

BRINGING THE LATEST IN PAEDIATRIC ENDOCRINOLOGY TO YOU

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Welcome

It is always inspiring to see the list of the year's ESPE Award winners (pages 4 and 5), who come from the breadth of our field and all career stages. It is a joy to work with such knowledgeable, talented colleagues and we congratulate them all. Do make your nominations for the 2023 ESPE Awards by 10 December.

Being reunited with so many colleagues at the recent 60th Annual Meeting of ESPE was truly exciting. On page 11, you will find a reminder of how delegates can continue to access the superb meeting content, while on page 3 you can read about the launch of the YES Group at ESPE 2022, and the result of elections at the Annual Business Meeting.

This issue gives insights into the genetics of disease. On page 7, Márta Korbonits provides a valuable summary of the genetics of pituitary tumours. Of course, these tumours are incredibly diverse; Márta's article explains how they may be categorised, as well as which genetic alterations are most common, and how the associated conditions may present.

Diana Le Duc and Antje Körner consider the genetics of childhood obesity on page 9. They also look forward to a potential era of precision medicine and personalised treatment, made possible by the detection of genetic variants.

Extensive genetic studies of monogenic diabetes and congenital hyperinsulinism have been undertaken by V Mohan and his team, and he shares his findings on page 10. Understanding the aetiology of these diseases has ensured that his patients receive the most appropriate treatment.

I am delighted to welcome two new members to our Editorial Board: Meera Shaunak and Chris Worth. They will bring fresh perspectives and valuable contributions.

Sadly, I am nearing the end of my happy 6-year term as Editor. As you will see elsewhere on this page, there is a chance for one of you to take over from me early in 2023. I can only say how much I have enjoyed working with the wonderful Editorial Board and Production Team. Creating each issue is immensely satisfying, and I didn't realise that being on a Committee could be so much fun! I strongly encourage you to put your name forward and make your mark on the evolution of *ESPE News*.

Happy reading!

Sarah Ehtisham
Editor, *ESPE News*

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OPPORTUNITIES

Could you be our next Editor?



This is your chance to lead the friendly, lively Editorial Board of *ESPE News*, your Society's well-respected newsletter. The current Editor, Sarah Ehtisham, completes her second term of office in March 2023. We welcome applications from ESPE members for an initial 3-year appointment.

Applicants should be organised, comfortable with medical writing and keen to disseminate interesting information from across the global paediatric endocrine community. You will have the opportunity to oversee the next phase of the newsletter's evolution, as it becomes more accessible and more interactive.

The Editorial Board, which is chaired by the Editor, meets quarterly (usually virtually) and communicates by email at other times. They are supported by the Sub-editor, who manages the production process, and by the ESPE Team.



Apply by **12 December 2022**



For further information, contact the ESPE Team at espe@eurospe.org

Your chance to host Science Symposium 2024

Could you be the host of our next ESPE Science Symposium, sharing the latest scientific knowledge on a special interest and bringing together scientists and clinicians in paediatric endocrinology? We welcome applications from any ESPE member and their team/group.



Apply by **1 April 2023**



See www.eurospe.org/education/espe-science-symposium-apply-to-host

RESOURCES

Screening for type 1 diabetes

The ESPE Position Statement on screening for type 1 diabetes has been published in *Hormone Research in Paediatrics*. It highlights the benefits of screening for the disease in the general population, such as reducing the incidence of diabetic ketoacidosis at onset, preserving β -cell function and possibly offering secondary prevention to the affected children. The Position Statement will facilitate further discussion of this approach.



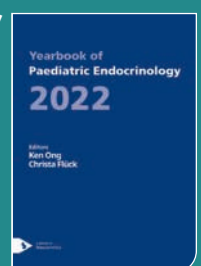
See www.eurospe.org/news/article/18804 and <https://doi.org/10.1159/000525824>

Yearbook of Paediatric Endocrinology

Remember that the 2022 *Yearbook of Paediatric Endocrinology* is now available. This provides a valuable summary of major advances in the field during the last year, with commentaries.



Download the Yearbook at www.espeyearbook.org



YOUR SOCIETY

ESPE Council update

At the Annual Business Meeting in September, Anita Hokken-Koelega was re-elected as President of ESPE for a further term of 3 years. Rasha Hamza was re-elected as Education and Training Committee Chair and Stefano Cianfarani was elected as Clinical Practice Committee Chair. Mehul Dattani has rejoined Council, as Annual Meeting Host 2024.

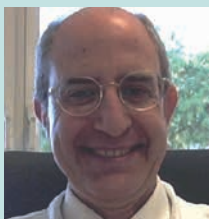
A call for nominations for Council vacancies in 2023 will be issued in December, so look out for the email in your inbox.



Anita Hokken-Koelega



Rasha Hamza



Stefano Cianfarani



Mehul Dattani

YES Group launch



The Young ESPE (YES) Group welcomed close to 100 young endocrinologists from across the world to its very successful launch at ESPE 2022 in Rome, Italy.

Events for members included a meeting on Young Endocrinologist Opportunities in Paediatric Endocrine Research, arranged by the ESPE Science Committee, and a social networking evening in Rome.

