OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

**DO NOT EXCEED FIVE PAGES**.

NAME: Steven J. Schrodi, PhD

eRA COMMONS USER NAME (credential, e.g., agency login): SCHRODIS

POSITION TITLE: Tenure-Track Associate Research Scientist

EDUCATION/TRAINING

| INSTITUTION AND LOCATION | DEGREE  (if applicable) | Completion Date  MM/YYYY | FIELD OF STUDY |
| --- | --- | --- | --- |
| University of California, Davis | B.S. | 06/1995 | Genetics |
| University of California, Irvine | M.S. | 12/1998 | Biological Sciences |
| University of California, Irvine | Ph.D. | 03/2001 | Biological Sciences |

# A. Personal Statement

My primary research interests lie in complex disease gene mapping in the areas of systemic inflammatory diseases and statistical genetics. My work has synthesized disease gene mapping approaches and statistical methods with the aim of identifying variants that underlie inflammatory disease phenotypes. Current areas of investigation include the development of probability-based methods to analyze genetic data, linkage disequilibrium patterns from disease-susceptibility variants, probabilistic tests of multiple hypotheses, applied machine learning methods, and shared chromosomal region analyses. My experimental research focuses on the discovery of alleles and biomarkers that predispose individuals to autoimmunity and dysfunction in immune tolerance, aberrant immune responses to pathogens, and systemic inflammation. Of particular interest is the use of feature selection algorithms and classifiers to generate robust predictive models and clustering algorithms for applications to human genetics. I have played key roles in numerous human genetics consortia investigating autoimmunity, systemic inflammation, diabetes, iron metabolism, and autism. The ultimate goals of my research are to develop widely-applicable genetic and biomarker statistical methods, gain an understanding of molecular pathogenesis of diseases, and provide results useful for disease treatment and remediation.

1. Bansal, N.K., Maadooliat, M., **Schrodi, S.J.** (2018) Empirical Bayesian approach to testing multiple hypotheses with separate priors for left and right alternatives. *Stat Appl Genet Mol Biol* 17(4):20180002.
2. Maadooliat M., Bansal N.K., Updhya J., Farazi M.R., Li X., He M., Hebbring S.J., Ye Z., **Schrodi S.J.\*** (2016) The decay of disease association with declining linkage disequilibrium: A fine mapping theorem. *Frontiers in Genetics*, 7:217. (**\***Corresponding Author)
3. Carter, T.C., Rein, D., Padberg, I., Peter, E., Rennefahrt, U., David, D.E., McManus, V., Stefanski, E., Martin, S., Schatz, P., **Schrodi S.J.\*** (2016). Validation of a metabolite panel for early diagnosis of type 2 diabetes. *Metabolism*, 65(9):1399-1408. (**\***Corresponding Author)
4. Hebbring SJ, Slager SL, Epperla N, Mazza JJ, Ye Z, Zhou Z, Achenbach SJ, Vasco DA, Call TG, Rabe KG, Kay NE, Caporaso NE, Camp NJ, Strom SS, Goldin LR, Cerhan JR, Brilliant MH, **Schrodi, S.J.\*** (2012) Genetic evidence of PTPN22 effects on chronic lymphocytic leukemia. (2012). *Blood*, 121(1):237-238.(**\***Corresponding Author)
5. Cargill, M.ǂ, **Schrodi, S.J.**ǂ, Chang, M., Garcia, V.E., Brandon, R., Callis-Duffin, K.P., Matsunami, N., Ardlie, K.G., Civello, D., Catanese, J.J., Leong, D.U., Panko, J.M., McAllister, L.B., Papenfuss, J., Prescott, S.M., White, T.J., Leppert, M.F., Krueger, G.G., Begovich, A.B. (2007) A large-scale genetic association study confirms IL12B and leads to the identification of IL23R as psoriasis-risk genes. *American Journal of Human Genetics*, 80(2):273-290. (ǂContributed equally)

