Clinical traits and molecular genetics analysis of monogenic diabetes caused by mutations in the GATA6

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Research Article

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Abstract

Aim:

This study aims to analyze the clinical and genetic features of monogenic diabetes with GATA6 mutations in order to improve clinicians' understanding of the disease.

Method:

We report a de novo GATA6 mutation in a family and review related literature to summarize the clinical and genetic characteristics of monogenic diabetes with GATA6 mutations.

Results:

This GATA6 missense mutation(c.749G>T, p.Gly250Val) is not reported presently, characterized by adult-onset diabetes with pancreatic dysplasia and located in transcriptional activation region. Carriers with GATA6 mutations(n=55) have a variable spectrum of diabetes, ranging from neonatal(72.7%), childhood-onset(20%) to adults-onset(7.5%). 83.5% of patients with abnormal pancreatic development. Heart and hepatobiliary defects are the most common abnormalities of extrapancreatic features. Most mutations with GATA6 are loss of function(LOF,71.8%) and located in functional region.

Conclusion:

The heterogeneous hallmarks result in monogenic diabetes with GATA6 mutations easy misdiagnosis and missed diagnosis. A comprehensive assessment and follow-up is needed in the clinic. Genetic counseling and genetic testing are recommended to patients with mutations.

Introduction

Monogenic diabetes, which accounts for 1–5% of diabetes cases^[1], including neonatal diabetes, maturity-onset diabetes of the young and monogenic diabetes syndromes^[2]. So far, more than 30 subtypes have been identified in these monogenic diabetes with specific clinical phenotypes and genetic patterns. Most of them coding proteins which play critical roles in pancreatic and beta cell development and function^[3, 4]. Monogenic diabetes is frequently misdiagnosed and treated as either type 1 or type 2 diabetes^[5]. Thus, getting a correct diagnosis for monogenic diabetes has important implications for management, prognosis and counselling of an individual's diabetes and other family members regarding likely inheritance.

GATA6-binding factor 6 (GATA6), a zinc finger transcription factor, is crucial in pancreatic development. It is important in the differentiation of endoderm, the development of pancreatic fate, the generation of endocrine/exocrine cells and the function of mature endocrine/exocrine cells^[6, 7]. GATA6 heterozygous mutations are rare causes of monogenic diabetes with broad clinical presentation, including many forms of diabetes, complete or partial defect of pancreas, and/or loss of exocrine function^[8, 9]. Furthermore,

GATA6 mutations patients exhibit abnormalities in extrapancreatic tissues such as congenital heart defects and endodermis anomalies, like hepatobiliary disorders, gallbladder hypoplasia and intestinal hernias^[8–10]. In a few cases, identical GATA6 mutations have variable phenotypic manifestations in different family members^[11–13].

We report a de novo GATA6 mutation (c.749G > T, p.Gly250Val) family with paternal inheritance. The proband is characterized by adult-onset diabetes, pancreatic agenesis, without exocrine pancreatic insufficiency or extrapancreatic abnormalities. His daughter just presents with pancreatic abnormality. Moreover, we outline 39 different GATA6 mutations with pancreatic dysfunction and/or developmental defect have been reported in the literature so far and explore the genotype-phenotype correlations of them, in order to improve clinicians' understanding of the disease.

Materials And Methods

1. Clinical evaluation and genetic testing

The proband with adult-onset diabetes and pancreatic agenesis was recruited at our hospital. Whole-exome sequencing was performed in the proband, his wife and daughter on DNA isolated from peripheral blood leucocytes at the Beijing Genomics Institute (Shenzhen, China). Detailed phenotypic data were obtained by medical history interviews and from clinical records. The informed consent was obtained from each subject after full explanation of the purpose and nature of all procedures used. The study was approved by ethical committee of the Third Hospital of Changsha. All methods were performed in accordance with the relevant guidelines and regulations.

