1 Answer **B**. However, response **D** is also correct: indeed, if we assume for example that “1” is active and “2” is inactive, then the proteins controlled by “1” and “2” are inactive and active, respectively. The final protein is inactivated because one of its inhibitors is active. Thus, apoptosis is inhibited.

2 Both are correct.
1) For the cell’s life: cytochrome c, inside the mitochondrial interspace, is an indispensable electron carrier protein for the mitochondrial electron-transport chain. It transfers electrons between complex III and IV. Hence, it is crucial for cells to express cytochrome c in the mitochondria.
2) For the cell’s death: if released in the cytosol, cytochrome c is converted into a pro-apoptotic molecule. It will bind Apaf-1 to trigger the activation of procaspase- 9, altogether forming the “apoptosome” complex, which will then activate caspase-3 and cause apoptosis. Hence, it is crucial for the life of the cells to prevent cytochrome c release into the cytosol.

3 B. Mitochondria are inherited maternally, and a genetic disease caused by mutations in the mitochondrial genome in a founder female would be inherited by all descendants.

4 (a) Mitofusin1 and -2 are essential proteins expressed in the outer membrane of the mitochondria, which make oligomers in *trans* to make connections between adjacent mitochondria and initiate fusion. In mitochondria that do not express the Mitofusin1 gene, fusion will probably be impaired. Hence, the cells will display small, fragmented mitochondria. However, we can imagine a partial (or even complete) compensation provided by the expression of Mitofusin2. Experiments should be done to test which scenario prevails.

(b) The fusion defect (assuming there is one) will not be corrected by adding more OPA gene, because OPA acts in the inner membrane, but fusion is initiated at the outer membrane, by Mitofusins.
(c1) To work efficiently in the fusion process, Mitofusins require their intact GTPase activity. Therefore, a mutant that cannot bind GTP will be inactive, and will not rescue the fusion defect.

(c2) To anchor mitochondria together and initiate the process of fusion, the localization of Mitofusins at the outer membrane is absolutely required. Hence, a mutant expressed at the internal membrane will not be able to rescue the fusion defect.

(c3) This is harder to predict. Because Mitofusin1 and -2 have partially redundant roles, increasing the expression of Mitofusin2 in Mitofusin1-deficient cells may compensate, at least partially but perhaps not entirely, for the absence of Mitofusin1. To get a definitive answer, the experiment should be done during the bachelor’s project.

(d1) Although the sequencing indicates there is no mutation, we cannot conclude there is no problem from these genes. One of them could, for example, not be.

expressed, or not be expressed at its correct mitochondrial localization. Hence, other methods should be used to complement gene sequencing, to ensure the proteins are expressed, localized where they should, and functional.
(d2) Cells with too long mitochondria can typically result from a deficit of fission (what we tried to exclude in (d1)), or too much fusion. Hence, fusion genes should be examined closer, to evaluate if one of them could have a gain-of- function mutation, or be expressed too much, which could augment fusion efficiency and rate, hence shifting the balance fusion-fission toward too much fusion.

5 (c). The signal sequences on a protein destined for the mitochondria are usually on its N-terminus (choice (a)). Although some mitochondrial proteins are synthesized inside the mitochondria from the mitochondrial genome, most mitochondrial proteins are encoded by genes in the nucleus and imported into the mitochondria after synthesis in the cytosol (choice (b)).

6 The binding of methotrexate to the active site prevents the enzyme from unfolding, which is necessary to import proteins into the mitochondria. Indeed, methotrexate binds so tightly to DHFR that it locks the enzyme into its folded conformation and prevents chaperone proteins from unfolding it.

7:
A) False. The mitochondrial genetic code differs slightly from the nuclear code, and also varies slightly from species to species.
B) False. The presence of introns in organellar genes is surprising precisely because corresponding introns are so uncommon in related bacterial genomes.
C) True. Inheritance of organellar genomes is very different from the inheritance of nuclear genes, which is governed by Mendelian rules. A pattern of inheritance that does not obey Mendelian rules is unlikely to be due to a nuclear gene, which leaves the organellar genomes—the only other genomes in a cell.

8:
A) Caspase
B) Apoptosome
C) Apoptosis
D) Death-inducing signaling complex (DISC)
E) Extrinsic pathway
F) Survival factor
G) Intrinsic pathway
H) Death receptor
I) Executioner caspase

9: Because apoptosis occurs on a large scale in both developing and adult tissues, it is important that it does not trigger the alarm reactions normally associated with cell injury. In tissue injury, for example, signals are released that can cause a destructive inflammatory reaction. Moreover, the release of intracellular contents could elicit an immune response against molecules that are normally not encountered by the immune system. In normal development, such reactions would be self-defeating, even dangerous, if they occurred in response to apoptosis.

10: Upon microinjection of cytochrome c, both cell types undergo apoptosis. The presence of cytochrome c in the cytosol is a signal for the assembly of apoptosomes and the downstream events that lead to apoptosis. Cells that are defective for both Bax and Bak cannot release cytochrome c from mitochondria in response to upstream signals, but there is no defect in the downstream part of the pathway that is triggered by cytosolic cyto- chrome c. Thus, microinjection bypasses the defects in the doubly defective cells, triggering apoptosis.