The need for more "driving" pathways in Down Syndrome

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One of these "driving" pathways may be related to the increased presence of a protein called CBS (cystathionine-beta-synthase) in the cells of persons with Down syndrome. The notion that this protein may play a special role in Down syndrome was already hypothesized by Pr Jerome Lejeune, the doctor who discovered the syndrome. Later on, another French scientist, Pr Pierre Kamoun has further advanced Lejeune's hypothesis and hypothesized that it is a gaseous factor, the swamp gas called hydrogen sulfide (H_2S) that CBS is producing that is in fact responsible for some of the pathological alterations in Down syndrome. H_2S is known to suppress the ability of the cells to generate energy, because it inhibits a key enzyme in a cellular compartment called mitochondrion (which is the "power station" of all of our cells). Without power, it is impossible to develop properly; the brain cells cannot fire and communicate properly, and the cells are slowly poisoned and eventually degenerate. This exciting hypothesis was not tested for decades because the experimental tools to do so were not available. Last year my group, supported by a grant from the Jerome Lejeune Foundation in Paris, took up the challenge to test the hypothesis directly. Our data (published in PNAS USA, one of the top scientific journals in the world) show that, indeed, CBS and its product H_2S causes a severe energetic deficit in Down Syndrome cells. The data also show that there are pharmacological ways to normalize the activity of CBS and this restores the function of the cell's "power plant" and improves functionality. We believe that drugs that target this pathway may provide future benefit to persons with Down syndrome.

There are, perhaps, investigators, who think that it is futile to seek for therapeutic solutions when we have such a massive cluster of misregulated genes and such an enormous array of pathophysiological processes – all of which starting from the time of embryonic development, and already massively manifest by the time of birth. Others – including my research group – takes the position that, while it is unlikely that correction or therapy of any single gene, gene product or pathway would cure or reverse all of the symptoms, it may be theoretically and practically possible to identify "driving" biochemical pathways that are more central to the pathogenesis of certain features of Down syndrome, and that by pharmacologically correcting some of these pathways, significant improvements in the life of persons with Down syndrome may be possible.

Down syndrome is the most common chromosomal disorder. The prevalence of Down syndrome is estimated at approximately 250 000 worldwide, which corresponds to a prevalence of approximately 8 people with Down syndrome per 10 000 population. People with Down syndrome carry an extra Chromosome 21, which encodes many 'extra' gene products, resulting in developmental, morphological, neurological, metabolic and cardiovascular disturbances. There are also many more genes that are not located on the extra chromosome (but are nevertheless mis regulated) in individuals with Down syndrome. All of these gene expression changes result in a variety of pathological alterations, among which the progressive intellectual impairment, and at later years, a high likelihood of developing Alzheimer Disease are some of the most severe ones.

The above is just one example of how continuing basic research in the field of Down syndrome is not at all futile: it is possible to identify significant fundamental pathways of this condition, which could lead to future therapeutic approaches. Naturally, in order to conduct such research, funding, in the form of grants (or, even better, focused "request for application" type announcements) would be important and the EU should increase its efforts in this direction. It is often very fruitful, for example, to bring in experts from other fields into a given field, in order to cross-fertilize and revitalize the research. In my case, I was "brought in" as a H_2S and cell metabolism expert. Even though I was not at all trained in Down syndrome (other than my general M.D. training), and I was able to discover a significant biochemical alteration. Others, coming perhaps from other fields, might be able to do the same.