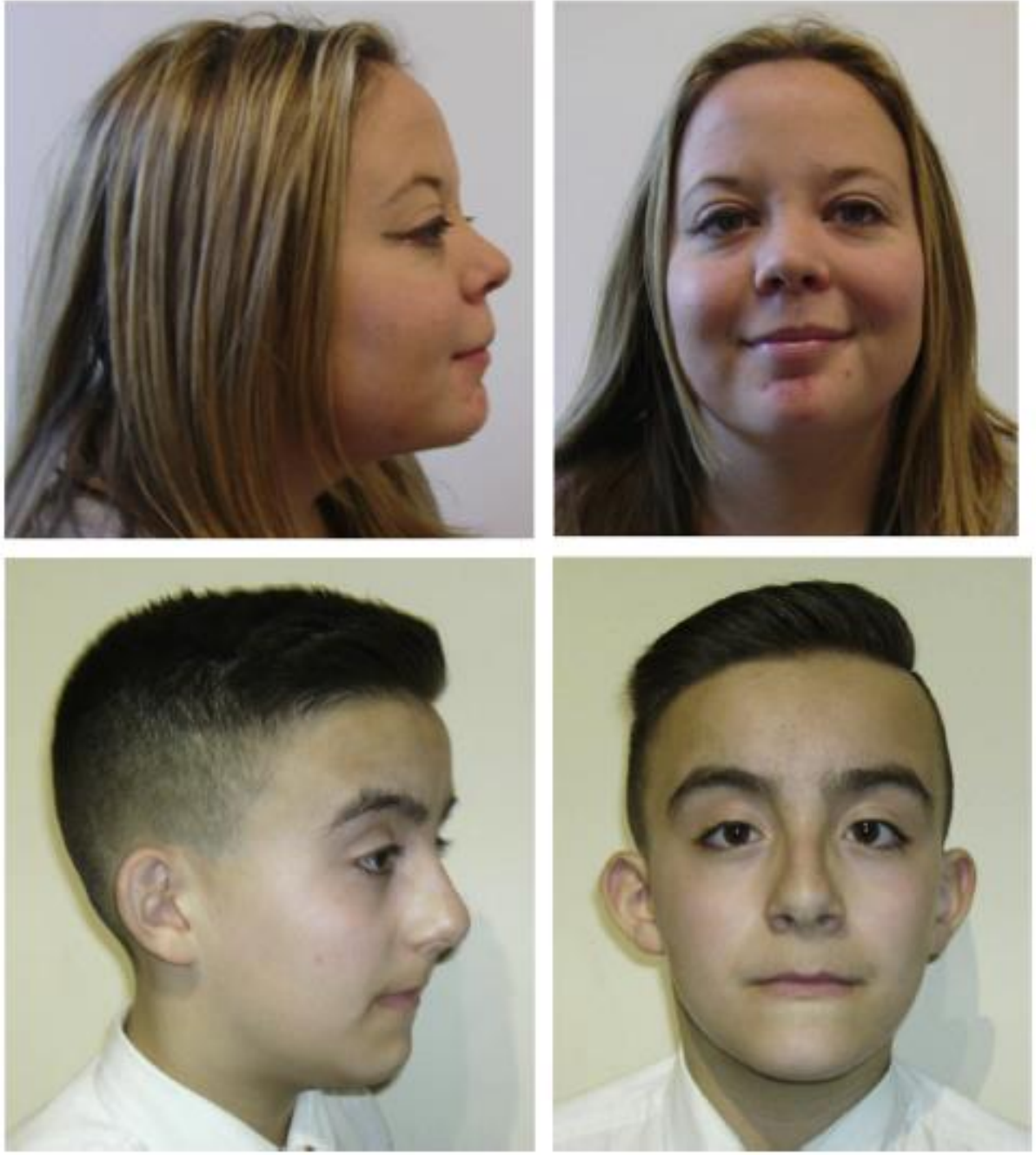
Neonate with permanent diabetes mellitus

Andrzej Kochański

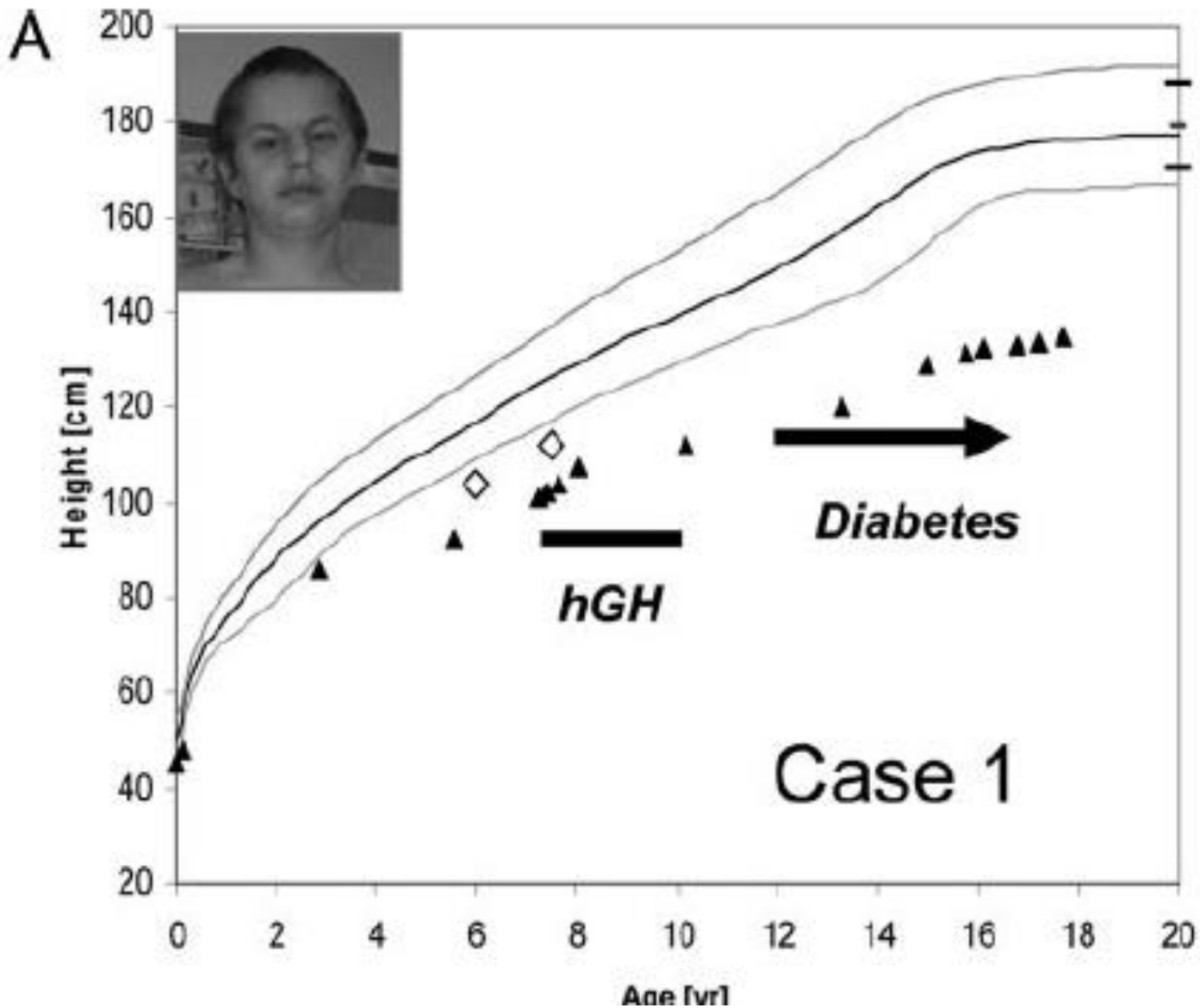


Clissold RL et al. Kidney International 2016; 90, 203-211

Expanded Clinical Spectrum in Hepatocyte Nuclear Factor 1B-Maturity-Onset Diabetes of the Young

Klemens Raile,* Eva Klopocki,* Martin Holder, Theda Wessel, Angela Galler, Dorothee Deiss, Dominik Müller, Thomas Riebel, Denise Horn, Monika Maringa, Jürgen Weber, Reinhard Ullmann, and Annette Grüters

Department of Pediatric Endocrinology and Diabetes (K.R., T.W., A.G., D.D., A.G.), and Institute of Medical Genetics (E.K., D.H.), Charité Campus Virchow, 13353 Berlin, Germany; Pediatric Diabetology (M.H.), Olgahospital, 70031 Stuttgart, Germany; Departments of Pediatric Nephrology (D.M.) and Pediatric Radiology (T.R.), Charité Campus Virchow, 13353 Berlin, Germany; Human Genetics, Private Practice (M.M.), 53115 Bonn, Germany; IntegraGen GmbH (J.W.), 53115 Bonn, Germany; and Max Planck Institute for Molecular Genetics (R.U.), 14195 Berlin, Germany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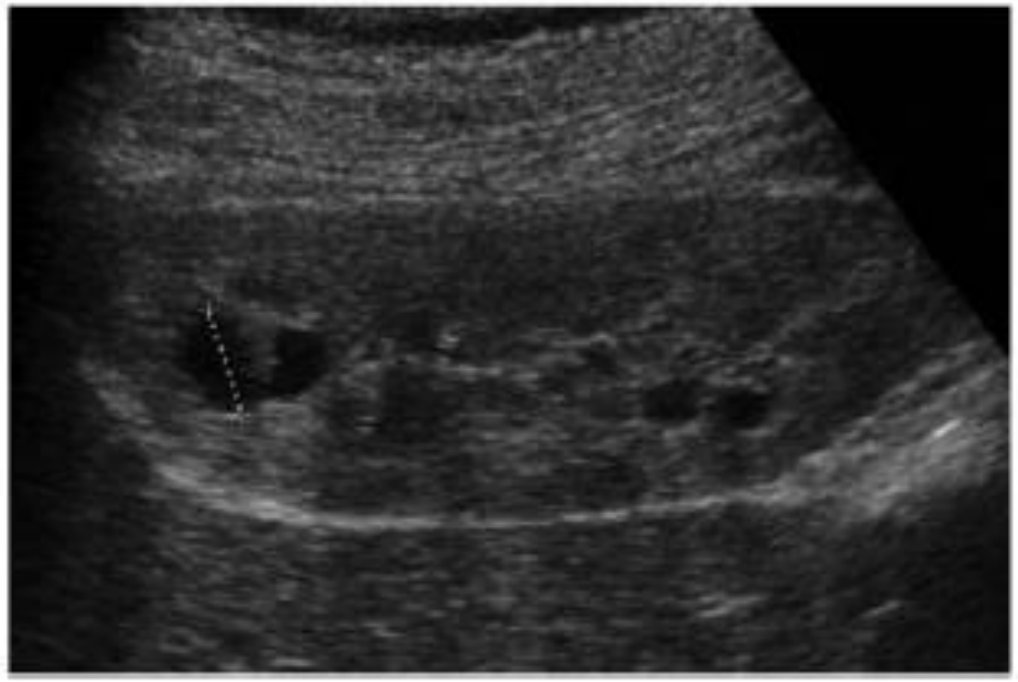
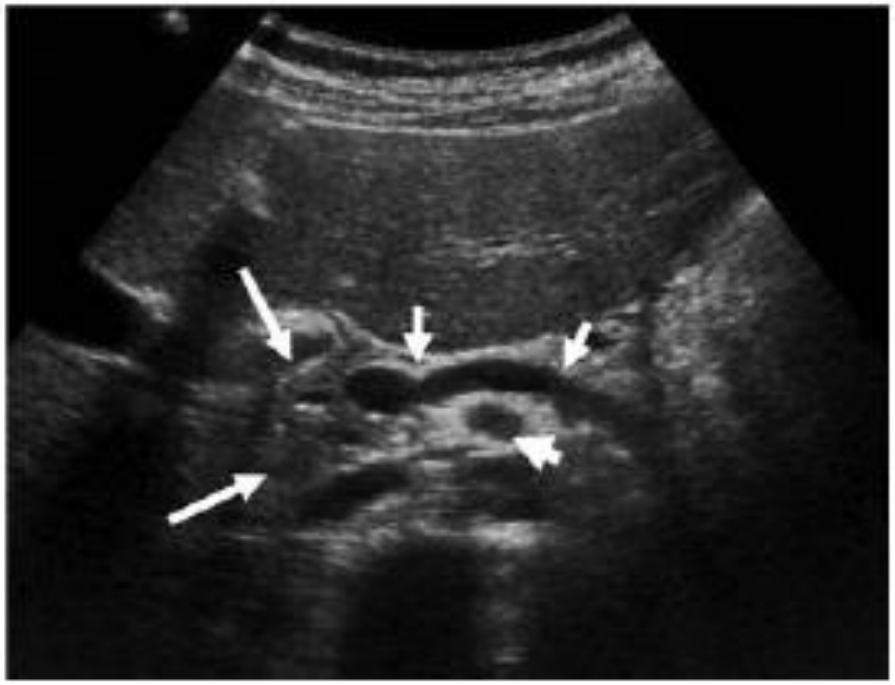
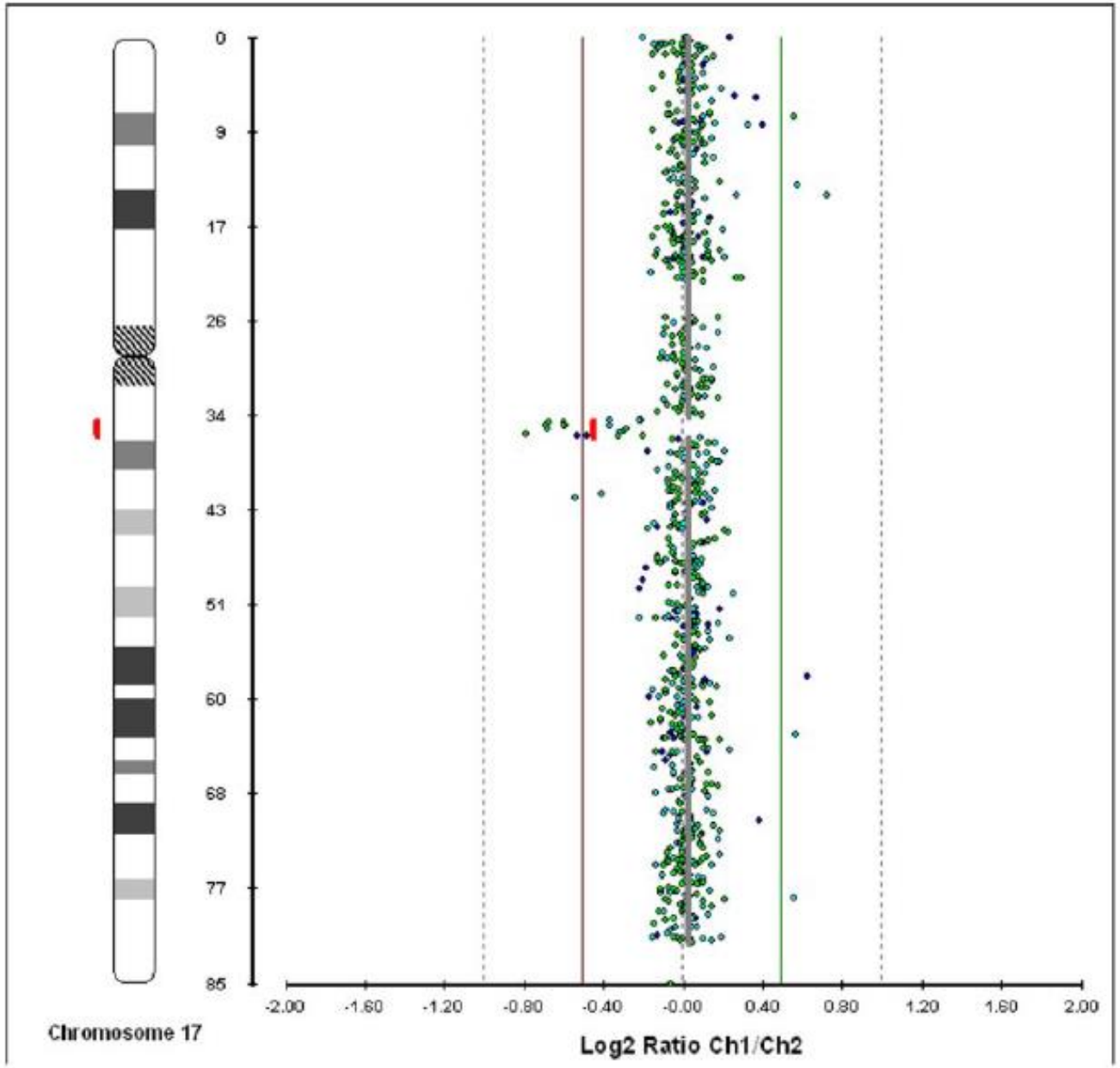
hGH
Diabetes
Case 1

