Invaluable Role of Consanguinity in Providing Insight into Paediatric Endocrine Conditions: Lessons Learnt from Congenital Hyperinsulinism, Monogenic Diabetes, and Short Stature

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**Abstract**

Consanguineous families have often played a role in the discovery of novel genes, especially in paediatric endocrinology. At this time, it has been estimated that over 8.5\% of all children worldwide have consanguineous parents. Consanguinity is linked to demographic, cultural, and religious practices and is more common in some areas around the world than others. In children with endocrine conditions from consanguineous families, there is a greater probability that a single-gene condition with autosomal recessive inheritance is causative. From 1966 and the first description of Laron syndrome, through the discovery of the first \(K_{\text{ATP}}\) channel genes \(ABCC8\) and \(KCNJ11\) causing congenital hyperinsulinism (CHI) in the 1990s, to recent discoveries of mutations in \(YIPF5\) as the first cause of monogenic diabetes due to the disruption of the endoplasmic reticulum (ER)-to-Golgi trafficking in the \(\beta\)-cell and increased ER stress; positive genetic findings in children from consanguinity have been important in elucidating novel genes and mechanisms of disease, thereby expanding knowledge into disease pathophysiology. The aim of this narrative review was to shed light on the lessons learned from consanguineous pedigrees with the help of 3 fundamental endocrine conditions that represent an evolving spectrum of pathophysiological complexity – from CHI, a typically single-cell condition, to monogenic diabetes which presents with uniform biochemical parameters (hyperglycaemia and glycosuria), despite varying aetiologies, up to the genetic regulation of human growth – the most complex developmental phenomenon.

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**Introduction**

Five per cent of all live births have genetic disorders that are recognizable until 25 years of age [1]. These genetic disorders are being increasingly diagnosed in the human population due to developments in genetic testing technology and tools such as next generation sequencing (NGS).

The knowledge on the genetic cause of disease allows precise and individualized clinical management, faster diagnosis without the need of invasive diagnostic tests (in...
some cases), prediction of long-term outcome and family planning. The decision on carrying out genetic examination is not only based on the potential therapeutic benefit, but on the feasibility, availability, and cost-effectiveness as well [2]. Prior to the indication of genetic testing, a comprehensive medical history should be obtained; this should include the presence of consanguinity in the family.

Due to the impact that paediatric endocrine disorders can have on a child’s metabolism, electrolyte balance, and growth and development, they represent a substantial part of paediatric morbidity and mortality. However, multiple conditions remain genetically and/or pathophysiologically unexplained.

Positive genetic findings in patients continue to contribute in a significant way towards elucidating the specific pathophysiological mechanisms of disease in complex phenotypes and clarifying genotype – phenotype relationships. Consanguineous families have especially played a role in the discovery of novel genes.

**Consanguinity**

“Consanguinity” or “inbreeding” in population genetics refers to non-random mating where humans mate with others who are more genetically similar, rather than mating at random in the population. Consanguinity is linked to demographic, cultural, and religious practices [3]. These practises served many purposes from ancient times, and are more common in some areas around the world than others, especially in Asia, Africa, and the Middle-East [3]. In modern times, despite increased awareness on the possible health consequences for children of consanguineous families, it has been estimated that over 20% of the world population live in communities which prefer such marriages and that over 8.5% of all children worldwide have consanguineous parents [4].

In a large genetic study performed in Egypt, recessive disorders were found mainly among families with consanguinity (78.8%). Consanguinity was present in 100% of cases of mental retardation and in 92.6% of patients with limb anomalies. Child deaths and stillbirths were more prevalent among children from consanguineous parents when compared to non-consanguineous families as well [4].

The higher frequency of recessive genetic conditions in descendants of consanguineous parents than those of unrelated parents can be attributed to less common alleles manifesting as homozygous. For example, first cousins are predicted to share 1/8th of their genes. Therefore, their progeny will be homozygous (or autozygous) at 1/16th of gene loci. In other words, this means that they will have identical gene copies from each parent at these sites in their genome; these are called “runs of homozygosity” [5]. Thereby, consanguinity represents a substantial genetic burden for the offspring.