Sign up to the YES Group at the link below and follow ESPE on Facebook and Twitter for further YES Group events and opportunities.



Join the YES Group at www.eurospe.org/about/yes-group



Members of the YES Group

GRANTS

Apply for ESPE grants now

IFCAH-ESPE Grant for Congenital Adrenal Hyperplasia

The IFCAH-ESPE Grant is dedicated to improving understanding and management of congenital adrenal hyperplasia. Selected research projects will receive up to €150 000.



Apply by **15 January 2023**



Find out more at www.eurospe.org/grants-awards/grants/ifcah-espe-grant

Early Career Scientific Development Grant

This grant of up to €2500 enables paediatric endocrinologists and basic scientists to gather information and experience regarding a specific research issue or laboratory technique.



Apply by **31 January 2023**



Find out more at www.eurospe.org/grants-awards/grants/early-career-scientific-development-grant

ESPE Research Unit

This collaborative research grant provides up to €50 000 per year for 2 years and aims to foster, facilitate, co-ordinate and identify topics for high quality research in paediatric endocrinology, for both physicians and scientists.



Apply by **15 February 2023**



Find out more at www.eurospe.org/grants-awards/grants/research-unit

EVENTS

Winter School



mareandmare/Stock

ESPE Winter School supports paediatricians who are either established in, or intending to develop a deep and continuing interest in, paediatric endocrinology and diabetes. The next Winter School will take place in Belgrade, Serbia, on 25 February–2 March 2023.



Apply by **1 December 2022**



Find out more at www.eurospe.org/education/winter-school

Summer School

ESPE Summer School provides senior trainees with up-to-date teaching on selected topics in the field, and promotes discussions between younger and more senior paediatric endocrinologists. The 2023 Summer School will take place on 18–20 September 2023 at Rockanje, near The Hague, The Netherlands, just before ESPE 2023.



Look out for applications opening in **December 2022**



See www.eurospe.org/education/summer-school

ESPE Award Winners 2022

We congratulate the many award winners who received their prizes at the ESPE Annual Meeting in Rome, Italy, in September.

ESPE Andrea Prader Prize



Juliane Léger (Paris, France) received the ESPE Andrea Prader Prize, in recognition of her lifetime achievement in teaching and research, outstanding leadership and overall contribution to the field of paediatric endocrinology.

ESPE Outstanding Clinician Award



Abdullah Bereket (Istanbul, Turkey) was presented with the ESPE Outstanding Clinician Award, in recognition of his outstanding clinical contribution to the practice of paediatric endocrinology.

ESPE International Research Award



Fernando Cassorla (Santiago, Chile) received the ESPE International Research Award. This is presented to an outstanding paediatric endocrinologist from a country outside Europe and the Mediterranean basin.

ESPE International Outstanding Clinician Award



Mitchell Geffner (Los Angeles, CA, USA) received the ESPE International Outstanding Clinician Award, in recognition of his contribution and commitment to clinical paediatric endocrinology in a country outside Europe and the Mediterranean basin.

ESPE Research Award



Mehul Dattani (London, UK) received the ESPE Research Award, in recognition of research achievements of outstanding quality in basic endocrine science or clinical paediatric endocrinology.

ESPE Young Investigator Awards



Dulanjalee Kariyawasam



Angela Lucas-Herald

These awards for paediatricians who are still in training or who have been in a senior (principal investigator) role for no more than 5 years were presented to the following, in recognition of their scientific publications:

- **Dulanjalee Kariyawasam** (Paris, France), whose award lecture was entitled 'Lopinavir-ritonavir impairs adrenal function in infants/New genetics in congenital hypothyroidism'
- **Angela Lucas-Herald** (Glasgow, UK), whose award lecture was entitled 'Vascular dysfunction and increased cardiovascular risk in hypospadias'.

Nominations are now open for our 2023 Awards



Nominate your colleagues by
10 December 2022



www.eurospe.org/grants-awards/awards

ESPE awards

Henning Andersen Prizes (supported by Novo Nordisk)

These awards for the most highly rated abstracts were presented to:

- **Christian Roth** (Seattle, WA, USA) for 'Development of anorexigenic and glucoregulatory chimeric peptides'
- **Ledjona Toni** (Prague, Czech Republic) for 'The genetic landscape of children born small for gestational age with persistent short stature'.



Christian Roth



Ledjona Toni

ESPE Hormone Research in Paediatrics Prizes (supported by Karger)

These prizes for the best original papers published in *Hormone Research in Paediatrics* were presented to:

- **Laetitia Martinerie et al.** (Paris, France) for 'Fertility of women treated during childhood with triptorelin (depot formulation) for central precocious puberty: the PREFER Study' *Hormone Research in Paediatrics* 2020 **93** 529–538 (best original paper)
- **Annalisa Deodati et al.** (Rome, Italy) for 'CRK haploinsufficiency is associated with intrauterine growth retardation and severe postnatal growth failure' *Hormone Research in Paediatrics* 2021 **94** 456–466 (best 'Novel Insights from Clinical Practice' paper).



