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FIRST PERSON

First person – Derek Reznik

First Person is a series of interviews with the first authors of a selection of papers published in Disease Models & Mechanisms, helping researchers promote themselves alongside their papers. Derek Reznik is first author on '*Magel2* truncation alters select behavioral and physiological outcomes in a rat model of Schaaf-Yang syndrome', published in DMM. Derek is a PhD student in the lab of Rodney Samaco at Baylor College of Medicine, Houston, TX, USA, investigating the underlying mechanisms of rare neurodevelopmental disorders using novel model systems to bring actionable therapies to patients.

Derek Reznik

How would you explain the main findings of your paper to non-scientific family and friends?

Most of the genes in our DNA are expressed from both alleles we inherited from our parents. However, there are select genes that are naturally expressed from only one parental allele, while the other remains silent. These genomic imprinted genes display a parent-of-origin-based expression where only one copy is active and the other remains silent. The active copy of a genomic imprinted gene is susceptible to mutation events that can lead to debilitating disorders, especially since the other allele remains naturally silent, as is the case for the imprinted *MAGEL2* gene. Mutations in the active copy of *MAGEL2* that create a truncated version of the protein are the genetic cause of multiple rare neurodevelopmental disorders including Schaaf-Yang syndrome, the patients of which experience debilitating behavioural and physiological symptoms. Historically, studies have utilized genetically modified mouse models that delete or disrupt the expression of the *Magel2* gene to study the consequences of its absence. Our study uses a novel genetically engineered rat model that has a truncating mutation in *Magel2*, serving two purposes: (1) the truncating mutation more accurately represents the mutations observed in individuals with Schaaf-Yang syndrome; and (2) rats are genetically closer related to humans and are an excellent organism to study for disruptions in both behavioral and physiological domains. We determined that the rat *Magel2* is imprinted, that a truncated protein is detectable in the brain of mutant rats, and that these mutant rats display disruptions in multiple behavioral domains along with alterations in organ systems that appear to be clinically relevant. Further studies using this novel rat model may increase our understanding of the biological underpinnings of genomic imprinting disorders and enable the creation of actionable therapies for individuals with Schaaf-Yang syndrome.

"The novel rat model will provide a meaningful tool to test and develop new therapeutic approaches that may improve clinical features of Schaaf-Yang syndrome […]"

What are the potential implications of these results for your field of research?

The novel rat model will provide a meaningful tool to test and develop new therapeutic approaches that may improve clinical features of Schaaf-Yang syndrome, and possibly inform therapeutic development for Prader-Willi syndrome more broadly. This is the first reported empirical confirmation of a truncated MAGEL2 protein species, which before this study was not possible using *Magel2* deletion mouse models or antibody-based detection approaches. The phenotypic results from this study demonstrate that a truncated MAGEL2 creates not only alterations in anxiety-like and social behaviours, but also measurable changes in body composition and both the cardiac and respiratory systems. These outcome measures will serve as the foundation for future studies focusing on the molecular underpinnings that emerge as a consequence of truncated MAGEL2.

What are the main advantages and drawbacks of the experimental system you have used as it relates to the disease you are investigating?

The novel rat model used in this study offers several benefits specific to examining a rare neurodevelopmental disorder such as Schaaf-Yang syndrome. The genetic construct of the mutant allele is the first confirmed mutation to result in a detectable truncated MAGEL2 protein. This truncated form is very similar in size and lacks the functional domains comparable to the predicted forms in Schaaf-Yang syndrome. The rat as a model species is also well situated to study Schaaf-Yang syndrome; they display a well-defined catalogue of behaviours, some of which are uniquely present in rats. The ability to interrogate the sociability of mutant

Derek Reznik's contact details: Baylor College of Medicine, Department of Molecular and Human Genetics, Houston, TX 77030, USA.
E-mail: Derek.Reznik@bcm.edu