If a variant with a heterozygosity frequency of 1 in 100 is considered, there is a 1 in 10,000 chance that both unrelated spouses are carriers (1/100 × 1/100 = 1/10,000). However, if they are first cousins, the chance of both being carriers of this pathogenic variant is 12.5 times higher, thereby the chance is 1 in 800 (1/100 × 1/8 = 1/800). In families with multiple consanguinity, this risk would be even higher [6].

Thus, when a rare and complex monogenic condition is suspected, consanguineous families provide the best chances for novel gene discovery. This has been proven over time in scientific research, even in research into paediatric endocrine disorders, which will be elaborated in the individual sections below.

**Genetic Testing Methods**

Karyotype testing was the only available method for identifying genetic defects until the 1970s. It was possible to identify chromosome aberrations and other structural abnormalities (major translocations, deletions, and inversions) using karyotyping [7]. In 1977, Sanger et al. [8] first described the basic concepts of DNA sequencing as a method to detect point mutations and with the growing popularity of polymerase chain reaction, and this method was widely used allowing amplification of a targeted region of DNA. Sanger sequencing still remains the gold standard for identification of mutations, using the “candidate gene approach” in situations where a specific gene is suspected based on the patient phenotype [7].

In the 1990s, methods of fluorescent in situ hybridization, array comparative genomic hybridization, and linkage analysis were developed. These techniques lead to the discovery of many novel genes, though limited to the detection of large copy number variants [7].

The successful sequencing of the entire human genome in 2001 led to a boom of genetic testing techniques including NGS over the last 2 decades [7]. NGS methods (the present standard when genetically examining patients with complex phenotypes) have unified all abovementioned methods and provide a way to detect all mutation types – single nucleotide variants, insertions or deletions,
structural variants, and copy number variants. However, a vital factor is the selection of the library to be adopted (due to cost and interpretation of results) [9]. The library refers to the extent of the human genome which is examined, and some types of libraries are custom-targeted panels (t-NGS), whole-exome sequencing (WES – which is focused on the 1% protein coding region of the genome), or whole-genome sequencing. T-NGS is a suitable, affordable tool to analyse many patients with a specific diagnosis (which is caused by a known group of genes) if a suitable gene panel has been created and tested [9].

The data obtained by NGS methods need to be analysed by a process called a bioinformatics pipeline [7]. Technical advancements have facilitated the storage and rapid exchange of these data, allowing more efficient analysis (using bioinformatics software capable of gathering comprehensive information about a single variant), consulting of variants, and international collaboration [7, 9]. The gold standard in variant classification is the American College of Medical Genetics and Genomics (ACMG) guidelines, which classifies possible variants in a range from benign to pathogenic [10]. Pathogenic variants are confirmed by Sanger sequencing [8].

Genetic testing methods used in consanguineous families are not largely different from methods used in non-consanguineous families. It is important to note the higher percentage of “runs of homozygosity” in consanguineous individuals and the importance of using homozygous

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**Table 1. Overview of genes mentioned in the manuscript (in the order of mention) and the role of consanguinity in their discovery**