2. Literature search

We searched in PubMed <https://pubmed.ncbi.nlm.nih.gov/> using “GATA6 Transcription Factor” [Mesh] AND “GATA6 protein, human” [Supporting Information Concept]. This resulted in 225 items. Suitable papers were selected based on the abstract. Inclusion criteria were: GATA6 mutations patients with pancreatic dysfunction and/or developmental defect where the full text was available. We checked the references in these papers and screened papers that cited the included papers. Lastly, we scanned Clinvar <https://www.ncbi.nlm.nih.gov/clinvar/> and OMIM <https://www.omim.org/> to identify any missing mutations. We summarized and analyzed the genotype-phenotype correlations of GATA6 mutations patients which described in 21 papers^[8–28] (in the supplement). Statistical comparisons were performed using Fisher's exact test, and Bonferroni corrected p values were used for determination of statistical significance ($p = 0.01$).

Results

1. Clinical descriptions of the proband and his daughter in the de novo GATA6 mutation family

The proband, a 62-year-old male born to healthy nonconsanguineous parents, was diagnosed with type 2 diabetes mellitus (DM) for 4 years. He visited our department for hypoglycemia with abnormalities in insulin secretion. Discovery of the GATA6 mutation initiated a renewed examination of the etiology of the DM and revealed pancreatic hypoplasia (Fig. 1A,B). In addition, his daughter presented with pancreatic abnormality and normal glucose tolerance (NGT) at her oral glucose tolerance test (OGTT) (Fig. 1C,D). Clinical and laboratory findings characteristics of them are described in Table 1. The proband was able to obtain good glycemic control with acarbose. The glycated hemoglobin value measured after 3 months was 6.4%.

2. Genetic testings of the de novo GATA6 mutation family

The results of whole-exome sequencing in the proband, his wife and daughter (Fig. 2). The same GATA6 mutation (c.749G > T, p.Gly250Val, chr18:19751854) was identified in the proband and his daughter. At present, such mutation is either classified as variants of unknown significance (VUS) or is not reported.

3. The genotype-phenotype analysis of GATA6 mutations with pancreatic dysfunction and/or developmental defect in the literature

3.1 Clinical traits

There were 39 GATA6 mutations, including nonsense, frameshift, splice site and missense mutations, in 45 independent probands. In 7 probands, the mode of inheritance was not tested. In the remaining, the variant arose de novo in 73.6% (28/38). Inherited mutations were found in 10 cases, of which maternally-expressed^[8, 11, 12, 15, 27] and paternally-expressed^[8, 16] each account for 50%.

3.2 Phenotypic manifestations

In total, there were data available on 59 GATA6 mutation carriers (45 probands and 14 family members from 10 families) with available pancreatic dysfunction and/or developmental defect in 55 of them. 96.3% of the carriers (n = 55, Fig. 3A) exhibited diabetes mellitus. Among them, 72.7% manifested neonatal diabetes mellitus, 20.0% manifested childhood-onset diabetes mellitus and 7.3% manifested adults-onset diabetes mellitus. Two cases with transient neonatal diabetes developed permanent diabetes mellitus in 3 and 5 years old^[12, 24]. There were 83.6% with agenesis of the pancreas and 67.3% with exocrine pancreatic insufficiency in carriers (n = 55). The most common other extrapancreatic features were heart (89.8%, mainly ventricular septal defect) and hepatobiliary (mainly gallbladder agenesis) in 59 GATA6 mutation carriers (n = 59, Fig. 3B). Diaphragmatic hernia with an incidence of 10.2% and hypothyroidism was the most frequently reported endocrine dysfunction in these cases.

3.3 Genotype-phenotype correlations

We stratified the patients according to inheritance (de novo vs. inherited) and found that patients with a de novo mutation more often presented neonatal diabetes mellitus and pancreas agenesis than those with an inherited mutation (Table S2, $P < 0.01$). In mutation families, all probands had neonatal diabetes

mellitus and pancreas agensis, clinical and phenotypic diversity resulted from family members. Members displayed different clinical phenotypes in the same mutation family, thus, the phenotype and genotype do not correlate. Intriguingly, carriers without pancreatic dysfunction and/or developmental defect occurred within maternal inheritance families(4/5), 3 of them were parents^[11, 12, 15, 27] and the remaining was younger brother^[12]. 4 were adult-onset diabetes^[8, 16] and 1 was childhood-onset diabetes^[8] mellitus in paternal inherited families. No significant differences were found between maternally and paternally inheritance in other abnormalities. Inter-sex differences also were not detected.

