Prenatal diagnosis of a complex skeletal dysplasia case deciphered by exome sequencing and postmortem pathological examination

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INTRODUCTION

We present a prenatal and postmortem diagnosis of diastrophic dysplasia (DD) in a fetus conceived by a mother with hypochondroplasia.

Hypochondroplasia is a skeletal dysplasia characterized by short stature, stocky build, disproportionately short arms and legs, broad short hands and feet, mild joint laxity and macrocephaly. The diagnosis is difficult in children under the age of three years, as skeletal disproportion tends to be mild and many of the radiographic features are subtle during infancy. It can occur randomly for unknown reasons with no apparent family history of the disorder. However there are also cases that the disorder is familial with autosomal dominant inheritance, correlated to pathogenic variants detected in ***FGFR3*** **gene**.

Overlapping prenatal phenotypes are observed between **hypochondroplasia** and **diastrophic dysplasia**, which is characterized by limb shortening, normal-sized skull, hitchhiker thumbs, spinal deformities, contractures of the large joints with deformities and early-onset osteoarthritis. Additionally typical findings are ulnar deviation of the fingers, gap between the first and second toes, and clubfoot. Most affected individuals survive the neonatal period and develop physical limitations with normal intelligence. Diastrophic dysplasia is considered a familial disorder with autosomal recessive inheritance, correlated to homozygous or compound heterozygous variants detected in ***SLC26A2*** **gene**

MATERIALS AND METHODS

Prenatal testing at 13 weeks gestation was requested due to a maternal hypochondroplasia phenotype of unknown genetic background. Clinical exome sequencing was performed on DNA extracted from chorionic villi and maternal blood, using Sophia Genetics' Clinical Exome Solution v2. Following preparations according to the manufacturer's protocol, DNA libraries were sequenced on an Illumina NextSeq-500 genetic analyser. Data processing, variant calling and pre-classification were conducted by SOPHiA DDM® bioinformatics pipelines.

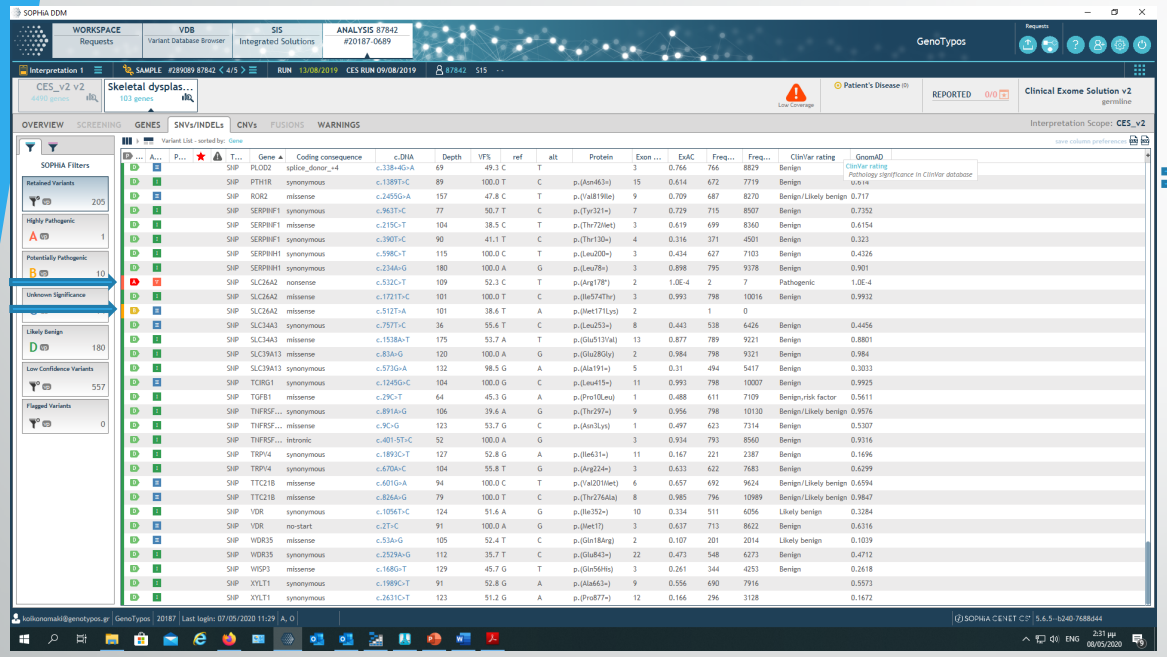
GENES ANALYSED RELATED TO SKELETAL DYSPLASIA

