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What's already known about this topic?

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What does this study add?

We have introduced a new target resequencing NGS approach in prenatal diagnosis for the screening of a wide range of genetic disorders.
Our method is applicable to high-risk pregnancies when an ultrasound screening fails to show a definite clinical phenotype, when ultrasound indications must be supported by a molecular genetic diagnosis, or in cases where one or both parents are carriers of a genetic disorder.

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To the best of our knowledge, this is the first report that describes the use of a multi-gene NGS panel optimized for clinical prenatal diagnosis with a relatively fast turn-around time that can be multiplexed to allow simultaneous analysis of multiple samples.

In this report the NGPD method was applied for the prenatal genetic diagnosis of Charcot Marie Tooth (CMT) disease in a fetus whose mother was affected by early onset CMT. Of all the types of hereditary sensory-motor polyneuropathy, CMT syndrome is the most frequent. From a clinical point of view, the disorder is characterized by distal muscular atrophy associated with malformation of the feet, osteotendinous hyporeflexia and alterations in sensibility. Based on motor conduction velocity, it is possible to identify type 1 (demyelinating form with a particularly reduced conduction speed) and type 2 (axonal form

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We identified a missense mutation in gene *MFN2* (OMIM 608507) c.1126A>G (NM_014874), p.Met376Val (NP_055689.1), previously described as CMT2A2 (OMIM 609260) disease causing[7,8]; this mutation was present in heterozygous form both in the mother and her fetus and was absent in the father; Sanger sequencing method confirmed the presence of the mutation (Figure 1). Given the autosomal dominant form of the pathology, the patient and her fetus were both found to be affected by CMT disease type 2A2[9]. No other pathogenic mutation was found.

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Table 1

NGPD panel: genetic diseases are listed on the left and on the right the associated genes included in NGPD panel.

GENETIC DISEASE	ASSOCIATED GENES
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HYPOCHONDROGENESIS/ACHONDROGENESIS, TYPE II	*COL2A1*
ACHONDROPLASIA	*FGFR3*
ALAGILLE SYNDROME 1/TETRALOGY OF FALLOT	*JAG1*
APERT SYNDROME	*FGFR2*
ATELOSTEOGENESIS, TYPE I	*FLNB*
ATAXIA-TELANGIECTASIA VARIANT	*ATM*
BARDET-BIEDL SYNDROME 1	*BBS1/BBS10*
BLOOM SYNDROME	*BLM*
CANAVAN DISEASE	*ASPA*
CARDIOFACIOCUTANEOUS SYNDROME 1	*BRAF*
CHARCOT MARIE TOOTH DISEASE	*BSCL2, DNM2, EGR2, FGD4, FIG4, GARS, GDAP1, GJB1, HSPB1, HSPB8,KIF1B, LITAF,LMNA, MFN2, MPZ, MTMR2, NDRG1, NEFL, PMP22, PRPS1, PRX, RAB7A,SBF2, SH3TC2, TRPV4*
RHIZOMELIC CHONDRODYSPLASIA PUNCTATA, TYPE 1	*PEX7*

COFFIN-LOWRY SYNDROME	*RPS6KA3*
CORNELIA DE LANGE SYNDROME 1	*NIPBL*
CORNELIA DE LANGE SYNDROME 2	*SMC1A*
COSTELLO SYNDROME	*HRAS*
CROUZON SYNDROME	*FGFR2*
DYSAUTONOMIA, FAMILIAL	*IKBKAP*
CORTICAL DYSPLASIA, COMPLEX, WITH OTHER BRAIN MALFORMATIONS 1	*TUBB3*
CAMPOMELIC DYSPLASIA WITH AUTOSOMAL SEX REVERSAL	*SOX9*
EHLERS-DANLOS SYNDROME, TYPE VIIC/TYPE I/AUTOSOMAL RECESSIVE, CARDIAC VALVULAR FORM/TYPE IV/TYPEVI	*ADAMTS2/COL1A1/COL1A2/COL3A1/COL5A1/COL5A2/PLOD1*
ELLIS-VAN CREVELD SYNDROME	*EVC*
EPIDERMOLYSIS BULLOSA SIMPLEX, DOWLING-MEARA TYPE/GENERALIZED	*KRT5/KRT14*
PHENYLKETONURIA	*PAH*
CYSTIC FIBROSIS	*CFTR*
GALACTOSEMIA	*GALT*
HOLT-ORAM SYNDROME	*TBX5*