When stratifying patients according to the type of mutation (missense vs. LoF mutation, Fig. 4), we did not observe any statistically significant differences in the terms of pancreatic dysfunction and/or developmental defect(Table S3).

Four mutations were found in more than one independent proband (c.1242C > A^[14, 18] c.1366C > T^[9, 19, 26] c.1367G > A^[9, 20] c.1504_1505del^[11, 13]) and one of these, c.1366C > T p.(Arg456Cys) was even found in 4 independent probands. It is located in the C-zinc finger domain of the protein, essential for modifying the DNA-bind function by active with GATA6 protein. All of these 4 probands varied in other extrapancreatic defects with pancreas agensis and cardiac abnormalities. 3 of them presented neonatal diabetes, the remaining was childhood-onset diabetes. 2 probands had pancreatic exoendocrine dysfunction.

3.4 Genic location of GATA6 mutations

Topologically, the GATA6 protein has at least three functional domains: a transcriptional activation domain essential for its transcriptional activity and two zinc finger domains(C- and N-) required for DNA sequence recognition and binding to the consensus motif^[29]. We plotted all mutations on a diagram of the GATA6 protein (Fig. 4). Most mutations were located within the functional domains of GATA6 (28/39, 71.8%). Furthermore, missense mutations were more often located in the zinc finger domains, whereas LOF mutations were more often located in the transcriptional activation domain. There were no statistically significant differences in clinical manifestations between mutations located inside and outside of the functional domains. The mutation we have reported was a missense, located in transcription activation domain, as far no reported.

Discussion

Heterozygous GATA6 patients with a wide spectrum of phenotypes ranging from non-diabetic, mildly diabetic in adults, to severely diabetic in newborns. This phenotypic heterogeneity of diabetes is clear within families, where identical mutations may have variable phenotypic manifestations in different family members. Only 7.3% of adults present at diabetes diagnosis in GATA6 mutations. We have reported a de novo GATA6 mutation (c.749G > T, p.Gly250Val) family with paternal inheritance. The proband is characterized by adult-onset diabetes, pancreatic agenesis, without exocrine pancreatic insufficiency or extrapancreatic abnormalities. His daughter just presents with pancreatic

abnormality. Unlike our case, all probands from inherited families present with neonatal diabetes. But, no difference differences are found between de novo and inheritance in the prevalence of diabetes. It suggests that phenotypic heterogeneity can indicate but does not imply genetic heterogeneity. Moreover, diabetes in GATA6 mutations patients may be a progressive disease, 2 carriers with transient neonatal diabetes progress into permanent childhood-onset diabetes in 3 and 5 years old, respectively^[12, 24]. GATA6 mutations patients with neonatal diabetes depend on the administration of low-dose exogenous insulin (0.15-0.5u/h) for survival; however it often causes glycaemic excursions. Some Childhood-onset and adults-onset diabetes despite improved oral glucose-lowering agents (most of metformin) available, all of them with long-standing diabetes eventually require insulin^[8, 18, 21]. A GATA6 mutation case represented a 19-year-old female with a 3-year history of insulin-dependent diabetes. Her pancreas obtained by the surgeon was very small, though the insulin area (%) of this atrophic sample and β cells of islets were within the normal range. Multiple islets with amyloidosis and adipose-infiltrating were observed, which is compatible with a histopathological diagnosis of type 2 diabetes. It suggested that residual β cells may have enough function before puberty^[26].