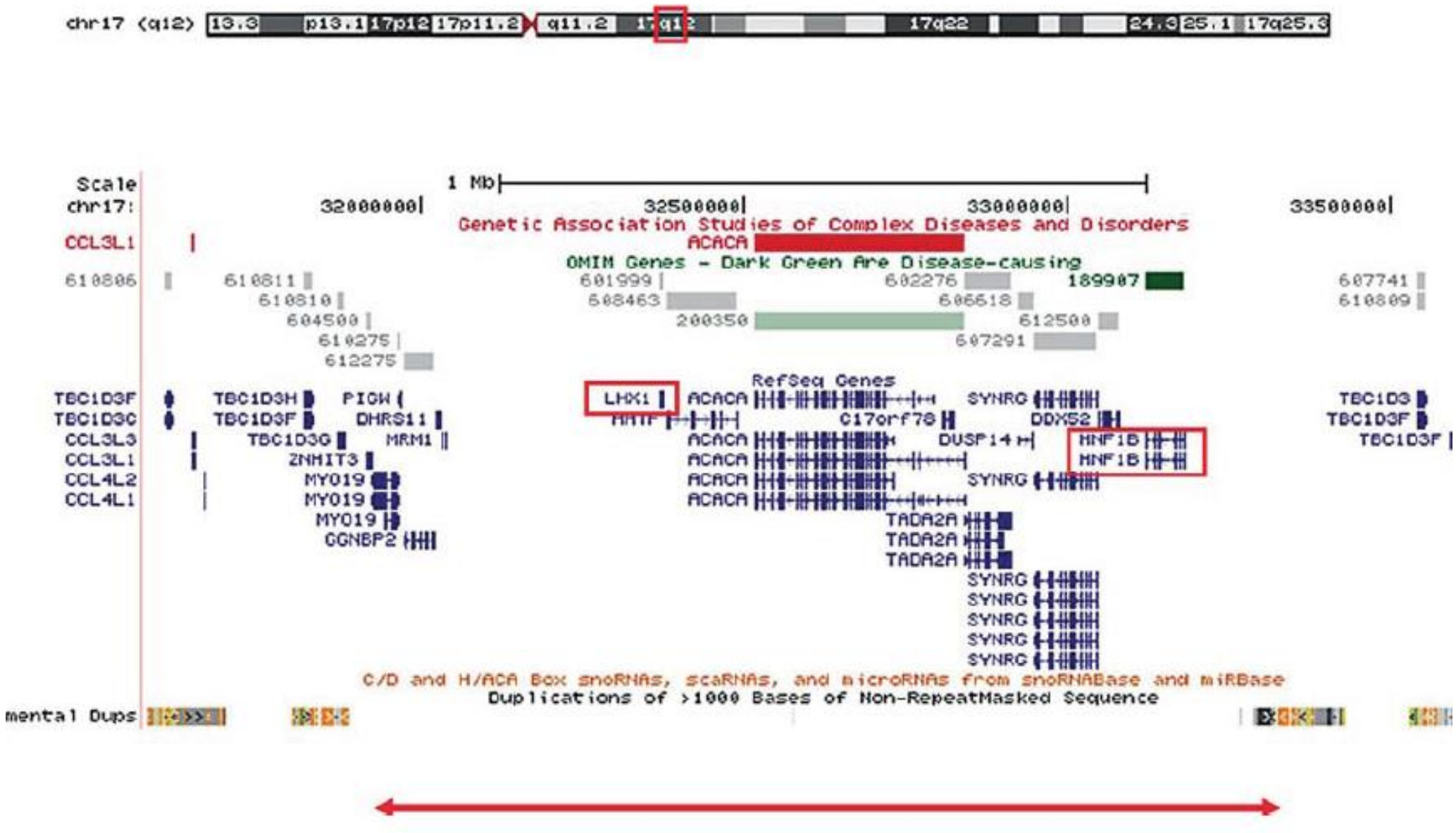
Kidney- cortical cysts;







Array CGH profile of chromosome 17


chr17 (q12)
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ZNHIT3
CCL4L2
MYO19
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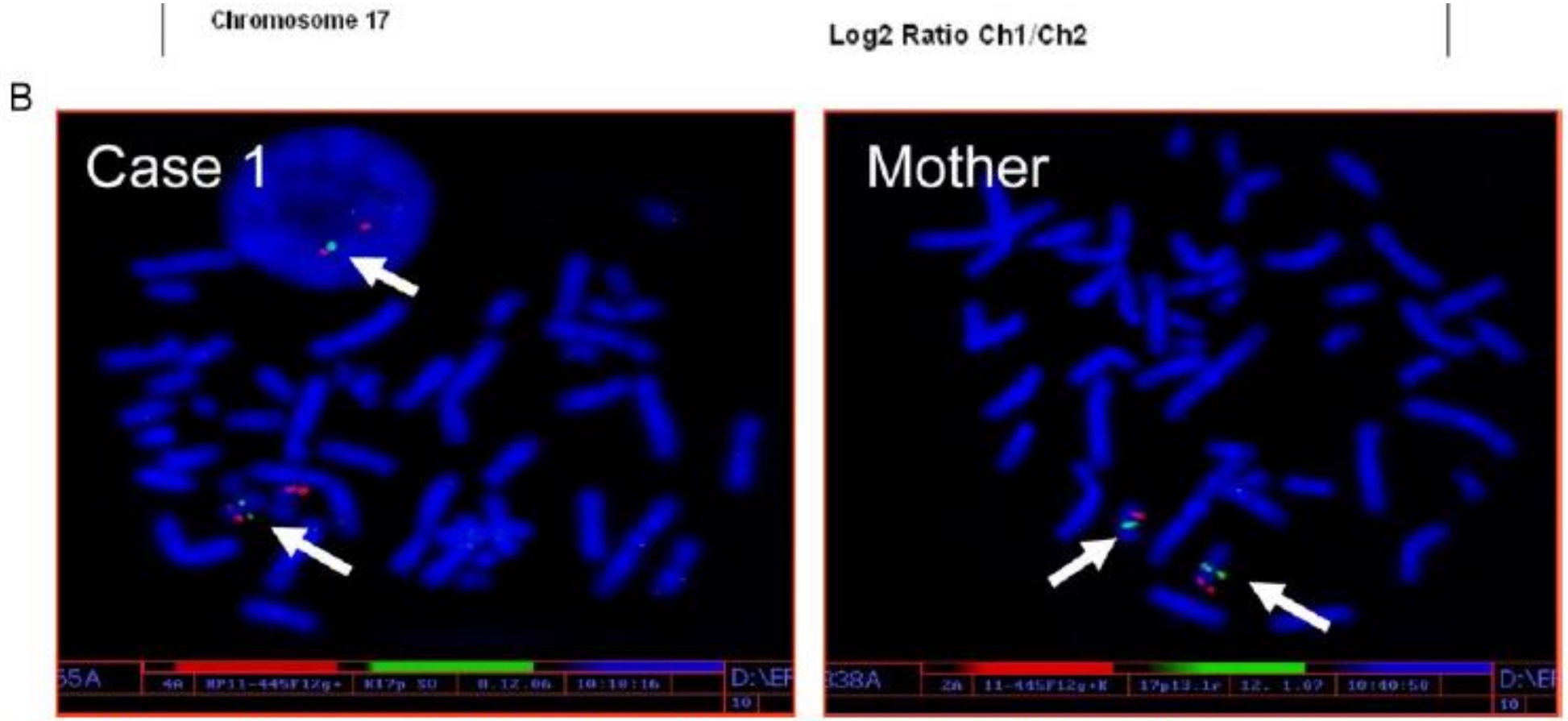


FIG. 2. Characterization of deletion size by array CGH (A) and confirmation of the heterozygous deletion of 17q12 by FISH (B). Array CGH profile of chromosome 17 was used to characterize the deletion size. The detected deletion is indicated by the *arrow* and the *red bar*. *Red and green lines* indicate a log2 ratio of −0.5 and 0.5, respectively. BAC probe RP11-445F12 (*green*) mapped to 17q12, whereas control probe RP11-404G1 (*red*) mapped to 17p13.1. Note only one green signal on metaphase chromosomes 17 and on interphase nucleus indicating a deletion in case 1 (*arrows*, *left image*), whereas two signals of both probes are present on metaphase chromosome of the patient's mother (*arrows*, *right image*). Similar signal patterns were observed for the other four patients (data not shown). Thus, we assume a *de novo* deletion in at least three cases.

- Of the 15 genes localized to the 17q12 microdeletion region, 2 may play a role in the variable phenotypes seen in affected carriers. Expression of the HNF1B gene is associated with vertebrate hindbrain development [Chometteet al., 2006; Pouilhe et al., 2007] and the translationproduct of this gene, hepatocyt nuclear factor-1, guidesthe embryological development of the kidneys, pancreas,liver and Müllerian ducts [Bingham and Hattersley,2004]. LHX1 is a candidate gene for the learning diff

Case report

- A male newborn born to a consanguineous parent at 37 weeks gestation with a low birth weight of 1.730 kg. Antenatal ultrasound- intrauterine growth restriction (IUGR). Mother- hypothyroidism, gestational diabetes. Father- mild fasting hyperglycemia controlled by diet.
- Baby’s initial examination was normal apart from low birth weight. From day 4 of life his blood glucose ranged from 180-250 mg/dl (10-13.8 mmol/l); no sepsis, no stress; on day 10 of life- he developed glucosuria. The HbA1c raised up 6.1% at age of three months

Whole exome analysis

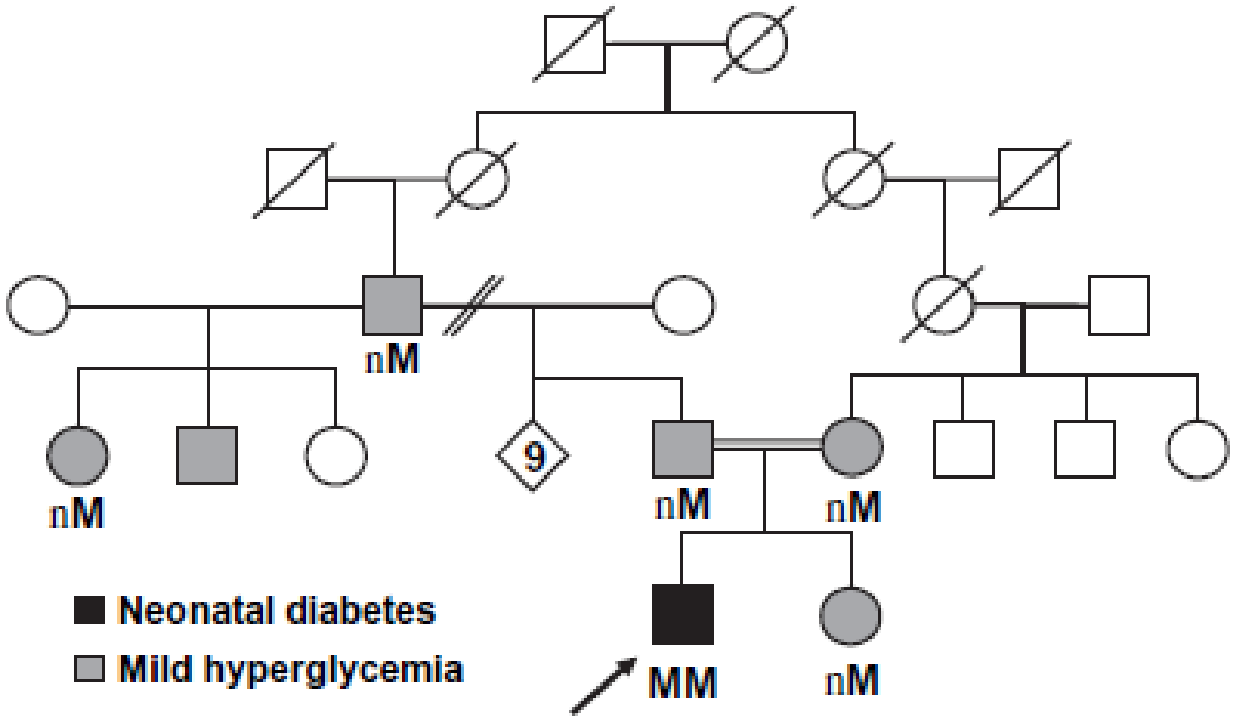
- c.667G>A ; p. Gly223Ser in the GCK (glucokinase) gene

Case report 2

- A baby male admitted to the neonatal intensive care unit (NICU) with respiratory distress and intrauterine growth restriction (IUGR). Birth weight was 1800 g, length 46 cm (-2.17 standard deviation scores) and head circumference 33 cm (-1.92 SDS). On admission at NICU serum glucose concentration was low (37 mg/dl). Over the next 24 h glucose concentration increased to 288 mg/dL and glucosuria was noted. He received broad-spectrum antibiotic treatment (*Escherichia coli* blood infection).The patient was transferred to subcutaneous insulin. Then he suffered a number of infections: otitis, bronchiolitis, pneumonia, urinary tract infection, parotitis, gastroeneteritis.

