Genetics of Growth

Jan M. Wit^a Primus E. Mullis^{b, c}

^aDepartment of Pediatrics, Leiden University Medical Center, Leiden, The Netherlands; ^bDivision of Paediatric Endocrinology, Diabetology and Metabolism and ^cDepartment of Clinical Research, University Children's Hospital, Bern, Switzerland

This first 'special topic issue' of *Hormone Research in Paediatrics* is completely dedicated to genetics of growth, a rapidly developing area of paediatric endocrinology. The main reason of this fast development is the stormy progress of genetic techniques. We believe that in the coming years genetic studies on growth and other areas of paediatric endocrinology will generate numerous novel insights, particularly due to the rapidly increasing availability of next generation sequencing. Since a few years whole exome sequencing is available at a reasonable price, and it is expected that whole genome sequencing will soon follow. These techniques will be primarily used for unravelling the genetic causes of congenital disorders, and recent examples illustrate that this can lead to the discovery of novel gene defects of known clinical syndromes such as mutations in *SRCAP* causing Floating-Harbor syndrome [1], and even to uncovering novel endocrine syndromes such as *IGSF1* deficiency syndrome [2]. However, it is expected that next generation sequencing will soon also be used in genome-wide association studies, which so far have been based on multiple single nucleotide polymorphisms [3].

This special topic issue can be roughly divided into four parts. The first part consists of a paper describing the role of zinc in the process of secretory granule biogenesis

in somatotrophs, illustrating that for proper growth hormone (GH) secretion more is needed than a normal *GH1* gene, and that multiple genes are involved in the full trajectory from *GH1* transcription to pulsatile GH secretion. The second part describes patients with mutations in various parts of the GH-IGF axis, including *GH1*, *GHR*, *IGFALS* and *IGF1R*, and ends with a paper describing a website containing clinical, biochemical and genetic information about presently known genes in this axis. The third part consists of two papers describing clinical features of large groups of patients with relatively frequent (epi)genetic defects: *SHOX* defects and Beckwith-Wiedemann syndrome. Finally, the fourth part contains two papers using association analysis and pharmacogenetics in relation to growth and growth response to GH.

We wish to emphasize three important messages from the papers in this issue. In the first place, the clinician should be aware of the limitations of a genetic test that was carried out at a certain time, and should consider re-testing if the genetic techniques have been changed or if novel defects have been published in parts of the gene that were not investigated in the patient's DNA. This is even more indicated if the clinical presentation is typical for that particular gene defect. In this issue this message is illustrated for type II GH deficiency (usually caused by

splicing mutations in *GH1*) and a specific intronic mutation in *GHR*. It shows that close collaboration between clinicians and geneticists is becoming even more necessary than it already was. Secondly, we wish to stimulate clinicians as well as geneticists to enter clinical and genetic data into web-based databases, so that more information will become available about the spectrum of the phenotype and genotype. For many genes it will become increasingly difficult to publish reports on single mutations. Thirdly, the papers on *SHOX* defects and Beckwith-Wiedemann syndrome illustrate the importance of collecting data on patients with genetic syndromes for improving the criteria for genetic testing and for performing additional investigations.

We hope that this special topic issue of *Hormone Research in Paediatrics* will be a pleasure to read, and will help the paediatric endocrinologist to become up to date on the genetics of growth.

Disclosure Statement

J.M.W. has served on advisory boards for Tercica, Ipsen, Pfizer, Prolog, Teva and Biopartners, and has received speaker honorariums from Pfizer, Lilly, Ipsen and Ferring. No grants or fellowships were received supporting the writing of the paper.

P.E.M. declares that no financial or other conflict of interest exists in relation to the content of the article.

References

- Hood RL, Lines MA, Nikkel SM, Schwartzentruber J, Beaulieu C, Nowaczyk MJ, Allanson J, Kim CA, Wieczorek D, Moilanen JS, Lacombe D, Gillissen-Kaesbach G, Whiteford ML, Quaio CR, Gomy I, Bertola DR, Albrecht B, Platzer K, McGillivray G, Zou R, McLeod DR, Chudley AE, Chodirker BN, Marcadier J, Majewski J, Bulman DE, White SM, Boycott KM: Mutations in *SRCAP*, encoding SNF2-related CREBBP activator protein, cause Floating-Harbor syndrome. *Am J Hum Genet* 2012;90:308–313.
- Sun Y, Bak B, Schoenmakers N, van Trotsenburg AS, Oostdijk W, Voshol P, Cambridge E, White JK, Le TP, Gharavy SN, Martinez-Barbera JP, Stokvis-Brantsma WH, Vulsma T, Kempers MJ, Persani L, Campi I, Bonomi M, Beck-Peccoz P, Zhu H, Davis TM, Hoken-Koelega AC, Del Blanco DG, Rangasami JJ, Ruivenkamp CA, Laros JF, Kriek M, Kant SG, Bosch CA, Biermasz NR, Appelman-Dijkstra NM, Corssmit EP, Hovens GC, Pereira AM, den Dunnen JT, Wade MG, Breuning MH, Hennekam RC, Chatterjee K, Dattani MT, Wit JM, Bernard DJ: Loss-of-function mutations in *IGSF1* cause an X-linked syndrome of central hypothyroidism and testicular enlargement. *Nat Genet* 2012;44:1375–1381.
- Lango AH, Estrada K, Lettre G, Berndt SI, Weedon MN, et al: Hundreds of variants clustered in genomic loci and biological pathways affect human height. *Nature* 2010;467:832–838.