A study showed that the progressive defect in glucose homeostasis in adult mouse models with GATA6 depletion of β -cell dysfunction and might be due to increased metabolic stress associated to age and concomitant increase in body weight^[31]. Further follow-up of the proband's daughter for progression to diabetes is needed. The beneficial approach to retard the progression of the proband may be to use insulin early and have good metabolic control. Exocrine and endocrine dysfunction can occur independently of each other. The former with relatively low incidences (67.3%) was determined using a pancreatic elastase based on faecal samples. Most patients were defined as steatorrhea requiring pancreatic enzymes supplementation. Our patients denied any relative symptoms and were not further evaluated. Pancreatic agenesis is a common phenotype in GATA6 mutations patients with an incidence of 83.6%. Besides, heart (89.8%) and liver (33.9%) abnormalities are major in GATA6 mutants, other extrapancreatic defects including diaphragmatic hernia, hypothyroidism and growth retardation. We did not find extrapancreatic abnormalities in the proband and his daughter. Like the daughter, case only presented pancreatic agenesis was also reported in the published report^[8]. A case have been reported progress to protein-losing enteropathy^[8, 20]. Therefore, whether extrapancreatic defects seen in the proband and his daughter remains unknown and requires more observers.

Abnormal formation, differentiation, maturation and function of endoderm and pancreas is the pathological basis for GATA6 mutations with pancreatic dysfunction and/or developmental defect, but the specific mechanism is unknown. Gata6 encodes two highly conserved zinc finger-containing transcription factors that serve as its DNA binding domain and recognize the cognate consensus motif (A/T)GATA(A/G). As a regulator of chromatin structure and function, GATA6 and other co-transcription complexes, including PDX1-GATA4-EOMES-FOXA2-SOX17-NKx2.2, play crucial roles in gene expression of endodermal cells and pancreas progenitors.

Abnormal differentiation of definitive endoderm and decreased number of pancreatic progenitors in GATA6 mutants related to the dose of retinol, abnormal hedgehog signaling pathway,

H3K9me3 accumulation and alleviated DNA methylation^[34–36]. Studies showed that GATA6 mutations present different types of diabetes caused by endocrine dysfunction with abnormal proliferation/apoptosis of islet cells, change of endoplasmic reticulum and mitochondria in β cells, increase of immature granules^[26, 31]. Independent to endocrine, exocrine dysfunction is associated with abnormal proliferation/apoptosis of acinar, acinar to ductal or adipocytes transdifferentiation^[37].

The mutations accounting for monogenic diabetes include missense mutations, frameshift mutations, nonsense mutations, partial/complete deletions, splice, and inframe deletion/insertions.

Clinical manifestations of monogenic diabetes vary depending on the affected gene^[38]. Therefore, we analyzed the genotype-phenotype correlations in GATA6 mutations. We found that most mutations were located within the functional domains of GATA6(28/39,71.8%), most of them are LOF(28/39,71.8%). Furthermore, missense mutations were more often located in the zinc finger domains, whereas LOF mutations were more often located in the transcriptional activation domain. There were no statistically significant differences in clinical manifestations between mutations located inside and outside of the functional domains. Family members or different probands carrying the same mutation have different clinical manifestations. There were no statistically significant differences in clinical manifestations between de novo and inheritance, missense mutations and LOF, inside and outside of the functional domains. Collectively, our findings demonstrate that GATA6 mutations exhibited marked phenotypic and genotypic heterogeneity. This heterogeneity is likely due to a multitude of factors, including genetic background, environment, and epigenetic status, which relative to haploinsufficiency, chimerism, gene expression incompletely and time window of mutations^[8, 9, 12, 36, 39]. More extensive testing in GATA6 mutations patients will help to refine genotype–phenotype correlations in the future. The mutation we have reported was a missense, located in transcription activation domain, as far as no reported. This extends the spectrum of gene and phenotype associated with GATA6 mutations. However, clarifying the mechanistic relationship between this mutation and diabetes requires further study, including gene testings for other members in the family, mutational analysis and functional experiments for our model. These efforts may help guide us toward more understanding about this disease.

