FALL 2021 NEWSLETTER

International Replication Repair Deficiency Consortium

Welcome

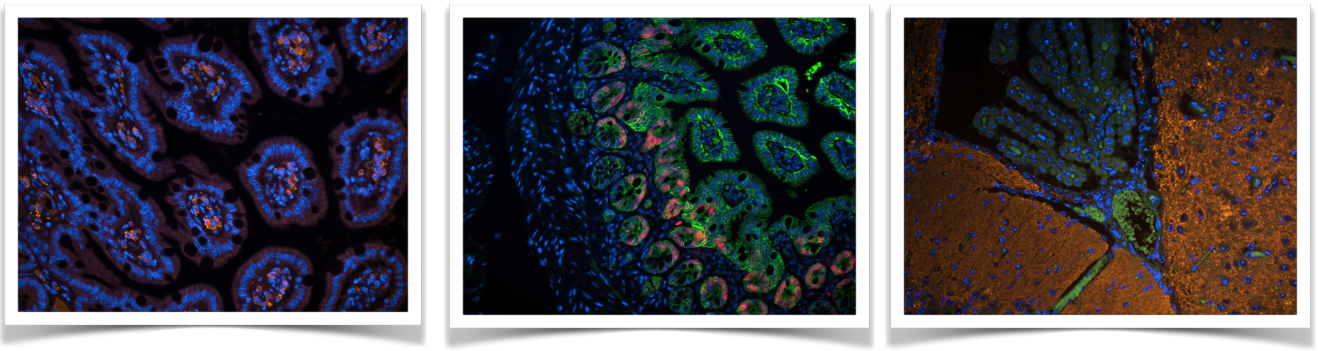
To our families, patients, and healthcare practitioners, The International Replication Repair Deficiency Consortium (IRRDC) is pleased to be bringing you this inaugural newsletter, as part of our new initiatives. Along with our bi-annual educational seminar series, these newsletters aim to bring awareness to syndromes of DNA replication repair deficiency and disseminate new clinical and research findings. The articles you will see presented here are all written by those who are part of our consortium, and include stories from physicians, genetic councillors, families, and scientists. With each edition of the newsletter, we aim to bring you engaging content from our own team as well as our collaborators and families globally.

Meeting of the IRRDC , 2017

The IRRDC, formally known as the BMMRD Consortium was conceptualized in the early 2000's and formally established as a consortium in 2007. At this time, our focus was on a rare and under-recognized genetic syndrome knows as biallelic mismatch repair deficiency (BMMRD). We postulated however, that BMMRD was more common than reported, and made it our mission to increase awareness, research initiatives, and understanding of this syndrome.

Since 2007 our consortium has grown exponentially, and we now have over 600 individuals from all over the globe currently enrolled in our consortium registry and research studies. We have collaborated with families, physicians, and scientists from over 45 countries. With this influx of patients, research and information, we learned that BMMRD, also known as constitutional MMRD (CMMRD) was not the only syndrome associated with defective DNA replication repair, and patients without CMMRD can still develop tumours that behave and can be treated in the same way as those with CMMRD. Therefore, in 2019, we formally changed our name to The International Replication Repair Deficiency Consortium (IRRDC), to represent all syndromes causing replication repair deficiency.

We hope you all enjoy this inaugural newsletter. Please feel free to share this with your friends, families, and colleagues.



Immunofluorescent (IF) staining by the Tabori Lab colourfully displays protein localization in human and mouse tissue.

Our Team - The Consortium Leadership Committee

Members of The Consortium Leadership Committee

Uri Tabori, MD
Consortium Lead

Anirban Das, MD
Paediatric Oncologist and Cancer Geneticist

Melissa Edwards, PhD
Clinical Research Project Manager

Vanessa Bianchi, PhD
Clinical Research Coordinator

Lucie Stengs, BSc
Biobanker

CMMRD and Genetics

Written by Melyssa Aronson (IRRDC Genetic Counsellor)

I am excited to contribute to the first newsletter for the International CMMRD consortium. My name is Melyssa Aronson, and as the genetic counsellor for the consortium, I review each family that contacts us to help determine if the family has CMMRD. I started in 1998 at the Zane Cohen Centre at Sinai Health System in Toronto specializing in hereditary colorectal cancer, and co-started the CMMRD consortium in 2005 with Drs. Uri Tabori and Carol Durno.

