## Editorial

Thomas Eggermann* and Bernhard Horsthemke

# Imprinting disorders: novel findings and translation into diagnostics and management

https://doi.org/10.1515/medgen-2020-2041

Imprinting disorders (ImpDis) are a group of human congenital diseases involving one or more genes that are expressed from only the paternal or the maternal allele. Currently ~100 imprinted human genes and twelve imprinting disorders have been recognized. From a clinical point of view, imprinting disorders are a heterogeneous group of diseases, which mainly affect growth, neurodevelopment and metabolism, but there is a considerable phenotypic overlap between some disorders (e. g. the Prader-Willi, Temple and Schaaf-Yang syndromes). Though each ImpDis is rare, they altogether affect approximately 7,500–10,000 patients in the European Union. Furthermore, it is likely that ImpDis are much more common than realised and therefore there is an increasing demand for ImpDis testing. The reasons for this underestimation are diverse, ranging from clinical heterogeneity, non-specificity of key features, clinical as well as molecular overlaps, to (epi)genetic mosaicism as a diagnostic challenge. Though many of these limitations are far from being overcome, there is a remarkable progress in diagnosing ImpDis. The recent identification of new molecular disturbances, the implementation of comprehensive molecular and clinical diagnostic tools, and novel approaches towards causal therapies already contribute to a more directed management of the patients and their families.

In this issue, we highlight novel insights into mechanisms of genomic imprinting and epigenetic regulation, which have been obtained in the last years. Prawitt and Haaf not only review the basic mechanisms of imprinting and the major types of molecular alterations, but they also refer to recently identified trans-acting factors causing aberrant imprinting marks. These fetal and maternal factors with an impact on early embryonic development are currently in the focus of research, but first results from these studies are already in use in genetic and reproductive counselling.

Each imprinting disorder can have multiple genetic or epigenetic causes, and in some patients these are present in a mosaic form. Furthermore, different causes carry different recurrence risks, which also depend on the sex of the transmitting parent. All of this makes molecular testing and reporting challenging (Beygo et al., in this issue). The interpretation of the test results has to consider the broadness of expectable disturbances, but also the growing number of unexpected findings. Consequently, laboratories offering molecular testing for ImpDis have to be aware of unusual and even – at first glance – contradictory results, and should update their knowledge continuously. Finally, diagnostics of ImpDis should be embedded in a suitable quality management system, and both wet lab results and reporting should be evaluated in external quality assessment schemes.

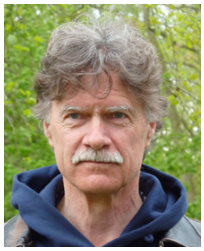
The molecular heterogeneity is reflected by the broad spectrum of clinical features in ImpDis patients (Elbracht et al., in this issue). The "classical" ImpDis (i. e. Prader-Willi syndrome (PWS), Angelman syndrome (AS), Beckwith-Wiedemann syndrome (BWS)) are defined by a combination of specific features, but in daily practice it turns out that a significant number of patients does not exhibit the typical phenotypes: The severity of features ranges considerably, often non-specific features are present, the phenotypes change from the neonate period to adulthood, and the phenotypes can overlap. Furthermore, additional phenotypes associated with aberrant imprinting patterns can be expected as the identification of new ImpDis shows. To face these clinical challenges, clinical scoring systems have been suggested for some of these disorders, but these systems can only partly face the clinical diagnostic challenges. Thus, the decision on the application of a suitable diagnostic test often remains difficult, and therefore a broad imprinting testing has to be considered in specific situations. As is well known from monogenetic disorders, the precise characterisation of the underlying molecular defect is a prerequisite for genetic counselling.

The clinical management of ImpDis patients is a further major challenge, as common clinical guidelines have

***Corresponding author: Thomas Eggermann,** Institut für Humangenetik, Medizinische Fakultät der RWTH Aachen, Aachen, Deutschland, e-mail: teggermann@ukaachen.de
**Bernhard Horsthemke,** Institut für Humangenetik, Universitätsklinikum Essen, Universität Duisburg-Essen, Essen, Deutschland, e-mail: bernhard.horsthemke@uni-due.de

only rarely been available before 2015 (see Elbracht et al., in this issue), therefore therapeutic strategies were inconsistent and unsatisfactory. With the publication of consensus guidelines or comprehensive reviews on treatment of the major ImpDis (PWS, AS, BWS, SRS, Pseudohypoparathyreoidism) first steps towards a standardised treatment (and diagnostics) have been undertaken, but further improvements, standardisation and dissemination are required. These improvements are currently based on conventional therapeutic and monitoring strategies (i. e. growth hormone treatment in PWS and SRS), but novel approaches to cure ImpDis are under development (see Horsthemke and Zechner). One promising approach is aimed at compensating for the loss of an active allele by unsilencing the inactive allele on the other chromosome. Already in 2020, the first clinical study in Angelman syndrome with antisense oligonucleotides has started. It remains to be seen, how efficient these and other "epigenetic therapies" will be.

**Thomas Eggermann**
Institut für Humangenetik, Medizinische Fakultät der RWTH Aachen, Aachen, Deutschland
**teggermann@ukaachen.de**



**Bernhard Horsthemke**
Institut für Humangenetik, Universitätsklinikum Essen, Universität Duisburg-Essen, Essen, Deutschland
**bernhard.horsthemke@uni-due.de**