# B. Positions and Honors

## Positions and Employment

2000-2001 Scientist, DNA Sciences, Fremont, CA

2001-2006 Senior Scientist, Celera, Alameda, CA

2006-2008 Staff Scientist, Celera, Alameda, CA

2008-2010 Senior Staff Scientist, Celera, Alameda, CA

2013-Pres Faculty Trainer, Computation and Informatics in Biology and Medicine, University of Wisconsin-Madison, Madison, WI

2010-Pres Tenure-Track Associate Research Scientist, Center for Precision Medicine Research, Marshfield Clinic Research Institute, Marshfield, WI

## Other Experience and Professional Memberships

1992-1993 Internship, Theoretical Space Science Division, NASA Ames

2000-2001 Scientific Advisory Board, DNA Sciences

2008-2010 Statistical Genetics Consultant, Biotechnology and Pharmaceutical Companies

2012 Critical Assessment of Massive Data Analysis, Scientific Committee

2014 Multiple Sclerosis Research Australia Grants Review Panel

2006-2014 American Association for the Advancement of Science, Member

2000-2014 American Society of Human Genetics, Member

2014-2015 Marshfield Clinic Research Institute Strategic Planning Committee

2013-2016 Marshfield Clinic Research Compliance Committee

2005-2017 International Society of Bayesian Analysis, Member

2014-2015, 2018 Institute of Clinical and Translational Research Grant Review Panel

2018 Clinician Scientist Collaborative Research Award Grant Review Panel

2013-2018 Marshfield Clinic Research Institute Seminar Series Committee

1993-Pres Thirty-three Invited Oral Presentations

1998-Pres Fifty Accepted Scientific Conference Abstracts

1999-Pres *Ad hoc* Reviewer for Twenty Scientific Journals

2015-Pres Associate Editor, *Frontiers in Genetics, Statistical Genetics and Methodology*

