Genome Medicine

RESEARCH HIGHLIGHT

Unexpected findings of variability in microRNAs suggest roles in human genetics

Stefano Volinia[1-3,*]

See research article http://genomemedicine.com/content/4/8/62/abstract

Abstract

Short RNA molecules were considered to be junk for decades, but in recent years they have been shown to have important functional roles. MicroRNAs (miRNAs) in particular have attracted much attention. They have been assumed to be highly conserved in humans and other species; however, a recent study published in *Genome Medicine* reveals an unexpected level of variability in human miRNAs, including variations within the seed region. This challenges the current view of miRNAs, and may explain previous reports of pathogenic mutations in miRNAs.

Keywords MicroRNA, non-coding RNA, pathogenic mutations, variation.

The human genome keeps revealing surprises about the structure and function of its hereditary repertoire. When the draft structure of the human genome was unveiled just over ten years ago, many scientists spoke about the 'end of genetics'. But in reality the opposite happened, and arguably human genetics has grown at a faster rate than ever before.

Among the many surprises has been the discovery of a pervasive role of non-coding RNAs (ncRNAs), including miRNAs, which was a major upset for those who thought that nothing new and paradigm changing could still be unveiled. Extremely short RNA molecules, treated for decades as junk in northern blots and other assays, turned out to be a formidably underestimated component of the natural history of multicellular organisms. The ncRNA revolution, which caught all of us unprepared, is ongoing, with the discovery of new classes such as long ncRNAs.

*Correspondence: s.volinia@unife.it
[1]Data Mining for Analysis of Microarrays, Department of Morphology and Embryology, Università degli Studi di Ferrara, 44100 Ferrara, Italy
Full list of author information is available at the end of the article

But now, after so many intensive studies and perhaps hasty assumptions, could another genetics dogma - this time about the level of variation within miRNAs in the genome - be on the verge of being wiped out? A report by Dopazo and colleagues [1] in this issue of *Genome Medicine* suggests so.

miRNA mutations

In the study, the investigators analyzed the genomic sequences, or more accurately the genomic variations, from over 1,100 individuals to examine the level of variation in miRNAs. The majority of sequences were collected from the 1000 Genomes Project, but to these data they added 60 new exome sequences from healthy individuals from southern Spain who participated in the Medical Genome Project. A total of 527 variants from 1,152 individuals were found, with the average number of variants in miRNAs per person being 28.

Most geneticists, when interrogated on this subject, would reply that miRNAs are among the most conserved genes across species. Indeed, this is the property that aided their discovery. And some will probably continue by saying that this is true within the human species. The common sense notion being that no mutations would be found in miRNA genes after more than a decade of studies of many diseases.

The article by Dopazo and colleagues strongly challenges this view, indicating that there are enough data in the databases (with back-up novel exome sequences) to convince us of the need to, at the very least, become acquainted with the notion of miRNA mutations.

Most of the variation found in the study is not within the conserved seed region: only 44 of the 527 variants were in this recognition region. Yet the small, but perhaps more interesting, percentage of miRNA mutations the authors identified that do lie within this region might affect miRNA functions, and seem to deviate from Hardy-Weinberg equilibrium. This would hint at the existence of a selective pressure working against these variant alleles.

Pathogenic mutations in miRNAs

There have been previous reports of pathogenic mutations in miRNAs and other short ncRNAs. Calin *et al.* [2]

in 2005 detected a mutation in the miR-15/16 precursor associated with chronic lymphocytic leukemia (CLL). This mutation negatively affected the processing of the precursor to mature miRNA and was not found in normal individuals. An almost identical mutation was later found in mice, where the development of CLL in the New Zealand Black murine model was shown to be associated with a point mutation in the primary mir-15a/16-1 region, which in turn correlated with a decrease in mature miR-16 and miR-15a levels [3].

Mutations in ncRNAs can be tricky to detect, because the changes do not produce obvious functional changes in the way that mutations in protein-coding genes do. Finding mutations within such ncRNAs takes persistence; for example, a mutation affecting a ncRNA was reported recently in microcephalic osteodysplastic primordial dwarfism type I (MOPD I), a severe developmental disorder characterized by extreme intrauterine growth retardation and multiple organ abnormalities, after many years of careful genomic investigations [4].

Viewed within this context, the article by Dopazo *et al*. [1] shows that we need to challenge some of the assumptions made about miRNAs, which would perhaps help us to understand better how miRNAs function. Certain questions arise from their results. Are the star forms (the complementary or passenger strand of miRNAs) more subject to variability? Are many of the 'novel miRNAs' really acting as classical miRNAs? And most of all, how do miRNAs, with their multiple gene target modulation, really affect cellular functions? It is likely that the discovery of mutations in miRNAs will, in the coming years, allow geneticists to answer these, and other questions.

Abbreviations
CLL, chronic lymphocytic leukemia; miRNA, microRNA; ncRNA, non-coding RNA.

Competing interests
The author declares that he has no competing interests.

Acknowledgements
SV is supported by Grant IG 8588 from the "Associazione Italiana per la Ricerca sul Cancro - AIRC" and by a "Progetti di Ricerca di Interesse Nazionale" PRIN 2008 Grant from the Ministero dell'Istruzione dell'Università e della Ricerca, Italy.

Author details
[1]Data Mining for Analysis of Microarrays, Department of Morphology and Embryology, Università degli Studi di Ferrara, 44100 Ferrara, Italy. [2]Comprehensive Cancer Center, Ohio State University, Columbus, OH 43210, USA. [3]Biomedical Informatics, Ohio State University, Columbus, OH 43210, USA.

Published: 31 August 2012

References

1. Carbonell J, Alloza E, Arce P, Borrego S, Santoyo J, Ruiz-Ferrer M, Medina I, Jimenez-Almazan J, Mendez-Vidal C, Gonzalez-del Pozo M, Vela A, Bhattacharya, Dopazo J: **A map of human microRNA variation uncovers unexpected levels of variability.** *Genome Med* 2012, **4:**62.
2. Calin GA, Ferracin M, Cimmino A, Di Leva G, Shimizu M, Wojcik SE, Iorio MV, Visone R, Sever NI, Fabbri M, Iuliano R, Palumbo T, Pichiorri F, Roldo C, Garzon R, Sevignani C, Rassenti L, Alder H, Volinia S, Liu CG, Kipps TJ, Negrini M, Croce CM: **A microRNA signature associated with prognosis and progression in chronic lymphocytic leukemia.** *New Engl J Med* 2005, **353:**1793-801.
3. Raveche ES, Salerno E, Scaglione BJ, Manohar V, Abbasi F, Lin YC, Fredrickson T, Landgraf P, Ramachandra S, Huppi K, Toro JR, Zenger VE, Metcalf RA, Marti GE: **Abnormal microRNA-16 locus with synteny to human 13q14 linked to CLL in NZB mice.** *Blood* 2007, **109:**5079-5086.
4. He H, Liyanarachchi S, Akagi K, Nagy R, Li J, Dietrich RC, Li W, Sebastian N, Wen B, Xin B, Singh J, Yan P, Alder H, Haan E, Wieczorek D, Albrecht B, Puffenberger E, Wang H, Westman JA, Padgett RA, Symer DE, de la Chapelle A: **Mutations in U4atac snRNA, a component of the minor spliceosome, in the developmental disorder MOPD I.** *Science* 2011, **332:**238-240.

doi:10.1186/gm370
Cite this article as: Volinia S: **Unexpected findings of variability in microRNAs suggest roles in human genetics.** *Genome Medicine* 2012, **4:**69.