| Gene     | Condition caused             | First published | Method used for gene discovery                      | Role of consanguinity                                           | Ref  |
|----------|------------------------------|-----------------|-----------------------------------------------------|-----------------------------------------------------------------|------|
| ABCC8    | CHI, neonatal diabetes       | 1995            | FISH, direct Sanger sequencing                       | By testing affected individuals from 9 consanguineous families  | [19] |
| KCNJ11   | CHI, neonatal diabetes       | 1996            | Direct Sanger sequencing                             | By testing 1 affected individual from a consanguineous family   | [20] |
| PTF1A    | Neonatal diabetes            | 2003            | Genome-wide linkage analysis                         | By testing 3 affected individuals from a consanguineous family  | [26] |
| YIPF5    | Neonatal diabetes            | 2020            | WGS                                                  | By testing 6 affected consanguineous children                   | [27] |
| WFS1     | Syndromic/neonatal diabetes  | 1998            | Genetic linkage analysis                             | One of 5 tested families was consanguineous                     | [29] |
| EIF2AK3  | Syndromic/neonatal diabetes  | 2000            | Genome-wide linkage analysis                         | By testing done in 2 affected consanguineous children           | [30] |
| SLC19A2  | Syndromic diabetes           | 1999            | Positional cloning and direct Sanger sequencing      | By testing in 6 families, 3 reported a history of consanguinity | [31] |
| IL2RA    | Autoimmune monogenic diabetes| 1997            | RT-PCR and sequencing                               | By testing an affected child from a first-cousin marriage       | [37] |
| LRBA     | Autoimmune monogenic diabetes| 2012            | Genetic linkage analysis                             | By studying 5 affected individuals from 4 consanguineous families| [38] |
| GHR      | Short stature                | 1989            | Genetic linkage analysis                             | By studying affected children from 2 consanguineous families   | [42] |
| GH1      | Short stature                | 1981            | Restriction endonuclease analysis                    | By studying 2 siblings from first-cousin parents               | [46] |
| GHRHR    | Short stature                | 1996            | Direct Sanger sequencing                             | By testing several severe affected members of a consanguineous family | [47] |
| POU1F1   | Short stature                | 1992            | Direct Sanger sequencing                             | By testing an affected child from 1 consanguineous family      | [50] |
| PAPPA2   | Short stature                | 2016            | WES                                                  | One of 2 tested affected families was consanguineous           | [51] |
| PCNT     | Short stature                | 2008            | Genome-wide linkage analysis                         | By testing 4 affected children from 3 consanguineous families  | [55] |

RT, reverse transcriptase; PCR, Polymerase Chain Reaction; WGS, Whole Genome Sequencing; WES, Whole Exome Sequencing; FISH, fluorescent in situ hybridization.
markers (homozygosity mapping) to discover the true genetic cause, especially when having many variants of unknown significance [11].

**Genetic Causes of Specific Disorders: Insight into the Role of Consanguinity**

In this review, we will focus on the 3 groups of paediatric endocrine conditions to highlight the contribution of consanguineous offspring to elucidate their genetic and pathophysiological background (Table 1). These conditions are representative of gradients of pathophysiological complexity, congenital hyperinsulinism (CHI) (a “single cell condition”) being the most straightforward and short stature the most complex. We believe that highlighting the evolution of genetic knowledge in these 3 conditions will provide an overall picture, shared by almost all paediatric endocrine disorders. It is important to note that this review does not include all genes that were discovered with the help of consanguinity; the genes mentioned in detail under each condition were selected due to their prominence and frequency in literature.

**Congenital Hyperinsulinism**

CHI is a heterogeneous genetic condition caused by a primary genetic defect of the pancreatic β-cell resulting in uncontrolled insulin secretion. The incidence of CHI has been estimated to be around 1:2,500 in communities with a higher rate of consanguinity, whereas it is 1:50,000 in non-consanguineous populations [12]. Similar to some other conditions, it has been clearly shown that not only the incidence and genetic causes of CHI, but also the mode of inheritance differs crucially between high- and low-consanguineous areas, with recessive (biallelic) transmission prevailing in high-consanguineous, and monoallelic (dominant/uniparental isodisomy) transmission prevailing in low-consanguineous areas [13]. In CHI, the mode of inheritance directly impacts disease severity, for example, recessive biallelic variants mostly cause (more severe) diffuse CHI and paternally inherited monoallelic variants cause focal CHI, where complete surgical resection of the lesion can be curative [14].

The pancreatic β-cell has the capability to detect the current blood glucose concentration and to produce, store, and release insulin to the bloodstream to maintain a normal blood glucose concentration without the risk of hypoglycaemia [15]. The pathophysiology of CHI is mostly based around genetic defects of β-cell function (shown in Fig. 1). Genetic testing in children with CHI is crucial for confirming diagnosis and tailoring therapy; it may play an important role in genetic counselling, or to explain fatal outcomes in previous offspring [16].