## Honors

2004 Top 10 Arthritis Advances of 2004, Arthritis Foundation

2005 UCSF Frontiers in Neurology & Neuroscience, Keynote Speaker

2007 Applera Demonstrated Noteworthy Achievement Award

2010 US Patent 7,833,706; Inventor

2011 US Patent 7,863,021; Inventor

2011 US Patent 7,947,451; Inventor

2011 US Patent 7,993,833, Inventor

2015 US Patent 8,975,022; Inventor

2016 US Patent 9,371,565; Inventor

2016 Mathematics, Statistics and Computer Science Colloquium Speaker, Marquette Univ.

2017 Computation and Informatics in Biology and Medicine, Seminar Speaker

2018 US Patent 10,006,088; Inventor

2018 Chinese Academy of Medical Sciences, Shanghai, Keynote Speaker

# C. Contribution to Science

1. **Temporal Variation in DNA Substitution Processes**. Early in my career, I investigated theoretical models in population genetics and molecular evolution where I developed a novel method for testing competing models of DNA substitution processes through measuring temporal patterns of DNA substitution variation. Applying this to mammalian protein-coding sequence data, I discovered that leading models of molecular evolution were rejected in favor of models where selection coefficients vary slowly over time.
   1. **Schrodi, S.J.** (2001) *Mathematical models in population genetics, molecular evolution and genomics.* UMI Dissertation Services, Ann Arbor, MI.
2. **First Exome-wide Association Scan for a Common Disease: Discovery of *PTPN22* and *TRAF1* Rheumatoid Arthritis Susceptibility Genes.** In 2003, I led the design and analysis and interpreted results from the first large-scale exome-wide SNP association disease scan using 30,000 putatively functional coding variants, interrogating RA susceptibility. I tested initial findings in a replication sample set of severe rheumatoid arthritis. The study resulted in the discovery of the R620W polymorphism in the protein tyrosine phosphatase, *PTPN22*, being strongly correlated with RA susceptibility. The 620W allele was subsequently found to confer profound effects on T-cell activation, B-cell pruning, NK cell stimulation, and impact numerous other innate and adaptive immune responses. R620W is a key factor in autoimmunity and has now been significantly associated with 11 common, chronic inflammatory diseases. Further, I led a fine-mapping effort which discovered *TRAF1* haplotypes as critically important RA susceptibility alleles. I was placed as chief architect for all Applied Biosystems and Celera fine mapping studies. I have been awarded two United States Patents describing this work.
   1. Begovich, A.B., Carlton, V.E., Honigberg, L.A., **Schrodi, S.J.**, et al. (2004) A missense single-nucleotide polymorphism in a gene encoding a protein tyrosine phosphatase (PTPN22) is associated with rheumatoid arthritis. *American Journal of Human Genetics*, 75(2), 330-337.
   2. Carlton, V.S., Hu, X., Chokkalingam, A.P., **Schrodi, S.J.**, et al. (2005) PTPN22 genetic variation: evidence for multiple variants associated with rheumatoid arthritis. *American Journal of Human Genetics*, 77(4), 567-581.
   3. Chang, M., Rowland, C.M., Garcia, V.E., **Schrodi, S.J.**, et al. (2008) A large-scale rheumatoid arthritis genetic study identifies association at chromosome 9q33.2. *PLoS Genetics*, 4(6), e1000107.
   4. Begovich, A.B., Carlton, V.E.H., **Schrodi, S.J.**, Alexander, H.C. (Filed Jan 30, 2003; Awarded Nov 16, 2010) *United States Patent* 7,833,706. Genetic polymorphisms associated with rheumatoid arthritis, methods of detection and uses thereof.
   5. **Schrodi, S.J.** and Begovich, A.B. (Filed Sept 5, 2007; Awarded Jan 4, 2011) *United States Patent* 7,863,021. Genetic polymorphisms associated with rheumatoid arthritis, methods of detection and uses thereof.
3. **First Large-Scale Genetics Association Scan for Psoriasis: Discovery of *IL23R*, *IL12B* and *IL13* Psoriasis Susceptibility Genes**. Starting in 2005, I designed, managed and analyzed the first exome-wide association scan of psoriasis. I developed a novel, pooled, multi-staged experimental design to interrogate 30,000 putatively functional coding variants to study psoriasis etiology. The study confirmed the *IL12B*-association with psoriasis and was the first investigation to discover the involvement of *IL23R* variants in disease. The findings solidified the view that Th17 signaling plays a fundamental role in autoinflammatory conditions. In addition, the study discovered polymorphisms segregating at *IL13* playing a role in psoriasis-predisposition. The *IL12B/IL23R* findings provided evidence supporting the use of anti-IL-23 and anti-IL-17 monoclonal antibodies as targeted therapies for autoinflammatory diseases. I was awarded five United States Patents describing these psoriasis and autoinflammatory disease results.
   1. Cargill, M.ǂ, **Schrodi, S.J.**ǂ, Chang, M., Garcia, V.E., et al. (2007) A large-scale genetic association study confirms IL12B and leads to the identification of IL23R as psoriasis-risk genes. *American Journal of Human Genetics*, 80(2):273-290. (ǂEqual contributions)