This paper has some limitations: our cases are reported in probands presenting with pancreatic abnormalities, causing bias due to selective inclusion. Then, a part of GATA6 mutation-positive individuals were derived from cohort studies where patients lack of detailed clinical evaluation about other associated features. As it is impossible to detect how extensive the clinical phenotype was in each patient, when there was no mention of pancreatic or other extrapancreatic features, we scored these data as unavailable. For family members we assumed that, if there was a pancreatic or other extrapancreatic feature described in the proband, this was also detected in carriers from the same family. If an abnormality was not mentioned in these family members, we scored this data as normal.

We hope that this study will enable treating physicians to increase the understanding of monogenic diabetes with GATA6 mutations. Subsequently, these patients should be provided for appropriate diagnostic testing and genetic counseling. Conversely, patients in whom a GATA6 pathogenic mutation has been identified should undergo a comprehensive clinical assessment and follow-up, in order to study the full disease spectrum in these individuals. Moreover, genetic testing and clinical analysis for members in family with inherent GATA6 pathogenic mutation will hopefully contribute to a better estimation of the mutational yield and to clear genotype-phenotype correlations.

Declarations

Conflicts of Interest

The authors declare that there is no conflicts of interest that could be perceived as prejudicing the impartiality of the research reported.

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References

1. Shepherd, M., et al., Systematic Population Screening, Using Biomarkers and Genetic Testing, Identifies 2.5% of the U.K. Pediatric Diabetes Population With Monogenic Diabetes. *Diabetes Care*, 2016. 39(11): p. 1879–1888.
2. Thomas, C.C. and L.H. Philipson, Update on diabetes classification. *Med Clin North Am*, 2015. 99(1): p. 1–16.
3. De Franco, E., et al., The effect of early, comprehensive genomic testing on clinical care in neonatal diabetes: an international cohort study. *Lancet*, 2015. 386(9997): p. 957–63.
4. Rubio-Cabezas, O., et al., ISPAD Clinical Practice Consensus Guidelines 2014. The diagnosis and management of monogenic diabetes in children and adolescents. *Pediatr Diabetes*, 2014. 15 Suppl 20: p. 47–64.
5. Shields, B.M., et al., Maturity-onset diabetes of the young (MODY): how many cases are we missing? *Diabetologia*, 2010. 53(12): p. 2504–8.
6. Lentjes, M.H., et al., The emerging role of GATA transcription factors in development and disease. *Expert Rev Mol Med*, 2016. 18: p. e3.
7. Carrasco, M., et al., GATA4 and GATA6 control mouse pancreas organogenesis. *J Clin Invest*, 2012. 122(10): p. 3504–15.

