Knowledge multiplies when shared — when calling things by their right name: improving the validation and exchange of genetic data in research and diagnostics

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Curriculum Vitae

Ivo Fokkema was born on August 20th, 1980, in Alphen aan den Rijn, but moved to Hoofddorp at age three and lived there most of his adult life. After completing the VWO in Heemstede, he studied Life Sciences in Amsterdam and, after the University of Applied Sciences in Amsterdam closed the program, in Utrecht. Ivo completed his studies in 2002 with an internship at the department of Clinical Genetics at the LUMC in Leiden, attempting to optimize a new method for high-throughput diagnostics for several common hemoglobinopathies. During his internship, he was more interested in developing the tool that interpreted the lab results than the lab work required to obtain these results, so Ivo left the lab and joined dr. Johan den Dunnen's group at the department of Human Genetics to build a tool for publishing genetic variants on dr. den Dunnen's web page about muscular dystrophies.

Starting with simple Excel macros to create DNA variant tables for web pages based on data in Excel, Ivo worked toward becoming a self-educated software developer and iteratively rebuilt the static variant listings into a database project to collect, curate, and display genetic variants and relevant patient data, for any gene in the human genome. He named this software "Leiden Open Variation Database", or LOVD for short, and released it as an open-source project to the world. LOVD quickly became the most popular variant database software worldwide, and today still powers the largest network of curated gene variant databases in the world.

In 2013, Ivo started the development of a tool for the Clinical Genetics department at the LUMC for whole-exome sequencing analysis of trios and single patients, built on top of LOVD. This package, called LOVD$^+$, gained the interest of the Melbourne Genomics Health Alliance, who wished to aid its development. In 2016–2018, Ivo skipped three consecutive European winters and visited the summers in Melbourne instead, meeting the MGHA team and working with them on new LOVD$^+$ features. In Melbourne, around 10 different institutes started using LOVD$^+$ for whole-exome sequencing analysis on patients with rare diseases and for training personnel on variant curation. LOVD$^+$ is still used today in the LUMC's Clinical Genetics department.

Ivo started his PhD trajectory in 2018 in parallel to his full-time position at the LUMC after it became clear that prof. dr. den Dunnen's retirement required a postdoc to lead the LOVD project. During his PhD trajectory, Ivo focused on improving data sharing between systems by developing new or improving existing Application Programming Interfaces (APIs), data exchange formats, data licensing, guidelines for variant descriptions, data validation tools, and automation. To achieve this, Ivo collaborates with a large number of database curators, researchers, and diagnostic labs, partially through committees set up by the Human Genome Organization (HUGO). Ivo is an active member of HUGO's HGVS Variant Nomenclature

Committee (HVNC), Reporting of Sequence Variants Working Group (Variants in Journals committee, VIJ), and the HUGO Forum. Ivo chairs HUGO's Gene/Disease Specific Database Advisory Council (GDSDBAC). A large part of the results of these endeavors are described in this dissertation.

Ivo has been working as acting PI of the LOVD project since 2021. After obtaining his PhD, Ivo will continue as PI of the LOVD project, setting up collaborations with publishers to automate data validation and submission to LOVD and working towards improving the integration of LOVD data in national and international diagnostic pipelines.

List of publications

1. Coline H.M. van Moorsel, Erwin E. van Wijngaarden, **Ivo F.A.C. Fokkema**, Johan T. den Dunnen, Dirk Roos, Rob van Zwieten, Piero C. Giordano, and Cornelis L. Harteveld. *β-Globin mutation detection by tagged single-base extension and hybridization to universal glass and flow-through microarrays.* European Journal of Human Genetics 2004; 12(7):567–573.

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3. Annemieke Aartsma-Rus, Judith C.T. van Deutekom, **Ivo F.A.C. Fokkema**, Gert Jan B. van Ommen, and Johan T. den Dunnen. *Entries in the Leiden Duchenne muscular dystrophy mutation database: an overview of mutation types and paradoxical cases that confirm the reading-frame rule.* Muscle and Nerve 2006; 34(2):135–144.

