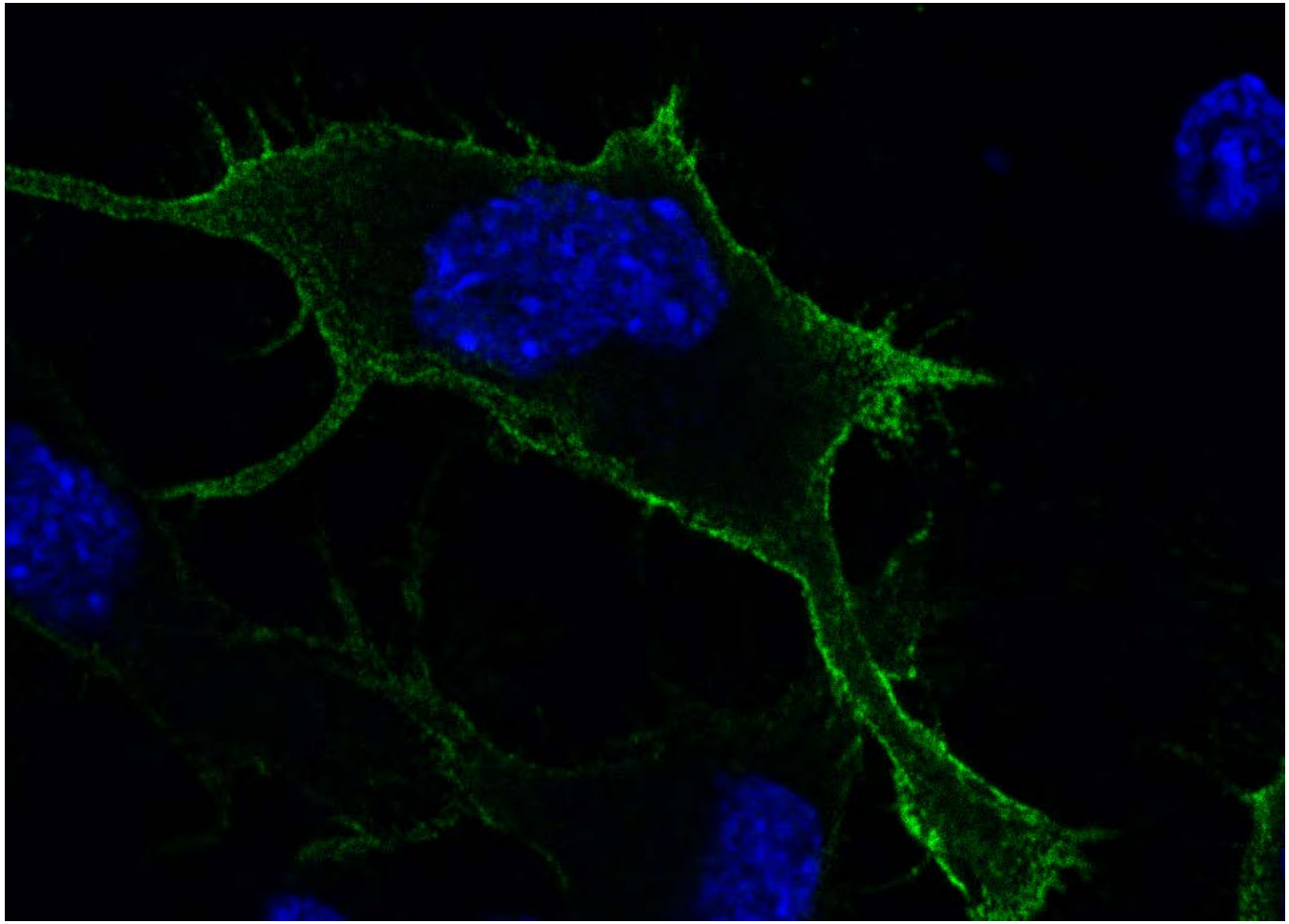
Bridging the gap between research and education using rare disease research

Robert N. Jinks, Ph.D.
Franklin & Marshall College



Collaboration with The Clinic for Special Children
Inherited disorders of the nervous system in Plain Communities

Fall 2000
Alicia Haupt ’02 (MSUD)

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2009-10 – Pierce Lab – Pediatric inherited retinal degeneration

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2009-10 – CSC – Pediatric inherited retinal degeneration – exome sequencing

FLVCR1 c.361A>G (N121D) – Retinitis pigmentosa and posterior column ataxia

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A few days later…

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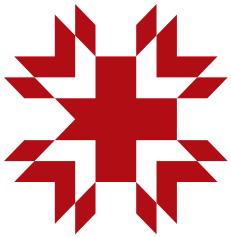