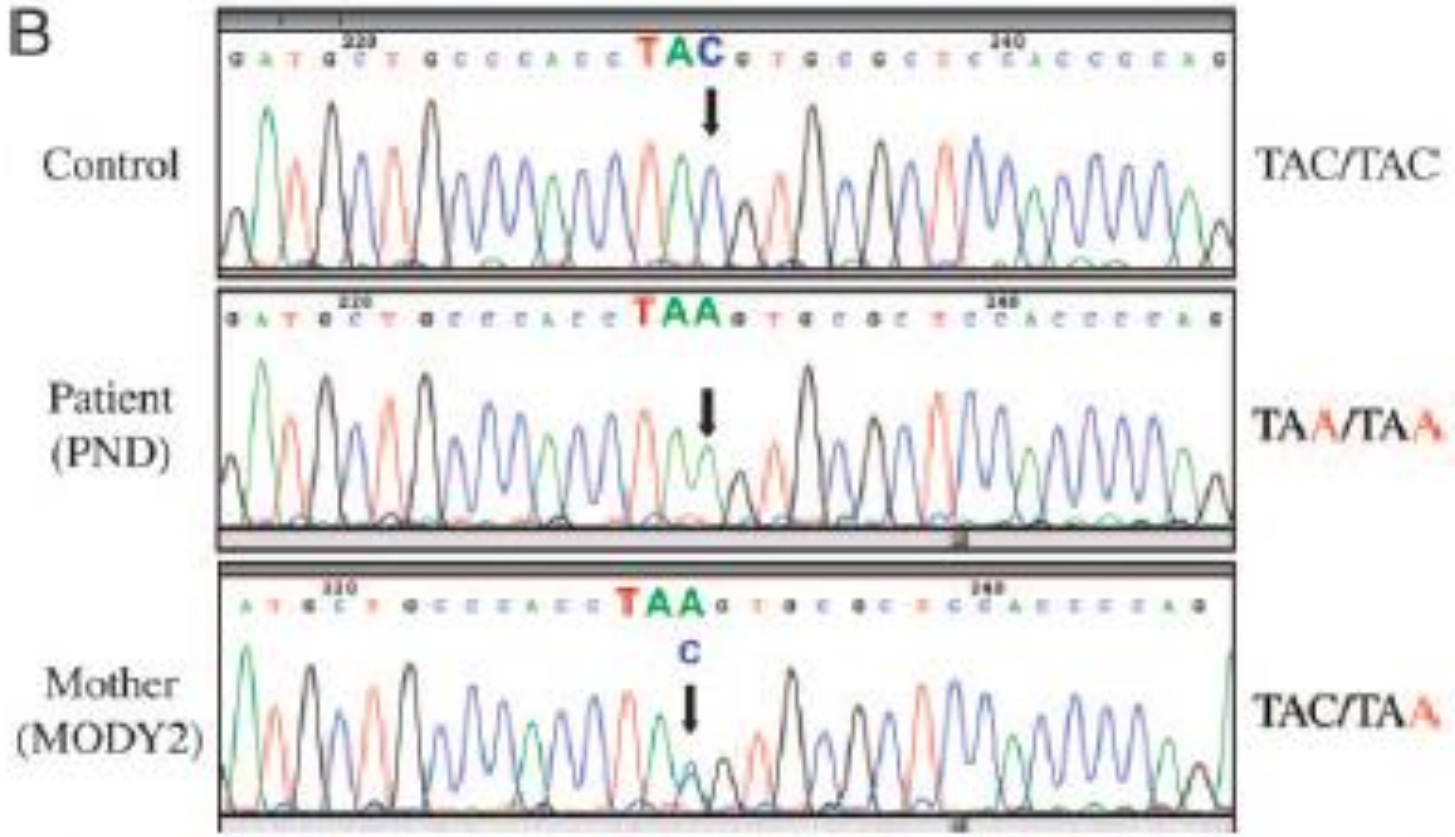
Rubio-Cabezas O et al. Pediatric Diabetes 20028; 9 (Part I): 245-249

Y61X mutation in *GCK* gene

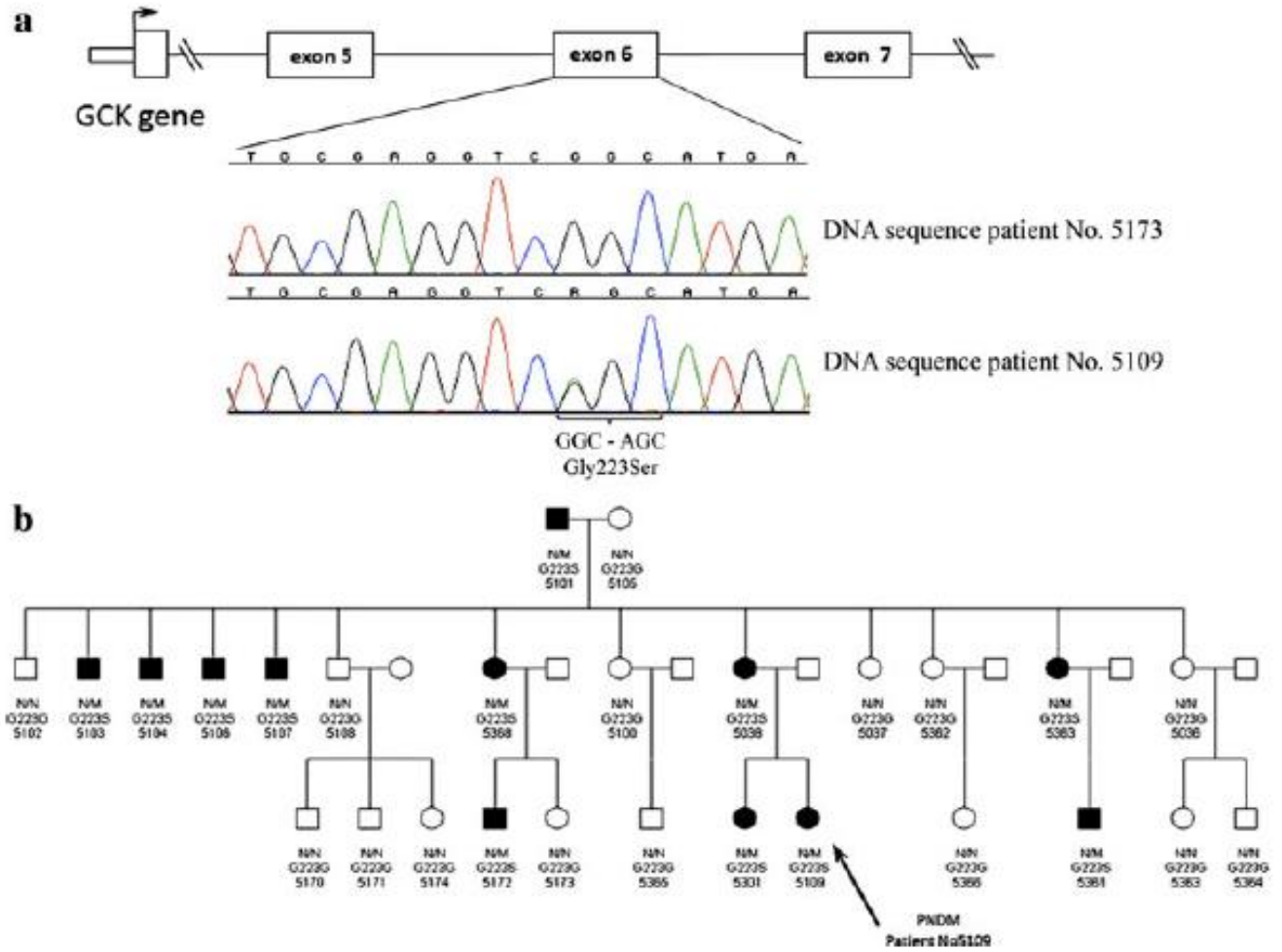


Rubio-Cabezas O et all. Pediatric Diabetes 2008; 9 (Part I): 245-249

Direct sequencing of the GCK exon 2



Rubio-Cabezas O et al. Pediatric Diabetes 2008; 9(Part I): 245-249



Borowiec M et al. Acta Diabetologica 2011

Continous glucose monitoring results

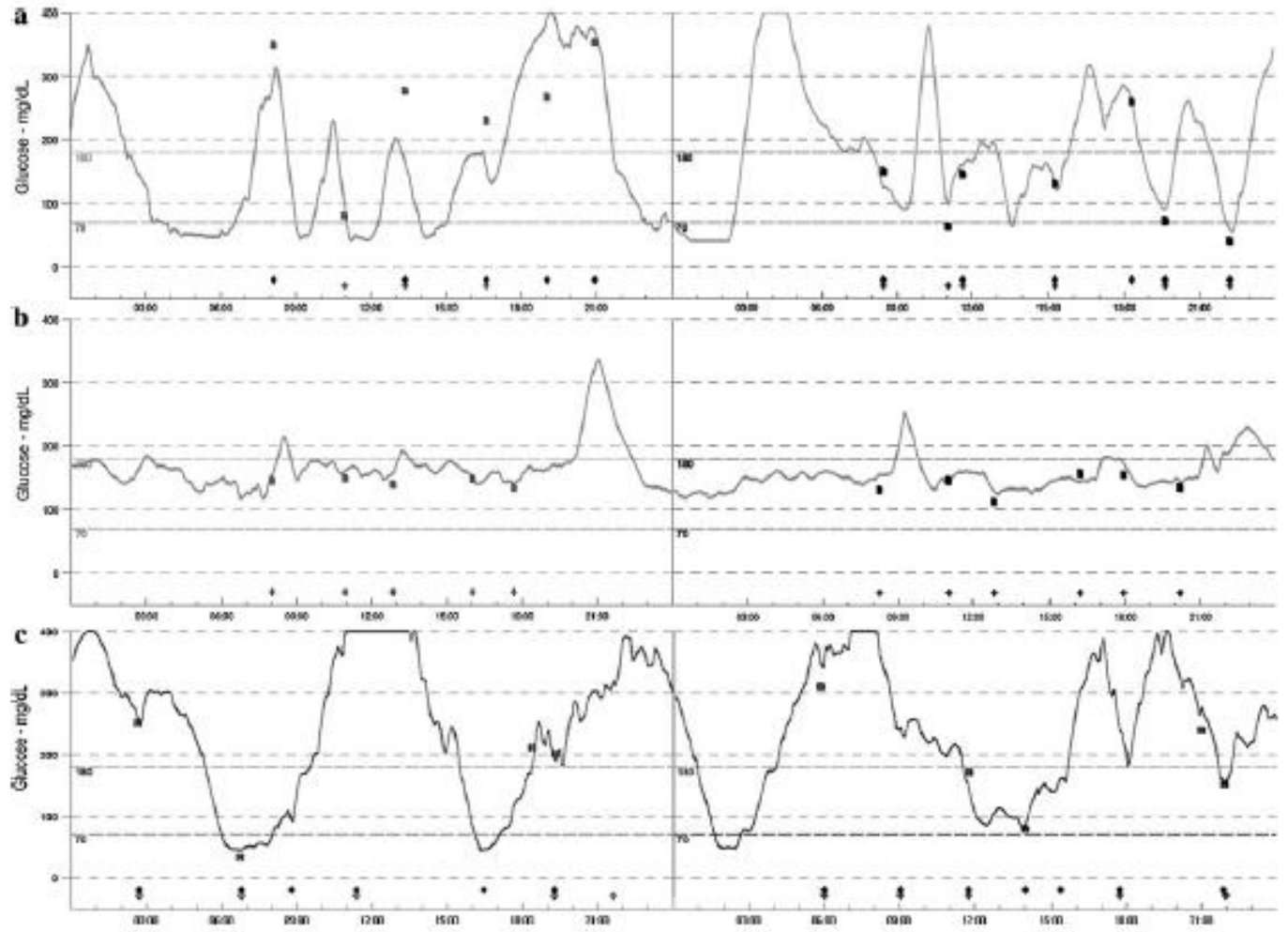
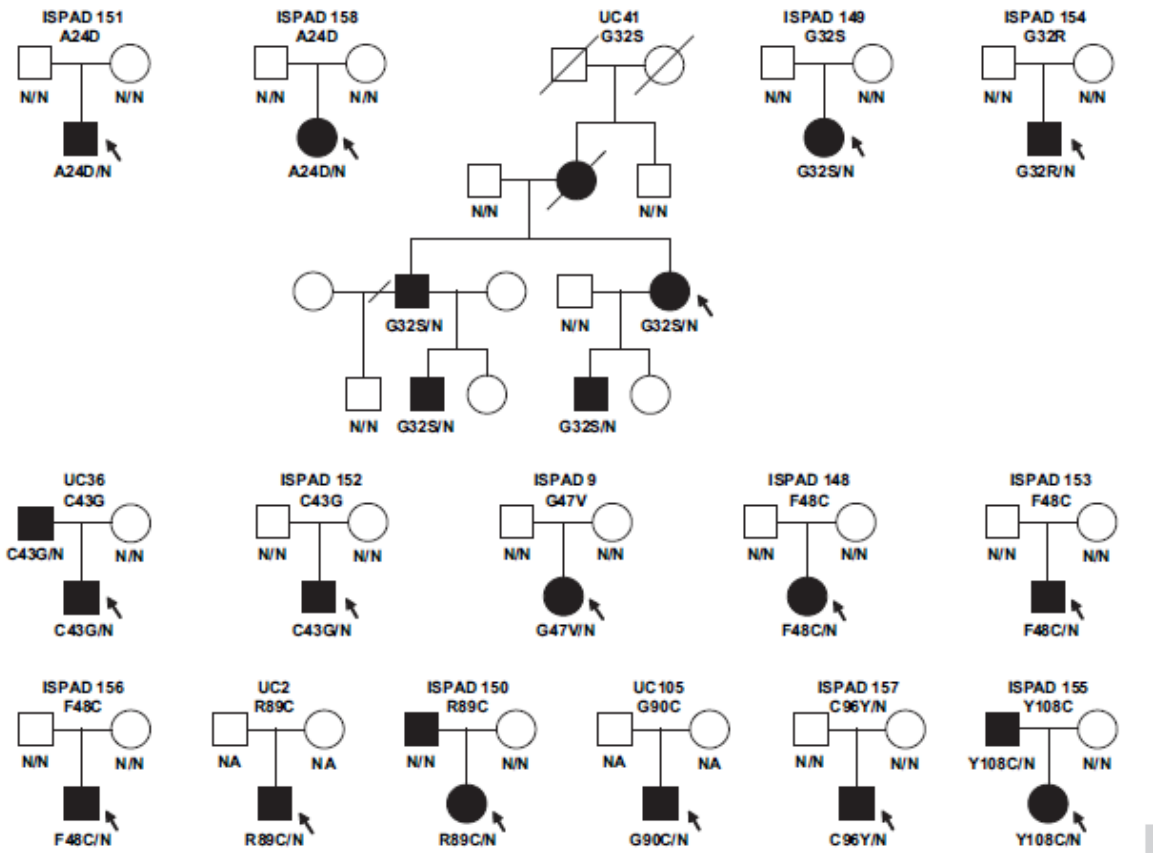
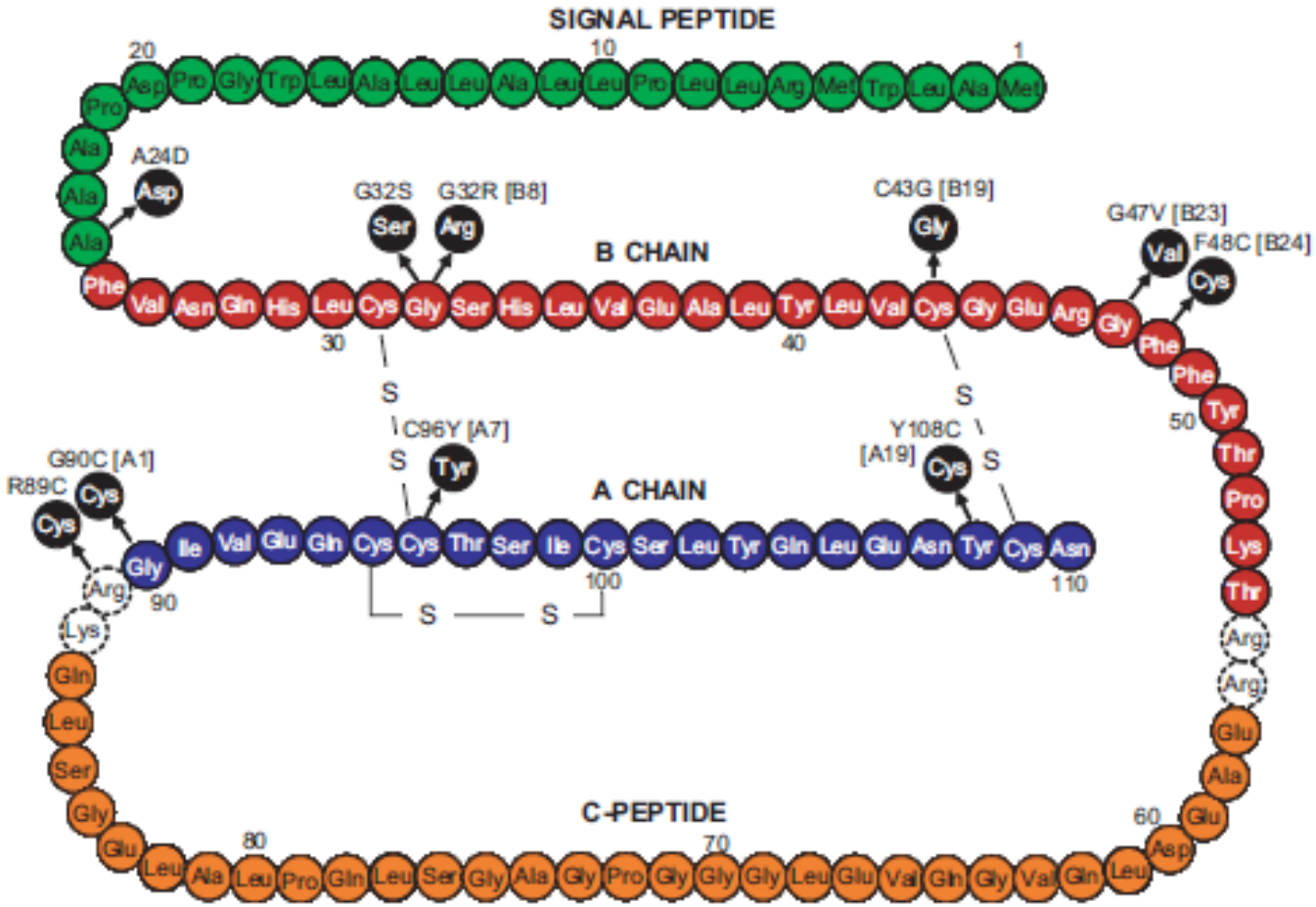