Laetitia Martinerie



Annalisa Deodati

IFCAH-ESPE Grants

The following awards were presented for research into congenital adrenal hyperplasia (CAH):

- **Alexander Ian** and **Lara Graves** (Sydney, Australia) for 'Genomic editing as a therapeutic approach to congenital adrenal hyperplasia' (€150 000 for 3 years)
- **Andreas Schedl** (Nice, France) for 'Adrenocortical cells and organoids derived from human iPSCs' (€150 000 for 3 years).

President's Poster Awards

This year's prizes for the best posters at the meeting were awarded for the following abstracts:

- 'Efficacy and safety of once-weekly somatrogen in pediatric subjects with growth hormone deficiency: lack of impact of anti-drug antibodies' by **Cheri Deal et al.** (Canada/USA)
- 'Aromatase inhibitor (anastrozole) versus placebo delays bone age maturation in prepubertal children with Silver–Russell or Prader–Willi syndrome and pathological adrenarche' by **Marie-Noëlle Dufourg et al.**, collected by **Irène Netchine** (France)
- 'Impaired gonadal function among pediatric Fanconi anemia patients following hematopoietic stem cell transplantation' by **Jane Koo et al.**, collected by **Jonathan Howell** (USA)
- 'Conditional *Pten* knockout in mouse osteoprogenitor cells impacts bone structure and turnover' by **Judith Lorenz et al.** (Germany)
- 'SF1next Study: spectrum of SF-1/*NR5A1* gene variants in this large international cohort' by **Idoia Martinez de Lapiscina et al.** (Switzerland/Spain/Belgium).



Cheri Deal



Irène Netchine



Jonathan Howell



Judith Lorenz



Idoia Martinez de Lapiscina

ESPE Research Fellowship (supported by Novo Nordisk)

This Fellowship, which enables talented young scientists, investigators and paediatric endocrinologists to conduct research at leading institutions worldwide, has been awarded to:

- **Terence Garner** (Manchester, UK) for 'Utilising novel markers of cortisol replacement for the management of paediatric adrenal insufficiency', supervised by Adam Stevens, Philip Murray and Peter Clayton at the University of Manchester, UK, and University of Gothenberg, Sweden (€140 000 for 2 years)
- **Jonna ME Männistö** (Kuopio, Finland) for 'Identifying new genetic mechanisms of congenital hyperinsulinism with whole genome sequencing', supervised by Sarah Flanagan at the University of Eastern Finland, University of Helsinki and Exeter Centre of Excellence for Diabetes Research (€140 000 for 2 years).

ESPE Research Unit

Jarmo Jääskeläinen (Finland), **Christa Flück** (Switzerland), **Anders Juul** (Denmark), **Kati Hanhineva** (Finland), **Timo Lakka** (Finland), **Jani Liimatta** (Switzerland) and **Therina Du Toit** (Switzerland) have been awarded the ESPE Research Unit, which supports collaborative research among members, for their project entitled: 'Unravelling the mystery of adrenarche: comprehensive steroid and metabolome profiling of the event and its association with growth and puberty' (€100 000).

Bringing you recent highlights from the world of research

Sexual dimorphism in fibrosis in a model of NASH

One of the known risk factors for progression from non-alcoholic fatty liver disease to non-alcoholic steatohepatitis (NASH) is male sex. The mechanisms responsible for this probably involve oestrogen signalling, since women in menopause or with Turner's syndrome, who have low levels of natural oestrogen, are less protected from developing NASH. The molecular pathways involved in this phenomenon, however, still need to be clarified.

Montefusco *et al.* generated mice lacking sphingosine kinase 1 (*SphK1*) in hepatocytes and compared the effects on the liver of a high fat diet between male and female knockout mice. They discovered that female mice lacking *SphK1*, although protected from hepatic inflammatory processes, were more prone to severe fibrosis.

Mechanistically, this was due to a lack of the *SphK1* product sphingosine-1-phosphate, which is released from hepatocytes upon oestrogen exposure. Sphingosine-1-phosphate is needed to prevent aberrant expression of *Col1a1* which leads to fibrosis. This pathway could potentially be targeted to treat NASH in both males and menopausal women.



Read the full article at Montefusco *et al.* 2022
Molecular Metabolism 62 101523

Dulaglutide treatment of youths with type 2 diabetes

This double-blind, multicentre, placebo-controlled randomised trial studied 146 youths (10–18 years) with obesity and type 2 diabetes, who were managed using lifestyle modification with or without metformin and/or basal insulin. They were treated with dulaglutide or placebo once-weekly, and followed for 52 weeks.

At week 26, glycated haemoglobin (HbA1c) was reduced by 0.8% in the group receiving dulaglutide versus an increase of 0.6% in the group receiving placebo. A higher percentage of participants in the dulaglutide arm had HbA1c < 7% (51% versus 14%; $P < 0.01$) and a lower fasting blood glucose (−18.9 mg/dl versus +17.1 mg/dl; $P < 0.01$). The effect of dulaglutide was sustained until 52 weeks. However, the degree of HbA1c reduction was lower than in week 26.