A few days later…

FLVCR1 c.361A>G (N121D) – Retinitis pigmentosa and posterior column ataxia

HARS c.1361A>C (Y454S) – Usher syndrome 3b

BRAT1 c.638_639insA – Lethal neonatal rigidity and multifocal seizure syndrome

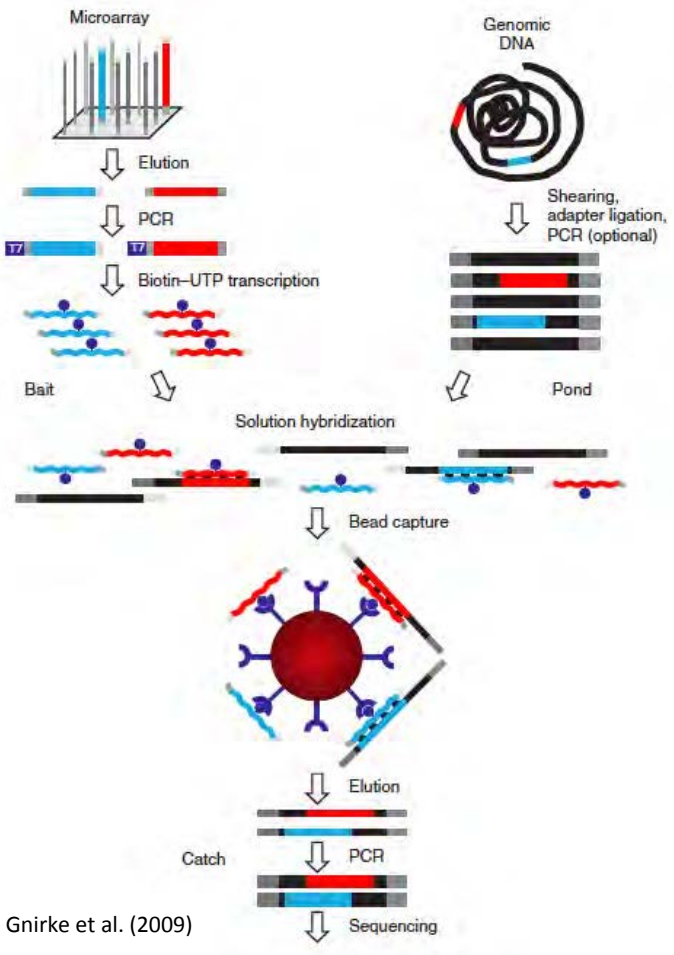
TUBGCP6 c.5458T>G (X1820G) – Mennonite microcephaly with chorioretinopathy

CRADD c.382G>C (G128R) – Non-syndromic intellectual disability

SNIP1 c.1097A>G (E366G) – psychomotor retardation, epilepsy, and craniofacial dysmorphism

Challenges

Rapid pace of disease gene discovery → need for corresponding functional data



Gnirke et al. (2009)

Exon capture

Exome sequencing

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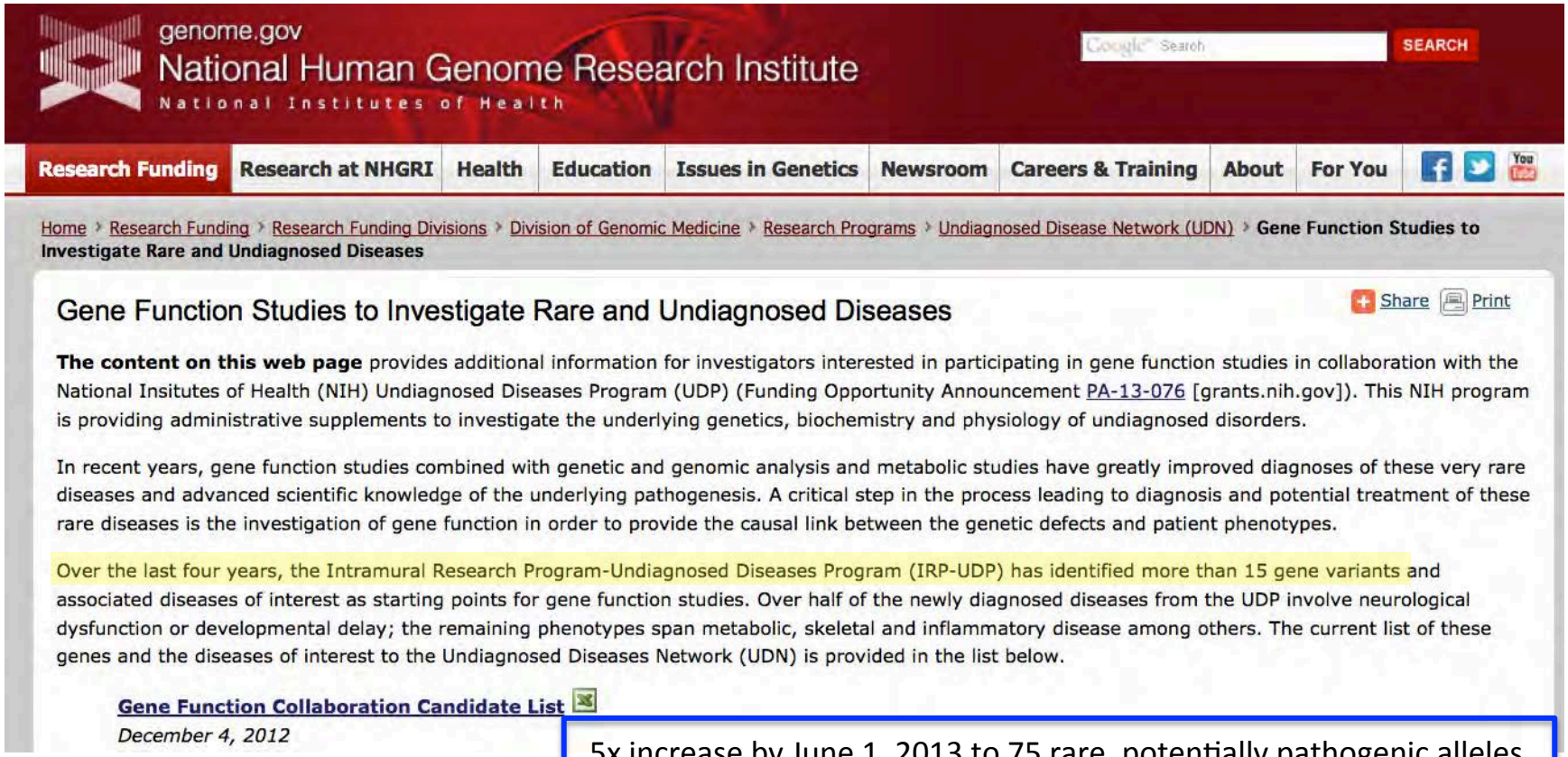

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Gene Function Studies to Investigate Rare and Undiagnosed Diseases

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The content on this web page provides additional information for investigators interested in participating in gene function studies in collaboration with the National Insitutes of Health (NIH) Undiagnosed Diseases Program (UDP) (Funding Opportunity Announcement PA-13-076 [grants.nih.gov]). This NIH program is providing administrative supplements to investigate the underlying genetics, biochemistry and physiology of undiagnosed disorders.