Fig. 2 Continuous glucose monitoring results of patient No5109 with a phenotype of neonatal diabetes and heterozygous p.Gly223Ser mutation in glucokinase (**a**), her sister with mild phenotype and the same heterozygous p.Gly223Ser mutation (**b**) and a 3-year-old patient with type 1 diabetes mellitus (**c**)

Insulin gene mutations



Stoy J et all. PNAS 2007; 104 (38): 15040-15044



StoJ, et all. PNAS; 104(38): 15040-15044

- 13-year-old girl, no consanguinity in family admitted to paediatric emergency department with headache and vomits during the last 48 hours; hyperglycemia of 177 mg/dL, HBA1c-6.8%. Islet cel antibodies (ICAs) were positive, C-peptide value was normal.

Oliveira RV, et all. BMJ Case Reports 2021; 14: e231837. doi: 10.1136/bcr-2019-231837

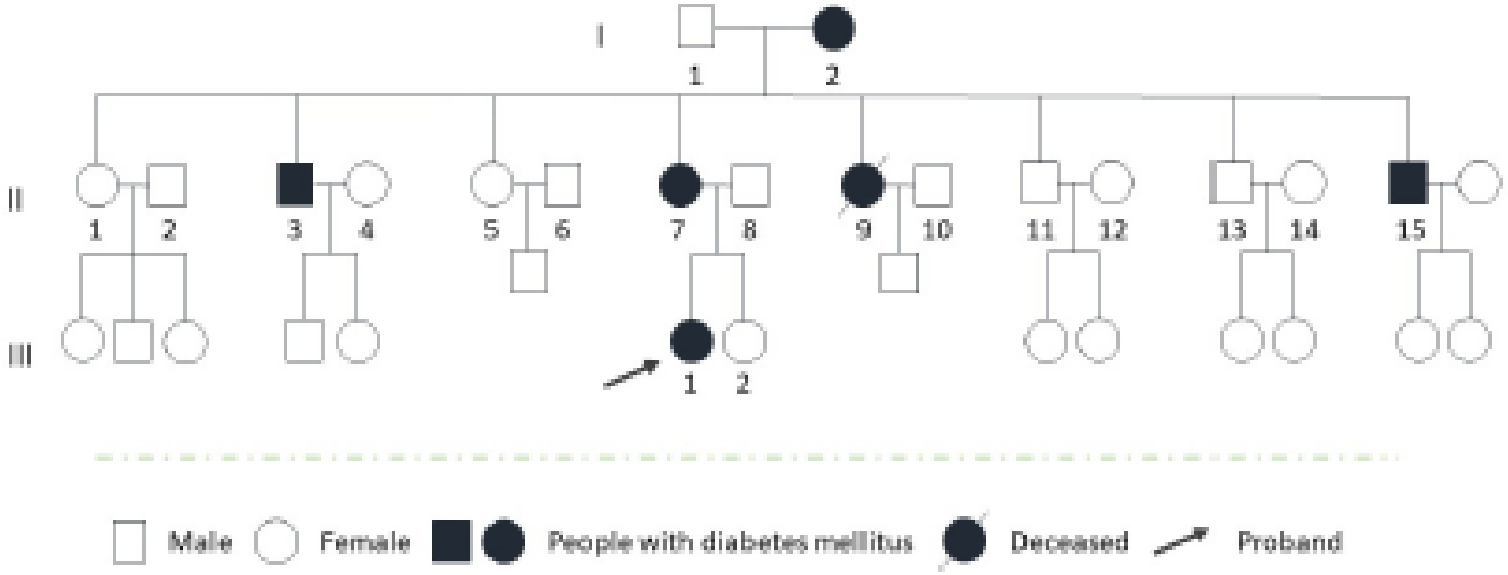


Figure 1 Patient's family history regarding a diabetes mellitus (DM) diagnosis. I 2—Grandmother with DM2 diagnosed in her youth, medicated with oral antidiabetic medication; II 7—Mother with DM2 diagnosed at 21 years old, medicated with slow-acting insulin; II 3, 9, 15—Three uncles with DM2 diagnosed in youth and medicated with oral antidiabetic medication or with long-acting insulin (one deceased). III 1—maturity onset diabetes of the young diagnosed at 13 years old.

- c.687_707del; p.Glu230_Cys236del in *HNF1A* gene

Familial Hypercholestrolemia (FH)

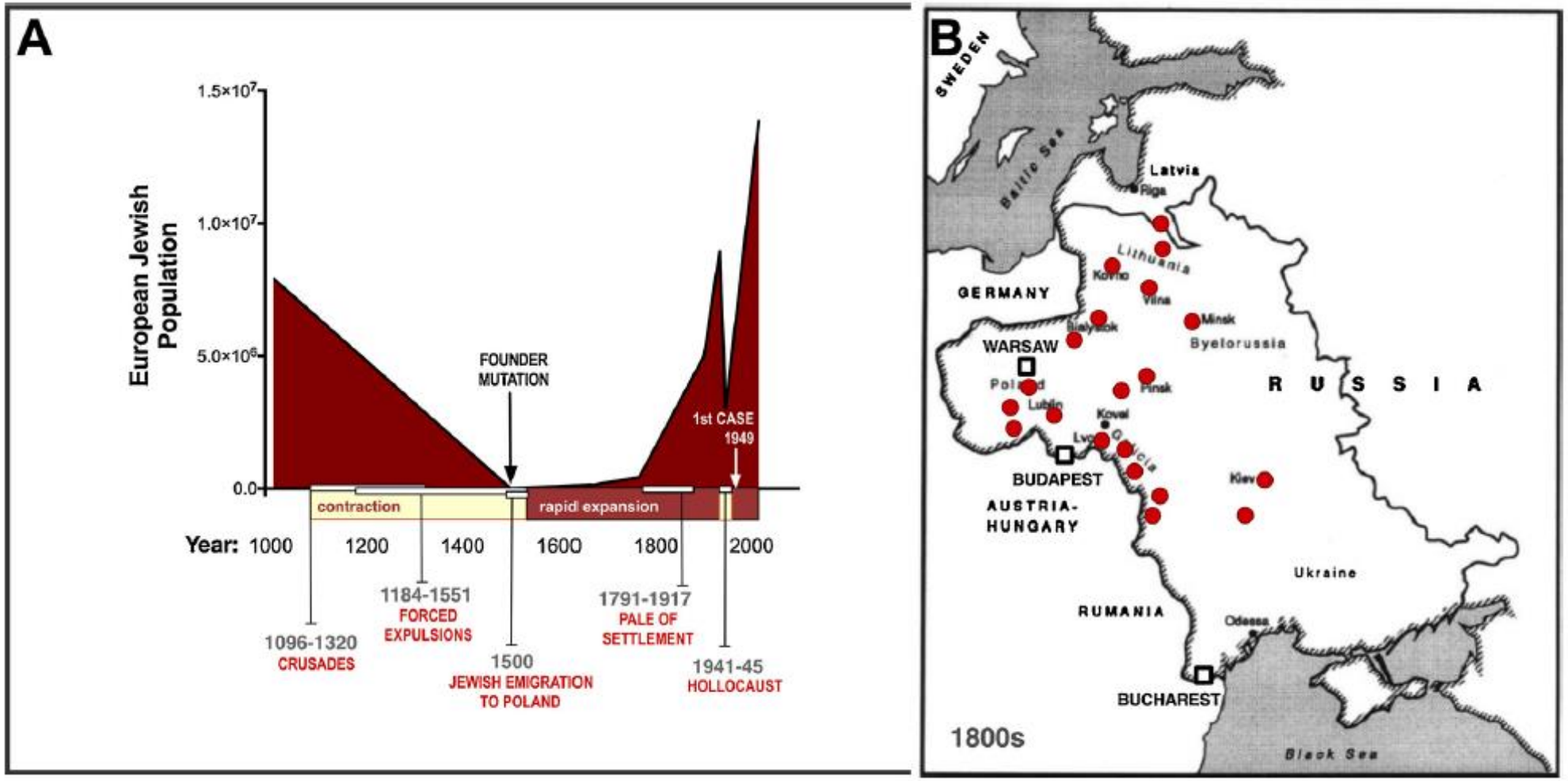
Prevalence of FH

- Homozygous FH is rare, ie, 1 in 1 milion but may be as high as 1 in 300000
- Founder effect (Lebanese, South African Afrikaners, South African Jews, South African Indians, French Canadians, Tunisians)
- Heterozygous FH- 1:500
- Less than 20% of all estimated cases are diagnosed
- Only 42% (US FH registry) receives statin therapy

Founder effect

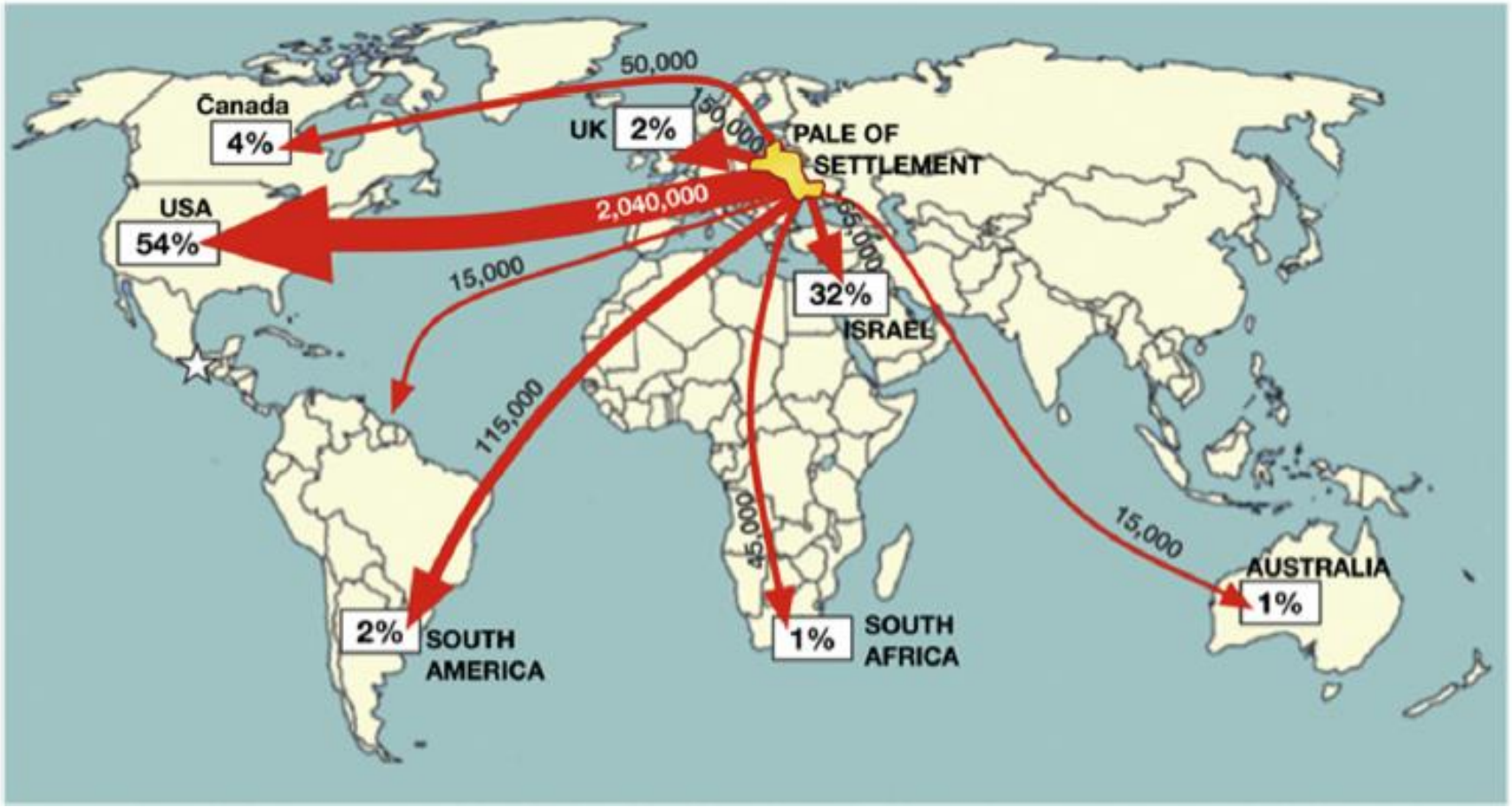
Catherine II[(born Sophie of Anhalt-Zerbst; 2 May 1729 – 17 November 1796), most commonly known as Catherine the Great, was the last reigning Empress Regnant of Russia (from 1762 until 1796)

