Deciphering the multifaceted pathways underlying MCPH pathogenesis in the mouse and human, (MicroKin)

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The microcephalies are common disorders of development characterized by abnormally small brains, leading to a small head size, and associated with mental retardation. These small brains are the result of the inadequate production of neurons during development, a complex process involving several progenitor types. The orientation of these progenitors, their plane and mode of division, the number of divisions undergone by each as well as their precise timing are all strictly controlled during normal embryonic development, and are crucial to generate the large number and variety of neurons that populate the mature brain. Any deviation from this highly detailed blueprint results in anomalies of brain development, and consequently, behavioral and intellectual disorders in childhood and adulthood. While several different factors, both genetic and environmental, have been identified as being associated with the different types of microcephaly, little is known about the process by which these factors interfere with normal neuronal production. The MCPH (or congenital autosomal recessive primary microcephaly) family of disorders is caused by mutations in at least 12 identified genes, which, despite their diversity, mostly appear to play very specific roles in the division of progenitor cells during development. Based on this limited knowledge, we propose to study the pathways by which defects in these genes could lead to aberrant cell divisions and/or the large-scale death of progenitors that attempt to divide under sub-optimal energetic or other conditions, leading to a shortage of adult neurons of the correct type. We will use both mouse models of MCPH in which one or more of these genes is genetically modified to be suppressed or overproduced, as well as cell lines derived from patients with MCPH microcephaly to (i) study how alterations in the expression or function of these genes could lead to the defective cell division or premature death of progenitors and, consequently, microcephaly, (ii) identify the molecules with which they interact within progenitor cells, and in particular to determine the role of cell-cycle kinases in guiding MCPH proteins to their appropriate locations and their subsequent function, and (iii) study differences in these processes between the mouse and human brain, in order to use this knowledge to guide future investigations and eventually, design appropriate treatment strategies.