INSTITUTE OF CHILD HEALTH

Great Ormond Street Hospital for Children NHS Trust

Understanding the Genetic and Molecular Mechanisms of Complex Syndromes of Diabetes Mellitus

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BACKGROUND

The two most commonly known types of Diabetes Mellitus (DM) are DM type 1 and DM type 2, characterized by insulin deficiency or insulin resistance respectively. DM can also be associated with rare mutlisystemic syndromes such as Alstrom, Bardet-Biedl, Wolfram and pigmentary hypertrichosis insulin dependent diabetes (PHID) syndromes.

OBJECTIVES

To understand the genetic and molecular basis of rare and novel syndromes of DM in a large cohort of patients.

METHODS

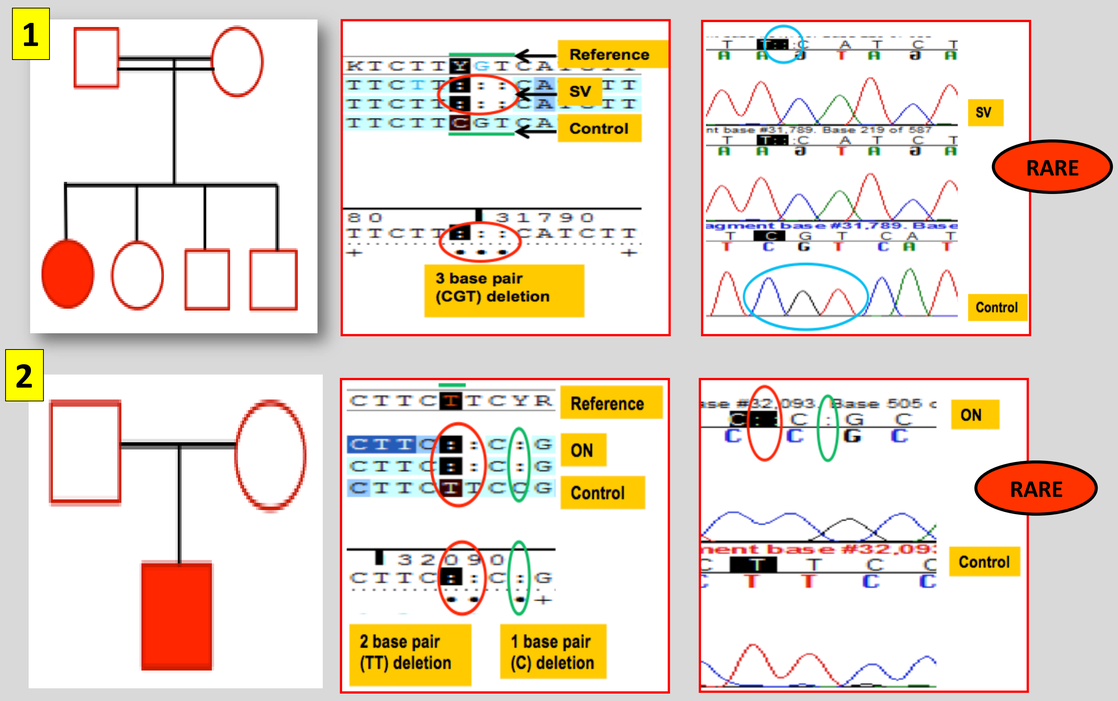
1. Polymerase Chain Reaction
2. Target Gene Sequencing
3. Homozygosity Mapping **(HZM)**
4. Western Blotting **(WB)**

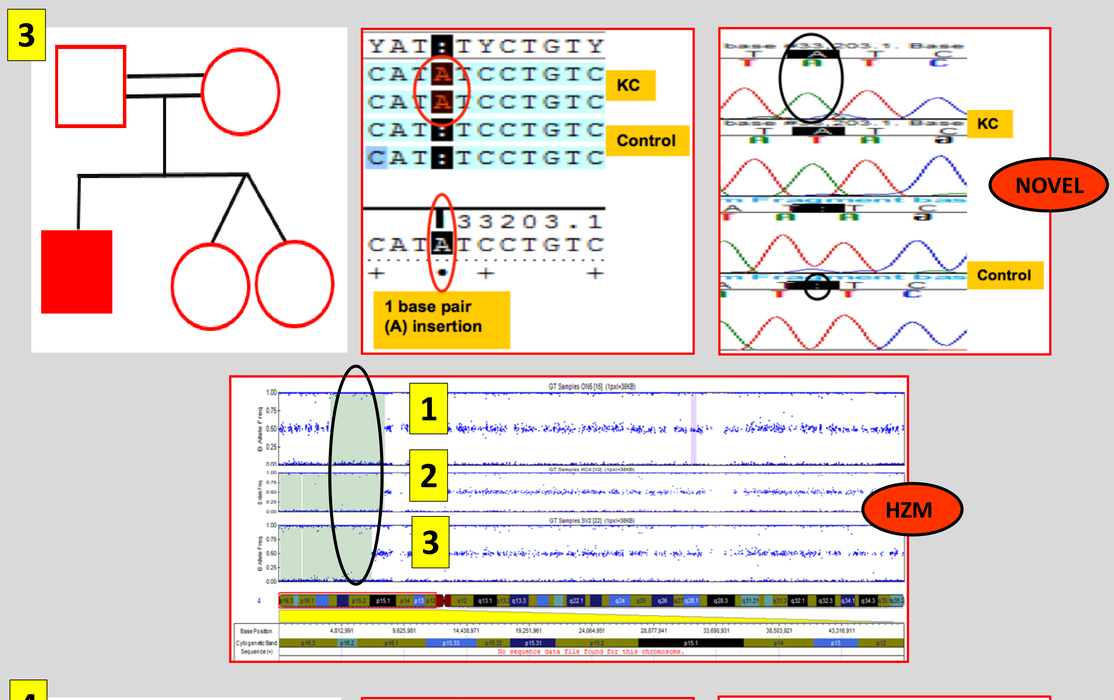
PHENOTYPE

Patient	Phenotype
1 , 2 , 3	- Diabetes Mellitus **(DM),** Diabetes Insipidus **(DI)** - Deafness **(D) &** Optic Atrophy **(OA)**
4, 5	- **DM**, **DI**, **OA &** no **D**
6	- **DM**, **OA**, **D**, no **DI &** Microcephaly
7, 8	- **DM**, Hyperpigmentation, Hypertrichosis **&** Growth Failure