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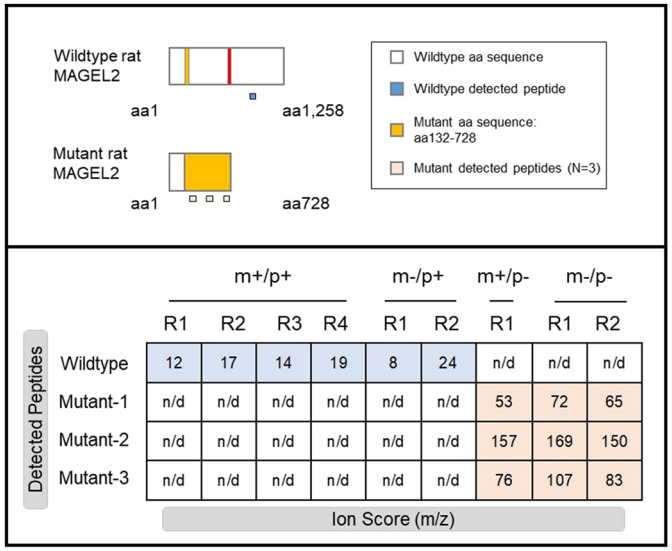

The first reported detection of a truncated MAGEL2 protein.
Top: predicted wild-type or mutant truncated proteins. Bottom: data confirming the detection of wild-type or mutant-specific peptides from rat brains. aa, amino acids; n/d, not detected. R corresponds to each biological replicate.

Magel2 rats offered insight into the alterations of a behavioural domain that is frequently disrupted in individuals with Schaaf-Yang syndrome yet is not readily apparent in mice. Finally, future efforts examining the molecular pathways that may be disrupted by a truncated MAGEL2 will benefit from comparative studies using this additional rodent model system. With respect to drawbacks of the experimental system, when we compare our rat studies to our human cell lines studies, our current approach was able to empirically detect the typical full-length but not truncated MAGEL2 in Schaaf-Yang syndrome-derived samples. Future studies of human specimens using induced neuronal cells or brain tissue samples may better elucidate whether the predicted truncating mutations result in a human truncated MAGEL2 protein.

What has surprised you the most while conducting your research?

The lack of phenotypic cognitive deficits detected in this novel rat model was surprising, given the significant prevalence of intellectual disability in the human condition. It remains a possibility that impairments in cognitive performance may be revealed by using more complex and challenging cognitive behavioural tasks.

What do you think is the most significant challenge impacting your research at this time and how will this be addressed over the next 10 years?

Among the biggest challenges facing not only this area of research, but throughout all science, are the aspects of data reproducibility and the identification of robust and biologically relevant disease markers. In the case of studying rare neurodevelopmental disorders, rodent models are frequently the most utilized mammalian system because of their experimental tractability. However, it has become increasingly clear that the approaches we use to examine these rodent models, especially in the realm of behavioural analyses, can vary significantly between institutions, and even within labs. It is imperative that the measurements, whether they be behavioural or molecular, that are to be used for preclinical evaluations have been systematically retested and reproduced, ideally by different sets of experimenters across different institutions, are robust enough to accurately determine the efficacy of a preclinical intervention. Another significant, but extremely necessary challenge for the field researching select individuals with known deleterious truncating mutations in Schaaf-Yang syndrome, will be developing a polytherapy approach that addresses a targeted removal of the mutant truncated MAGEL2 protein alongside re-establishing neurotypical levels of the wild-type MAGEL2 form (via gene therapy or activation of the silent allele).

“It is especially important for those scientists whose research directly correlates to human genetic conditions to engage with the patients and their caregivers.”

What changes do you think could improve the professional lives of scientists?

I believe it is incredibly useful for scientists to expand their professional engagement with the larger public community and that it should be highly supported by academic institutions. To create a more connected society, especially one that understands and trusts the scientific community, we have the obligation to be more engaging with public interaction. It is especially important for those scientists whose research directly correlates to human genetic conditions to engage with the patients and their caregivers. Understanding the struggles and hurdles that many patients suffer daily offers a necessary clarity to the importance of the research we do, why we do it, and the lives it will hopefully change for the better.

What’s next for you?

Upon completing my PhD, I will look to transition into either an industry or non-profit-focused research career in which I wish to continue providing scientific support to patient populations of rare diseases.

Reference

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