In recent years, gene function studies combined with genetic and genomic analysis and metabolic studies have greatly improved diagnoses of these very rare diseases and advanced scientific knowledge of the underlying pathogenesis. A critical step in the process leading to diagnosis and potential treatment of these rare diseases is the investigation of gene function in order to provide the causal link between the genetic defects and patient phenotypes.

Over the last four years, the Intramural Research Program-Undiagnosed Diseases Program (IRP-UDP) has identified more than 15 gene variants and associated diseases of interest as starting points for gene function studies. Over half of the newly diagnosed diseases from the UDP involve neurological dysfunction or developmental delay; the remaining phenotypes span metabolic, skeletal and inflammatory disease among others. The current list of these genes and the diseases of interest to the Undiagnosed Diseases Network (UDN) is provided in the list below.

Gene Function Collaboration Candidate List
December 4, 2012

5x increase by June 1, 2013 to 75 rare, potentially pathogenic alleles

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Challenges

Rapid pace of disease gene discovery → need for corresponding functional data

Long-term "teachable moment"…

Challenges

Rapid pace of disease gene discovery → need for corresponding functional data

Long-term "teachable moment"…

HHMI

HHMI *Bulletin*, Fall 2012

Teaching Genomics, Plainly

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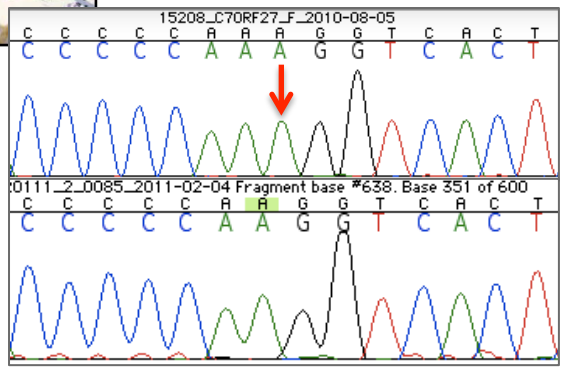
Approach

Diagnosis through deep phenotyping:

- Thorough description of physiological, anatomical, biochemical, and genetic characteristics of a particular disease.

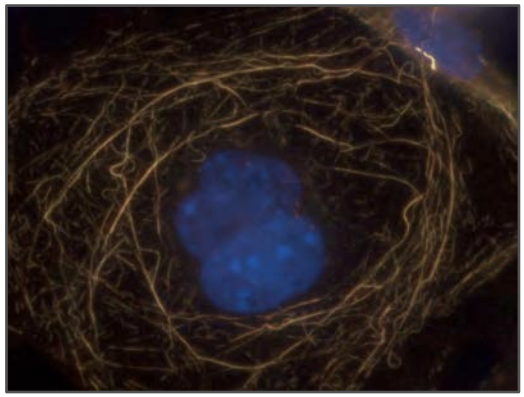
Disease gene identification:

- Identification of the specific gene mutation that underlies the phenotype. (~25,000 genes; 3 billion base pairs)



Functional studies:

- Determine pathophysiological consequences of disease gene variants at molecular, cellular, systems, and organismal (knock-out/in transgenics) levels.



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Approach

Develop treatment strategies:

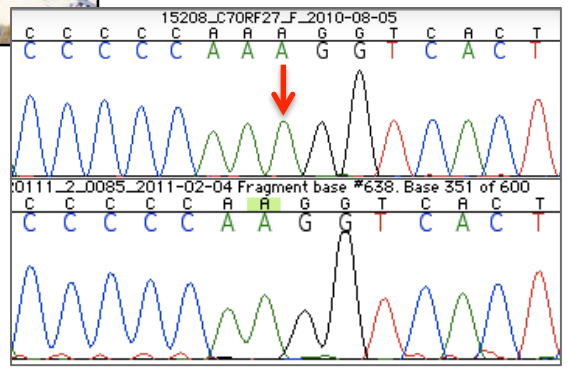
- Can disease course be altered to improve outcomes using research-grade phenotyping and functional data? E.g. – GM3 synthesis/ purification.

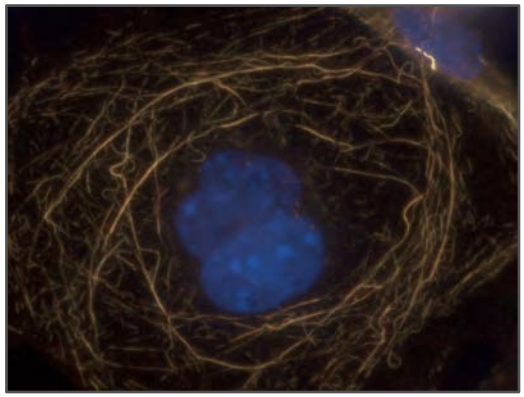
Public Health Research & Outreach:

- Develop courses and student-faculty research focused on:

  production of educational materials for patients, families, and caregivers, and

  epidemiological surveys of disease burden for novel inherited disorders.