8. Franco, E.D., et al., GATA6 Mutations Cause a Broad Phenotypic Spectrum of Diabetes From Pancreatic Agenesis to Adult-Onset Diabetes Without Exocrine Insufficiency. *Diabetes*, 2013. 62(3): p. 993–997.
9. Allen, H.L.F.S., GATA6 haploinsufficiency causes pancreatic agenesis in humans. *Nature Genetics*, 2011. 44(1): p. 20–22.
10. Chao, C.S., et al., Novel GATA6 mutations in patients with pancreatic agenesis and congenital heart malformations. *PLoS One*, 2015. 10(2): p. e0118449.
11. Bonnefond, A., et al., GATA6 inactivating mutations are associated with heart defects and, inconsistently, with pancreatic agenesis and diabetes. *Diabetologia*, 2012. 55(10): p. 2845–2847.
12. Yau, D., et al., Case report: maternal mosaicism resulting in inheritance of a novel GATA6 mutation causing pancreatic agenesis and neonatal diabetes mellitus. *Diagn Pathol*, 2017. 12(1): p. 1.
13. Yorifuji, T., et al., Dominantly inherited diabetes mellitus caused by GATA6 haploinsufficiency: variable intrafamilial presentation. *J Med Genet*, 2012. 49(10): p. 642–3.
14. Tühan H, Catli G, Anik A, et al. Neonatal diabetes mellitus due to a novel mutation in the GATA6 gene accompanying renal dysfunction: A case report[J]. *American Journal of Medical Genetics Part A*, 2015, 167(4):925–927..
15. O Gaisl, D Konrad, P Joset. A novel GATA6 variant in a boy with neonatal diabetes and diaphragmatic hernia: a familial case with a review of the literature[J]. *Journal of pediatric endocrinology & metabolism: JPEM*, 2019, 32(9).
16. Yang T D, Moore L, Poplawski N K, et al. Familial GATA6 mutation causing variably expressed diabetes mellitus and cardiac and renal abnormalities[J]. *Endocrinology Diabetes and Metabolism Case Reports*, 2019, 2019(1).
17. Suzuki S, Nakao A, Sarhat A R, et al. A case of pancreatic agenesis and congenital heart defects with a novel GATA6 nonsense mutation: evidence of haploinsufficiency due to nonsense-mediated mRNA decay.[J]. *American Journal of Medical Genetics Part A*, 2014, 164(2):476–479..
18. Miles, M.L., N. Cowan and G. Jackson, A NONSENSE GATA6 MUTATION EXPLAINS HISTORY OF CONGENITAL HEART DEFECTS AND 10 YEARS OF POORLY-CONTROLLED DIABETES LACKING DKA IN A NON-OBESE 30 YEAR-OLD INCIDENTALLY FOUND TO HAVE PANCREATIC HYPOPLASIA. *AACE Clin Case Rep*, 2020. 6(3): p. e123-e126.
19. Raghuram, N., et al., Congenital hypothyroidism, cardiac defects, and pancreatic agenesis in an infant with GATA6 mutation. *Am J Med Genet A*, 2020. 182(6): p. 1496–1499.
20. Skoric-Milosavljevic, D., et al., GATA6 mutations: Characterization of two novel patients and a comprehensive overview of the GATA6 genotypic and phenotypic spectrum. *Am J Med Genet A*, 2019. 179(9): p. 1836–1845.
21. Sanchez-Lechuga, B., et al., Case report: adult onset diabetes with partial pancreatic agenesis and congenital heart disease due to a de novo GATA6 mutation. *BMC Med Genet*, 2020. 21(1): p. 70.
22. McMillan, T., R. Girgis and E.A. Sellers, Neonatal diabetes and protein losing enteropathy: a case report. *BMC Med Genet*, 2016. 17: p. 32.

23. Eifes, S., et al., A novel GATA6 mutation in a child with congenital heart malformation and neonatal diabetes. *Clinical Case Reports*, 2013. 1(2).
24. Catli, G., et al., A novel GATA6 mutation leading to congenital heart defects and permanent neonatal diabetes: a case report. *Diabetes Metab*, 2013. 39(4): p. 370–4.
25. Gong, M., et al., Two novel GATA6 mutations cause childhood-onset diabetes mellitus, pancreas malformation and congenital heart disease. *Horm Res Paediatr*, 2013. 79(4): p. 250–6.
26. Sanyoura, M., et al., Pancreatic Histopathology of Human Monogenic Diabetes Due to Causal Variants in KCNJ11, HNF1A, GATA6, and LMNA. *J Clin Endocrinol Metab*, 2018. 103(1): p. 35–45.
27. Ferreira, S., et al., GATA6 Mutation: A Rare Genetic Cause of Hepatobiliary Disease. *J Pediatr Gastroenterol Nutr*, 2017. 64(5): p. e134-e135.
28. Stanescu, D.E., et al., A novel mutation in GATA6 causes pancreatic agenesis. *Pediatr Diabetes*, 2015. 16(1): p. 67–70.
29. Tremblay M, Sanchez-Ferras O, Bouchard M. GATA transcription factors in development and disease[J]. *Development*, 2018, 145(20):dev164384..
30. Jay, J.J. and C. Brouwer, Lollipops in the Clinic: Information Dense Mutation Plots for Precision Medicine. *PLoS One*, 2016. 11(8): p. e0160519.
31. Villamayor, L., et al., GATA6 Controls Insulin Biosynthesis and Secretion in Adult beta-Cells. *Diabetes*, 2018. 67(3): p. 448–460.
32. Heslop, J.A., et al., GATA6 defines endoderm fate by controlling chromatin accessibility during differentiation of human-induced pluripotent stem cells. *Cell Rep*, 2021. 35(7): p. 109145.
33. Sharma, A., et al., GATA6 mutations in hiPSCs inform mechanisms for maldevelopment of the heart, pancreas, and diaphragm. *Elife*, 2020. 9.
34. Laina, Freyer, Christian, et al. A loss-of-function and H2B-Venus transcriptional reporter allele for Gata6 in mice.[J]. *BMC developmental biology*, 2015..
35. Xuan, S. and L. Sussel, GATA4 and GATA6 regulate pancreatic endoderm identity through inhibition of hedgehog signaling. *Development*, 2016. 143(5): p. 780–6.
36. Chia, C.Y., et al., GATA6 Cooperates with EOMES/SMAD2/3 to Deploy the Gene Regulatory Network Governing Human Definitive Endoderm and Pancreas Formation. *Stem Cell Reports*, 2019. 12(1): p. 57–70.
37. Martinelli, P., et al., Gata6 is required for complete acinar differentiation and maintenance of the exocrine pancreas in adult mice. *Gut*, 2013. 62(10): p. 1481–8.
38. Bansal, V., et al., Spectrum of mutations in monogenic diabetes genes identified from high-throughput DNA sequencing of 6888 individuals. *BMC Med*, 2017. 15(1): p. 213.
39. Zhong-Dong S, Kihyun L, Dapeng Y, et al. Genome Editing in hPSCs Reveals GATA6 Haploinsufficiency and a Genetic Interaction with GATA4 in Human Pancreatic Development[J]. *Cell stem cell*, 2017, May04;20(5): 675–688.