Gastrointestinal side effects were reported more often in the dulaglutide group, and one participant discontinued dulaglutide.



Read the full article at Arslanian *et al.* 2022
New England Journal of Medicine 387 433–443

Biphasic pattern of reproductive hormones in female infants

Ljubicic conducted a prospective longitudinal study to evaluate the dynamics of the hypothalamic-pituitary-gonadal hormonal axis in infant girls, and to establish continuous age-specific reference ranges for the most clinically relevant reproductive hormones from birth until 1 year of age.

Healthy pregnant women were recruited as part of the study, and 98 healthy, term, female infants were followed up by means of six examinations, including blood and urine samples, during the first year of life.

Reference ranges were established for luteinising hormone (LH), follicle-stimulating hormone (FSH), inhibin B, anti-Müllerian hormone (AMH), oestrone (E1), oestradiol (E2) and sex hormone-binding globulin (SHBG). A biphasic pattern was observed for all hormones in the first 6 months of life: the first peak was around postnatal days 15–27, followed by a second peak at around days 107–125 for inhibin B, AMH, E1, E2 and SHBG, and days 164–165 for LH and FSH.



Read the full article at Ljubicic *et al.* 2022
Journal of Clinical Endocrinology & Metabolism
107 2598–2605

Neuroimaging in central precocious puberty

It is clear that girls with central precocious puberty (CPP) who present under 6 years of age should undergo neuroimaging. However, the requisite for brain imaging in girls with CPP in the 6–8-year age range has been questioned, with a low rate of imaging abnormalities found in previous studies.

Fava and colleagues have now published a retrospective cohort study of 112 girls aged 6–8 years of age with CPP, who all had brain MRI between 2005 and 2019. This study found normal MRI scans in 47 girls (42%), but 54 girls (48%) had hypothalamic-pituitary or other abnormalities, and 11 girls (10%) had brain tumours. The girls with brain tumours had a higher luteinising peak in a gonadotrophin-releasing hormone test, with larger pituitary diameters than those with normal scans.

The authors conclude that MRI scanning remains important in girls aged 6–8 with CPP, with a significant number having intracranial lesions despite the absence of other neurological signs.



Read the full article at Fava *et al.* 2022
Journal of Clinical Endocrinology & Metabolism
107 e4132–e4143

Genetics of pituitary tumours

Márta Korbonits summarises our latest understanding of the genetic changes associated with pituitary tumours.



Márta Korbonits



While most pituitary tumours are sporadic, in about 5% of cases they can arise in a familial setting

Pituitary tumours can come in many shapes and forms, the most common being tumours of anterior pituitary hormone-producing cells (pituitary adenomas or pituitary neuroendocrine tumours) or craniopharyngiomas.

Pituitary adenomas were not one of the typical genetic diseases that the previous generation of doctors learned about at medical school. How much this has changed in the 21st century, especially as regards paediatric patients with pituitary tumours!

To present a short overview of the current state of the art, we will discuss DNA sequence changes¹ (see Figure), concentrating on paediatric cases, while leaving epigenetics for another time.

Categorisation

Different categories of genetic changes could occur:

- (a) **germline** – inherited or *de novo*, for example, as in most patients with multiple endocrine neoplasia type 1 (MEN1) syndrome
- (b) **mosaic** – affecting some parts of the body, for example in McCune–Albright syndrome
- (c) **somatic** – only affecting the tumorous tissue, for example *USP8* mutations in corticotroph tumours.

Another way to classify genetic diseases that affect the pituitary gland is according to whether:

- (a) only the pituitary gland is affected (i.e. ‘isolated’ disease, familial isolated pituitary adenoma due to *AIP* mutations, X-linked acrogigantism due to *GPR101* duplication, or familial disease due to currently unknown genes), or
- (b) there is syndromic disease (e.g. MEN1 and 4, Carney complex, McCune–Albright syndrome and, rarely, pituitary adenomas associated with familial paragangliomas/phaeochromocytomas, DICER1 syndrome and Lynch syndrome).

Identification of causative mutations

While most pituitary tumours are sporadic, in about 5% of cases they can arise in a familial setting. The identification of causative mutations through genetic testing allows a search for other manifestations of the disease in syndromic cases, with cascade screening of relatives at risk. This results in relief of anxiety regarding disease in non-carriers, and earlier diagnosis and treatment in carriers, with potentially targeted therapies for that particular disease.

Acromegaly and gigantism

Acromegaly is the most common genetically determined pituitary disease. Gain-of-function somatic mutations in the *GNAS* gene may occur in up to 40% of sporadic somatotroph adenomas, typically in older patients, while mosaic disease with *GNAS* mutations (McCune–Albright syndrome), pituitary hyperplasia or tumour occurs at a young age. Familial cases with pituitary adenomas also predominately present with acromegaly, especially in young patients.

Indeed, in half of all cases with pituitary gigantism, the disease develops due to identifiable genetic alterations² in *AIP*, *GPR101*, *GNAS*, *PRKAC1A*, *MEN1*, *CDKN1B* and *MAX*. The tallest-ever giants have duplication of *GPR101*, an orphan G protein-coupled receptor, with misregulation of its expression, usually *de novo* germline in females and mosaic in males, although three families with mother-to-child transmission have now also been described.