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Outcomes

BRAT1 c.638_639insA – Lethal neonatal rigidity and multifocal seizure syndrome (RMFSL)

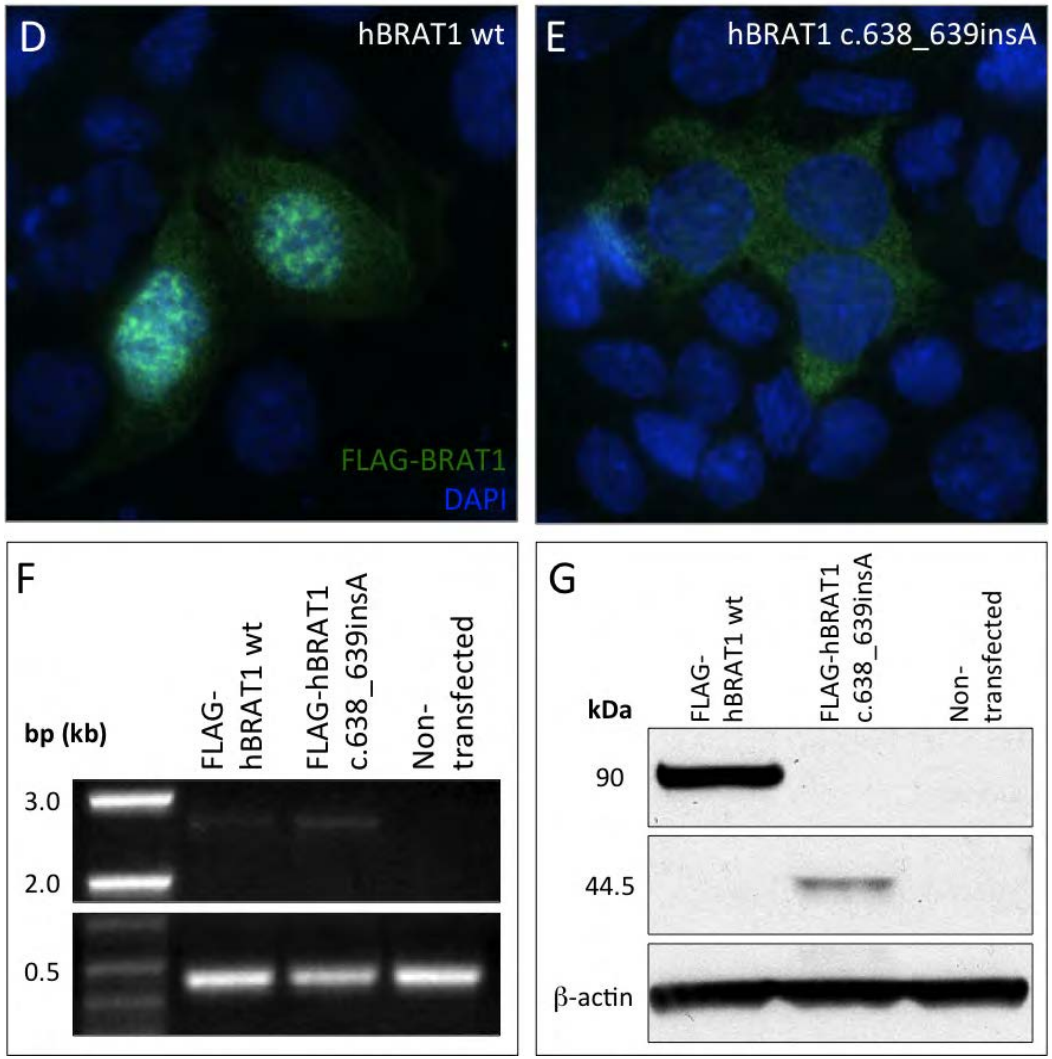
BRAT1 interacts with BRCA1 and ATM – Inhibits ATM phosphatase in DNA damage response.

BRCA1 "chaperones" BRAT1 to the nucleus (Aglipay et al., 2006).

BRAT1 ins. c.638_639A mutation → reading frame shift for amino acids 214-401, and premature truncation at Leu^{401}.

Mutation likely eliminates the BRCA1 and ATM binding sites in BRAT1.