Melyssa Aronson, MSc, CGC

As a start, let me explain what CMMRD means. **CMMRD stands for Constitutional Mismatch Repair Syndrome. It is a hereditary syndrome that increases a person's risk to develop cancers, starting in childhood.** The most common cancers seen are brain, blood (lymphomas or leukemias) and digestive (colon and small bowel) cancers, although other types of cancers can occur with less frequently. Individuals with CMMRD may also have birthmarks that are light-dark brown patches on the skin, called café-au-lait macules. It is important to note that these patches can be seen in children who do not have CMMRD, however, if someone has many of these birthmarks especially in combination with early onset cancers, it can be a hint of CMMRD.

Café-au-lait Macule

Disclaimer: a CALM alone does not mean a person has CMMRD, but in combination with other risk factors, may be investigated.

CMMRD is a hereditary condition caused by genetic changes (or mutations) in our mismatch repair genes (which is the MMR part of CMMRD). Each of us have 2 copies of our genes, one we inherit from our mother and one from our father. There are 4 mismatch repair genes, named *PMS2*, *MSH6, MLH1* and *MSH2*, and the role of these genes are to correct spelling mistakes (or replication repair errors) in our cells. They are our spellchecker genes and important in preventing cancer. CMMRD is caused by inheriting a mutation in both copies of one of our MMR genes – one mutation inherited from the mother's copy and one mutation inherited from the father's copy. **The most common of the MMR genes impacted in CMMRD is the *PMS2* gene, which is the cause in more than half of the CMMRD families**.

Genetic testing on a blood sample is able to identify mutations in both MMR genes in approximately 60% of our families. **That means that 40% of our families cannot be diagnosed through standard genetic testing and it can be challenging to figure out if they have CMMRD.** Our consortium helps by performing additional functional tests, and combining that information with the genetic and clinical information provided to try and determine a diagnosis. We also worked with an international group of experts to outline diagnostic criteria for CMMRD, which we hope will be published soon. Being able to properly diagnose CMMRD is essential to provide accurate cancer screening recommendations and treatment for cancers. We hope to continue our understanding of CMMRD, the cancer risk, the screening required and the best way to prevent and treat these cancers.

Recent Highlights

Written by Dr. Vanessa Bianchi (IRRDC Clinical Research Coordinator)

This past year alone has been full of so many advances, both research and clinical. Before diving into the articles written so thoughtfully by our amazing global family, we wanted to share some updates from our consortium, many of which we hope to present in more detail in upcoming events.

Clinical Trials / Immune Checkpoint Inhibitor (ICI) Therapy

Dr. Eric Bouffet

OZM-075: Our pilot study of Nivolumab in paediatric patients with recurrent or refractory hyper-mutant tumours is now closed. Results from this study are being assembled for publication. More information on this study can be found at ClinicalTrials.gov (Identifier: NCT02992964)

Dr. Daniel Morgenstern

The 3CI Study: On January 28th, 2021 we officially opened a new clinical trial in multiple centres across North America investigating combination ICI therapy (nivolumab and ipilimumab) for patients with relapsed or refractory hyper-mutant cancers. More information on this study can be found at ClinicalTrials.gov (Identifier: NCT04500548)

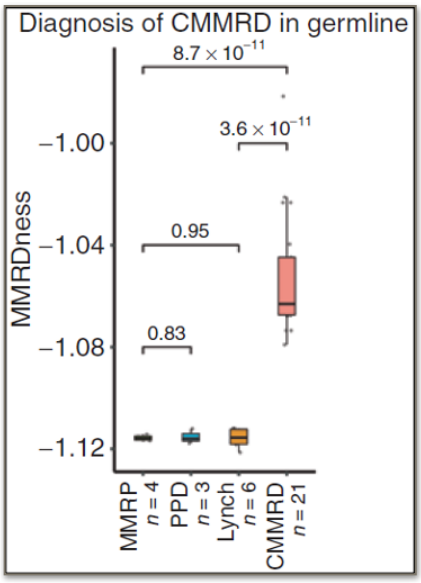
Summary of IRRDC patients treated with ICI Therapy: Our study of IRRDC patients treated with ICI is currently under review. This manuscript highlights the clinical response of CMMRD patients to ICI across cancer types and identifies genomic biomarkers which may predict response. Keep an eye out for the published data!

