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PERSPECTIVE

The development and growth of EJHG 1995–2017

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This year, the European Society of Human Genetics celebrates its 50th anniversary. On this occasion, the European Human Genetics Conference returned to Copenhagen, where the first ESHG meeting was held in 1967.

In the early nineties I was one of the faculty members of the European School of Human Genetics organised by Giovanni Romeo. In 1991 I was heading the Department of Human Genetics at Leiden University Medical Center (LUMC), succeeding Peter Pearson who left to head the Genome Data Base and OMIN in Baltimore. We were involved, among others, in Duchenne Muscular Dystrophy and Huntington's Disease research. Together with Johan den Dunnen, I had developed pulsed field electrophoresis to size the DMD gene, and yeast artificial chromosome (YAC) cloning of Human DNA to study the DMD gene in more detail. These advanced techniques were much needed, as we had found the DMD gene to span over 2.3 Mb, with deletions of up to 1.2 Mb and more. I taught several of these genomics technologies in the Sestri course. Hans Dauwerse, from our group, had developed fluorescent in situ hybridisation (FISH), notably a multi-colour chromosome paint that allowed chromosomes to be distinguished in up to 12 different colours. I won't easily forget the 1992 Sestri course when I presented this, building up from three to six to 12 colours; the whole room with 130 or so pupils, faculty and technical people, broke out in spontaneous applause when the 12 differently coloured chromosome pairs hit the screen.

One of the high points of the Sestri course was the 'Cinque Terre walk', an afternoon outing, usually on Wednesday, where we all took the train to the farthest of five little coastal villages nearby and from there walked back to the nearest village, or sometimes the other way around, and then took the train back. The Sestri course was co-organized by Victor McKusick, and, despite his age, he generally joined this walk, together with his wife Anne. I remember that in 1993 or 1994, since they did not keep up with the stamina of the young turks in the front, Sue Naylor and I kept them company. Then we decided to play the front runners a trick: in the second village, we went to the station and took the train to the third one. We knew that just before this village, there was a tiny bar at the top of the hill with a spectacular sea view. This would typically be overrun well past capacity by the horde of thirsty geneticists, after the most strenuous walk of all. So the four of us left the train, went back up on the village's stairs, sat in the bar in all quietness, ordered our Cokes, put our feet on the table, and when the young turks finally came chugging around the bend, we asked them 'What took you so long?'.

In April 1995, I was walking the Cinque Terre with Jean Louis Mandel, a good friend and also a faculty member, who had just arrived. He had plunged straight into the walk with his everyday shoes and his satchel and having a bit of a hard time, so once again we took a train back to Sestri at an earlier village and spent the rest of the afternoon on a terrace talking shop. Then we teamed up with Marcus Pembrey for dinner in one of the tiny restaurants in the main street leading towards the castle. During dinner Marcus mentioned that the ESHG board was having a problem. Giovanni Romeo, who had founded the EJHG in 1992, had indicated that it was time after 3 years to look around for a successor as Editor in Chief. Marcus asked us both if we knew of potential candidates. Only half seriously, I ventured that they might want to consider myself, as I was familiar with writing and editing, also outside of science, having been a pop music critic in a national newspaper from 1968–1975 and editor of a computer journal from 1984–1989. And that my wife was in publishing too, and that I generally liked this type of work. Not expecting to hear anything back, I was both honoured and scared when he got back to me around a month later with the ESHG board offering me this job. But I accepted.

I was in the lucky situation that the sister Department to our Human Genetics at LUMC, that of Radiation Genetics, was the seat of the journal *Radiation Genetics* and their publishing assistant, Jane Pleging-Vale, had half a day per week available to also 'do' the editorial office for the EJHG.

After a transition period, in which I got to know the systems with much help from Giovanni and the people from the Karger publishing company, Linda Haas and Pamela Koppay-Pinto, I was on my own. With a stack of manuscript print outs, I would sit down in the afternoons on the terrace of a nearby pub in my home town, Amsterdam, reading papers from A–Z, thinking of reviewers and wondering how on earth I could get some sort of line and direction into the EJHG contents. It has been the great merit of our authors and reviewers that this managed to shape—and keep shaping—itself. I remember comparing it at the time to building a house without precise drawings, with bricks people were handing you over your shoulders. And remarkably enough it still feels like that.