Outcomes



Lethal neonatal rigidity and multifocal seizure syndrome (RMFSL)
OMIM 614498

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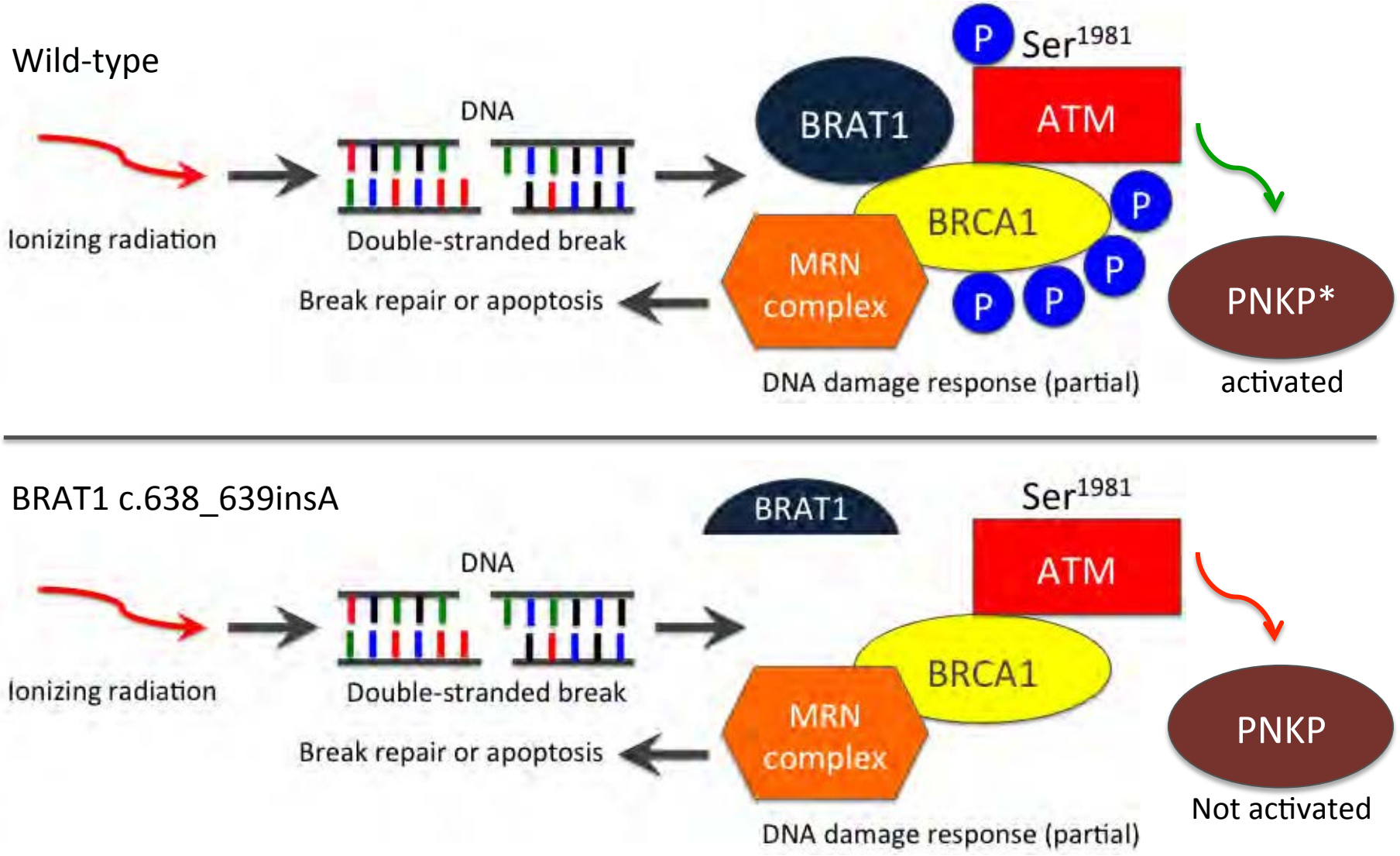

Loss-of-function mutations in PNKP → microcephaly, early-onset, intractable seizures and developmental delay (Shen et al., 2010; *Nat. Genetics* **42**:245).

Outcomes

OPEN ACCESS Freely available online

PLoS one

Genetic Mapping and Exome Sequencing Identify Variants Associated with Five Novel Diseases

Erik G. Puffenberger[1,2*], Robert N. Jinks[2], Carrie Sougnez[3], Kristian Cibulskis[3], Rebecca A. Willert[2], Nathan P. Achilly[2], Ryan P. Cassidy[2], Christopher J. Fiorentini[2], Kory F. Heiken[2], Johnny J. Lawrence[2], Molly H. Mahoney[2], Christopher J. Miller[2], Devika T. Nair[2], Kristin A. Politi[2], Kimberly N. Worcester[2], Roni A. Setton[2], Rosa DiPiazza[2], Eric A. Sherman[4], James T. Eastman[5], Christopher Francklyn[6], Susan Robey-Bond[6], Nicholas L. Rider[1,2,7], Stacey Gabriel[3], D. Holmes Morton[1,2,7], Kevin A. Strauss[1,2,7]

Abstract

The Clinic for Special Children (CSC) has integrated biochemical and molecular methods into a rural pediatric practice serving Old Order Amish and Mennonite (Plain) children. Among the Plain people, we have used single nucleotide polymorphism (SNP) microarrays to genetically map recessive disorders to large autozygous haplotype blocks (mean = 4.4 Mb) that contain many genes (mean = 79). For some, uninformative mapping or large gene lists preclude disease-gene identification by Sanger sequencing. Seven such conditions were selected for exome sequencing at the Broad Institute; all had been previously mapped at the CSC using low density SNP microarrays coupled with autozygosity and linkage analyses. Using between 1 and 5 patient samples per disorder, we identified sequence variants in the known disease-causing genes *SLC6A3* and *FLVCR1*, and present evidence to strongly support the pathogenicity of variants identified in *TUBGCP6*, *BRAT1*, *SNIP1*, *CRADD*, and *HARS*. Our results reveal the power of coupling new genotyping technologies to population-specific genetic knowledge and robust clinical data.

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Outcomes

HHMI

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Outcomes

RESEARCH ARTICLE

Science Translational Medicine **4**, 154ra135 (2012)

DIAGNOSTICS

Rapid Whole-Genome Sequencing for Genetic Disease Diagnosis in Neonatal Intensive Care Units

Carol Jean Saunders,[1,2,3,4,5]* Neil Andrew Miller,[1,2,4]* Sarah Elizabeth Soden,[1,2,4]* Darrell Lee Dinwiddie,[1,2,3,4,5]* Aaron Noll,[1] Noor Abu Alnadi,[4] Nevene Andraws,[3] Melanie LeAnn Patterson,[1,3] Lisa Ann Krivohlavek,[1,3] Joel Fellis,[6] Sean Humphray,[6] Peter Saffrey,[6] Zoya Kingsbury,[6] Jacqueline Claire Weir,[6] Jason Betley,[6] Russell James Grocock,[6] Elliott Harrison Margulies,[6] Emily Gwendolyn Farrow,[1] Michael Artman,[2,4] Nicole Pauline Safina,[1,4] Joshua Erin Petrikin,[2,3] Kevin Peter Hall,[6] Stephen Francis Kingsmore[1,2,3,4,5†]