Impact for Patients: Clinical trials help us identify new ways to treat Replication Repair Deficient (RRD) tumours and support the implementation of new standards of care. For patients in North America at or near our partnering centres, access to this trial may be a therapeutic option.

Low-pass Genomic Instability Characterization (LOGIC) Assay

This year our team developed a new diagnostic assay which can determine if a patient has CMMRD or an RRD cancer with a high level of sensitivity and specificity. This new test is over 25 times less expensive than standard genetic testing and may be used globally at centres all over the world once it has been approved for clinical use (currently in-progress). We hope that this test can help us find and treat more patients globally, especially in low-resource settings, where standard genetic testing is often not done due to cost restrictions. This article is published open access in Cancer Discovery (https://doi.org/10.1158/2159-8290.CD-20-0790).

Using these same methods, we recently showed that DNA from saliva samples can be used for diagnosis of CMMRD in germline (manuscript pending).



Detection of germline CMMRD using LOGIC.
Blood samples from CMMRD and relevant control patients were used. Statistical significance was calculated using the Mann–Whitney U test. MMRP= mismatch repair proficient. PPD= polymerase proofreading deficient. Lynch = Lynch Syndrome. CMMRD= constitutional mismatch repair deficiency syndrome.

Impact for Patients: LOGIC is simple and cost effective and can be established in multiple centres around the globe, even in low resource settings, allowing for enhanced screening. Identifying patients with CMMRD before they get cancer will allow physicians to employ surveillance protocols which are essential to the management and long-term survival outcomes of these individuals. Additionally, identifying cancers that are RRD, outside of the context of CMMRD, allows physicians to treat these patients upfront with therapies known to be more effective than standard therapies for RRD cancers. Finally, using DNA from saliva samples for this testing will allow for more access to testing globally.

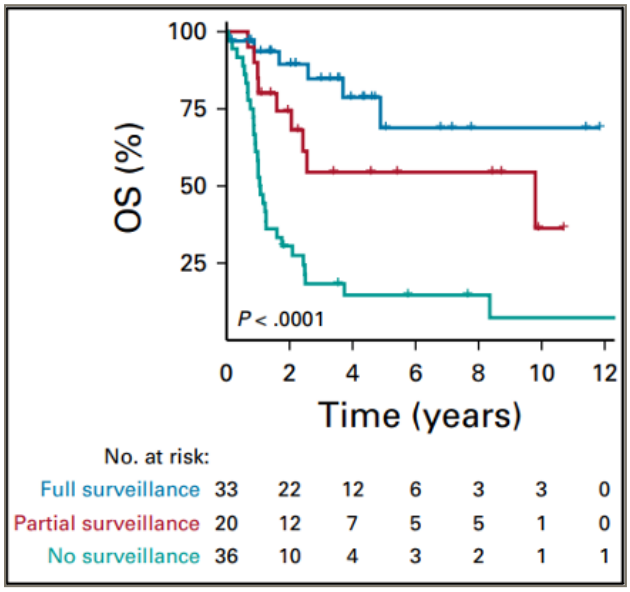
New Diagnostic Criteria for CMMRD

Melyssa Aronson, the IRRDC genetic counsellor, and other members of The International Consensus Working Group, published new diagnostic criteria for evaluating patients for CMMRD. This criteria is more comprehensive than all past criteria, and may help identify CMMRD patients in which genetic testing is not possible or results are not straightforward. The full article can be found published in The Journal of Medical Genetics (http://dx.doi.org/10.1136/jmedgenet-2020-107627).

Impact for Patients: Having comprehensive and well-defined guidelines for diagnosis, especially in cases in which genetic testing is not straightforward, will ensure that all individuals suspected of CMMRD are properly assessed.

