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LETTER TO THE EDITOR

Att. to Kabuki Syndrome (ORPHA: 2322)

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Introduction

Dear Editor of the International Journal of Rare Diseases and Disorders,

In the year 2017 I was asked if I would start a search for small molecule biomarkers for Kabuki syndrome. My history track record with finding biomarkers in rare diseases is lyso- Gb1 for Gaucher, lyso-Gb3 for Fabry, lyso-SM509 for NPC and lyso-Sulfatide for MLD. After a careful literature check (only a few publications available) the NIH description led me to urine as a possible matrix for finding e.g. diagnostic biomarkers. I expected differences between patients and healthy individuals with rather hydrophilic molecules.

Especially the metabolism around lysine seemed promising. I got from the parents of a Kabuki syndrome child a urine sample. The researcher who put me on this track was not able to deliver more urine samples within an appropriate time frame so our cooperation ended.

Although I looked intensely for medical doctors who treated Kabuki syndrome children (especially in Europe) I did not find anyone who could provide urine samples of Kabuki patients. Just a few months ago I got another urine sample of another young patient.

Our concept is using HPLC-MS (LTQ-Orbitrap XL, Xevo TQ-XS) for searching for biomarkers (targeted and untargeted). In 2017 I compared this only one patient urine sample with five urine samples of healthy children and checked targeted (and quantitatively) for lysine, methyllysine, dimethyllysine, trimethyllysine, hydroxylysine, dilysine and pipecolic acid. Only the levels of lysine were elevated for the patient.

After getting samples of another patient a few months ago I analyzed these lysine-derivates again, but as a conclusion only one patient had higher lysine levels, the other not. Then I analyzed and semi-quantitated 42 substances, mainly amino acids and certain amines as metabolites of amino acids (peak area comparisons). Only methionine in patient samples was 2 to 4 times higher.

Another approach was searching for more lysine typical MRMs by doing a research in precursor ion mode to the fragment ion of 84 (in positive mode a typical fragment for lysine). 29 different substances were identified there from and were analyzed doing again peak area comparison between healthy and sick, but only one, a lysine-amide or even more likely lysine-alanine, showed clearly lower levels in both patients (factor 3 to 10) compared to urine samples from healthy people. The MRM was 146/84 in positive mode. 146 could be the molecular ion (lysine-amide) or more likely an in-source fragment ion of 218 (lysine-alanine) since two MRMs of lys-ala also intensely showed the same peak.

We had no analytical reference standard but used MS/MS-spectra from the literature for spectra comparison and also used the plausibility of the retention time of the HPLC system compared to lysine.

I hope, that this information can be helpful for researchers in the field of Kabuki syndrome.

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