However, the most common genetic cause for pituitary gigantism, in one-third of cases, is a mutation in *AIP*, often presenting with macroadenomas with suprasellar and extrasellar extension and requiring multimodal treatment. Nonetheless, with combination treatment, further excessive height gain can be avoided and long term complications reduced.

Interestingly, patients with optic gliomas associated with neurofibromatosis type 1 may also have growth hormone (GH) excess and tall stature, probably due to dysregulation of the GH-releasing hormone (GHRH)–GH axis, rather than a pituitary tumour. We also should remember that in rare cases of MEN1 syndrome, pancreatic tumours secreting GHRH can also lead to pituitary hyperplasia and gigantism/acromegaly, even in childhood.

Corticotroph and other tumours

The most common genetic alteration in Cushing’s disease is a gain-of-function somatic *USP8* mutation; this is seen in over a third of paediatric cases, mostly girls. *USP8* has also been described as a germline mutation associated with developmental problems. Somatic *CABLES1*, *USP48* and *TP53* (coding for p53) cases have also been described.

Infants, usually under the age of 2 years, with large pituitary blastomas due to *DICER1* mutation show

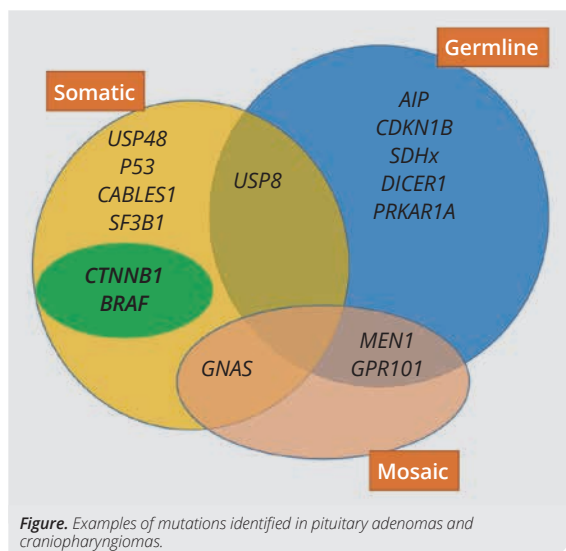


Figure. Examples of mutations identified in pituitary adenomas and craniopharyngiomas.

particularly severe disease, although with better outcomes in the last decade.³ Patients with MEN1 and MEN4 syndromes (due to germline loss-of-function *MEN1* and *CDKN1B* mutations) can develop corticotrophinomas. In Carney complex (germline loss-of-function *PRKAR1A* mutations), we usually see somatotroph or somatomammotroph hyperplasia or tumour, but corticotrophinomas have now also been described. In adults, especially aggressive, large, corticotroph tumours have been seen in a few patients with Lynch syndrome due to germline mutations in mismatch repair genes (*MLH1*, *MSH2*, *PMS2*) and with somatic *ATRX* mutations.

The genetic background of prolactinomas in childhood is usually related to *MEN1* and *AIP* mutations, either as part of a known kindred or in around 5% of what are apparently simplex cases. MEN1-related paediatric cases show a high percentage of invasive (Hardy 3 or 4) adenomas, especially in males (males 54%, females 14%). MEN4 and SDH-related cases have also been described, primarily in adults.

Thyrotrophinomas and clinically non-functioning cases rarely have a known genetic background, especially in children. However, we note that small, non-functioning lesions can be seen in patients carrying *MEN1* or *AIP* mutations. The relevance of these is currently unclear, but they often behave similarly to incidentalomas.

Craniopharyngiomas have now also been found with an identifiable genetic background in the majority of the cases. These have, until now, always been somatic mutations: the classical *BRAF p.V600E* mutation in papillary craniopharyngiomas and *CTNNB1* (coding for β -catenin) in the majority of adamantinomatous craniopharyngiomas,

with a few reported cases of *ACP* mutations in the WNT- β -catenin pathway.

In summary

All in all, the current consensus suggests that patients with paediatric-onset pituitary adenomas would benefit from genetic testing for germline mutations, with the highest chance of finding abnormalities in patients with somatotroph tumours and prolactinomas and, of course, in those with familial disease.

Currently, somatic mutation testing in the tumour tissue is not routinely indicated, but options are already there, for example, for craniopharyngiomas, and it is a subject for further research. The British Society for Paediatric Endocrinology and Diabetes and the Children's Cancer and Leukaemia Group have recently completed two comprehensive guidelines for craniopharyngiomas⁴ and for pituitary adenomas. These will hopefully be helpful in guiding clinicians in the management of these often challenging patients.

Colleagues who have patients with paediatric or familial pituitary adenomas are welcome to contact me for discussion.