Survival Benefit with Surveillance Protocol

In a study of over 100 individuals with CMMRD enrolled in the IRRDC, we demonstrated that following a surveillance protocol drastically improves long-term survival. When we catch cancers early, we can better manage and treat them. A study of this size was made possible through the help of our global collaborators. The full article is open access and can be found in the Journal of Clinical Oncology (DOI: 10.1200/JCO.20.02636).

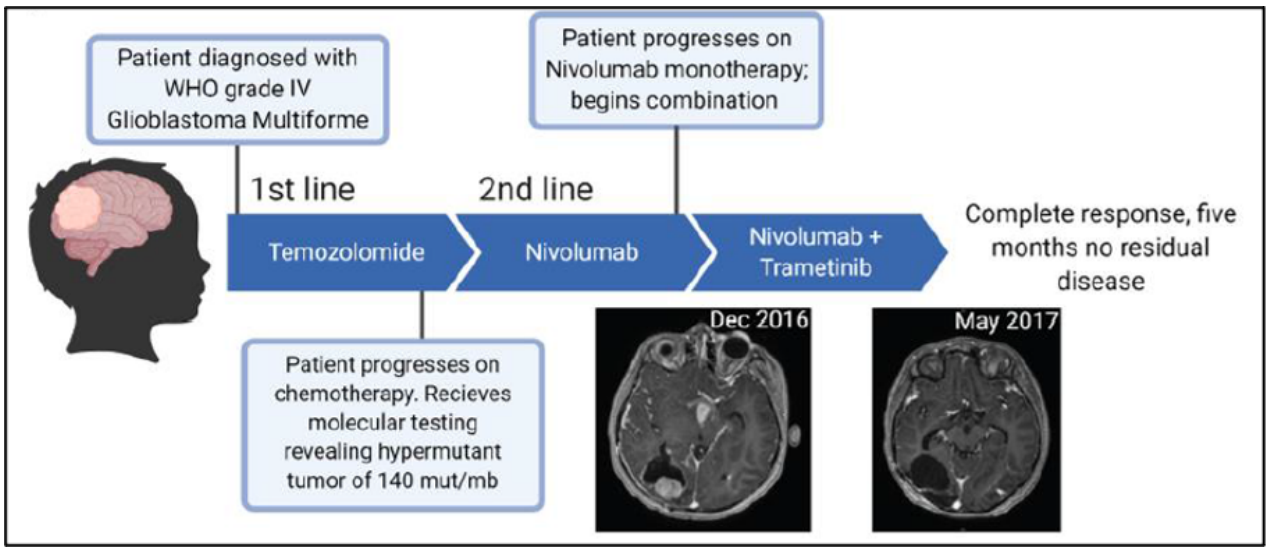


Survival for patients stratified by surveillance adherence. P values were calculated by log-rank test. OS, overall survival. Full surveillance= patients who received routine surveillance utilizing all modalities. Partial surveillance= patients who did not routinely receive screening including all modalities or for whom modalities were not performed at the recommended time intervals. No surveillance= patients who did not receive any of the recommended screening.

Impact for Patients: Until now, the importance of surveillance for individuals with CMMRD was not known, and therefore may not have been offered as a management strategy. With this information, we can now effectively argue in favour of full surveillance in all individuals affected with CMMRD, as the result on long-term survival is striking.

RRD Tumour Sensitivity to MEK Inhibition

In a new study we demonstrated that replication repair deficient (RRD) hypermutant cancers are enriched for RAS/MAPK mutations and further illustrated that these tumours respond to MEK inhibition. This study supports targeting oncogenic pathways and may provide therapeutic options for these hypermutant tumours. The full article is published in Cancer Discovery (DOI: 10.1158/2159-8290.CD-20-1050).



Clinical response of a patients with replication repair deficient high-grade gliomas to MEK inhibitor (Trametinib).

