

# The neglected genome

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Mitochondria harbour some of the most critical functions of life [1–3]. As the site of ATP synthesis by oxidative phosphorylation, they are the primary energy-generating system in almost all eukaryotic cells and are central to programmed cell death. Mitochondria also play major roles in a broad range of other key processes such as the synthesis of amino acids, haem, nucleotides and lipids, ion homeostasis, cell proliferation and motility. It is of major evolutionary and functional significance that they carry their own small DNA genome—a legacy of the endosymbiosis that created mitochondria, and possibly the eukaryotic cell, some 1.5–2 billion years ago [4]. In humans, mitochondrial DNA (mtDNA) is a double-stranded circular molecule of 16.5 kilobase pairs that carries only 37 genes, 13 of which encode proteins.

The coordinated expression of the mitochondrial genome with the nuclear genome is essential for the functioning of eukaryotic cells [5]. This interaction is subject to epigenetic regulation because chromosome phosphorylation, acetylation and methylation are modulated by energy availability and redox state [6]. As a consequence, mitochondrial dysfunctions have pleiotropic effects in multicellular organisms and give rise to a large spectrum of defects [7–10].

The vast majority of proteins involved in mitochondrial biogenesis and function are encoded by the nuclear genome and imported into mitochondria as precursors. Yet the 13 proteins encoded by human mtDNA are crucial for life as they are essential subunits of the oxidative phosphorylation system [11–13]. Moreover, changes in their expression affect nuclear genes through pathways as yet poorly understood.

Complete functional genomic analyses must consider nuclear–mitochondrial interplay by describing genetic, epigenetic and expression profiles of both genomes in healthy and pathological conditions.

Mutations in mtDNA are associated with a wide range of severe diseases, preferentially affecting tissues with high energy demand. These diseases include specific metabolic conditions, but also ageing, various degenerative diseases, and probably fertility [14] and cancer [13].

The advent of next-generation sequencing technologies is profoundly revolutionizing several areas of biological research and providing unprecedented possibilities for functional genomic studies. Genome sequencing and expression profiling are now routinely performed at increasing economy and speed. Indeed, we are facing a flourishing of papers reporting large-scale analysis of genome variation in different populations and diseases, for example, the 1000 Genomes Project and the Cancer Genome Atlas, genome-wide associations studies (GWAS) for several diseases, as well as high-throughput expression profiling in different cell types and conditions.

However, despite the increasing evidence for the fundamental role of nuclear–mitochondrial communication in eukaryotic cell functions, the overwhelming majority of functional genomic studies largely neglect the mitochondrial contribution at the level of genome sequence in the detection of mutations or polymorphisms, and in gene expression profiling.

Commercial kits for genome-wide investigations neglect the tiny but crucial store of genetic material in mtDNA, and genome sequencing protocols sometimes involve steps designed to minimize ‘mitochondrial contamination’ [15]. For example, DNA enrichment systems for exome sequencing do not include probes targeting mitochondrial genes, thus ignoring variations and mutations in mtDNA [16]. Furthermore, although the necessary raw data are often available, for example, RNA-Seq data include mtDNA transcription products, most popular bioinformatics

computer programs for transcriptome profiling do not take into account mitochondrially encoded transcripts. With the increased interest in understanding ‘missing heritability’ and epistatic interactions in GWAS studies, the lack of mtDNA markers ensures that ‘mito-nuclear’ epistases will be missed.

We strongly recommend that high-throughput investigations begin to integrate information from both mitochondrial and nuclear–cytosolic genetic systems to fully understand the behaviour of eukaryotic cells in health and disease. This integrative approach will open new avenues in studies focused on molecular evolution and on selective adaptation in eukaryotes as well as addressing the onset and treatment of degenerative and age-related diseases.

#### ACKNOWLEDGEMENTS

We thank David Horner for comments on the manuscript.

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EMBO reports (2012) 13, 473–474; published online 4 May 2012; doi:10.1038/embor.2012.57

## A tribute to the ERC—long live basic research

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The creation of the European Research Council (ERC) five years ago was a unique and singularly encouraging event. After long discussions among individual researchers and, later on, among national research organizations, a European-wide research council finally emerged. Its creation was a true grass-roots movement to address the shortcomings of the EU Framework Programmes (FPs) in supporting basic research, which were widely seen as suffering from excessive bureaucracy, top-down stipulation of what constituted topical research, politically motivated requirements for huge networks of laboratories, the fostering of proposals best written by consultants, and a generally uninspiring and uninspired vision of science. In reality, the situation might not have been as bleak: the huge sums of money spent by the FPs have certainly improved science, mobility, networking and training; and most scientists agree that concerted research efforts are needed to address pressing concerns about the economy, the environment, public health and so forth. Nonetheless, one might question the cost-effectiveness of the FPs, and the extent to which their research goals have been achieved.

The ERC was intended to add a completely different mechanism for supporting basic research in Europe and it has succeeded spectacularly. The only criterion for assessing grant proposals is the quality of

science. This is the case not only on paper, but also in practice, as ERC review panels are made up of independent researchers, and they have all the power. There are no Programme Directors in the sense of the US National Science Foundation, although there are highly motivated and competent staff in Brussels supporting the panels. There are more than 100 panels covering the sciences and humanities. With an average of more than 10 members per panel, this adds up to more than 1,000 independent researchers. The direct and indirect influence of the ERC is seen across Europe.

The ERC has been running two types of grant, the Advanced Grants for senior researchers and the Starting Grants for younger investigators. The first call for Starting Grants in 2007 attracted nearly 10,000 proposals, of which less than 3% could be funded. Since then, the acceptance rate has settled at around 10%. A new type of grant, ERC Synergy, was established last year and the first round of evaluations is taking place as I write. ERC Synergy supports 2–4 primary investigators working together on especially ambitious and challenging, big projects. Incidentally, I see ERC Synergy as a great opportunity to involve researchers with special skills from the smaller European nations. But it is up to the researchers to decide how they team up—once again, the only criterion is excellence of science.

The ERC's budget has accounted for around 15% of the total funding for research

and innovation in the 7th EU Framework Programme. In the planned Horizon 2020 Programme for 2014 to 2020, its share might increase slightly. Whether 15% strikes a good balance between basic research and the rest is debatable. I would prefer to see this figure approaching 20%.

In any case, the ERC has filled a vacuum in Europe to directly fund basic, investigator-driven research across the continent. The venerable argument for basic research is on the basis of the applications that inevitably follow on from new knowledge—even if we cannot predict how and when, and which particular piece of new knowledge will be especially influential. Being an ecologist and conservation biologist, I find the comparison with the value of biodiversity enlightening. Human well-being depends on biodiversity and the proper functioning of ecosystems, ('ecosystem services') but we cannot pinpoint exactly which species are most important, especially in a changing world. Species cannot be reinvented—notwithstanding the bizarre claims of some synthetic biologists—and truly new and, by definition, unexpected knowledge cannot be gathered at will; the trade of basic research must be kept alive.

New knowledge will lead to new applications, and the greater the pool of knowledge, the more diverse the set of applications. Sadly, such potential is under-appreciated in our societies. Nonetheless, it remains the responsibility of science and researchers to look beyond the short-term challenges. I think of scientists as co-pilots in a fast-moving rally car; they are the navigators, communicating the twists and turns to the driver by knowing in advance what is on the road ahead. The faster you move, the more you need good navigation. Alas, society often seems to want to increase the speed of the car by installing an extra gas pedal on the side of the co-driver. Navigation, well, that's regarded as expensive luxury.

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EMBO reports (2012) 13, 474; published online 11 May 2012; doi:10.1038/embor.2012.64