Márta Korbonits

Centre for Endocrinology, William Harvey Research Institute, Barts and the London School of Medicine, Queen Mary University of London, UK

References

1. Denes & Korbonits 2021 *Endocrine* **71** 663–674.
2. Rostomyan et al. 2015 *Endocrine-Related Cancer* **22** 745–757.
3. Liu et al. 2021 *Journal of Clinical Endocrinology & Metabolism* **106** 351–363.
4. Children's Cancer and Leukaemia Group 2021 *Craniopharyngioma: Guideline for the Management of Children and Young People aged <19 years* www.cclg.org.uk/guidelines/endocrine/craniopharyngioma.

Test yourself with e-Learning

The ESPE–ISPAD e-Learning web portal is an interactive resource for up-to-date information on paediatric endocrinology and diabetes mellitus, offering over 200 learning modules. It's freely accessible, simply by registering at the website.



For more details, see www.eurospe.org/education/e-learning



Register for free access at www.espe-elearning.org

This issue's clinical case highlight

Does Jimmy have diabetes? Jimmy is a 11-year-old boy with a body mass index Z-score of +2.7 (see chart, right). He participated in an obesity intensified weight loss programme and has lost around 20kg over the last 3 months. He has tiredness, thirst and lack of energy. A random capillary glucose measurement was 21mmol/l (378mg/dl). His grandmother has type 2 diabetes.

What is your diagnosis?

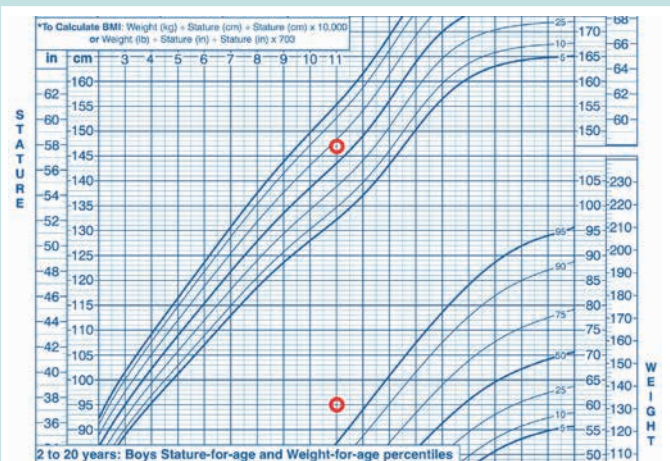
Type 2 diabetes

Type 1 diabetes

Stress-induced hyperglycaemia

Both type 1 and type 2 diabetes are possible options

For the answer, see **page 11**.



Jimmy's stature and weight plotted with respect to age-related percentiles.

Genetic testing in severe childhood obesity

Our understanding of the genetics underlying obesity is gradually developing, as Diana Le Duc and Antje Körner explain.



Diana Le Duc



Antje Körner

“

The wider availability of genetic testing in a high throughput set up will contribute to a better understanding of the genetic landscape underlying obesity”

Childhood obesity is rising at alarming speeds. The prevalence of overweight and obesity among children and adolescents aged 5–19 years has risen from 4% in 1975 to more than 18% in 2016.¹ Although, in the past, obesity was mainly regarded as a problem of the Western world, almost half of the children under 5 who had overweight or obesity in 2019 lived in Asia.¹

Obesity often develops in early childhood and, once manifest, has a high propensity to persist.² Obesity is a disease and never should be viewed as a failure to adhere to a healthy lifestyle or diet. Childhood obesity can profoundly affect children's social and emotional well-being and has tremendous consequences for physical health, with disorders impacting metabolic, cardiovascular, skeletal, neuronal, digestive, pulmonary and renal systems.³

There is a high heritability of body mass index, attributed mostly to multiple common, but also to rare, genetic variants.⁴ Accordingly, there are two main forms of obesity: common polygenic obesity and syndromic obesity. The latter includes monogenic syndromic obesity and obesity syndromes associated with neurodevelopmental disorders.⁵

Approximately 7% of severe cases are thought to be determined by highly penetrant genetic variants.⁶ This is considered to be an underestimate of the monogenic causes of obesity; our estimation is expected to improve with newer methods and wider availability of genetic testing.⁴ The criteria for genetic testing are: cases of extreme early-onset obesity (before 5 years of age) and clinical features of genetic obesity syndromes (in particular extreme hyperphagia) and/or a family history of extreme obesity.⁴

Non-syndromic monogenic obesity

Non-syndromic monogenic obesity is predominantly caused by pathogenic point variants in genes involved in the leptin–melanocortin pathway.⁶ These children typically present with hyperphagia and increased food-seeking behaviour. Many of them will also suffer from delayed puberty. The most frequently affected gene is *MC4R*. Affected individuals generally have a tall stature and severe hyperinsulinaemia.⁷

Leptin (*LEP*) deficiency and leptin receptor (*LEPR*)-associated obesity are, unlike cases associated with *MC4R*, autosomal recessive diseases that can present with short stature. Setmelanotide, an *MC4R* agonist, has only recently been approved for clinical use in children over 6 years and is currently in trial for younger ages. For individuals with disruption in the leptin–melanocortin pathway, setmelanotide appears to be a very promising treatment.