   2. Garcia, V.E., Chang, M., Brandon, R., Li, Y.J., Matsunami, N., Callis-Duffin, K.P., Civello, D., Rowland, C.M., Bui, N., Catanese, J.J., Krueger, G.G., Leppert, M.F., Begovich, A.B., **Schrodi, S.J.\*** (2008) Detailed genetic characterization of the interleukin-23 receptor in psoriasis. *Genes & Immunity*, 9(6):546-555. (\*Corresponding Author)
   3. Chang, M., Li, Y.J., Yan, C., Callis-Duffin, K.P., Matsunami, N., Garcia, V.E., Cargill, M., Civello, D., Bui, N., Catanese, J.J., Leppert, M.F., Krueger, G.G., Begovich, A.B., **Schrodi, S.J.** (2008) Variants in the 5q31 cytokine gene cluster are associated with psoriasis. *Genes & Immunity*, 9(2):176-181.
   4. Nair, R.P., Duffin, K.C., Helms, C., …, **Schrodi, S.J.**, et al. (2009) Genome-wide scan reveals association of psoriasis with IL-23 and NF-kappaB pathways*. Nature Genetics*, 41(2):199-204.
   5. Tsoi, L.C., Spain, S.L., Knight, J., …**Schrodi, S.J.**, et al. (2012) Identification of 15 new psoriasis susceptibility loci highlights the role of innate immunity. *Nature Genetics*, 44(12):1341-1348.
4. **Statistical Genetics**. I have an ongoing interest in developing novel statistical genetics methods and approaches. In 2000, I was recruited by Dr. Ray White to DNA Sciences where I led a very large Monte Carlo simulation study involving several scientific programmers and a genetic epidemiologist to simulate disease genetics in extended kinships in an effort to inform the development of powerful mapping methods in founder populations. Over the past 17 years, I have worked on methods of selecting tagging SNPs, TDT statistical approaches, Bayesian hypothesis testing for genetic association, Bayesian estimation applied to genetics, permutation approaches, and multiple testing.
   1. **Schrodi, S.J.\*** (2005) A probabilistic approach to large-scale association scans: a semi-Bayesian method to detect disease-predisposing alleles. *Stat Appl Genet Mol Biol*, 4, Article 31. (\*Corresponding Author)
   2. **Schrodi, S.J.\***, DeBarber, A., He, M., Ye, Z., et al. (2015) Prevalence estimation for monogenic autosomal recessive disease using population-based genetic data. *Human Genetics*, 134(6):659-669. (\*Corresponding Author)
   3. **Schrodi, S.J.\*** (2016) The use of multiplicity corrections, order statistics and generalized family-wise statistics with application to genome-wide studies. *PLoS One* 11(4):e0154472. (\*Corresponding Author)
   4. **Schrodi, S.J.\*** (2017) The impact of diagnostic code misclassification on optimizing the experimental design of genetic association studies. *J Healthc Eng* 2017:7653071. (\*Corresponding Author)
   5. Bansal, N.K., Maadooliat, M., **Schrodi, S.J.** (2018) Empirical Bayesian approach to testing multiple hypotheses with separate priors for left and right alternatives. *Stat Appl Genet Mol Biol* 17(3):20180002.
5. **Disease Genetics Theory and Prediction of Disease Traits.** My research on theoretical models of disease genetics has shown how linkage disequilibrium with a causal site varies with mode of inheritance, including a mathematical formulation for precisely how disease association statistics decays as linkage disequilibrium declines from a causal site. My colleagues and I show the utility of this work for developing new fine mapping approaches. Additionally, we have applied machine learning techniques to utilize molecular markers for disease prognosis and information theory metrics for characterizing the predictive capacity of such models. Of note, my colleagues and I developed a validated classifier for early type 2 diabetes diagnosis using metabolites, genetics and protein markers has shown very high discrimination power (AUC>0.91).
   1. **Schrodi, S.J.\***, Garcia, V.E., Rowland, C.M., Jones, H.B. (2007) Pairwise linkage disequilibrium under disease models. *Eur J Human Genetics*, 15(2), 212-220. (\*Corresponding Author)
   2. **Schrodi, S.J.\***, Mukherjee, S., Shan, Y., Tromp, G., et al. (2014) Genetic-based prediction of disease traits: prediction is very difficult, especially about the future. *Frontiers in Genetics*, 5:162. (\*Corresponding Author)
   3. **Schrodi, S.J.\*** (2016) Reflections on the field of human genetics: A call for increased disease genetics theory. *Frontiers in Genetics*, 7:106. (\*Corresponding Author)
   4. Carter, T.C., Rein, D., Padberg, I., Peter, E., Rennefahrt, U., David, D.E., McManus, V., Stefanski, E., Martin, S., Schatz, P., **Schrodi, S.J.\*** (2016). Validation of a metabolite panel for early diagnosis of type 2 diabetes. *Metabolism*, 65(9):1399-1408. (\*Corresponding Author)
   5. Maadooliat, M., Bansal, N.K., Updhya, J., Farazi, M.R., Li, X., He, M., Hebbring, S.J., Ye, Z., **Schrodi, S.J.\*** (2016) The decay of disease association with declining linkage disequilibrium: A fine mapping theorem. *Frontiers in Genetics*, 7:217. (\*Corresponding Author)