Tables

Table 1 is available in the Supplemental Files section.

Figures

Figure 1 Imaging of pancreas in the proband and his daughter. Magnetic resonance imaging of the proband showing only the head of the pancreas is visible (A,B). Computed tomography scan of his daughter with pancreatic body hypoplasia (C,D). Abnormalities are indicated by red arrows.

Figure 1

See image above for figure legend.

Figure 2 Genetic testings of the de novo GATA6 mutation family. (A) the proband. (B) his wife. (C) his daughter. The proband and his daughter with GATA6 heterozygous mutation(NM_005257.4;c.749G>T;p.Gly250Val).

Figure 2

See image above for figure legend.

Figure 3 Clinical phenotypes of GATA6 mutations carriers. A. The incidence of monogenic diabetes in 55 carriers. B. The incidence of extrapancreatic abnormalities in 59 carriers. Carriers with GATA6 mutations (n=55) have a variable spectrum of diabetes, ranging from neonatal (72.7%), childhood-onset (20%) to adult-onset (7.5%). Heart (89.8%) and hepatobiliary (33.9%) defects are the most common abnormalities of extrapancreatic features.

Figure 3

See image above for figure legend.

Figure 4 Presentations of the GATA6 protein and its protein domains with all described mutations. (a) A diagram of the GATA6 protein with the functional domains “N-terminal” (GATA-type transcription activator) and “GATA” (zinc finger domains). Our case and 39 mutations have been reported are plotted at their topological location on the GATA6 protein. Blue dots represent missense mutations, Red dots represent loss-of-function mutations, and brown dot represent our mutation. Splice site mutations are plotted at the closest amino acid position. Bigger dots represent different mutations at the same amino acid position. The figure is created using The Lollipop software^[30], which uses the Pfam protein domain database (<http://pfam.xfam.org/>) to retrieve domains. (b) Overview of all 39 mutations categorized by position on the protein. Most mutations were located within the functional domains of GATA6 (28/39, 71.8%), most of them are LOF (28/39, 71.8%).

Figure 4

See image above for figure legend.

Supplementary Files

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- [Table1.pdf](#)
- [TableS1OverviewofalldescribedGATA6mutations.pdf](#)
- [TableS2Differencesbetweenenovovs.inheritedmutation.pdf](#)
- [TableS3DifferencesbetweenmissenseandLoFmutation.pdf](#)