IKBKAP gene mutation-Poland -1500



Norcliffe-Kaufmann L i wsp. Progress in Neurobiology 2017; 152: 131-148

First Rileya-Day syndrome patient diagnosed in 1949



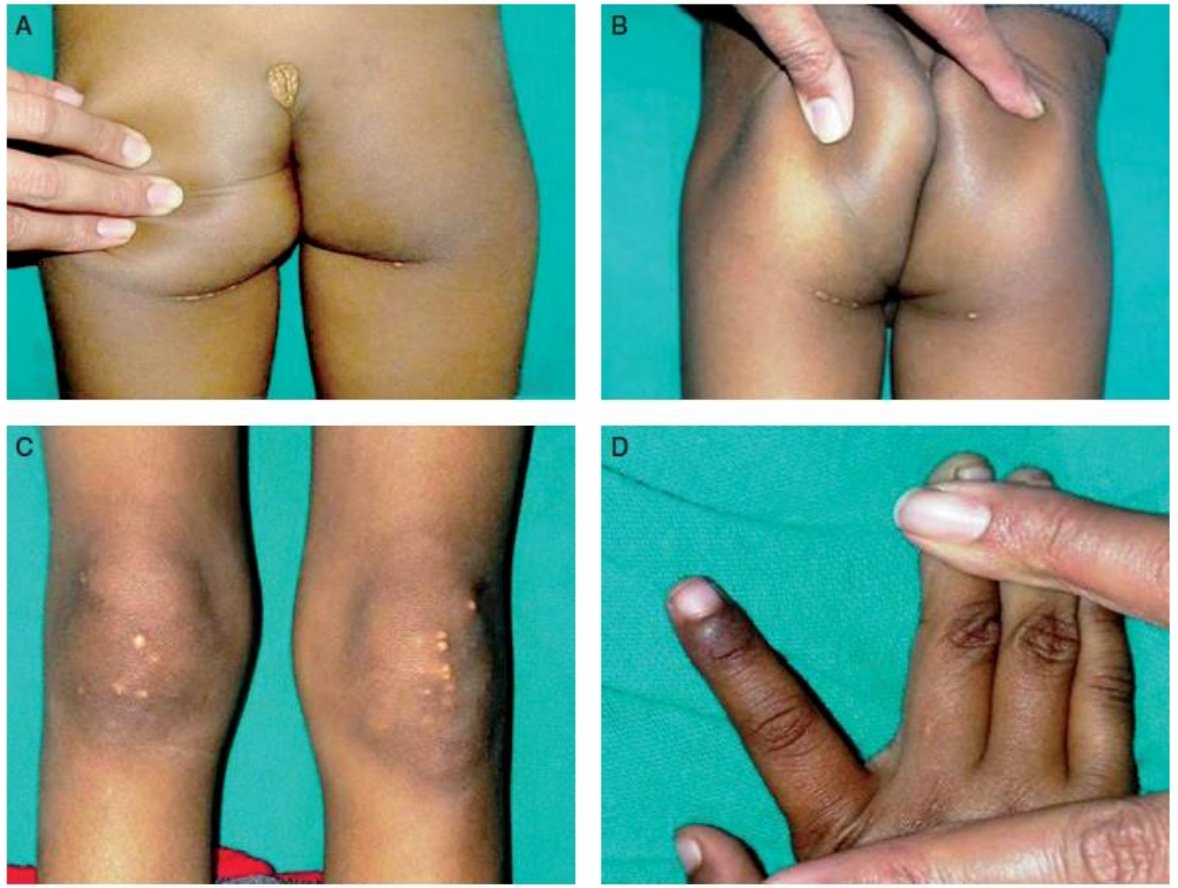
Norcliffe-Kaufmann L. i wsp. Progress in Neurobiology 201; 152: 131-148

Clinical presentation

- -significantly elevated LDL-C levels –typically elevated greater than the 90th percentile for age and sex
- -early onset ASCVD – atherosclerotic cardiovascular disease
- Pathognomonic signs of cholesterol deposits under the skin (xanthomas)
- Cholesterol deposits in the cornea (corneal arcus)

Xanthomas and Arcus

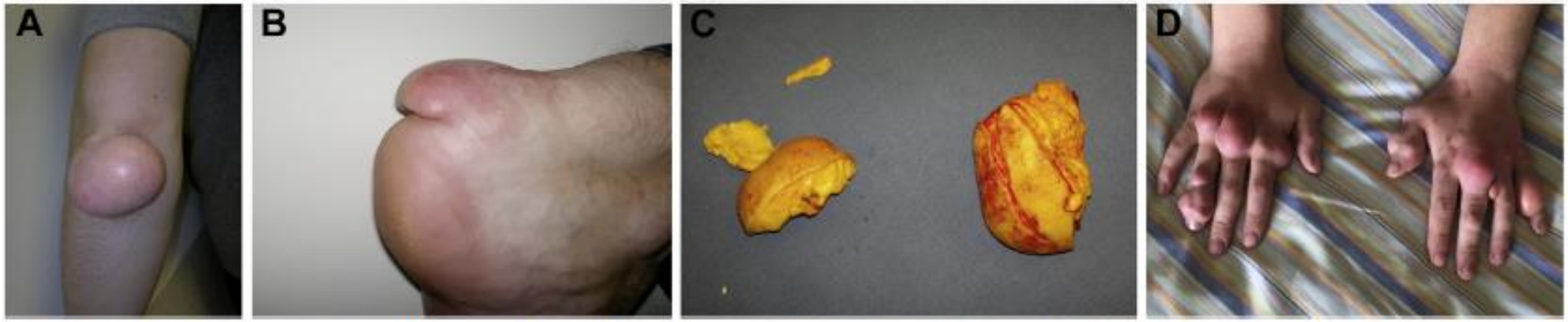
- Xanthomas on the extensor tendons-thickening of the Achilles tendon
- Corneal arcus –grayish-white ring opacity in the periphery of the cornea unilaterally or bilaterally – not asociated with visual impairement
- Ultrasound of the Achilles tendon- increase the sensitivity of detecting xanthomas by 80% and the specifity by up to 88%



Dewan P, Grover Ch. Pediatric Endocrionology Diabetes and Metabolism 2021

Figure 2. Bilateral *Arcus juvenilis*

Dewan P, Grover Ch. Pediatric Endocrionology Diabetes and Metabolism 2021



igure 1 A) Xanthomas on the elbows (24 years). (B) Xanthomas on the Achilles tendons (24 years). (C) Histology of Xanthomas 24 years). (D) Xanthomas on the metacarpal joint area of both hands (28 years).

History and examination

- History of personal and family occurrence of premature ASCVD must be elicited
- History of thyroid, renal, hepatic, or biliary disease as causes of hypercholesterolemia
- Physical examination: peripheral pulsies, the presence of aneurysms, xanthomas, corneal arcus, signs of aortic valve stenosis, aortic valve calcification

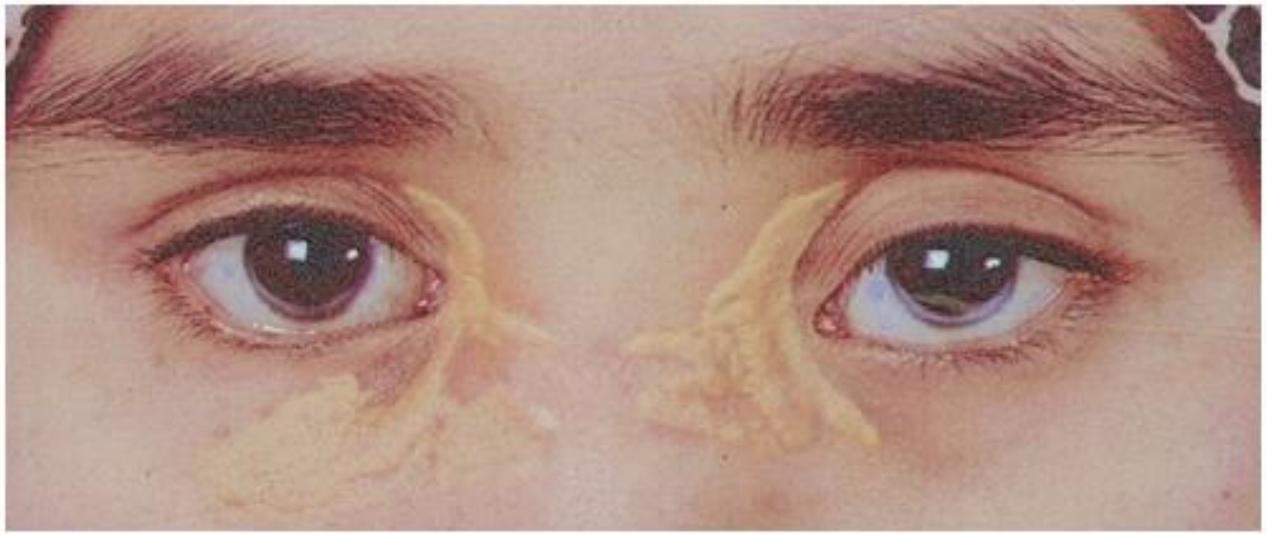


FIG. 1: Xanthelasma. Marked yellow plaques near the inner canthus of the eyelids with bilateral corneal arcus.

MK Alicezah et al. Malaysian J Pathol 2014; 36(2): 131-137

Clinical criteria

- Homozygous FH: Plasma LDL-C levels> 500 mg/dl
- Biallelic mutation in FH-related gene: *LDLR, APOB, PCSK9 or LDLRAP1*
- Heterozygous FH:
- Plasma levels of LDL-C(mg/dL)- Low density lipoprotein cholesterol
- >325 (8 points)
- 251-325 (5 points)
- 191-250 (3 points)
- 150-190 (1 point)
- Molecular genetic testing: pathogenic variants in *LDLR, APOB, PCSK9* (8 points)
- Het FH- total score is greater than 8 points.

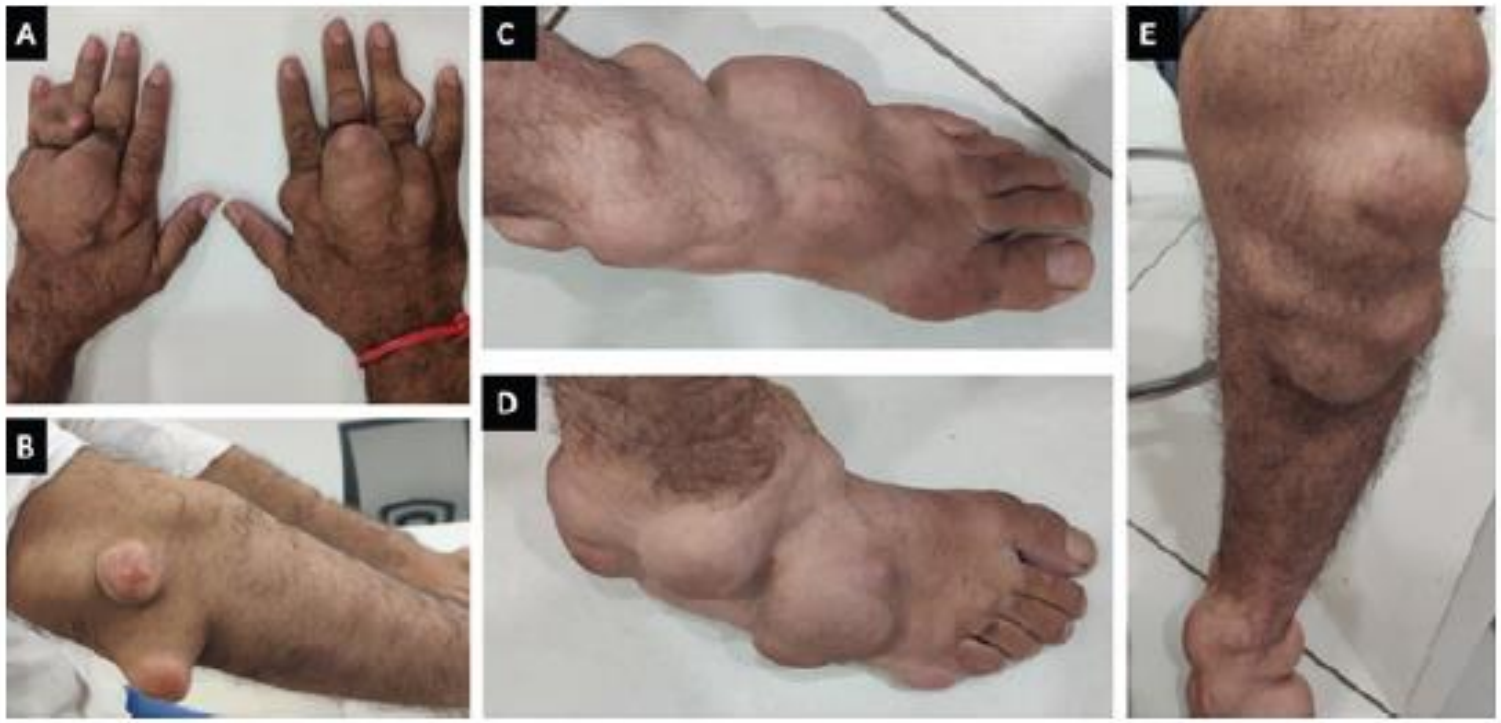


Figure 1: Clinical photographs of the patient showing xanthomas over extensor aspect of Hands (a), Elbow (b), Bilateral Feet (c and d), and Knee (r).