The 2 most common genes known to cause CHI are ABCC8 and KCNJ11 (encoding the SUR1 and Kir6.2 subunits of the ATP-sensitive K+ (K<sub>ATP</sub>) channel in the pancreatic β-cell). Pathogenic variants in these genes cause the most severe forms of CHI, due to the loss of K<sub>ATP</sub> channel activity, persistent membrane depolarization, and continuous insulin release, regardless of the blood glucose concentration [17].

Linkage analysis studies done by Glasser et al. [18] in 1994 in 15 families lead to CHI being mapped to chromosome 11p14–15.1. This confirmed the existence of a Mendelian disease locus for the condition [18]. Twelve were Ashkenazi Jewish families (most came from areas where marriage between second and third cousins was common), and 2 were Arabic (with confirmed consanguinity). In 1995, Thomas et al. [19] mapped SUR to chromosome 11p15.1 by using fluorescent in situ hybridization. By testing affected individuals from 9 consanguineous families, he identified 2 SUR gene splice site mutations, which segregated with disease, thereby confirming the existence of the ABCC8 gene. This signified the start of a deeper understanding into the pathophysiological relationship of the pancreatic β-cell function with K<sub>ATP</sub> channel proteins in CHI.

In 1996, Tomas et al. [20] considered Kir6.2 as another candidate gene for CHI because of its close location to the SUR gene and its necessity for the functioning of the β-cell K<sub>ATP</sub> channel. They found a homozygous missense variant in a child with CHI from a consanguineous family, confirming that variants in gene Kir6.2, currently called KCNJ11, cause CHI as well.

At the point of writing this article, pathogenic variants causing CHI have been found in over 15 genes including GLUD1, GCK, HNF4A, and HNF1A (shown in Fig. 1) [16]. In addition, some genetic syndromes in non-consanguineous populations such as Beckwith-Wiedemann, Kabuki, and Turner syndromes have been associated with hyperinsulinism as well [17, 21].

**Diabetes Mellitus**

Diabetes mellitus (DM) is a group of conditions that result from an absolute or relative insulin deficiency, with or without insulin resistance, which leads to hyperglyca-
mia and glycosuria. In addition to type 1 DM and type 2 DM, which are polygenic diseases with significant environmental components, the less frequent monogenic forms of diabetes continue to help uncover various biological processes causing diabetes due to insufficient insulin production or defects in insulin action [22].

Monogenic diabetes comprises of partially overlapping subtypes, such as neonatal DM (NDM), syndromic diabetes, autoimmune monogenic diabetes, and maturity-onset diabetes of the young. Maturity-onset diabetes of the young follows a pattern of autosomal dominant inheritance while syndromic diabetes is almost exclusively recessive, and NDM and autoimmune monogenic diabetest show both forms of inheritance [23]. The prevalence of monogenic diabetes in the UK paediatric diabetic population was 2.5% in a 2016 study examining 808 patients with positive urinary C-peptide creatinine ratio and negative islet cell-antibodies [23]. A similar Italian study showed a prevalence of 6.5% [24].

However, even though such studies have not yet been carried out in a population with prevalent consanguinity, it has been clearly shown that (among children with permanent NDM) the spectrum of genetic aetiologies differs largely between areas with high and low rates of consanguinity (shown in Fig. 2). In consanguineous regions, the most common gene was EIF2AK3 causing Wolcott-Ral-
optic atrophy, and deafness (DIDMOAD, later called Wolfram syndrome) were observed, particularly in consanguineous families with healthy parents and siblings, suggesting a condition with autosomal recessive inheritance [28]. It was later mapped due to homozygous mutations in gene WFS1-encoding wolframin (an ER protein involved in the regulation of the response to ER stress) [29]. Testing in 2 consanguineous families led to gene discovery (EIF2AK3 – an ER protein which is a key ER stress transducer) in previously mentioned Wolcott-Rallison syndrome which causes PNDM [30].

Another example is recessively inherited thiamine-responsive megaloblastic anaemia causing megaloblastic anaemia, DM, and sensorineural deafness. This was mapped to gene SLC19A2 in 1999 by testing in 6 families, 3 reported a history of consanguinity; however, they were all shown to be linked to a gene region based on homozygous markers, suggesting linkage disequilibrium and the existence of a founder mutation [31].