Syndromic monogenic obesity

There are many neurodevelopmental delay syndromes that are associated with obesity. Probably the most common

cause of syndromic obesity is Prader–Willi syndrome, an imprinting disorder.⁷ Other syndromes, like Bardet–Biedl and Alstrom, are autosomal recessive diseases with an overlapping phenotypical spectrum including retinal dystrophy and neurosensory deficits, which are caused mainly by point variants in the responsible genes. Copy number variations can also cause disease associated with obesity, such as the Smith–Magenis or 16p11.2 microdeletion syndrome.

The future of genetic diagnosis for obesity

According to current recommendations, genetic diagnostics of children with severe obesity should entail next generation sequencing of the genes postulated to be involved in the clinical phenotype. Yet, in the very limited examples mentioned above, we show that clinical diagnostics is not possible most of the time, given the non-specific symptoms. Thus, gene panels miss about 10% of disease-causing variants, which can be detected by whole exome sequencing.⁷ Moreover, using an exome-first approach, we can also detect copy number variations responsible for microdeletion/microduplication syndromes.

For Prader–Willi syndrome, we may still need methylation analyses, although exome sequencing can also give hints in respect to uniparental disomies.

Trio exome sequencing, in which the exomes of the parents are analysed together with the child, has been proven to increase diagnosis rates and gene discovery for intellectual disability.⁸ We argue that, in extreme cases of obesity without a family history, trio exomes may improve discovery of novel causal variants.

With the costs of next generation sequencing continually dropping, the wider availability of genetic testing in a high throughput set up will contribute to a better understanding of the genetic landscape underlying obesity, help to achieve rapid diagnosis of patients with known forms of monogenic or syndromic obesity, and also give hope for the discovery of causes of obesity which are so far unknown. Eventually, variant detection could pave the way for precision medicine and personalised treatment.

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References

1. World Health Organization 2021 *Obesity and Overweight* www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.
2. Geserick et al. 2018 *New England Journal of Medicine* **14** 1303–1315.
3. Sahoo et al. 2015 *Journal of Family Medicine & Primary Care* **4** 187.
4. Styne et al. 2017 *Journal of Clinical Endocrinology & Metabolism* **102** 709–757.
5. Hinney et al. 2022 *Nature Reviews Endocrinology* **18** 623–637.
6. Farooqi & O'Rahilly 2008 *Nature Clinical Practice Endocrinology & Metabolism* **4** 569–577.
7. Malhotra et al. 2021 *Journal of Pediatric Genetics* **10** 194–204.
8. Vissers et al. 2016 *Nature Reviews Genetics* **17** 9–18.

Monogenic diabetes among children

V Mohan relates his extensive experience in interpreting the causes of monogenic diabetes among paediatric patients.



V Mohan

Children and youth with a monogenic form of diabetes, caused by the mutation of a single gene, are often misdiagnosed as having type 1 diabetes, which can lead to them being asked to take insulin injections throughout their lives. Several types of monogenic diabetes have been identified.

Maturity-onset diabetes of the young (MODY)

This type of diabetes affects children or youth, and a family history of diabetes can be traced to three or more generations. There are several subtypes of MODY. In some of these, insulin injections are not necessary and patients can be treated with tablets.

We have conducted molecular genetic studies of monogenic diabetes at the Madras Diabetes Research Foundation, Chennai, India, for over 20 years. Among 96 young onset diabetic patients screened for *HNF1A* gene mutations, nine mutations were identified (9.6%).¹ A novel *HNF1A* gene mutation Arg263His co-segregated with diabetes in a family of 30 individuals.¹

We also screened 87 patients diagnosed with non-type 1 diabetes under the age of 25 years for *HNF4A* gene mutations (MODY 1), and identified three mutations (3.4%).² Subsequent screening of 55 patients for *GCK* gene mutations (MODY 2) led to the identification of two mutations – Met251Thr and Thr206Ala – of which Thr206Ala was novel. The individuals were managed without pharmacotherapy and had non-progressive mild hyperglycaemia.³

Among 50 cases who were clinically suspected of having MODY 5, based on renal abnormalities on ultrasound, such as renal cysts or horseshoe kidney, we identified six (12%) different *HNF1B* gene mutations and whole-gene deletion.⁴ More recently, we used an exome and whole genome strategy to analyse 153 clinically confirmed cases of MODY.⁵ We found MODY 3 (*HNF1A*; 7.2%) to be the most frequent mutation, followed by MODY 12 (*ABCC8*; 3.3%).

HNF1A, *HNF4A* and *ABCC8* are the most frequently observed MODY subtypes in India.

Neonatal diabetes (NDM)

This form of monogenic diabetes affects children below 6 months of age. The two major subtypes are transient NDM, which usually resolves before the first birthday, and permanent NDM, which is lifelong. It is due to genetic defects in pancreatic insulin secretion, and individuals with variants in the *KCNJ11* and *ABCC8* genes can be treated with sulphonylurea tablets.

Children with NDM are also often initially suspected of having type 1 diabetes and given insulin injections. If forms of NDM which respond to tablets are diagnosed, these children can stop insulin and be treated with tablets.