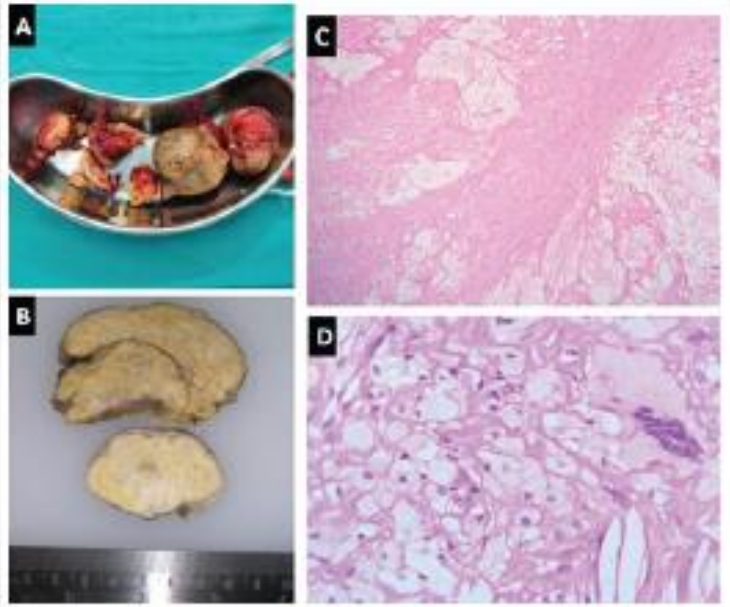


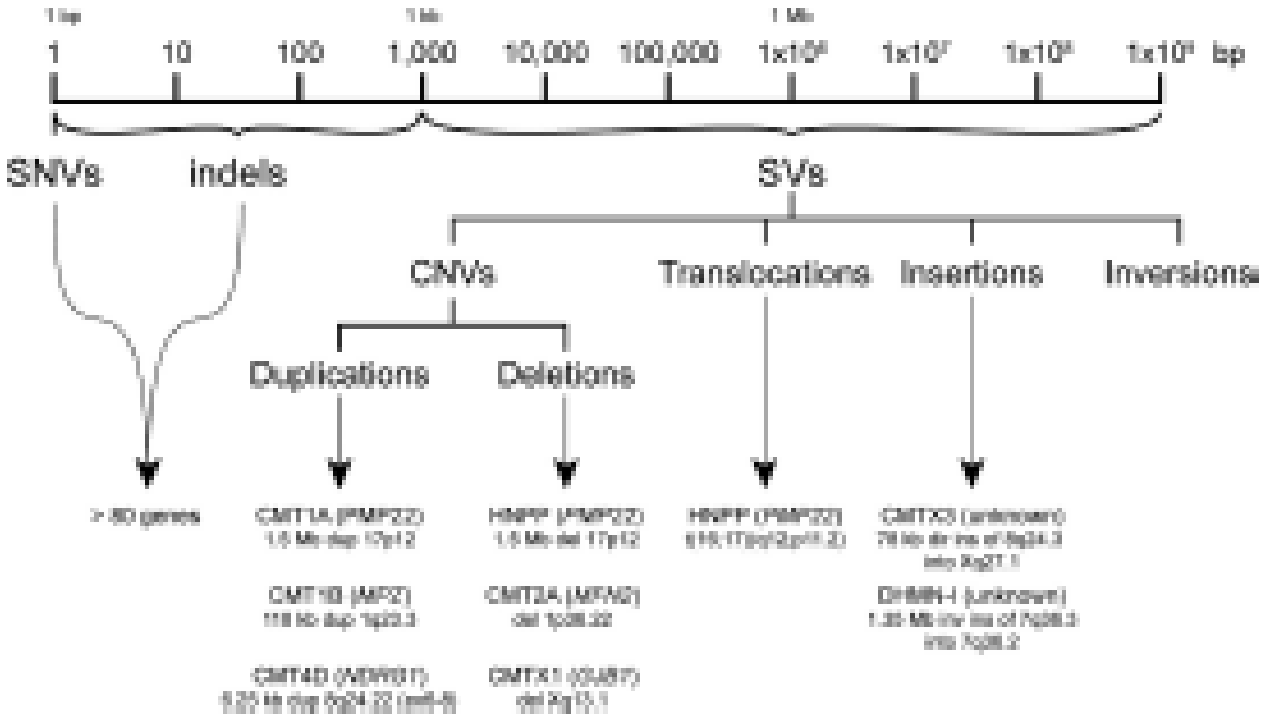
Figure 2: (a) Excised swellings post-surgery, (b) gross cut surface of the swellings having a yellowish nodular appearance, (c) dermis shows a pale lesion composed of foamy histiocytes and cholesterol clefts with areas of fibrosis (H and E, ×4), (d) sheets of foamy histiocytes having lipid droplets are present. Note cholesterol clefts and giant cell.

- To date, genetic testing has become more affordable in terms of laboratory procedures and costs , but data interpretaton has become more complex due to the large amounts of generated data.

Genetic testing

- 1. sequencing of *LDLR* supplemented by large deletion/duplication analysis
- 2. APOB: genotyping of two variants (R3500Q and R3500W)
- 3. sequencing of *PCSK9*

Small structural alterations



Treatment

- High-intensity lipid-lowering therapy with maximum tolerable dose of statin
- Treatment should be started as soon as diagnosis has been made and should be continued throughout the lifetime
- Patients with FH should be counseled on lifestyle changes, reduced intake of saturated and trans fats and cholesterol, limitation of alcohol consumption, smoking cessation and regular physical activity, blood pressure and glucose control

Case report

- A 30-year-old woman was admitted to the hospital with an inferior wall ST-segment elevation. She had yellowish nodules on the tendons of the hands and the Achilles tendon. The LDL-C level was of 285 mg/dL, coronary angiography revealed right coronary artery occlusion.

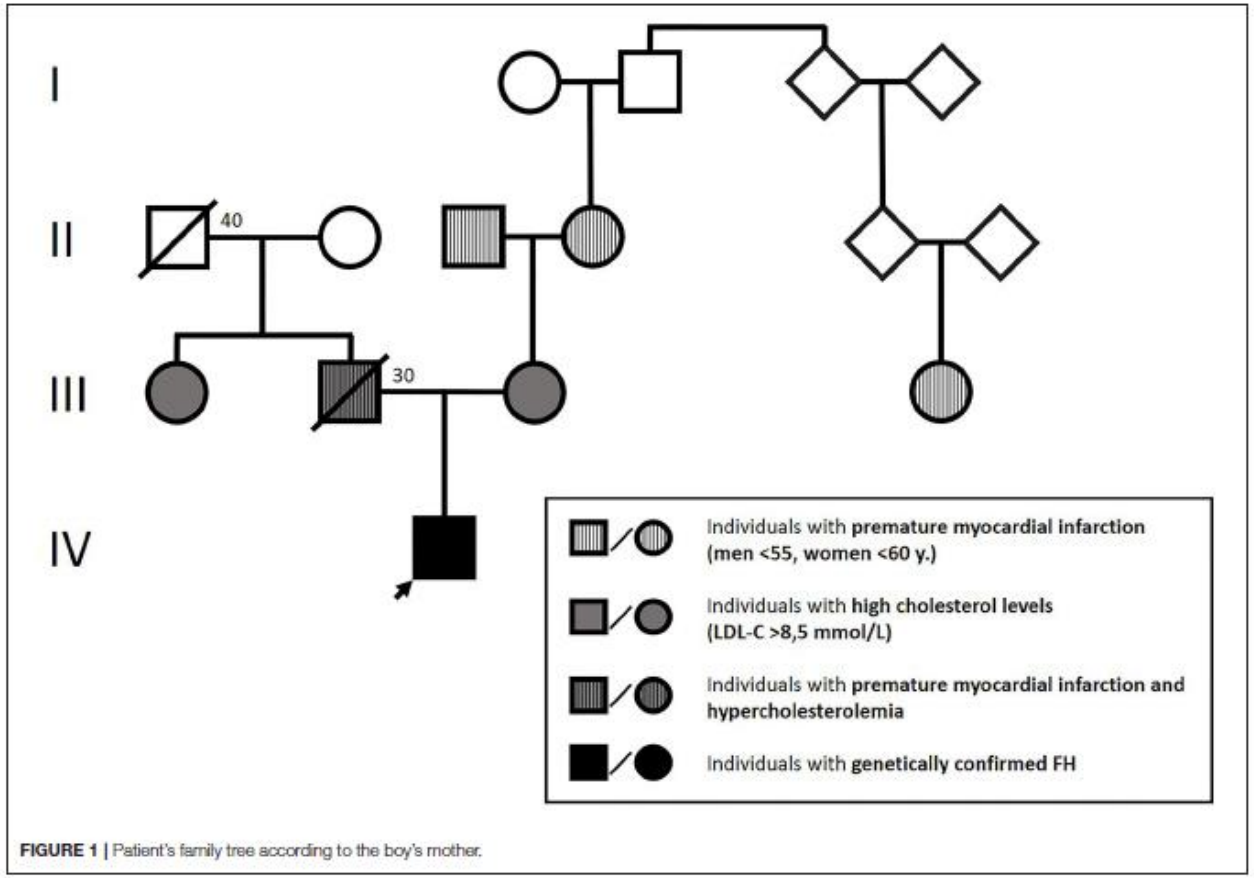


FIGURE 1 | Patient's family tree according to the boy's mother.

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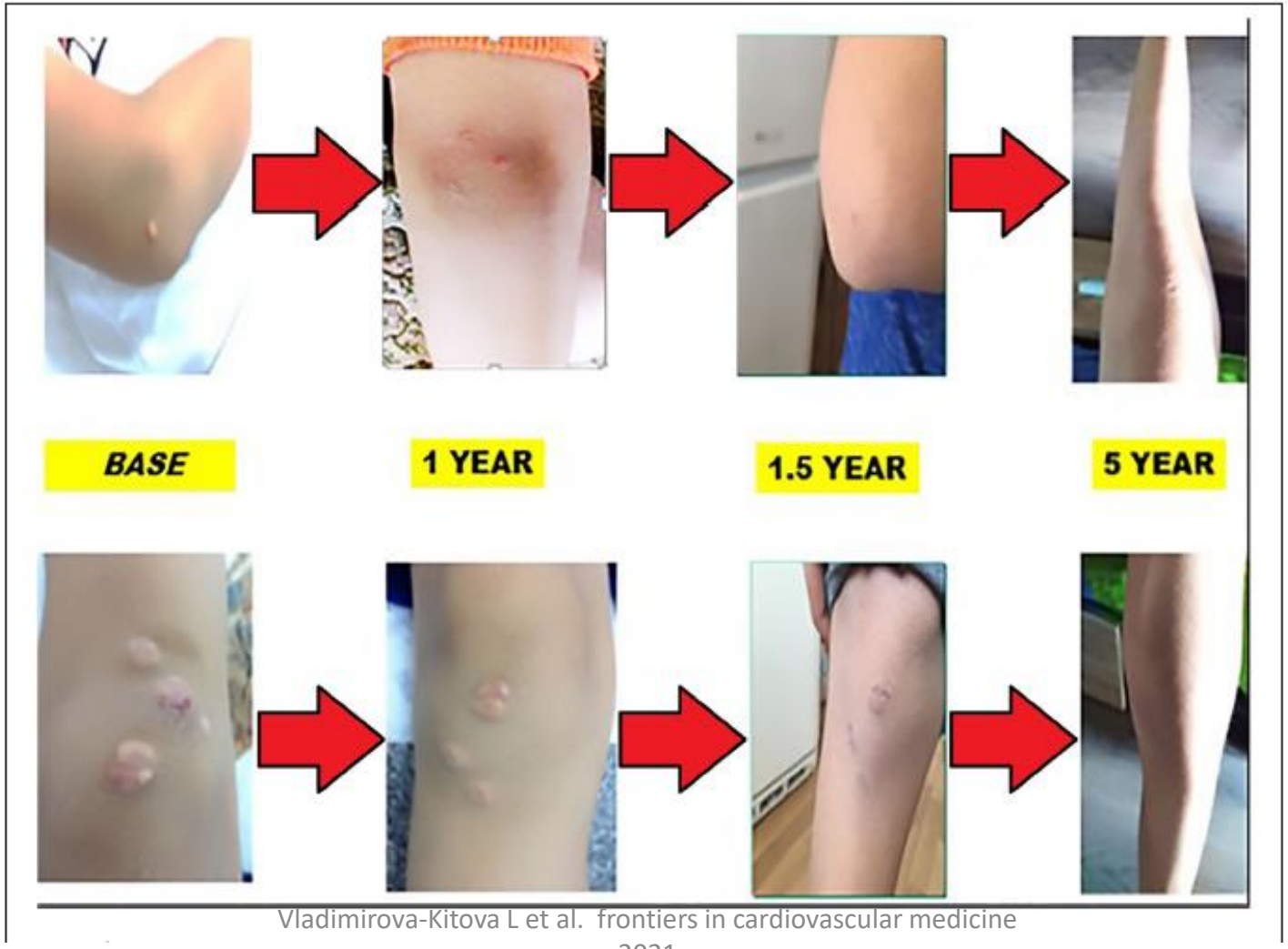
Involution of the xanthomas during the treatment