**Complete List of Published Work:**

<http://www.ncbi.nlm.nih.gov/sites/myncbi/steven.schrodi.1/bibliography/47248234/public/?sort=date&direction=descending>

# D. Additional Information: Research Support and/or Scholastic Performance

## Ongoing Research Support

Marshfield Clinic Research Institute Schrodi (PI) 07/15/2018 – 07/14/2020

*Detecting Shared Chromosomal Regions and Compound Heterozygous Effects for Diseases*

Role: Principal Investigator

UL1 TR000427 Drezner (PI) 06/01/2015 - 05/31/2019

University of Wisconsin

NIH-NCATS/UW-Institute for Clinical & Translational Research

The major goal of this study is to create an environment that facilitates the transformation or research at the University into a continuum extending from investigation through discovery to translation into practice, thereby linking even the most basic research to practical improvements in human health.

Role: Scientist

1RO1GM114128 Hebbring (PI) 09/01/2014 - 08/31/2019

*PheWAS of Loss-of-Function Variants*

The hypothesis being tested in this project is that loss-of-function variants – a class of variation with the highest probability of being clinically relevant – may cause disease phenotypes described in EMRs.

Role: Co-Investigator

5R01MH097464-03 Lainhart (PI) 04/01/2013 - 07/31/2019

*The Biological Basis of Variations in Brain Structure and Function in Autism*

The overarching hypothesis of this study is:  Looking at variability and extremes of autism-associated imaging data as phenotypic measures of autism we will be able to find new genetic variants that lead to biological pathways that explain the imaging findings and advance understanding of clinical impairing manifestations of the disorder.

Role: Site Principal Investigator

## Completed Research Support

Clinical Scientist Development Award Shelef (PI) 07/01/2017 - 06/30/2018

Doris Duke Charitable Foundation

Genetic variants, immune dysregulation, & rheumatoid arthritis

The major goals of this study are to examine how exome variants drive dysfunction in NET formation and autoantibody production in rheumatoid arthritis.

Role: Consultant

Second Genome Schrodi (PI) 08/09/2015 - 08/09/2016

*Inflammasome Host and Microbiome Genetics*

Role: Principal Investigator

Rheumatology Research Foundation Smith (PI) 07/01/2013 - 12/31/2015

*WIC - Analysis of Causal Variants in the IL-23/IL-17 Pathway Genes in Axial Spondyloarthritis*

Axial Spondyloarthritis, including the prototypic ankylosing spondylitis is a slowly progressive debilitating disease that may be caused by excess production of inflammatory mediators, in particular IL-17. Although previous genetic studies have implicated multiple genes in an “IL-23/IL-17” pathway that regulates pathogenic immune cells, the proposed research is necessary to explain how variations within the individual genes alter immune responses.

Role: Site Principal Investigator

Metanomics Health Schrodi (PI) 08/01/2012 - 07/13/2013

*Metanomics Health and Marshfield Type 2 Diabetes Prediction*

As a collaboration between Metanomics Health and MCRI, this study evaluates and develops predictive models for T2D using a panel of metabolites and additional biological markers as applied to PMRP samples.

Role: Principal Investigator

UL1 TR000427 Drezner (PI) 06/01/2012 - 05/31/2013

University of Wisconsin

NIH-NCATS/UW-Institute for Clinical & Translational Research

The major goal of this study is to create an environment that facilitates the transformation or research at the University into a continuum extending from investigation through discovery to translation into practice, thereby linking even the most basic research to practical improvements in human health.

*Genomics of IL-23/IL-17-Mediated Chronic Inflammation*

Role: T1 Pilot Grant Recipient, Principal Investigator