4. Jorge Oliveira, Isabel Soares-Silva, **Ivo F.A.C. Fokkema**, Ana Gonçalves, Alexandra Cabral, Luísa Diogo, Lucía Galán, António Guimarães, Isabel Fineza, Johan T. den Dunnen, and Rosário Santos. *Novel synonymous substitution in* POMGNT1 *promotes exon skipping in a patient with congenital muscular dystrophy.* Journal of Human Genetics 2008; 53(6):565–572.

5. Annemieke Aartsma-Rus, **Ivo F.A.C. Fokkema**, Jan Verschuuren, Ieke Ginjaar, Judith van Deutekom, Gert Jan van Ommen, and Johan T. den Dunnen. *Theoretic applicability of antisense-mediated exon skipping for Duchenne muscular dystrophy mutations.* Human Mutation 2009; 30(3):293–299.

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7. Astrid A. Out, Carli M.J. Tops, Maartje Nielsen, Marjan M. Weiss, Ivonne J.H.M. van Minderhout, **Ivo F.A.C. Fokkema**, Marie Pierre Buisine, Kathleen Claes, Chrystelle Colas, Riccardo Fodde, Florentia Fostira, Patrick F. Franken, Mette Gaustadnes, Karl Heinimann, Shirley V. Hodgson, Frans B.L. Hogervorst, Elke Holinski-Feder, Kristina Lagerstedt-Robinson, Sylviane Olschwang, Ans M.W. van den Ouweland, Egbert J.W. Redeker, Rodney J. Scott, Bruno Vankeirsbilck, Rikke Veggerby Grønlund, Juul T. Wijnen, Friedrik P. Wikman, Stefan Aretz, Julian R. Sampson, Peter Devilee, Johan T. den Dunnen, and Frederik J. Hes. *Leiden Open Variation Database of the MUTYH gene.* Human Mutation 2010; 31(11):1205–1215.

8. **Ivo F.A.C. Fokkema**, Peter E.M. Taschner, Gerard C.P. Schaafsma, J. Celli, Jeroen F.J. Laros, and Johan T. den Dunnen. *LOVD v.2.0: the next generation in gene variant databases.* Human Mutation 2011; 32(5):557–563.

9. Myles Byrne, **Ivo F.A.C. Fokkema**, Owen Lancaster, Tomasz Adamusiak, Anni Ahonen-Bishopp, David Atlan, Christophe Béroud, Michael Cornell, Raymond Dalgleish, Andrew Devereau, George P. Patrinos, Morris A. Swertz, Peter E.M. Taschner, Gudmundur A. Thorisson, Mauno Vihinen, Anthony J. Brookes, and Juha Muilu. *VarioML framework for comprehensive variation data representation and exchange.* BMC Bioinformatics 2012; 13(1):254.

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13. Nahuel A. Paolini, Kat S. Moore, Franca M. di Summa, **Ivo F.A.C. Fokkema**, Peter A.C. 't Hoen, and Marieke von Lindern. *Ribosome profiling uncovers selective mRNA translation associated with eIF2 phosphorylation in erythroid progenitors.* PloS one 2018; 13(4):e0193790.

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17. **Ivo F.A.C. Fokkema**, Mark Kroon, Julia A. López Hernández, Daan Asscheman, Ivar Lugtenburg, Jerry Hoogenboom, and Johan T. den Dunnen. *The LOVD3 platform: efficient genome-wide sharing of genetic variants.* European Journal of Human Genetics 2021; 29(12):1796–1803. (Chapter 4 of this thesis)

18. Peter J. Freeman, John F. Wagstaff, **Ivo F.A.C. Fokkema**, Garry R. Cutting, Heidi L. Rehm, Angela C. Davies, Johan T. den Dunnen, Liam J. Gretton, Raymond Dalgleish. *Standardizing variant naming in literature with VariantValidator to increase diagnostic rates.* Nature Genetics 2024; 56:2284–2286. (Chapter 6 of this thesis)

19. Reece K. Hart, **Ivo F.A.C. Fokkema**, Marina DiStefano, Ros J. Hastings, Jeroen F.J. Laros, Rachel L. Taylor, Alex Wagner, Johan T. den Dunnen. *HGVS Nomenclature 2024: improvements to community engagement, usability, and computability.* Genome Medicine 2024; 16:149. (Chapter 5 of this thesis)

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