Personalized medicine eliminates need for drug in two children

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Using genome-wide analysis, investigators at the Sainte-Justine University Hospital Research Center and the University of Montreal have potentially eliminated a lifetime drug prescription that two children with a previously unknown type of adrenal insufficiency had been receiving for 14 years.

Over a lifespan, the adjustment in treatment represents an approximate saving of $10,000 in drug and test costs per patient. Moreover, the less invasive treatment regime can potentially reduce the lifetime risk of hypertension in the patients. "This is a real case of personalized medicine made possible today through the use of novel techniques in genomics," stated Dr. Mark Samuels, lead author of a paper published on the subject in January 2013 in the *Journal of Clinical* Endocrinology and Metabolism. Dr. Johnny Deladoëy was the senior author of the article.

Fourteen years ago both children were diagnosed with adrenal insufficiency, a condition that occurs when the adrenal glands do not secrete enough hormones to control sugar and mineral levels in the blood. After having sequenced the part of the genome that codes for genes in one patient, the investigators identified mutations in POMC, the gene behind the disorder. They then showed that the disorder in the second patient was also caused by a similar mutation in the gene POMC. Identifying the causal gene allowed them to conclude that the only thing missing in the patients was the production of cortisol, the hormone that regulates blood sugar. They thus advised the patients to continue cortisol treatment, but that fludrocortisone treatment was unlikely to be

necessary. So far, fludrocortisone has been stopped in one patient without any adverse effects, while the condition of the second patient is still being evaluated.

In addition to reducing the risks of hypertension induced by fludrocortisone and allowing the patients and their family to feel more confident about the origin of the disease, the investigators' discovery made it possible to reduce by as much as $10,000 the health costs for patients with this type of adrenal insufficiency. Over a 70-year lifespan, this is what the fludrocortisone treatment and the blood tests required in the patients treated with it adds up to.

The physicians did not modify the treatment earlier in the children's lives due to lack of a clear molecular diagnosis hence an imperfect understanding of the disease. Not only could withholding one of the replacement hormones have potentially led to a fatal outcome, but also analyzing the whole genome that led to the diagnosis would have been unthinkable just a few years ago. "Due to the astronomical costs associated previously with analyzing the whole genome, certain genes had to be targeted that were potentially responsible for the disorder and only these genes were analyzed in spite of the risk of not finding the right gene," explains Dr. Samuels, a researcher in human genetics. Today, lower genome analysis costs make an analysis of the whole genome affordable.

Description of the study

The two children in the study were hospitalized at the ages of 4 months or 4 years respectively, for hypoglycemia and associated convulsions. A diagnosis of adrenal insufficiency was made and the two children were saved by administering replacement hormones. Their ACTH (the pituitary hormone that controls the adrenal gland) blood concentrations were very high, which seemed to implicate the adrenal gland. The

adrenal gland produces two vital hormones: cortisol to regulate glycemia and aldosterone to control minerals. When in doubt, in the event of adrenal insufficiency, both hormone types (cortisol and fludrocortisone, an aldosterone analogue) are prescribed. Nevertheless, fludrocortisone treatment can lead to side effects such as hypertension.

Hoping to better target patient treatment, the investigators went about tracking down the exact cause of adrenal insufficiency. They proceeded to analyze part of the genome that codes for genes in one patient's DNA (whole-genome sequencing being still too expensive for the time being). To their great surprise, the analysis indicated the presence of two mutations in POMC, the gene that codes for ACTH, in the patient. Direct sequencing of the POMC gene in DNA from the second patient confirmed the occurrence of one of the mutations in that child as well. The researchers then collaborated with Dr. Michel Bouvier (University of Montreal) and Dr. Nicole Gallo-Payet (University of Sherbrooke) to validate the discovery by performing in vitro tests on cells using two synthetic ACTHs produced for the experiment: one normal and the other carrying the mutation observed in both children. These studies showed that, while high levels were detected in the blood, the mutant ACTH was inactive. Due to technical limitations, the standard diagnostic test that detects ACTH was unable to distinguish between the normal and the mutated form found in the patients.

"The genome analysis allowed us to incriminate the POMC gene. Since the gene was not suspect according to the blood tests, we would have missed the cause of the disease without this new technique," concludes Dr. Deladoëy, a physician and researcher in endocrinology and diabetology.

This case of personalized medicine made possible through novel genomic techniques is just the tip of the iceberg. In the near future, investigators hope to succeed in refining the treatment of many patients

using these techniques.

Provided by University of Montreal