At the time *EJHG* was a bimonthly journal, and while initial and final decisions were made by the Editor-in-Chief, its reviewing was commissioned by a team of around ten Section Editors from all over Europe with different fields of expertise. In 1997, as our publishing contract with Karger ran out, we ventured onto the publishing market to assess our options, and among the interested parties Nature Publishing Group offered us a very comprehensive deal aiming at rapid growth. Considering all the extras of having such a well-known and esteemed scientific publisher, we decided to make the jump and signed with NPG for 1998. With submissions rising steeply due to major technological strides in genetics and genomics; in 1999, we were already producing eight issues per year and publishing 700 pages. In my early years, I would regularly ask the ESHG board if they could sponsor, from part of their Journal income, 50–100 pages over the yearly page budget to keep pace with the submissions and thus keep

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growing and maximise the benefit for authors and readers. In 2000, we fulfilled the long-standing wish of the ESHG by becoming a monthly. That year the ESHG sponsored no less than 200 extra pages over the 800-page budget, and thus for the first time reached the 1000-page boundary. At the time, we had an acceptance rate of 45–50%. In consultation with the board we felt it necessary to assist genetics publishing from all over Europe, and in order not just to become the 'West-European Journal of Human Genetics', we were perhaps a little more lenient in assessing papers of authors from less privileged regions than from technologically advanced places. However, after 2000, we soon left this bias behind, considering that passing the same high bar was in the best interest of all authors, the Journal and the Society. Currently, we have an acceptance rate of around 25% and publish 1834 pages, with authors from all over the world.

The strong growth of submissions in human genetics undoubtedly had much to do with its increasing impact on health care and broader society. This was heralded by the tremendous advances of the human genome project. The year 2000 was truly a landmark year: not even a year after the completion of the first human chromosome sequence, 22, the complete genome sequence was published, from 1–22, X and Y, by two groups in competition.[1,2] Notably, this all took place while the entire DNA-marker genetics field was barely two decades old. I noted in an editorial in January 2000 that the first healthy baby born following DNA marker prenatal diagnosis couldn't be older than 14!

After the publication of the genome sequence, 'medical genomics' took off in earnest. While in the 1990s, major discoveries were largely limited to well-equipped big centres and collaborations, the first effect of the genome sequence was to benefit many laboratories worldwide in the pursuit of their favourite disease gene. The 2001 EJHG editorial foresaw that '*Much painstaking mapping, sequencing and puzzling to piece together even the `wildtype' form of the culprit-at-hand, will now be replaced by a few mouse clicks and a little wait*'. *Looking back after 16 years, EJHG has made good on its promise to 'cover the diagnostic, prognostic and therapeutic advances, but also the studies and viewpoints on the ethical, socio- political, legal and economic aspects of this maturing field*'.

An important part of this has been the inclusion in EJHG of the PPPC Policy documents [see elsewhere in this issue]. After extensive deliberations in the committee, approval, in principle, by the ESHG Board, and a consultation round of the ESHG membership, typically two documents are generated and published in EJHG: the actual guidelines and an in-depth background document. Initially both were published in print, the guidelines in a regular issue and the background document in a supplement. To save page space and production time, recently the background documents have started to be published online only.

In 2004, a slew of in-depth articles in major journals literally 'filled in the gaps': reducing them from 150.000 in the draft genome to only ~350 in the 'finished' version, with average continuity up to 40 Mb from the initial 80 kb. The (protein-coding) gene count was further revised downward from 31.000 to 22.500.[3] One almost wondered what, other than genes that make humans embark on sequencing genomes, did set us apart from flies and worms. Well, of course the complexity wasn't in the parts, but in the architecture, and this was not including noncoding RNAs, which we now know to have major regulatory and evolutionary impact.

Major attention was also given to gene birth and death in the evolutionary context,[4] and the new field of segmental duplications[5,6] and genomic copy number polymorphism,[7,8] meanwhile broadened into genomic structural variation,[9] hit centre stage. In an *EJHG* commentary in December 2004,[10] relating copy number variability in chromosome 5[11] to human pathology, I wrote as a personal recollection: '*Chromosome 5 is a classroom example of what segmental duplication may do to an everyday piece of single-copy DNA. I still lively remember the fierce debate on the Mediterranean Ile des Embiez, in the early nineties, among members of the SMA community on the clinical criteria to distinguish SMA types I—III, or alternatively types I—VIII. If this community had known what they were getting themselves into, one wonders if they would have had the courage*'.

In those days, the early SNP association studies to find common disease risk factors were typically based on the hypothesis of qualitative and not quantitative polymorphism. We noted: "*So far, the prevailing idea, among scientists as well as the public at large, is that the source of common diseases is the combined effect of 'poorer' and 'better' genes. It would significantly ease our task as geneticists in communicating with the public, if we could put this in the perspective of more or fewer copies of perfectly normal genes*".

Notably, as early as 2004, this EJHG commentary closed as follows: 'With the scaling up of biology, the lagging of a well-funded European central database infrastructure undermines the core of European medical and biological research: the easy, continued access to a rising tide of high-density data. Without flourishing, well-accessible resources, which are being actively codeveloped in parallel to other regions in the world, we will not gain the required momentum in turning the data into insights'. Only today, with the increasing attention to the Big Data and the FAIR principles (Findable, Accessible, Interoperable and Reusable), and the advent of infrastructures like BBMRI and ELIXIR, this begins to take hold with the funding bodies in the European Research Area—and still not in a very sustainable way.