Monogenic diseases are frequent causes of neonatal morbidity and mortality, and disease presentations are often undifferentiated at birth. More than 3500 monogenic diseases have been characterized, but clinical testing is available for only some of them and many feature clinical and genetic heterogeneity. Hence, an immense unmet need exists for improved molecular diagnosis in infants. Because disease progression is extremely rapid, albeit heterogeneous, in newborns, molecular diagnoses must occur quickly to be relevant for clinical decision-making. We describe 50-hour differential diagnosis of genetic disorders by whole-genome sequencing (WGS) that features automated bioinformatic analysis and is intended to be a prototype for use in neonatal intensive care units. Retrospective 50-hour WGS identified known molecular diagnoses in two children. Prospective WGS disclosed potential molecular diagnosis of a severe *GJB2*-related skin disease in one neonate; *BRAT1*-related lethal neonatal rigidity and multifocal seizure syndrome in another infant; identified *BCL9L* as a novel, recessive visceral heterotaxy gene (*HTX6*) in a pedigree; and ruled out known candidate genes in one infant. Sequencing of parents or affected siblings expedited the identification of disease genes in prospective cases. Thus, rapid WGS can potentially broaden and foreshorten differential diagnosis, resulting in fewer empirical treatments and faster progression to genetic and prognostic counseling.

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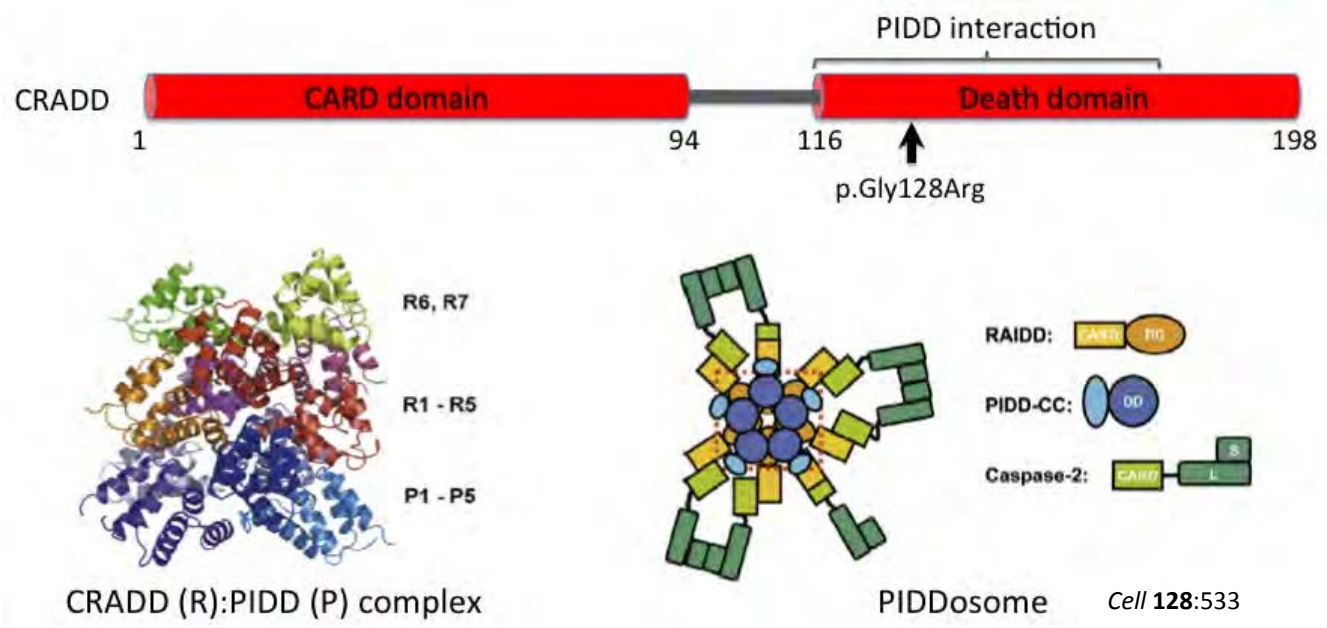
Functional studies: *CRADD* – caspase-recruitment-domain (CARD) and death domain (DD) adaptor protein

CRADD	c.382G>C; Gly128Arg	recessive non-syndromic mental retardation (Mennonite)

CRADD (*aka* RAIDD) links PIDD (p53-induced protein with death domain) and caspase-2 to form PIDDosome required for caspase-2 activation during apoptosis.

CRADD c.382G>C mutation alters a highly conserved residue (Gly^{128}) within the CRADD death domain. May alter CRADD:PIDD interaction and/or CRADD:RIPK1 interaction at DDs.



Cell **128**:533

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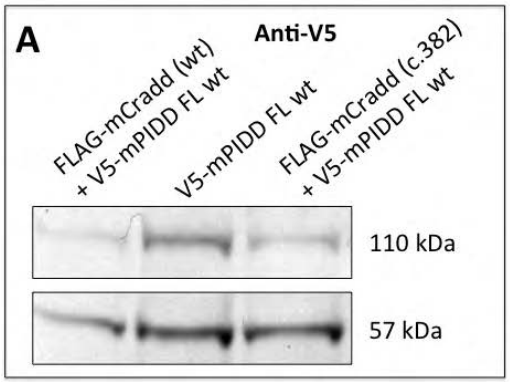

