ETHICS WATCH

Ethics guidelines for population genetics research

Large-population biobanks and their related databases have multiplied in recent years. The United Kingdom, Estonia and Iceland have led the way, and others are expected to follow soon. Even an international consortium, the HapMap Project, is currently regrouping partners from six countries and comparing haplotype variations in various populations around the world.

CARTaGENE is a population genomics project that plans to map genetic variation in a large reference population of Quebec. At the request of its leader, Claude Laberge, a multidisciplinary research team from the Genetic and Society Project (University of Montreal) has been studying the ethical and legal challenges that are raised by population genetics research. The team has found that despite the existence of many guidelines on genetics research, none was tailored to the specific challenges raised by these types of project.

The research team therefore drafted a *Statement of Principles on the Ethical Conduct of Human Genetic Research Involving Population*[1]. The statement, which was developed by a multidisciplinary team composed of M. Deschênes, G. Cardinal, B. Knoppers, T. Hudson, D. Labuda, G. Bouchard, É. Racine, C. Fecteau, S. Truong and C. Laberge, includes a vision of ethical conduct in population genetics research, based on ten fundamental principles that should be upheld in undertaking these types of project: individuality, diversity, complexity, reciprocity, solidarity, security, accountability, equity, citizenry and universality. The principles are articulated in practical recommendations and procedures to guide researchers in setting up these types of project. The statement covers topics such as consultation, recruitment, consent, confidentiality, governance, communication of research results, commercialization and contribution to the welfare of the population and of humanity.

Let us consider public consultation. In a population genetics research project, the entire population must be recognized as an important partner. Early international experiences have shown that public consultation is key to the overall success of such projects. Indeed, although the whole population (including participants and non-participants) will eventually benefit from such initiatives, it is also collectively taking potential risks. In addition, an important amount of public and private research resources must be devoted to a population genetics research project. These types of initiative need consent not only from the participants, but also meaningful public support and engagement. Open and continued dialogue, throughout the project, will help to foster the trust of the population; it can even serve as a preparatory stage for individual informed consent.

According to the statement: "Respecting the principles of reciprocity, diversity and accountability requires that research on a given population be based upon an open dialogue between the population and the research team. A guiding mechanism for population genetic research is prior and ongoing public consultation." In suggesting how to implement these recommendations, the statement emphasizes the importance of a proper information and public-engagement process that will enable the public to take part in the debate and voice their concerns or support for such a project.

Setting up a population genetics research project poses a scientific and logistic challenge, but also a legal and ethical challenge. Statements such as the one based on the CARTaGENE project promise to provide useful guidance to the research community and their partners, including participating populations.

Mylène Deschênes, B.C.L., LL.B, LL.M.
e-mail: MDeschenes@cihr-irsc.gc.ca

[1]Knoppers, B. M. (Ed.) in *Population and Genetics Legal and Socio Ethical Perspectives* 641 (Martinus Nijhoff, The Netherlands, 2003); *RMGA* [online], <http://www.rmga.qc.ca/en/index.htm> (2003)

GENE REGULATION

microRNA, control yourself!

From plants to fish to humans, microRNAs — arguably the most sought-after molecules in genetics — work by interfering with the expression of complementary mRNAs. Now, Hervé Vaucheret and colleagues show that microRNAs (miRNAs) are not averse to biting the hand that feeds them: the *Arabidopsis thaliana* ARGONAUTE PROTEIN 1 (AGO1) is needed for the proper function of miRNAs and is itself regulated by a miRNA. Proving the existence of this negative feedback involved engineering artificial miRNAs, potentially spurring a new approach to targeted gene silencing.

Circumstantial evidence indicated that the AGO1 protein worked in the miRNA pathway, specifically as a component of the RNA-induced silencing complex (RISC), the ribonucleoprotein complex in which miRNAs act. Animal AGO homologues are found in the RISC, but it was the combination of genetic analysis of *ago1* mutants in *A. thaliana* and some clever sequence manipulations that provided the proof.

Vaucheret and colleagues found that mRNAs that are normally targeted for cleavage by miRNAs accumulate in *ago1* null mutants; this indicates that AGO1 could be needed for proper miRNA function and that this is the only AGO family member — out of ten — to be predominantly associated with miRNAs in the plant RISC.

Among the mRNAs that accumulate in the mutants is the *AGO1* transcript itself, prompting the idea that *AGO1* mRNA is negatively regulated by a miRNA. A miRNA that is complementary to *AGO1* (miR168) suggested itself — correctly, as it turns out — as the negative-feedback regulator. An otherwise wild-type *AGO1* gene was engineered to reduce its complementarity to miR168; this increased the levels of *AGO1* mRNA and caused developmental defects that resemble those of *dcl1*, *hen1* or *hyl1* mutants that are impaired at other steps in the miRNA pathway. To be certain that *AGO1* mRNA was regulated by miR168, the authors reversed the defects by generating compensatory mutations in the miR168, so that it now bound to the mutant *ago1* mRNA and presumably allowed its normal degradation.

As the authors note, further experiments will be needed to prove that AGO1 is in the RISC, and, if it is, that it is the only AGO family member to be involved in miRNA function.

Tanita Casci

References and links

ORIGINAL RESEARCH PAPER Vaucheret, H. *et al*. The action of *ARGONAUTE1* in the miRNA pathway and its regulation by the miRNA pathway are crucial for plant development. *Genes Dev.* **18**, 1187–1197 (2004)

FURTHER READING Bartel, D. P. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell* **116**, 281–297 (2004)

WEB SITES

David Bartel's laboratory: http://web.wi.mit.edu/bartel/pub

Hervé Vaucheret's laboratory: http://www-ijpb.versailles.inra.fr/bc/equipes/Epigenetics/index.html