Autoimmune monogenic diabetes represents an overlap between classical T1DM and syndromic monogenic diabetes, and typically manifests at an early age. Two monogenic syndromes of polyglandular autoimmunity were genetically elucidated more than 20 years ago: the autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome and the X-linked (IPEX) syndrome caused by variants in the AIRE and FOXP3 genes, respectively [32, 33]. These are rare diseases but, for example, the autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome has been detected at high rates among certain populations such as the Finnish (1:25,000), Sardinian (1:14,000), and Iranian Jewish (1:6,500–1:9,000) as a result of founder mutations [34, 35]. The higher frequency in Iranian Jews can be additionally attributed to the presence of consanguinity in this population. Since then, multiple other genes responsible for autoimmune monogenic diabetes have been described (shown in Fig. 3) [36]. These genes can be divided further into genes causing autosomal recessive forms of autoimmune monogenic diabetes (IL2RA and LRBA), X-linked recessive forms (FOXP3), dominant forms (CTLA4 and STAT3), and genes that can be inherited both ways (AIRE).
Consanguinity and Its Impact on Paediatric Endocrine Research

Consanguinity played a role in the discovery of IL2RA (found in a boy from a first-cousin marriage with an immunodeficiency syndrome) and LRBA (due to genetic linkage analysis carried out in consanguineous families with hypogammaglobulinemia) [37, 38].

**Growth Regulation Disorders/Short Stature**

Many different genes impact growth by various mechanisms. The hypothalamic-pituitary axis of growth hormone (GH) and insulin-like growth factor (IGF)-1 was long believed to be the main linear growth regulator in children. However, recent studies have shown that it is rather regulated by 2 major tiered pathways – the GH-IGF-1 axis and the complex regulation of growth plate chondrocytes and the extracellular cartilaginous matrix (shown in Fig. 4) [39, 40].

**GH-IGF-1 Axis**

Mutations in genes regulating steps in the entire GH-IGF-1 axis, ranging from GH deficiency (GHD), primary IGF-1 deficiency to IGF-1 resistance may cause short stature. The first genetic syndrome related to this axis was clinically described by Laron et al. [41] in 1966. It was characterized by severe growth retardation, obesity, and small genitalia in 3 siblings from a consanguineous Jewish family and was later named Laron syndrome [41]. It was characterized by high serum GH concentrations and low to undetectable IGF-1 concentrations. In patients with this rare syndrome, GH resistance was demonstrated by the administration of exogenous human GH for 7 days, which did not lead to IGF-1 increase [42]. Later, in 1984, Eshet et al. [43] proved that the mechanism of GH resistance is due to an inability of GH to bind to the respective receptor. Soon thereafter, in 1989, the GH receptor gene was described as causative by Amselem et al. [42], by using gene linkage methods in 2 consanguineous families from the Mediterranean region.

![Fig. 3. Overview of the molecular pathophysiology of monogenic diabetes. Functional locations of proteins encoded by causative genes (mentioned in the manuscript) are assigned the following numbers: 1 – PDX1, 2 – CNOT1 (pancreas development genes), 3 – NEUROG3 (an endocrine differentiation gene), 4 – ABCC8, 5 – KCNJ11 (KATP channel genes), 6 – INS, 7 – EIF2AK3, 8 – WFS1, 9 – YIPF5 (insulin and ER genes), 10 – GCK (glucokinase gene), 11 – HNF4A, 12 – HNF1A, 13 – HNF1B, 14 - PTF1A, 15 – FOXP3, 16 – GATA6 (transcription factor genes present in the nucleus), 17 – SLC19A2, 18 – GLUT1 (transporter genes), 19 – AIRE, 20 – FOXP3, 21 – IL2RA, 22 – LRBA, 23 – CTLA4, 24 – STAT3 (immune regulating genes).](image-url)
During this time, the genetic transmission of severe isolated GH deficiency (IGHD) was studied as well. This occurs with an incidence of between 1 in 4,000 and 1 in 10,000 live births [44]. Classical genetic causes of IGHD include mutations of the gene-encoding GH (GH1) and the GH releasing hormone receptor (GHRHR). Thus far, there have been no instances of GHD as a result of mutations in GH releasing hormone (GHRH) itself [44].

