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C26-ceramide is a new and sensitive biomarker for Farber disease

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Farber disease (Farber's lipogranulomatosis, ceramidase deficiency), is an autosomal recessive, extremely rare disease caused and characterized by a deficient acid ceramidase activity encoded by ASAH1 gene. Low ceramidase activity is resulting in accumulation of fatty substances, mainly ceramides. At clinical level, Farber disease is manifesting through hallmark symptoms such as: periarticular nodules, lipogranulomas, swollen and painful joints and a hoarse voice or a weak cry; in addition to these, also hepatosplenomegaly, rapid neurological deterioration or developmental delay are reported. Seven different Farber types were described, with phenotypes varying from mild cases with a longer life expectancy to very severe cases, where the patients do not survive past their first year of life. The screening through over 40 different ceramide-like molecule show that only C26 is specifically increased in samples from Farber patients. We present here a new method of diagnosis of Farber disease by determining the concentration of C26 ceramide isoforms using LC/MRM-MS and C25 ceramide as internal standard. Moreover, we found that cis-isomer of the C26 ceramide is a specific biomarker for Farber disease, with pathological values in a range of 39.2-150.0 nmol/L blood (normal range 13.6-23.4 nmol/L blood, N=192, healthy individuals). The new biomarker can be determined directly in the dried blood spot extract with low sample consumption, easy sample preparation, high reproducibility and it presents the possibility of to be used in high throughput screenings.

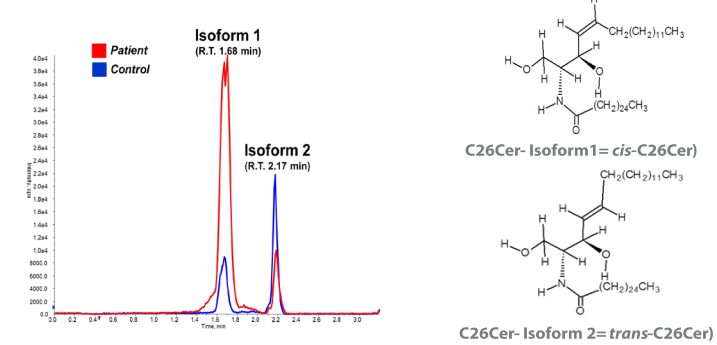

Figure 1. LC/MRM-MS TIC of C26Cer isoforms analysis in DBS vs Non-hemolytic plasma

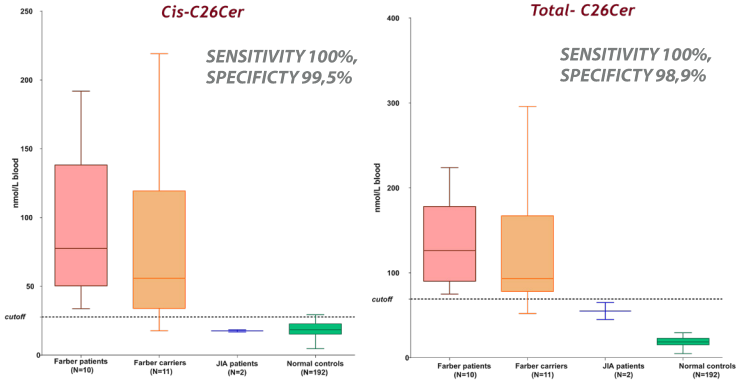

Figure 2. Cis-C26Cer and Total C26Cer levels in Farber patients vs healty controls.