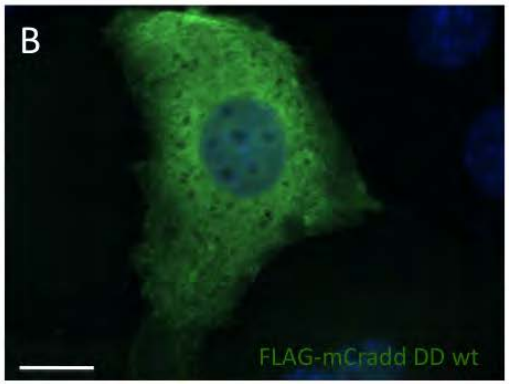

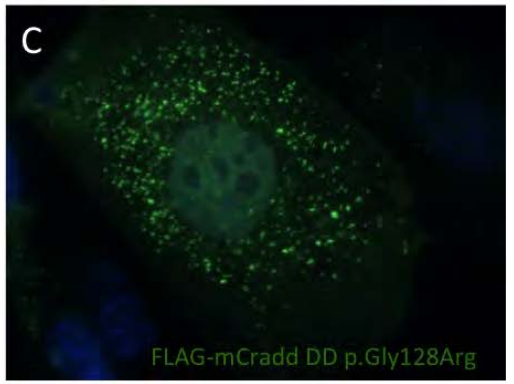

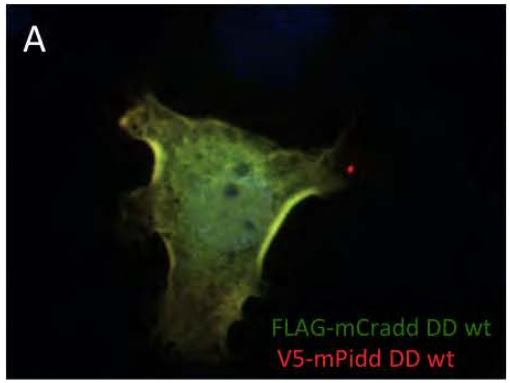

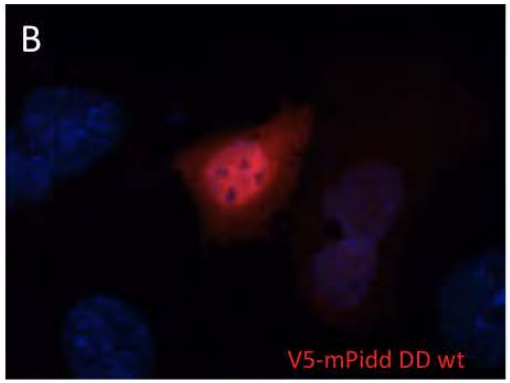

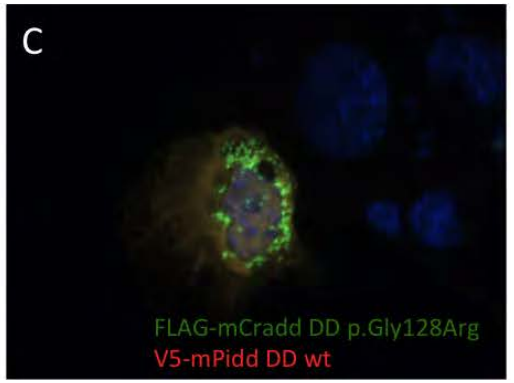

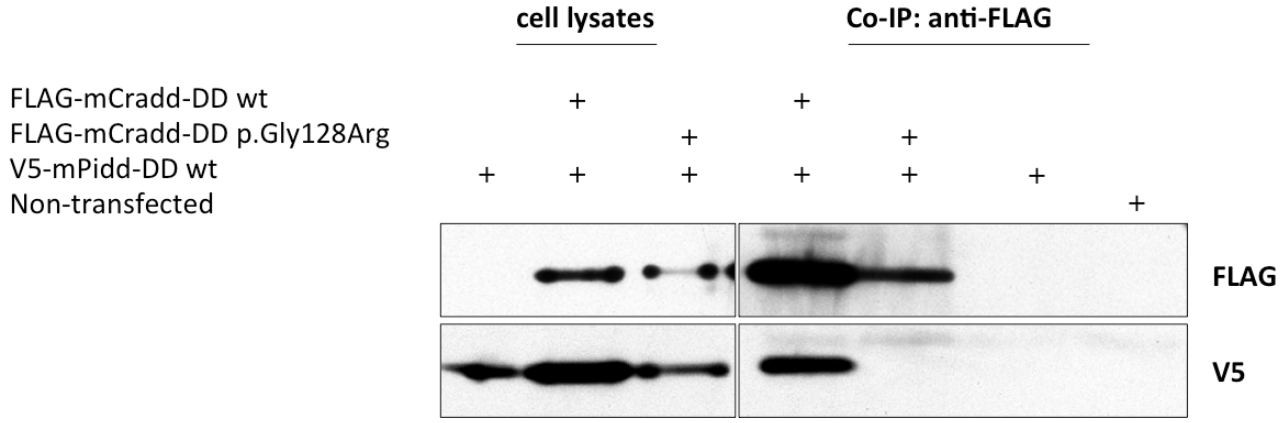

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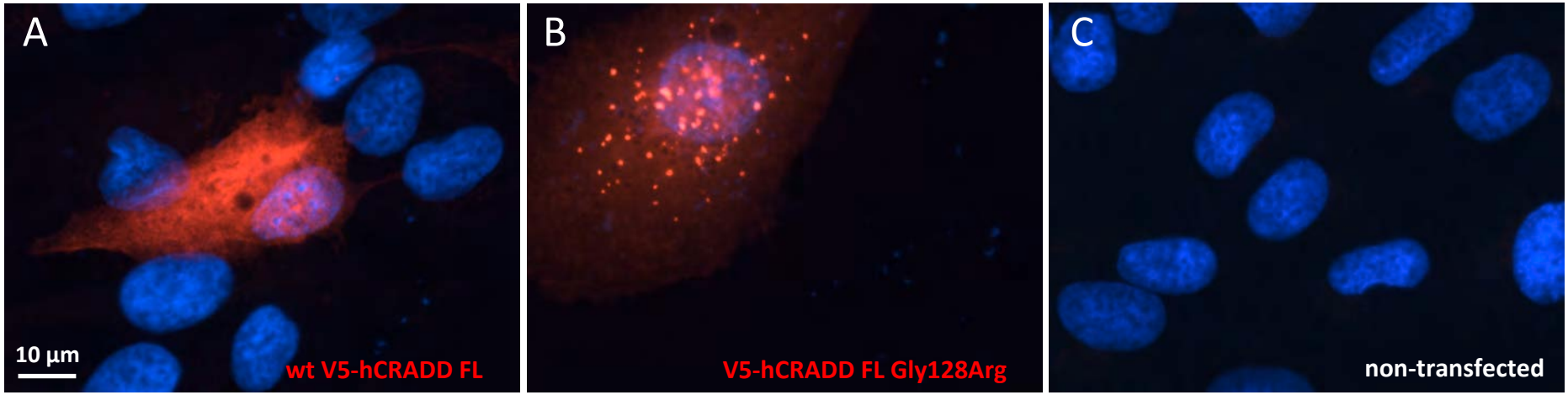
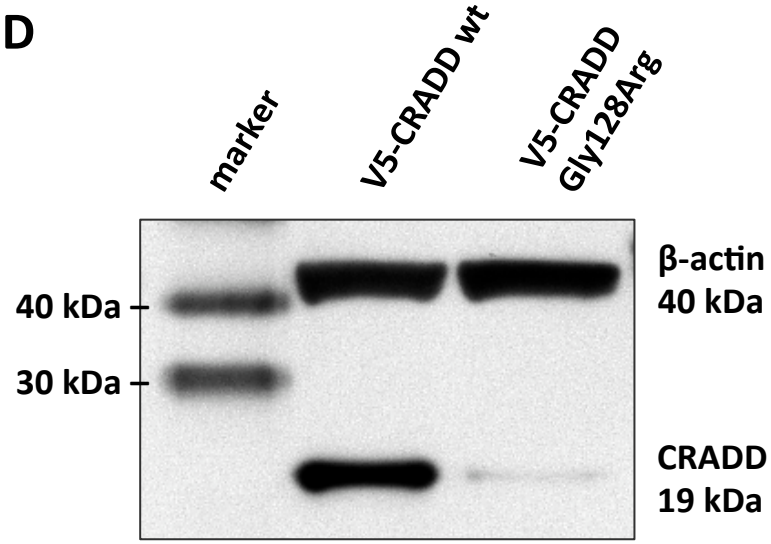
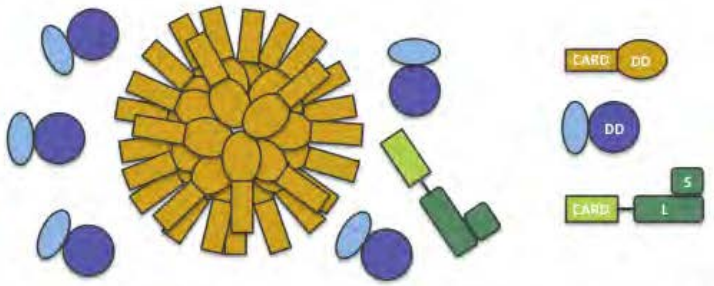
Functional studies: *CRADD* – caspase-recruitment-domain (CARD) and death domain (DD) adaptor protein







Putative impact of CRADD p.Gly128Arg variant on PIDDosome

Alteration of caspase-2 initiated apoptosis (resulting from disruption of the PIDDosome) during neuronal proliferation may lead to inappropriate neuronal cell death that results in cognitive impairment.

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SNIP1	c.1097A>G	Psychomotor retardation, epilepsy, and craniofacial dysmorphism
FLVCR1	c.361A>G	Posterior column ataxia, retinitis pigmentosa
TUBGCP6	c.5458T>G	Microcephaly with chorioretinopathy
BRAT1	c.638_639insA	Rigidity and multifocal seizure syndrome, lethal neonatal