Vladimirova-Kitova L et al. frontiers in cardiovascular medicine 2021

Statins

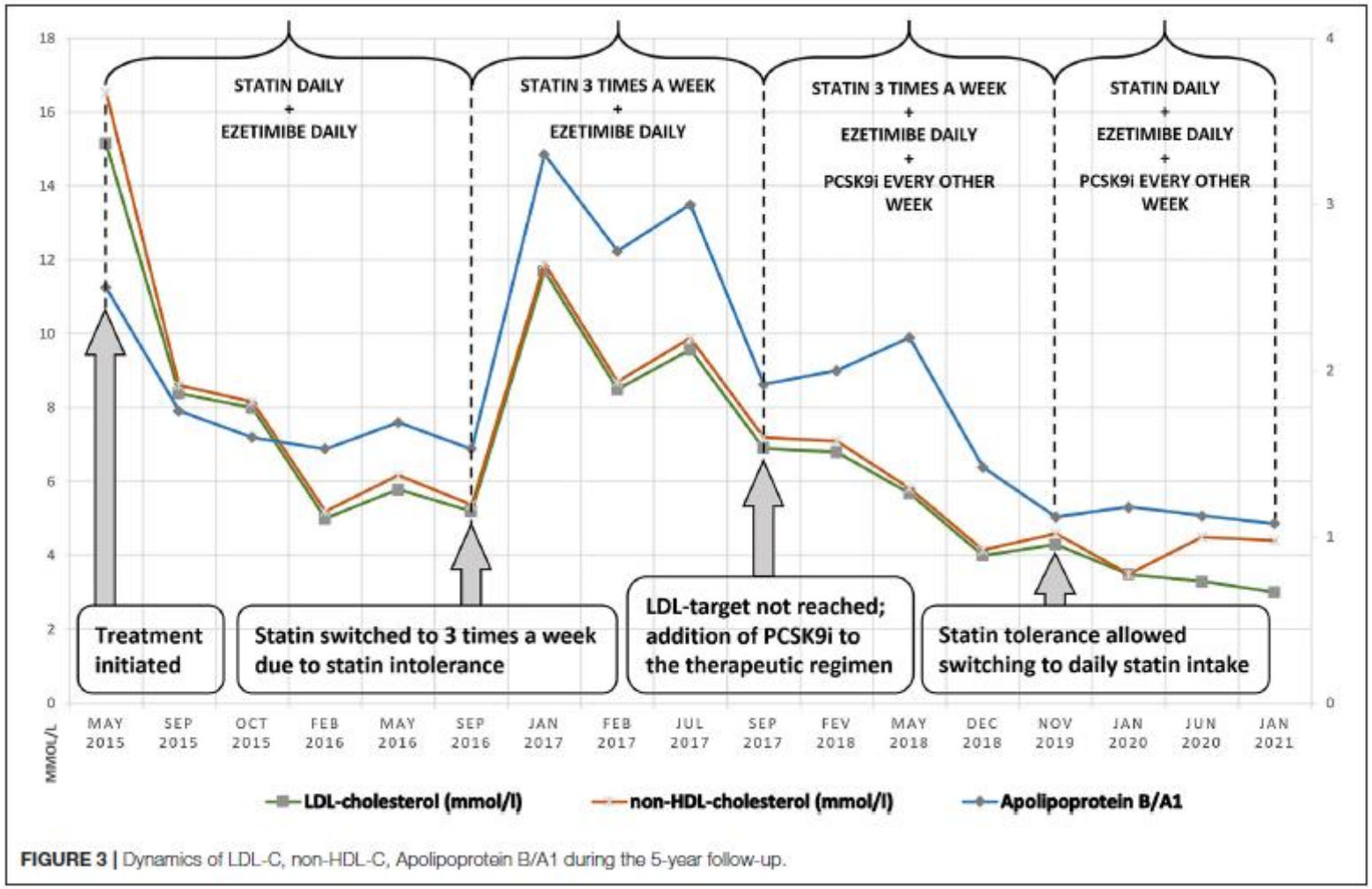
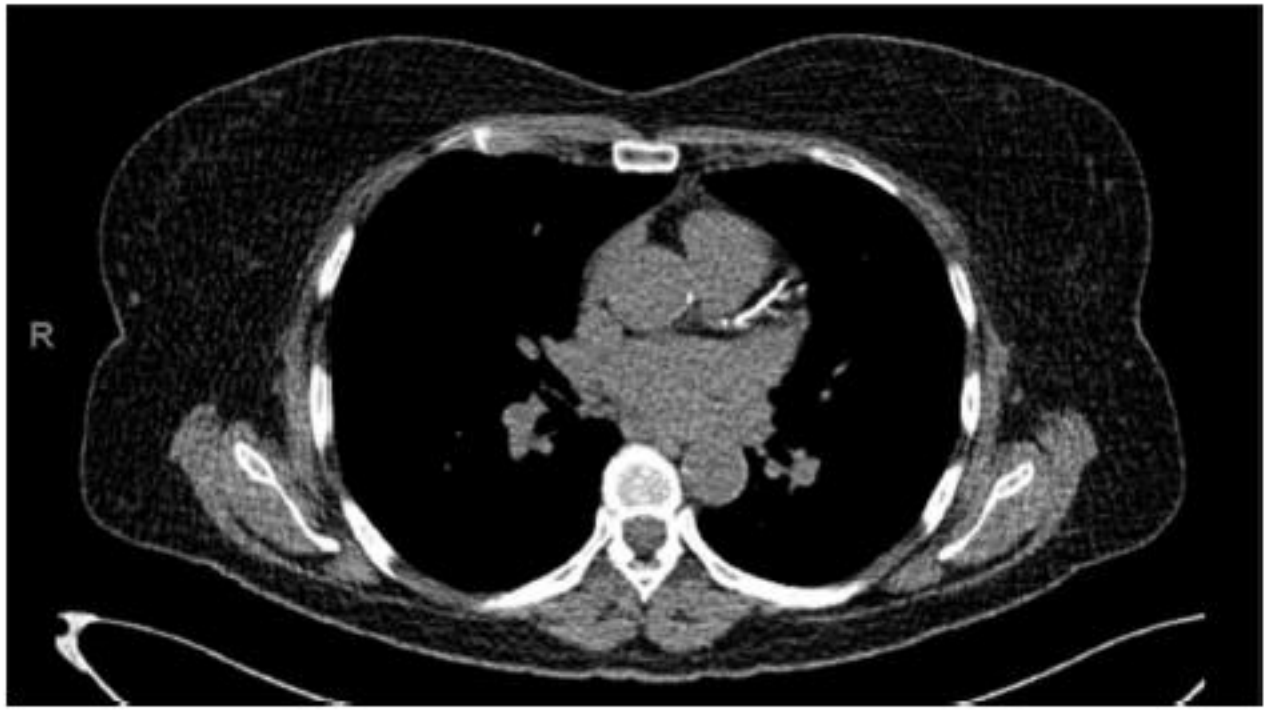


FIGURE 3 | Dynamics of LDL-C, non-HDL-C, Apolipoprotein B/A1 during the 5-year follow-up.

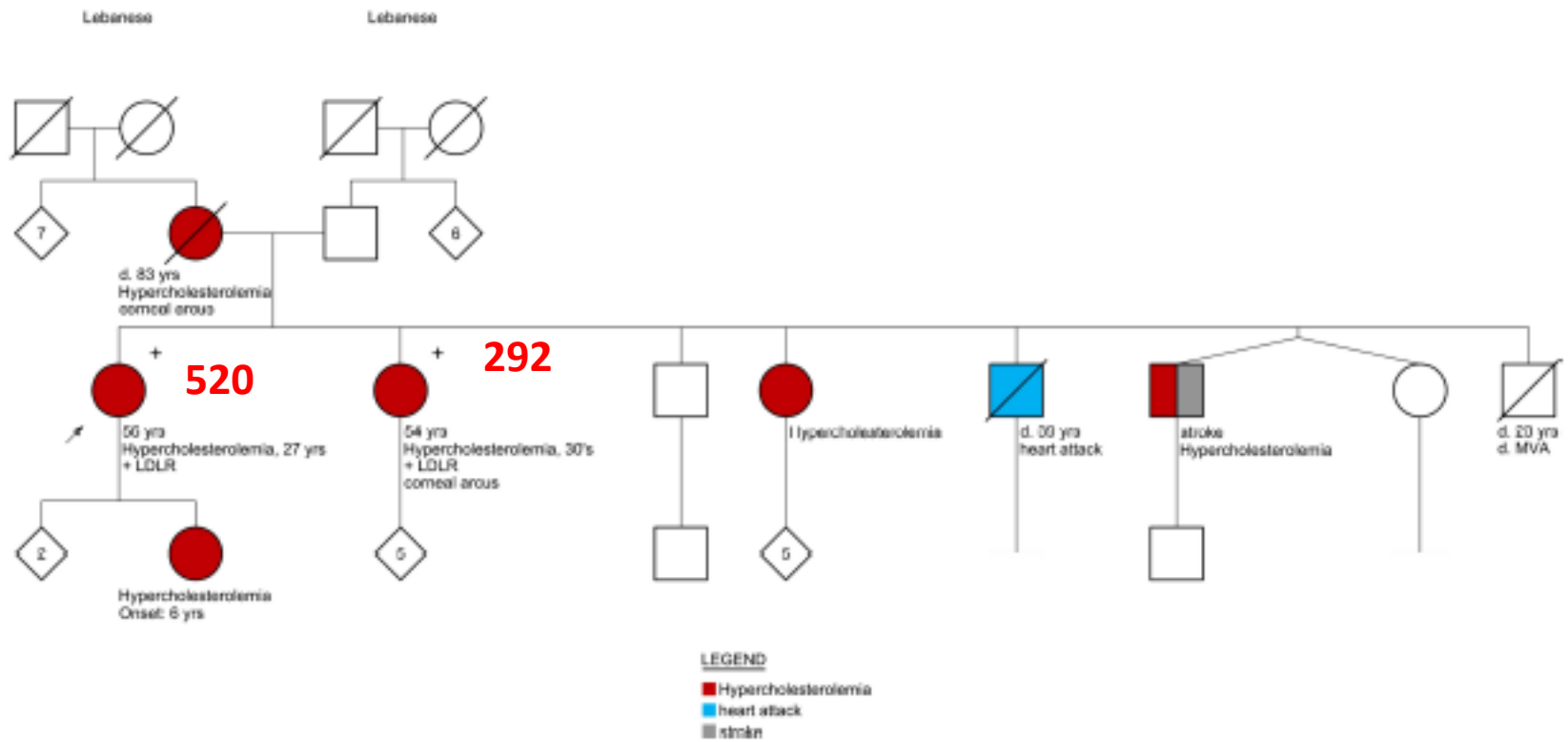
LDLR p.Cys681X – Lebanese allele

- 56-year-old female of Lebanese descent with abnormal coronary calcium scan



Chahine et al. Vascular Health and Risk Management 2021

- Hyperlipidemia diagnosed at age 27
- Smoking with a 20-pack year history
- Total cholesterol (TC)- 630 mg/dl [normal<200]
- LDL-C of **520 mg/dl** [normal <100]
- Triglycerides (TG) of 188 mg/dl [normal<150]
- No cholesterol deposits
- Not on any specific diet
- Sister of the patient: a 54-year-old female with LDL-C of **292 mg/dl**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Hypercholesterolemia, 27 yrs
+ LDLR
54 yrs
Hypercholesterolemia, 30's
+ LDLR
corneal arcus
Hypercholesterolemia
d. 30 yrs
heart attack
stroke
Hypercholesterolemia
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Hypercholesterolemia
Onset: 6 yrs
LEGEND
Hypercholesterolemia
heart attack
stroke

Expanded Clinical Spectrum in Hepatocyte Nuclear Factor 1B-Maturity-Onset Diabetes of the Young