ACAN, ACP5, ADAMTS10, ADAMTSL2, AGPS, ALPL, ANKH, ARSE, B3GALT6, BMP1, BMPR1B, CA2, CANT1, CDC6, CDKN1C, CDT1, CHST3, CLCN7, COL10A1, COL11A1, COL11A2, COL1A1, COL1A2, COL2A1, COL9A1, COL9A2, COL9A3, COMP, CRTAP, CTSK, CUL7, CYP27B1, DHCR24, DLL3, DYM, DYNC2H1, EBP, EIF2AK3, ENPP1, ESCO2, EVC, EVC2, FAM20C, FGF23, FGFR1, FGFR2, FGFR3, FKBP10, FLNA, FLNB, GDF5, GNPAT, HSPG2, IFT140, IFT172, IFT80, IHH, KAT6B, LBR, LIFR, LMX1B, LRP5, LTBP2, MATN3, MMP9, NEK1, NPR2, OBSL1, ORC1, ORC4, ORC6, P3H1, PAPSS2, PCNT, PEX7, PHEX, PLOD2, PPIB, PTH1R, ROR2, RUNX2, SERPINF1, SERPINH1, SHOX, SLC26A2, SLC34A3, SLC39A13, SMAD4, SMARCAL1 , SOX9, TCIRG1, TGFB1, TNFRSF11A, TNFRSF11B, TRIP11, TRPV4, TTC21B, VDR, WDR19, WDR35, WISP3, WNT5A, XYLT1

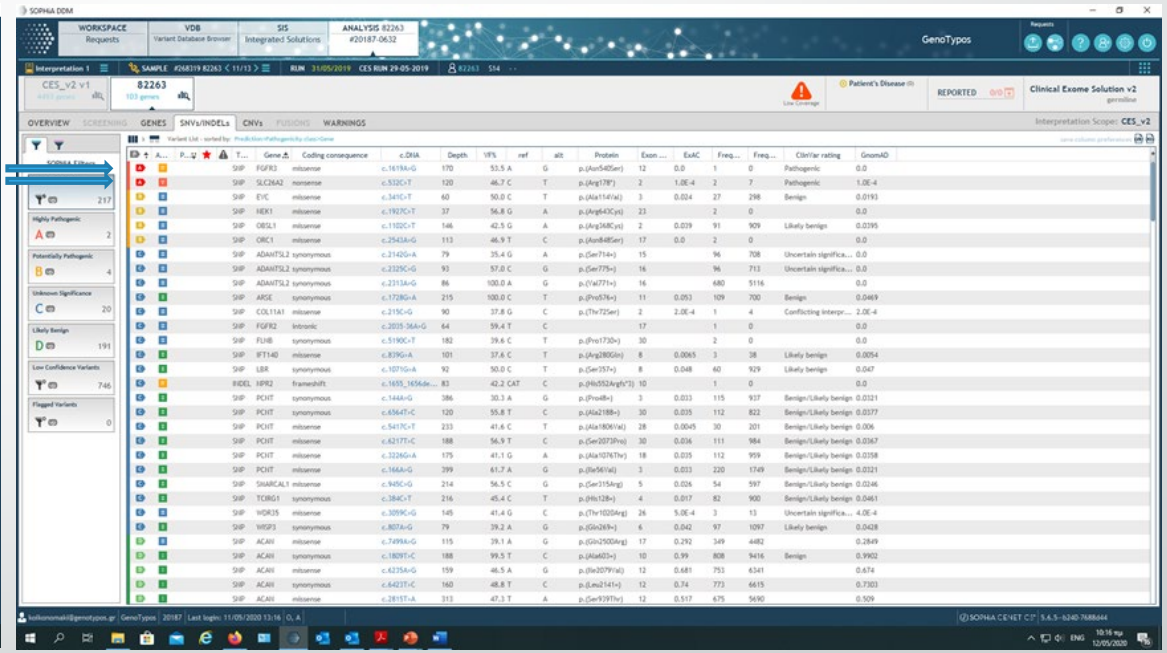
RESULTS

A *FGFR3* pathogenic variant was identified in the mother, confirming her phenotype; this variant was not detected in the fetus. However, one maternally inherited pathogenic and one of unknown significance *SLC26A2* variants were identified, related, according to the literature, to four distinct genetic skeletal dysplasias of various severity and prognosis. On 2nd trimester ultrasound the fetus presented short long bones and, following clinical genetic counselling, the pregnancy was terminated. Postmortem radiographical and histopathological findings were consistent with Diastrophic Dysplasia.

Variants detected in the fetus



Variants detected in the mother



DISCUSSION

Targeted *FGFR3* mutation testing, based on the mother's phenotype, would have missed the Diastrophic Dysplasia diagnosis in the fetus, preventing informed decision for this pregnancy and proper genetic counselling for the family. Therefore, this case highlights the utility of exome sequencing for complex overlapping prenatal phenotypes such as skeletal dysplasia, and underscores the contribution of postmortem pathological examination to the phenotype - genotype correlation, which is essential for the correct interpretation of exome sequencing results.