Our group has conducted extensive studies on the genomics of NDM in India. In our first study, we screened a total of 33 unrelated Indian probands with onset of diabetes below 1 year of age for the common genes implicated in NDM, such as *KCNJ11*, *ABCC8* and *INS*. A total of 12 mutations were identified, including *ABCC8* mutations in seven, *KCNJ11* mutations in three and *INS* mutations in two children. Our genetic diagnosis has made it possible to successfully shift some of the children with *KCNJ11* mutations (e.g. Cys42Arg and Arg201Cys) and *ABCC8* mutations (e.g. Val86Ala and Asp212Tyr) from insulin treatment to oral sulphonylurea therapy.⁶

We tried to identify the genotype-phenotype correlation of K_{ATP} channel gene defects in a large series ($n=181$) of Indian patients with permanent NDM. We identified the molecular basis of K_{ATP} -NDM in 39 of these patients (22%); 20 had *KCNJ11* mutations and 19 had *ABCC8* mutations. Three patients with *KCNJ11* mutations had developmental delay with DEND syndrome (a triad of developmental delay, epilepsy and NDM). In patients with *ABCC8* mutations, developmental delay was seen in 7 out of 19 (36.8%). This study demonstrates the importance of genetic screening in children suspected of having permanent NDM.⁷

Congenital hyperinsulinism (CHI) with hypoglycaemia

Congenital hyperinsulinism is characterised by persistent hypoglycaemia in infants and children. CHI occurs as a consequence of inappropriate and unregulated secretion of insulin by pancreatic β -cells. It typically presents in newborn babies and infants as severe and persistent hypoglycaemia, and is a major cause of hypoglycaemia-related brain injury and mental retardation. The molecular basis for CHI involves mutations in *ABCC8*, *KCNJ11*, *GLUD1*, *GCK*, *HADH*, *SLC16A1*, *HNF4A* and *UCP2*. Hence, the response to treatment heavily depends on genetics.

We identified molecular abnormalities in 45% (10 of 22) of children with CHI.⁸ Mutations were identified in 88.9% of diazoxide-unresponsive cases and in 11.1% of children who were treated with diazoxide. Genetic testing assists in the proper treatment of CHI.

Conclusion

Our experience with the genomics of MODY and NDM exemplifies the need to bring the genomics of diabetes to the diabetic clinic. This will help in tailoring drug treatment and is an important step in the precision diagnosis and treatment of diabetes.

V Mohan

Chairman and Chief of Diabetology, Dr Mohan's Diabetes Specialities Centre, and Director, Madras Diabetes Research Foundation Gopalapuram, Chennai, India

References

1. Radha et al. 2008 *Journal of Clinical Endocrinology & Metabolism* **94** 1959–1965.
2. Anuradha et al. 2011 *Clinical Genetics* **80** 541–549.
3. Kanthimathi et al. 2014 *Diabetes Technology & Therapeutics* **16** 180–185.
4. Kanthimathi et al. 2015 *Annals of Human Genetics* **79** 10–19.
5. Mohan et al. 2018 *BMC Medical Genetics* **19** 22.
6. Jahnvi et al. 2013 *Clinical Genetics* **83** 439–445.
7. Gopi et al. 2021 *Pediatric Diabetes* **22** 82–92.
8. Jahnvi et al. 2014 *Annals of Human Genetics* **78** 311–319.

“Our experience exemplifies the need to bring the genomics of diabetes to the diabetic clinic”



Success for ESPE 2022

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Thank you to everyone who attended, submitted abstracts or presented at the 60th Annual Meeting of ESPE. You made ESPE 2022 an overwhelming success. It was great to see so many people come

together after 3 years away. We are particularly grateful for the hard work of ESPE President Stefano Cianfarani, Vice-President Mariacarolina Salerno and their Local Organising Committee, and to the Programme Organising Committee, led by Nils Krone (UK).

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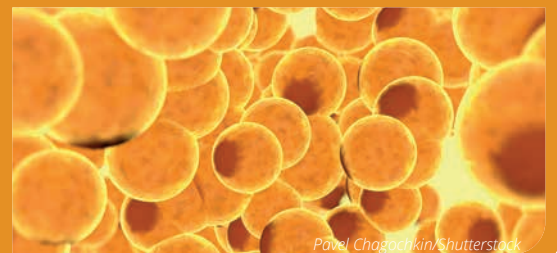
8th ESPE Connect Webinar

14 December 2022, 16.00 CET

The next ESPE Connect Webinar will be on **Management of Lipodystrophy.**



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ESPE e-Learning

Answer to the case query on [page 8](#).

What is his diagnosis?

Both type 1 and type 2 diabetes are possible options.

Based on the current information, both type 1 and type 2 diabetes are possible diagnoses. Type 1 diabetes mellitus is more common in prepubertal children. However, with Jimmy's morbid obesity and the family history, type 2 diabetes mellitus should also be considered.

For further reading see

www.espe-elearning.org/goto.php?target=lm_4291&client_id=espe.

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JANUARY

IFCAH-ESPE Grant applications – 15 January 2023

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