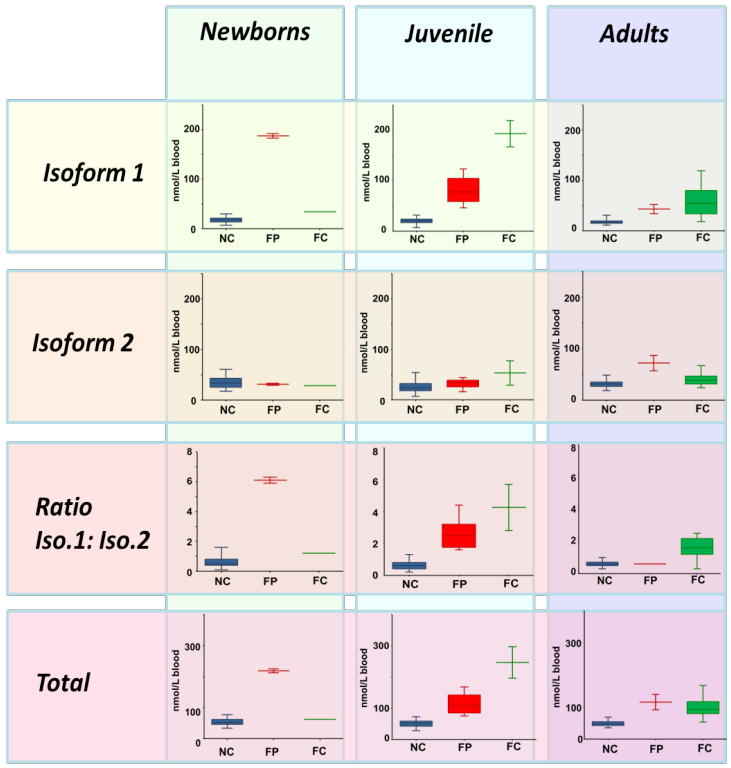

Figure 3. C26Cer isoforms levels in Farber patients (FP), Farber carriers (FC) and healthy controls (NC) in relation with the age of the donors

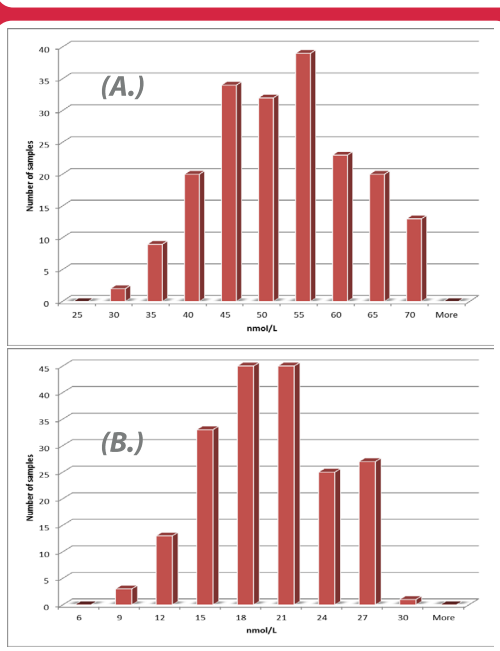

Figure 4. Normal distribution of cis-C26Cer (A.) and total-C26Cer in DBS of healthy controls

Ceramide C26 levels in DBS healthy controls, Farber patients and Farber carriers and samples from patients suffering of other LSDs

Samples	N	Ceramide C26:0 (nmol/L) : mean ± STD					
		Isoform1	*p-value	Isoform2	Ratio	Total	*p-value
Cut-off	-	28.3	-	-	-	69.0	-
Farber Patients	10	94.6 ± 55.4	< 0.0001	40.1 ± 19.6	2.9 ± 2.0	134.8 ± 52.2	< 0.0001
Farber carriers	11	81.6 ± 62.8	-	41.6± 16.7	2.0 ± 1.4	123.1 ± 71.92	-
Healthy controls	192	18.5 ± 4.9	-	33.8 ± 8.6	0.6 ± 0.2	49.8 ± 9.6	-
Gaucher Patients	5	24.0 ± 1.4	0.002	35.6 ± 6.8	0.7 ± 0.2	59.3 ± 6.8	0.002
JIA Patients	2	17.5 ± 0.7	0.030	37.5 ± 14.8	0.5 ± 0.3	55.0 ± 14.1	0.030
Pompe Patients	5	21.3 ± 3.0	0.002	28.8 ± 2.3	0.8 ± 0.1	50.0 ± 5.0	0.002
Niemann-Pick A/B Patients	5	19.5 ± 7.8	0.002	28.5 ± 9.9	0.8 ± 0.3	48.5 ± 13.3	0.002
Fabry Patients	5	25.5 ± 3.8	0.002	32.5 ± 1.0	0.8 ± 0.2	57.5 ± 3.0	0.002
Hunter Patients	5	23.3 ± 5.6	0.002	35.8 ± 7.0	0.7 ± 0.1	59.0 ± 10.8	0.002

*p-value found in Mann-Whitney test for Farber patients vs. patients affected by other LSDs

References:

1. *Rolfs A. et al., Patent application*
2. *Cozma C. et al., 2016, manuscript submitted*

Disclosure of conflict of interest:

- *This study was sustained in part by Centogene AG, Rostock, Author of the presentation, Claudia Cozma, and 2 co-authors are employees of Centogene AG, Rostock, Germany*