Not long thereafter, increasing sequencing power unleashed the search for risk factors in earnest. A steep rise started in 2007, and in the following years, the literature was, if anything, dominated by ever larger GWAS studies. In a 2008 comment, 'GWAS here, last year',[12] I came rather to the defense of these types of studies in the light of criticism from the more biologically and mechanistically inclined: '*For those of us who have had—or still have—difficult times with grant applications of a non-hypothesis-driven, prospective nature, who were seen to be out on fishing expeditions, the advent of the exploratory, high-throughput approaches is especially welcomed. Indeed, one might maliciously wonder if we are not (temporarily, in this field and pending subsequent functional studies) close to the ultimate consumption date of the Popperian approach of hypothesis-driven research? For was not a main goal of this to unravel the truth in the most efficient, that is, plausible way, faced with a daunting scarcity of collectible data? Well, if it becomes cheaper to just collect all data required, than to run after a hundred consecutive, plausible, but wrong hypotheses, starting with a hypothesis becomes an economic futility. The hypothesis as a guiding principle is then replaced by a truism: if one does not throw away anything before thoroughly assessing its irrelevance, one will always find what one is looking for...*'

Fortunately, the GWAS studies have borne fruit and are nowadays delivering valuable clinical utility, like the description of the role of PCSK-9 variants in cholesterol metabolism by Helen Hobbs and coworkers,[13] which is now the basis of several next-generation cholesterol-lowering medications.

The rest, as one says, is history: EJHG keeps growing and its impact factor is slowly on the rise—though with ups and downs, in 2016 4.58 and in 2017 4.28. Occasionally, we hit the headlines, with genetics from the distant past, such as an African Y-chromosome in Yorkshire;[14] the more recent past, like the refutation of Naundorf's claim to be the son of Louis XVI and Marie-Antoinette;[15] or even

non-genetic transgenerational effects.[16] New categories were developed, alongside the existing ones of Articles, Short Reports, Reviews and Policy papers, such as Practical Genetics and Clinical Utility Gene Cards, and recently, we initiated the possibility of sending in, in addition to your manuscript, a short video, for the 'EJHG-tube' on the website. This allows authors to outline more in their own words what made them embark on their research and what are in their view the salient outcomes. As of 2014, we have had the manuscripts checked for the accessibility of the data through widely-recognised public databases—not just their institution's website as half of these will have vanished or changed their name in a few years' time—and their adherence to the HGVS variant nomenclature guidelines. All of this with the aim of improving 'FAIR'ness: findability, accessibility, interoperability and reusability.

Now, in 2017, we have arrived at the moment that, when a patient reports in the clinic without an obvious and easily confirmed diagnosis, the first thing to be considered is a whole-exome sequence (WES), or even a whole-genome sequence (WGS) instead of a battery of time consuming lab tests. Unfortunately, a concomitant development relates to the technical and psychosocial conundrum of our ability to find more variants that we understand… That brings a new type of research in focus, related to, if and how to report back uncertain information to patients and parents. To assist in this field, EJHG has recently compiled a web focus with our papers published on this subject during the last two years http://www.nature.com/ejhg/focus/res-gen/index.html. Undoubtedly, insights will advance greatly with the increase in 'population genomics projects' and biobanking studies and registry activities in rare and common diseases, as these will be the true test-beds of the penetrance of rare variants of unknown significance.

In short: stay tuned to EJHG!

Finally, as many of the actors in the fabric of the ESHG are being highlighted in this issue, let me gratefully acknowledge here all the people without whom the EJHG would not have become what it is now. First and foremost, all our contributing authors and reviewers. Then, the real hard work of coordinating the reviewing process and assisting with the decision process, which is done by a team of 25 highly dedicated Section Editors, who have invaluably contributed to the diversity and strength of the EJHG. In addition, we owe our organizational robustness to the Production Editors at *Nature*, for many years now Helen Smith, but also her predecessors, with all of whom we had dozens of monthly contacts. I also wish to thank Mary Rice for assistance with the compilation and editing of the present History issue. And last but not the least, the single person with whom all of us, from authors and reviewers through Section Editors and Production Editors, have had the most frequent contacts of all, I thank the unstinting, modest and even-tempered support of our assistant Jane Pleging-Veale at the EJHG Editorial Office.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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His main professional aim is to help improving diagnosis, therapy and prevention of rare and common diseases and he has contributed to the finding of the gene defects and disease mechanisms of several rare diseases notably Duchenne Muscular Dystrophy and Huntington Disease. His group was an early developer of gene mapping and mutation detection techniques and molecular diagnostics. More recently his group pioneered the exon-skipping approach for therapy of Duchenne Muscular Dystrophy, Huntington and several other diseases.