Historically, genetic forms of IGHD were classified into 4 types, depending on the inheritance pattern, as autosomal recessive (types IA and IB), dominant (type II), or X-linked (type III) [45]. This classification no longer applies due to expanding knowledge into the pathophysiology of GHD. Autosomal recessive IGHD type IA was first described in patients with homozygous GH1 deletions, including 2 siblings from Italian first-cousin parents having IGHD due to a 7.6 kb deletion in the GH gene cluster [46]. Patients present with severe growth failure by 6 months of age with undetectable GH concentrations. Some of these children tend to develop antibodies on treatment, thereby resulting in poor response to GH therapy [46].

Subsequently, the first homozygous loss-of-function GHRHR mutation causing profound IGHD was described in 2 patients from a consanguineous family with a clinical presentation suggestive of cretinism. Hormonal workup showed profound deficiencies of thyroid-stimulating hormone, GH, and prolactin. These patients were the first described case of a defect of a transcriptional activator causing deficiency of multiple target genes [50].

Recently, 2 families (one of which was consanguineous) with children with progressive postnatal growth failure and markedly elevated serum concentrations of IGF-1, IGF-binding proteins (IGFBP3), IGFBP5, acid labile subunit, and IGF-2 concentrations were reported. This was shown to be resulting from homozygous loss of function of the PAPPA2 gene, which leads to low IGF-1 bioavailability. This indicates that PAPPA2 is a key regulator of IGF-1 bioavailability by regulating the proportion of IGF-1 that is bound to IGF-binding proteins [51].
Growth Plate Chondrocytes and Extracellular Matrix

Disorders of chondrocyte paracrine regulation (for example, NPR2 defects), defects in intracellular pathways such as “RASopathies” or mutations in transcriptional factor genes (for example, SHOX) cause short stature as well [40, 44, 52, 53]. Homozygous inactivating mutations in NPR2 cause severe acromesomelic Maroteaux dysplasia and was first described in 2004 via testing done in a predominantly consanguineous cohort [54].

Impairment of DNA repair can result in rare autosomal recessive forms of very severe short stature (such as microcephalic osteodysplastic primordial dwarfism type II – birth weight typically <1,500 g at term and an adult height of <100 cm). One example is the gene PCNT which encodes pericentrin (a centrosomal protein) first discovered by linkage analysis studies in 2 consanguineous families [55].

Extracellular matrix structure genes including collagen regulating genes such as COL1A2, COL2A1, COL11A1, fibrillin genes such as FBN1 and matrilin genes such as MATN3 impact growth as well [52, 56]. These gene mutations most often cause milder forms of short stature in heterozygous form and more severe forms in homozygous/recessive form. Consanguineous families have helped extend the disease phenotype and genotype-phenotype relationship such as in the case of gene MATN3 where a novel form of autosomal recessive spondylo-epimetaphyseal dysplasia caused by homozygous MATN3 mutations was described in a large consanguineous family with 5 affected individuals [57].

Conclusion

The presence of consanguinity in families with children with endocrine disease represents a substantial genetic burden for the offspring due to the higher probability of a single-gene condition with autosomal recessive inheritance. Not all pathogenic genes in the above-mentioned conditions were discovered with the help of related marriages; however, consanguineous families have been invaluable in elucidating novel genes and novel mechanisms of disease despite this genetic burden. Thus, it can be said that genetic examination in consanguineous families could trigger novel advancements in pathophysiological research and extend medical knowledge. Therefore, continued genetic testing (specialy using methods such as whole-genome sequencing) in areas with prevalent consanguinity could further help shed light on conditions where the genetic background and pathophysiology are not fully known.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

J.L. designed this review. S.A.A. wrote the manuscript. T.H.T. and P.D. provided insight into genetic findings and testing in consanguineous areas. S.A.A. and J.L. prepared the figures. S.P. and J.L. revised the manuscript critically. All authors contributed to the discussion, reviewed or edited the manuscript, and approved the final version to be published.

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