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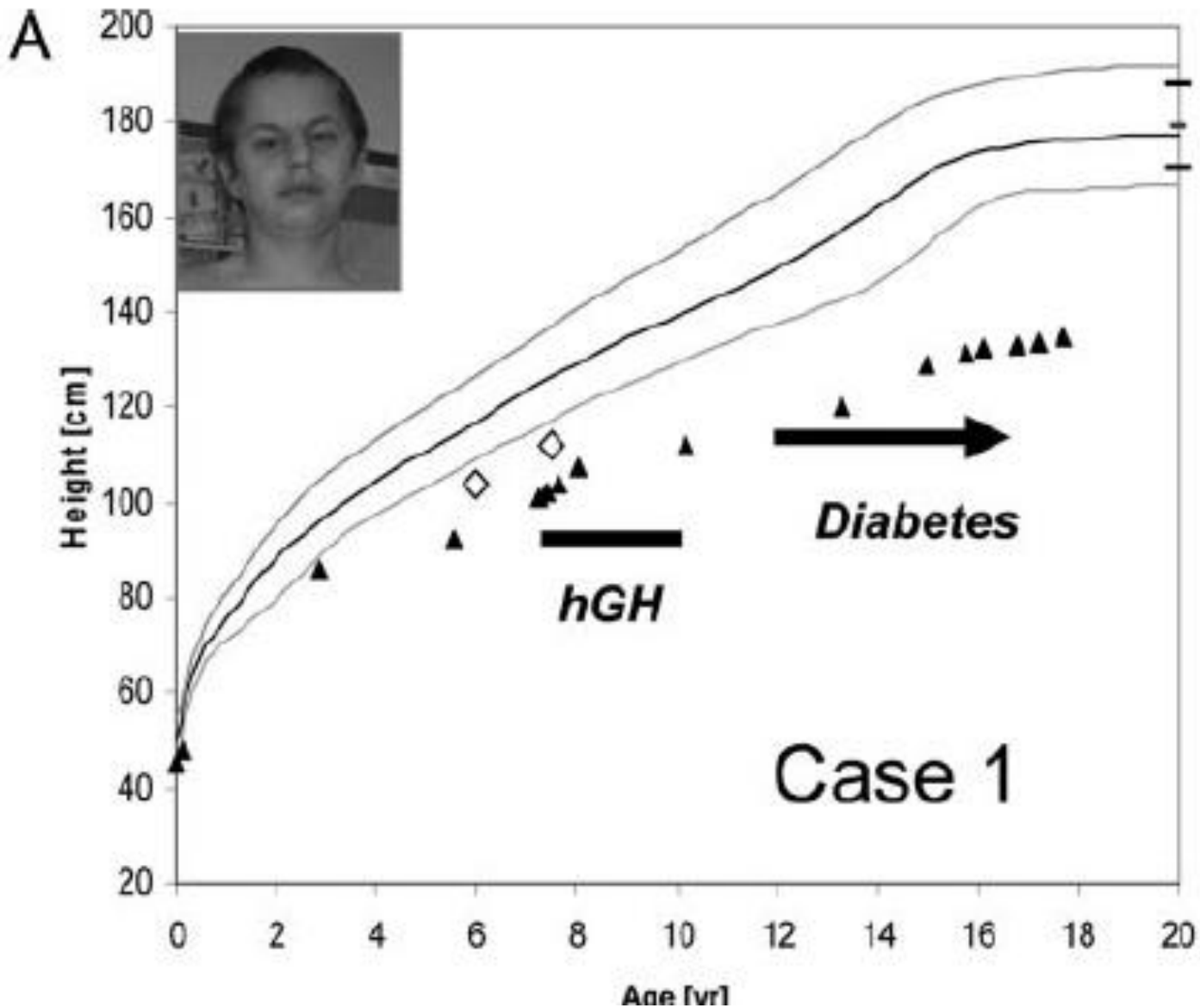
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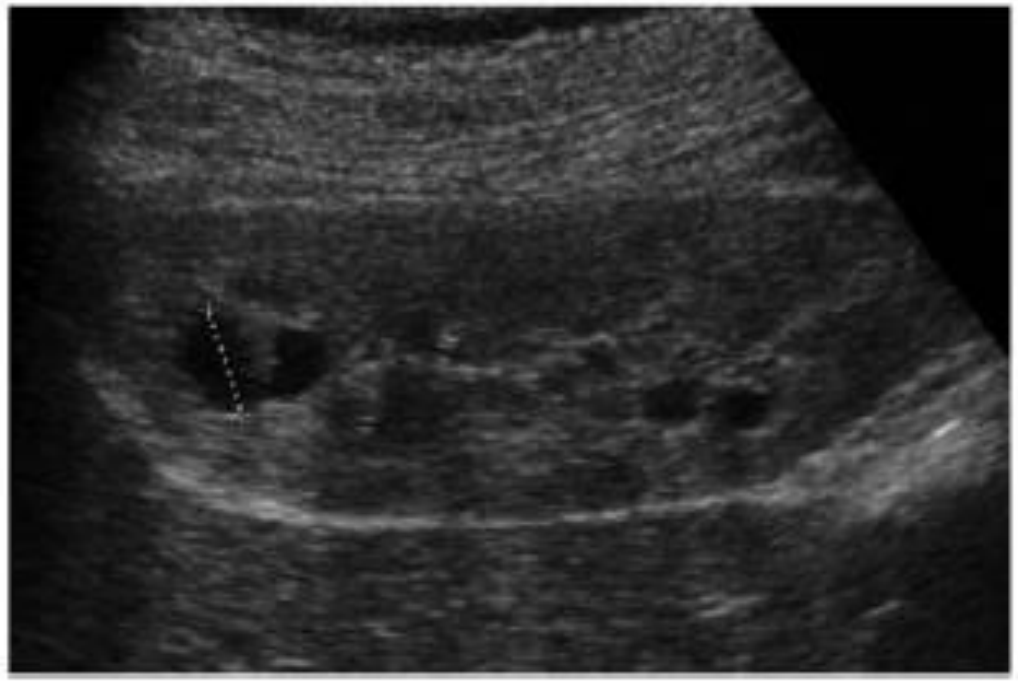
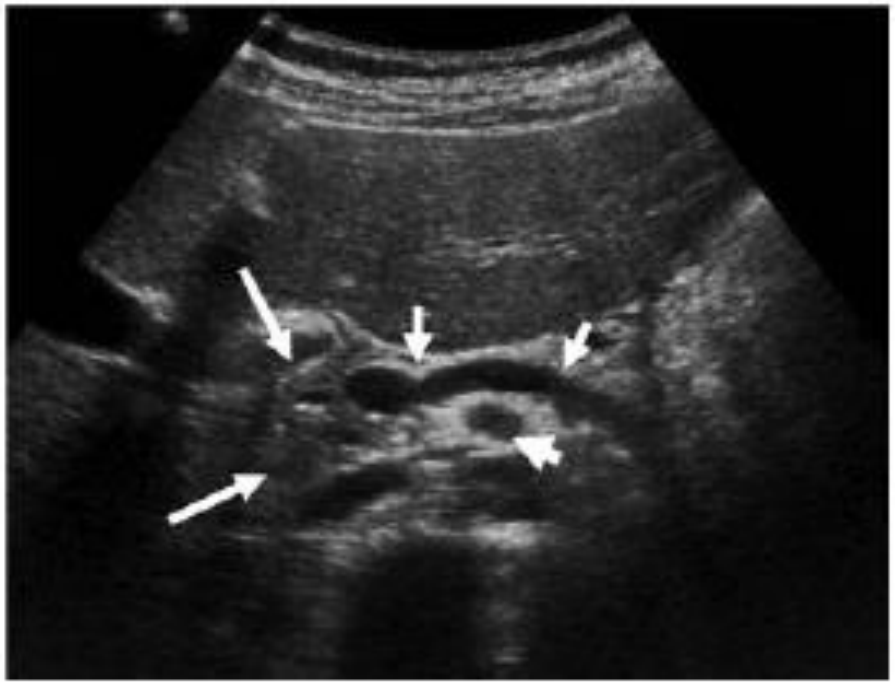
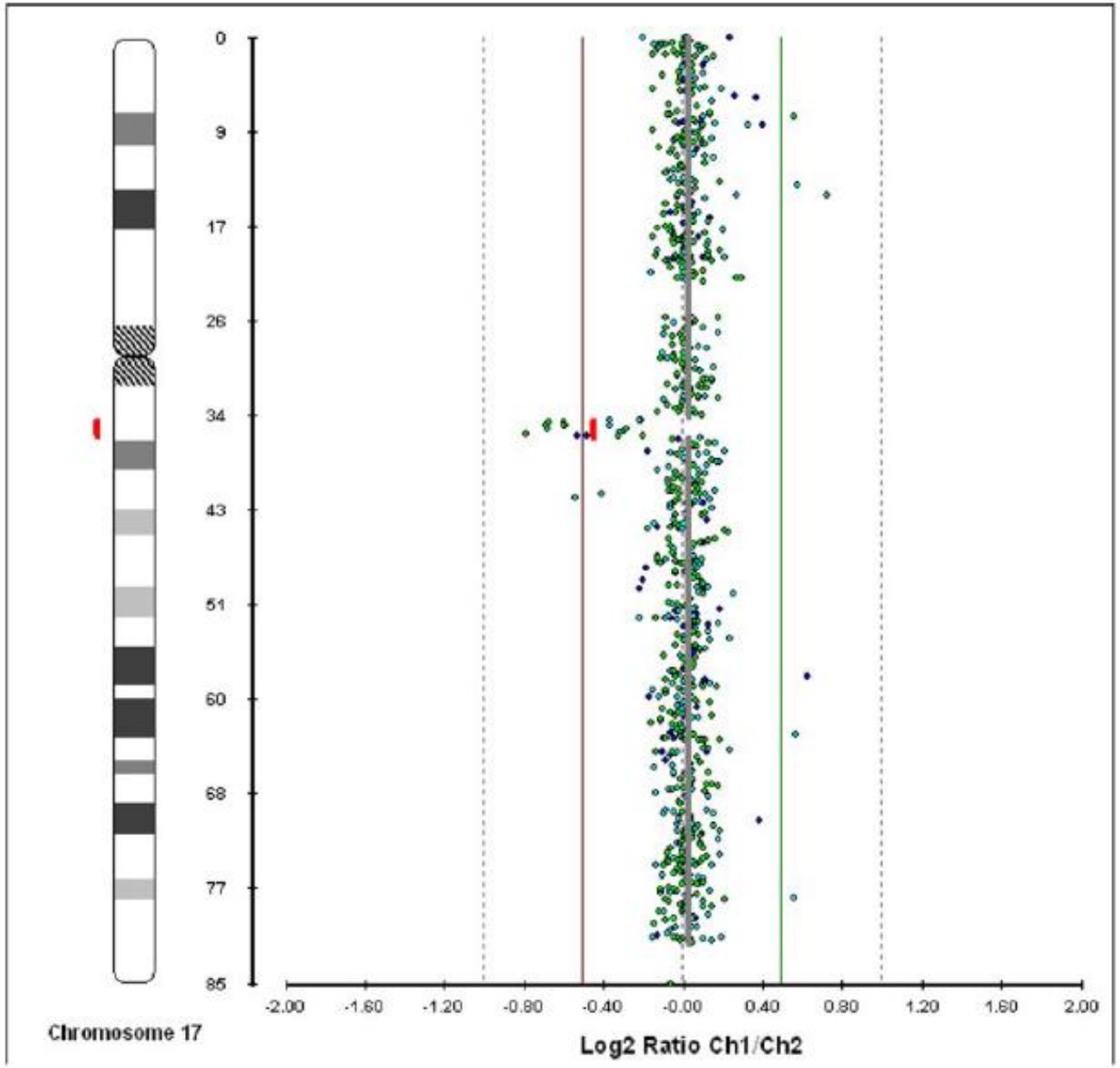
Diabetes
Case 1

Kidney- cortical cysts;







Array CGH profile of chromosome 17

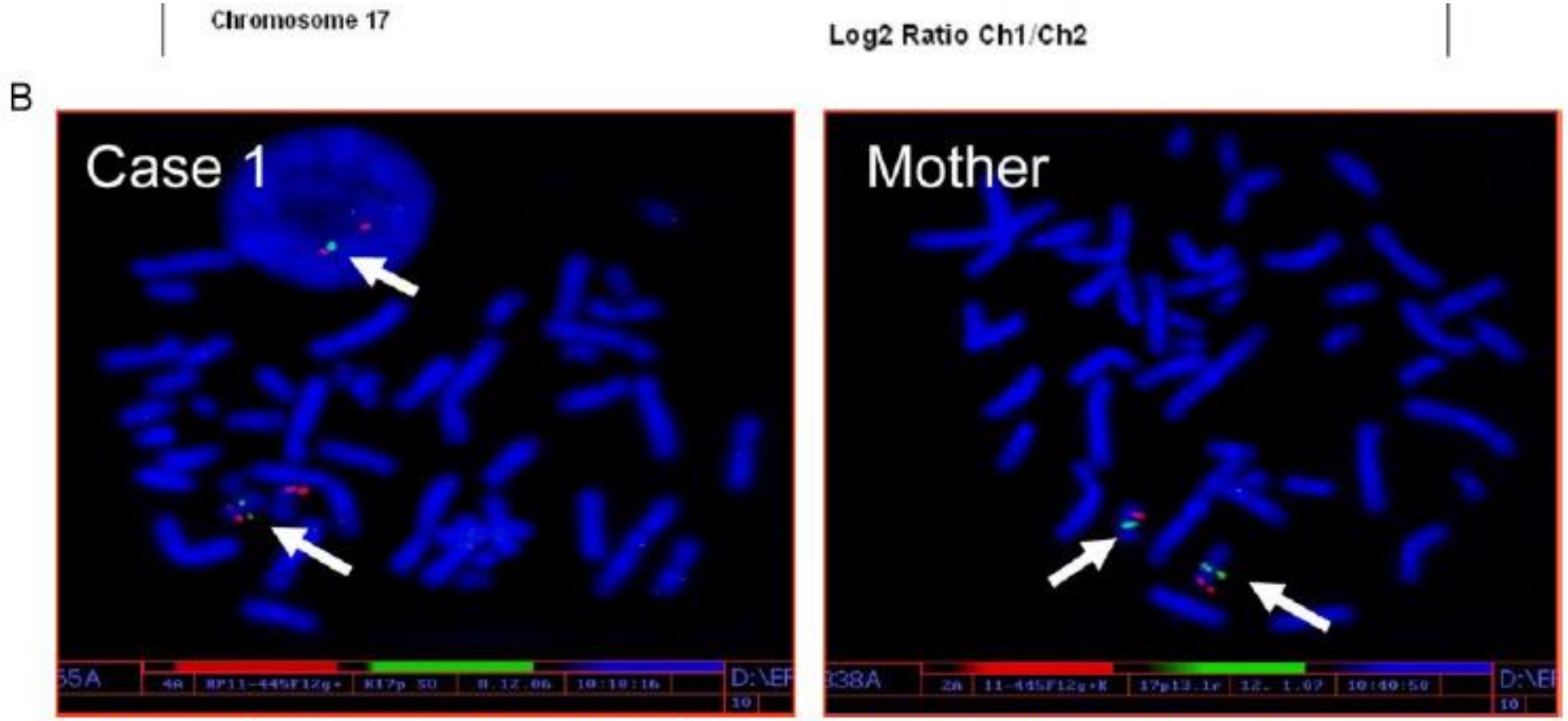
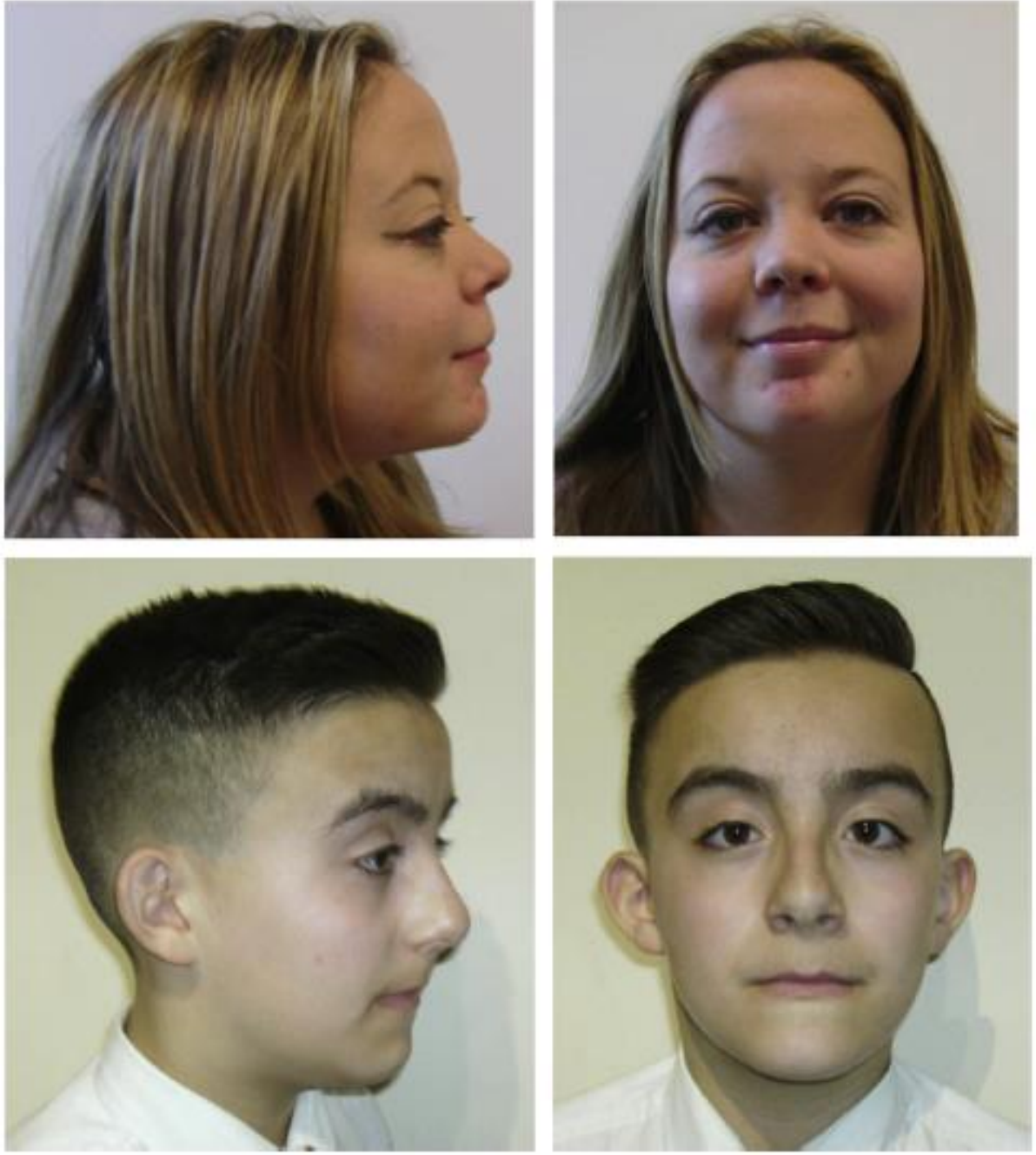


FIG. 2. Characterization of deletion size by array CGH (A) and confirmation of the heterozygous deletion of 17q12 by FISH (B). Array CGH profile of chromosome 17 was used to characterize the deletion size. The detected deletion is indicated by the *arrow* and the *red bar*. *Red and green lines* indicate a log2 ratio of −0.5 and 0.5, respectively. BAC probe RP11-445F12 (*green*) mapped to 17q12, whereas control probe RP11-404G1 (*red*) mapped to 17p13.1. Note only one green signal on metaphase chromosomes 17 and on interphase nucleus indicating a deletion in case 1 (*arrows*, *left image*), whereas two signals of both probes are present on metaphase chromosome of the patient's mother (*arrows*, *right image*). Similar signal patterns were observed for the other four patients (data not shown). Thus, we assume a *de novo* deletion in at least three cases.



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