Editorial

Ingo Kurth*

Peripheral Neuropathies

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Peripheral neuropathy, the result of damage mostly to peripheral motor and sensory nerves, often causes muscle weakness, numbness and pain, usually beginning in the hands and feet. Autonomic nerves that control blood pressure, heart rate, digestion and bladder function may also be affected. Peripheral neuropathies, or polyneuropathies, are relatively common with an estimated prevalence in the general population of 2.5 %, and as high as 8 % at over 55 years of age. The causes are manifold and include immunological, metabolic, toxic or infectious as well as hereditary etiologies with many different genes being involved. In this issue the journal *medizinischegenetik* deals with the different aspects of heritable neuropathies.

Can the duplication of a small part of the genome be disease-relevant? For a long time, this hypothesis was considered absurd and much persuasion was needed to convince the scientific community (and especially the editors of several top journals!) that a duplication of a gene – *PMP22* – is the cause for a common autosomal dominant trait, a polyneuropathy termed Charcot-Marie-Tooth (CMT) type 1A. *Vincent Timmerman and James R. Lupski*, the latter himself being affected by a subtype of CMT, report in a personal view on their groundbreaking independent finding on the first recurrent, submicroscopic DNA duplication 30 years ago [1, 2]. As Vincent Timmerman reports, such a genetic Odyssey could easily end with the offer to take home a rabbit when visiting a CMT patient with a forester as husband.

Sabine Rudnik-Schöneborn, Michaela Auer-Grumbach, and Jan Senderek give an update on the genetics of CMT-disorders (also: Hereditary Motor and Sensory Neuropathies, HMSN) and distal Hereditary Motor Neuropathies (dHMN). *PMP22* duplications are still the major cause for CMT, however, dozens of additional genes have turned out to be involved in CMT and more are still being discovered, as illustrated by the recent finding of mutations in *SORD* as common dHMN/CMT2-associated gene [3]. In terms of medical care and genetic counselling of affected women, the question whether there is a higher complication rate in pregnancy and delivery in CMT neuropathy, and if there is a possible influence of the pregnancy on a patient's muscles and nerves is answered by *Sabine Rudnik-Schöneborn and Miriam Elbracht*. They present the results from a cohort of 148 pregnancies of CMT patients.

30 years after the tedious discovery of the *PMP22* duplication, sequencing of whole exomes or genomes is possible and becomes increasingly cheaper and faster. Leading research nations now want to make greater use of genomic medicine to improve patient care and stimulate the development of new drugs. Whilst Germany lags far behind these international developments [4], the United Kingdom in 2012 initiated a 340 million euro project with the aim of sequencing 100,000 genomes [5]. *Menelaos Pipis, Henry Houlden, and Mary M. Reilly* report on their experiences with the "Genomics England" project from their perspective on CMT diseases. In this context it should be noted that in the German health care system routine next-generation sequencing diagnostics is still only reimbursable to up to 25 kilobases of coding sequence per year (GOP 11513). This is clearly backward, medically unreasonable and an adjustment is long overdue!

A subgroup of heritable neuropathies predominantly affects peripheral sensory nerves. This can result in excessive or chronic burning pain, as for example in Small Fiber Neuropathies (SFN) or Familial Episodic Pain Syndromes (FEPS). However, different mutations – sometimes within the same gene – can also lead to a complete lack of pain perception, resulting in permanent injuries and poorly healing wounds (Hereditary Sensory Autonomic Neuropathies, HSAN). *James J. Cox, C. Geoffrey Woods, and Ingo Kurth* summarize the current knowledge in this regard. Rare diseases with congenital insensitivity to pain (CIP) are at the same time of interest from a pharmacological perspective because they reveal target molecules for general pain therapies [6].

A neuropathy often does not occur as a single disease symptom, but as part of a neuromuscular or multisystemic disorder. *Sebahattin Cirak, Uluc Yis, Hülya-Sevcan Daimagüler, and Abubakar Moawia* describe syndromes with neuropathy being only part of a more complex disease. They also discuss the emerging model of a mutational burden and the possibility of a non-Mendelian multilocus inheritance in a number of yet "unsolved" neuropathy patients.

***Korrespondenzautor: Ingo Kurth,** Institute of Human Genetics, Medical Faculty, RWTH Aachen University, Aachen, Germany, E-Mail: ikurth@ukaachen.de

Recently, 5q–associated Spinal Muscular Atrophy (SMA), a disease of lower motor neurons, has come into focus due to novel therapeutic possibilities. The approval of Nusinersen as an antisense-oligonucleotide therapy for the treatment of SMA has shown how a profound (genetic) understanding of a disease can consequently be translated into therapy. On the other hand, the discussion on a gene replacement therapy for SMA (Zolgensma®/Novartis) has caused many controversies about what a drug may cost, about compassionate use, and finally about the idea of playing a lottery, where the drug is randomly raffled off to families. Many of these pitfalls should be avoided when further drugs for rare diseases are approved.

However, such therapeutic options argue for the implementation of a comprehensive newborn screening (the carrier frequency for SMA is approximately 1 in 35!) to allow an earlier therapy and thereby maximize the benefit for affected infants. *Katja Eggermann, Dieter Gläser, Angela Abicht, and Brunhilde Wirth* review the current status on this topic.

In summary, this issue of the journal *medizinischegenetik* highlights the broad spectrum of diseases of the peripheral nervous system, the genetics and underlying mechanisms of which are increasingly well understood, but also the new questions that arise from this progress.

Literatur

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Ingo Kurth
Institute of Human Genetics, Medical Faculty, RWTH Aachen University, Aachen, Germany
ikurth@ukaachen.de