HARS	c.1361A>C	Usher syndrome type IIIB; retinitis pigmentosa and prog. sensorineural hearing loss; fever-induced hallucinations
CRADD	c.382G>C	recessive non-syndromic mental retardation
HERC2	c.1781C>T	autism spectrum disorder, developmental delay
XXXX	XXXX	recessive non-syndromic mental retardation
SLITRK6	c.1240C>T	congenital hearing loss
XXXX	XXXX	CODAS syndrome
XXXX	XXXX	Yoder dystonia with chronic kidney disease
XXXX	XXXX	Mental health
XXXX	XXXX	Venous thromboembolism (dominant; non-Plain)
XXXX	XXXX	Syndromic developmental delay

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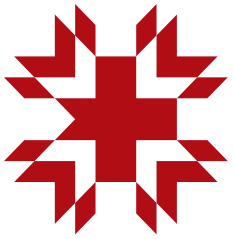

Impact on F&M

Integration of collaboration with Clinic into curriculum and student-faculty research

Jinks, Davis, Roberts, Miller, Rice, Yost, Hess, Fenlon, Brewer, Nadig, Billig

Neuroscience, Biology, Public Health, Biochemistry & Molecular Biology, Chemistry, Anthropology

Research-intensive courses reach over 150 undergraduates annually.

Summer research experiences in translational research and public health for over 20 undergraduate students