Recapitulating Disease in RRD Mouse Models

Written by Melissa Galati (Recent PhD Graduate)

Melissa Galati, PhD

Hi there! Nice to e-meet you, and welcome to the first RRD Consortium newsletter. My name is Melissa Galati, and I have just recently wrapped up my PhD studies in Dr. Uri Tabori's lab at the Hospital for Sick Children. I started my graduate degree in September 2015, shortly after completing my BSc at McGill University in Montreal, Canada. In the Tabori lab, I have had the privilege of working on several CMMRD-related research projects over the last few years, but most of my time has been spent developing and studying mouse models of cancers common to CMMRD and other replication repair deficient (RRD) individuals.

So why models? What's the benefit of modelling a disease in the lab? Well, while we've been able to learn a lot from tissues, samples, and tumour biopsies generously donated to us from patients and families within the consortium, these specimens only give us part of the story—a "snapshot" of the biology of one tumour at one specific time. If we can recreate the genetic basis for a disease like CMMRD in the lab, we can model tumour development and learn much more about the evolution of how tumours form, what other biological or genetic events might be driving the tumour to progress, and ultimately, understand more about how to treat these devastating cancers. The mouse is one of the most widely used animals in oncology research because we know they have considerable genetic similarity to humans (mice also have mismatch repair and polymerase genes, for example) and because it is relatively easy to genetically modify and breed mice.

" […] To validate these findings and more efficiently test potential therapies is critical."

- MELISSA GALATI, PHD

Over the last six years I developed several new mouse models of RRD-related cancers like brain tumours, gastrointestinal cancers, and lymphomas. RRD cancers can be driven by either mismatch repair deficiency and/or mutations in polymerase genes like POLE and POLD1. Since less is know about cancers driven by mutations in polymerase genes, I focused a lot of my early studies on the effects of different POLE mutations on tumour development. Based on this work we were able to group POLE mutations into clinically distinct groups, study tumour genetics as tumours evolve, and learn that immunotherapies like checkpoint inhibitors, which may be useful for RRD brain and GI cancers, may not be useful when it comes to treating hematopoietic malignancies like lymphomas. You can read more about our findings in Cancer Research.

My focus is the study of a new brain tumour mouse model of CMMRD. We're using this model to learn more about the role of the immune system in tumour development so that we can better understand how CMMRD brain tumours evade immune surveillance, resist immunotherapy, and how we can better boost a tumours response to immunotherapy. We have some ideas for potential therapeutic combinations that come from our research on human tumours, but having tools, like mouse models, to validate these findings and more efficiently test other potential therapies is critical.

Hello from Wisconsin!

Written by Jenell Holstead (Parent of Child with CMMRD)

We are the Holsteads, a busy family of seven with three daughters and two sons. Our fourth child, Elijah (age 5), was diagnosed with CMMRD in 2017 after both Michael and Jenell (parents) were diagnosed with Lynch Syndrome. We were extremely fortunate to discover Eli's condition prior to a cancer diagnosis. As a result, Eli has undergone regular cancer screenings recommended by the Consortium every six months so that we can monitor him closely.

The Holstead Family, 2021

During the last year and a half, Jenell has served as a Parent Advocate for the Consortium. She has a unique perspective, as she is a Professor of Psychology at the University of Wisconsin-Green Bay. As such, she has a distinct understanding of research policies and procedures, institutional rules and regulations, and the lengthy process of research while having the perspective of patients and families who seek answers for treating childhood cancer predisposition syndromes. In her Parent Advocate role, she ensures the research team understands the concerns of families. She has reviewed protocols and informed consent procedures, contributes to grant applications for funding, and also acts as a liaison between the researchers and the CMMRD family support group.

Elijah continues to be monitored closely. One would never know that he has a serious genetic condition. He is a typical little boy who LOVES dinosaurs and sharks, playing with his siblings and cousins, and is looking forward to playing soccer this summer!

Ways to Give

Thank you for considering making a donation towards the International Replication Repair Deficiency Consortium.

Thanks to your donations, we are able to continue funding the most promising cancer research, look for better treatments for this devastating condition, educate parents and families throughout the world about RRD and provide trusted information, resources and support for every patient and family who are on a journey to beat an RRD cancer.

If you are interested in making a donation, please reach out to us directly at replication.repair@sickkids.ca.