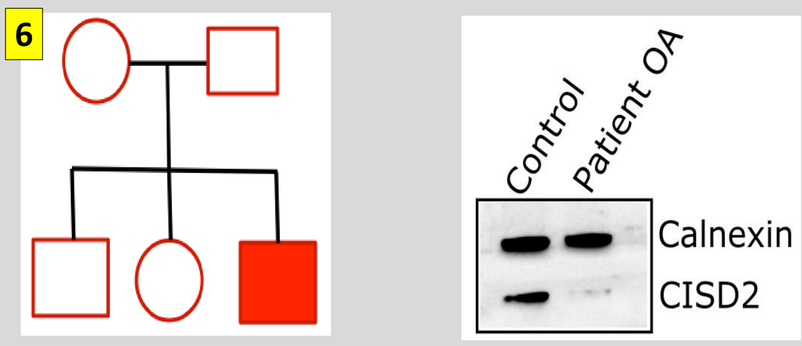
RESULTS

A. Wolfram Syndrome Type 1 in 5 Turkish Patients

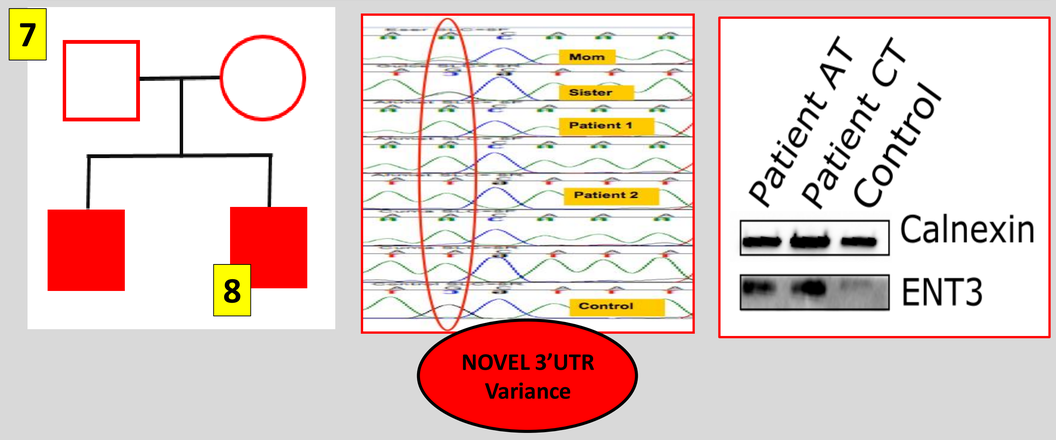




B. Wolfram Syndrome Type 2 in a Turkish Patient



C. PHID Syndrome in 2 Turkish Patients



Conclusions

This study so far has identified novel causes of Wolfram type 1 and PHID syndrome, highlighting a potentially new mechanism for the latter. Also, Western Blotting techniques revealed disrupted protein expression in the three diseases under study. Further work is ongoing to understand the molecular and genetic mechanisms of these and other rare DM syndromes in 17 patients.

References

AMR, S., HEISEY, C., ZHANG, M., XIA, X. J., SHOWS, K. H., AJLOUNI, K., PANDYA, A., SATIN, L. S., EL-SHANTI, H. & SHIANG, R. 2007. A homozygous mutation in a novel zinc-finger protein, ERIS, is responsible for Wolfram syndrome 2. *Am J Hum Genet,* 81**,** 673-83.

FONSECA, S. G., ISHIGAKI, S., OSLOWSKI, C. M., LU, S., LIPSON, K. L., GHOSH, R., HAYASHI, E., ISHIHARA, H., OKA, Y., PERMUTT, M. A. & URANO, F. 2010. Wolfram syndrome 1 gene negatively regulates ER stress signaling in rodent and human cells. *J Clin Invest,* 120**,** 744-55.

KANG, N., JUN, A. H., BHUTIA, Y. D., KANNAN, N., UNADKAT, J. D. & GOVINDARAJAN, R. 2010. Human equilibrative nucleoside transporter-3 (hENT3) spectrum disorder mutations impair nucleoside transport, protein localization, and stability. *J Biol Chem,* 285**,** 28343-52.

MINTON, J. A., RAINBOW, L. A., RICKETTS, C. & BARRETT, T. G. 2003. Wolfram syndrome. *Rev Endocr Metab Disord,* 4**,** 53-9.

SPIEGEL, R., CLIFFE, S. T., BUCKLEY, M. F., CROW, Y. J., URQUHART, J., HOROVITZ, Y., TENENBAUM-RAKOVER, Y., NEWMAN, W. G., DONNAI, D. & SHALEV, S. A. 2010. Expanding the clinical spectrum of SLC29A3 gene defects. *Eur J Med Genet,* 53**,** 309-13.

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Diabetes

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