-scale database of newly found editing sites can be explored in order to better characterize the editing reaction. Weak sequence preferences for the nucleotides preceding and following the editing sites are observed, presumably attesting for ADAR binding preferences. There is also some evidence that the local dsRNA structure may play a role in targeting of the ADARs. The editing level in a given *Alu* repeat can be shown to correlate with the existence of a nearby and reversely oriented repeat, in support of the paired *Alu* model. Analysis of thousands of examples has shown that effective editing requires a distance of roughly 2000 bp or less between the two *Alus*. Furthermore, the level of editing increases with the number of reverse complement *Alus* present within this distance.[38-40,42] These characteristics of the editing pre-requisites are instrumental in devising future searches for editing targets in human and other organisms. Interestingly, edited adenosines within the dsRNA structure are paired with a "U" or a "C" in the reverse strand, meaning that editing either strengthens or weakens the dsRNA structure, but virtually never has a neutral effect on the dsRNA pairing energy.[40] This observation hints at the possibility of RNA editing playing a regulatory role in controlling dsRNA stability.

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The role of *Alu* editing is yet to be explored. Recent observations suggest that editing is involved in molecular mechanisms based on dsRNA structure, such as RNAi[43] and miRNA.[44-46] Indeed, while searching for a functional role for the abundant editing of Alu repeats, it was noticed that many of these editing events alter putative targets of miRNAs.[47,48] Several additional regulation mechanisms, including degradation and nuclear retention of edited transcripts, were discussed in recent years, where occurrence of inosine clusters was shown to facilitate RNA expression regulation in a few examples. It is yet too early to call whether any of these regulation mechanisms is as widespread as *Alu* editing itself.[49-56]

Alu repetitive elements are unique to the primates, but the occurrence of repetitive elements in general is common to all metazoa. However, applying the same methods for editing detection to other organisms has shown that there are about 40 times less editing events in mouse as compared to the human genome.[37,38] A similar picture was observed in rat, chicken and fly.[37] The high editing level in humans is likely due to the fact that humans have only one dominant SINE, which is relatively well-conserved (only ~12% divergence between an average *Alu* and the consensus). In comparison, mouse has four different SINEs, which are shorter and more divergent (~20% average divergence).[57]

The exceptional level of editing in the primate brain makes it tempting to suggest a role in primate evolution. The over-representation of editing in brain tissues and the association of aberrant editing with neurological diseases are consistent with a possible connection between editing and brain capabilities. One thus may

speculate that the massive editing of brain tissues is responsible in part for the brain complexity. As this large-scale editing is a direct result of *Alu* abundance, it follows that if the above idea has any merit then the massive invasion of *Alus* into the primate genome had a major impact on primates' evolution.[37,58-60]

The recent identification of hundreds of non-repetitive human RNA editing sites may be followed by many more very soon. The wide availability of RNA-seq data will surpass the EST database for more predicted RNA editing sites. The dbSNP has also grown as a result of recent genomic sequencing efforts, improving one's ability to filter rare SNPs. As sequencing cost continues to drop, a comprehensive approach to identifying all RNA editing sites is becoming possible by sequencing the entire transcriptomes as well as the exomes or genomes. In addition to A-to-I sites, other types of RNA editing, such as C-to-U sites, will be revealed by these efforts.

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