HYPOCHONDROPLASIA	*FGFR3*
HYPOPHOSPHATASIA, INFANTILE	*ALPL*
LISSENCEPHALY, X-LINKED, 1	*DCX*
LISSENCEPHALY 3	*TUBA1A*
JOUBERT SYNDROME 3/5/6/8/7/9/2	*AHI1/CEP290/TMEM67/ALR13B/RPGRIP1L/CC2D2A/TMEM216*
KABUKI	*KMT2D*
MARFAN DISEASE	*FBN1*
MECKEL SYNDROME	*MKS1*
MICROCEPHALY	*ASPM*
MUCOLIPIDOSIS	*MCOLN1*
NAIL-PATELLA SYNDROME	*LMX1B*
NOONAN SYNDROME	*PTPN11/SOS1/KRAS/RAF1/BRAF/NRAS/CBL*
HOLOPROSENCEPHALY	*SHH/SIX3*
OSTEOGENESIS IMPERFECTA, TIPO I/II/III/IV/VII	*COL1A1/COL1A2/CRTAP/LEPRE1*
POLYMICROGYRIA	*TUBB2B*
POLYCISTIC KIDNEY DISEASE	*PKD1/PKD2/PKHD1*
PFEIFFER SYNDROME	*FGFR1*

RETT SYNDROME	*MECP2*
SAETHRE-CHOTZEN SYNDROME	*TWIST1*
SECKEL SYNDROME	*ATR*
SMITH-LEMLI-OPITZ SYNDROME	*DHCR7*
DEAFNESS	*GJB2/GJB6*
SOTOS SYNDROME	*NSD1*
TAY-SACHS DISEASE	*HEXA*
TIROSINEMIA	*FAH*
TREACHER COLLINS SYNDROME	*TCOF1*
WILSON SYNDROME	*ATP7B*
ZELLWEGER SYNDROME	*PEX1*

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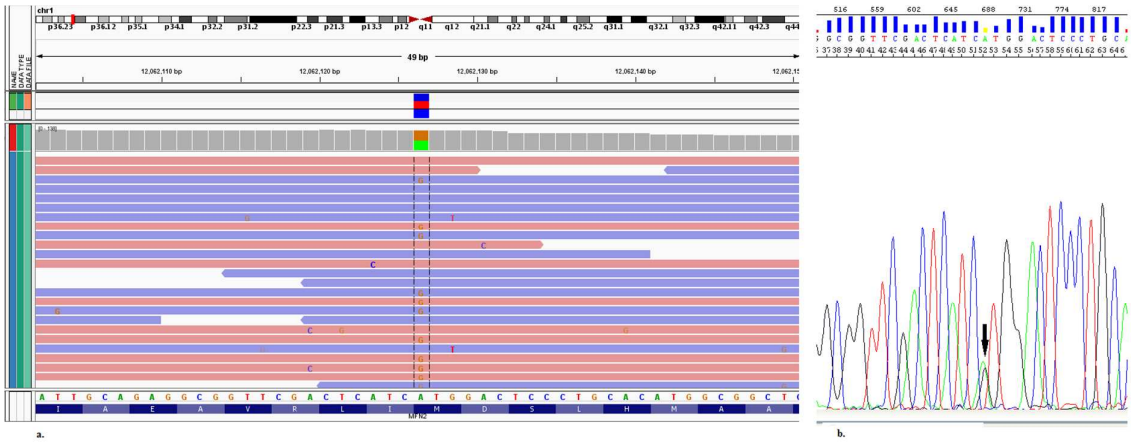
Figure 1

MFN2 c.1126A>G on CVS sample: a. NGS result displayed by Integrative Genome Viewer (IGV); b. variant confirmation by Sanger sequencing .



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CANAVAN DISEASE	*ASPA*
CARDIOFACIOCUTANEOUS SYNDROME 1	*BRAF*
CHARCOT MARIE TOOTH DISEASE	*BSCL2, DNM2, EGR2, FGD4, FIG4, GARS, GDAP1, GJB1, HSPB1, HSPB8,KIF1B, LITAF,LMNA, MFN2, MPZ, MTMR2, NDRG1, NEFL, PMP22, PRPS1, PRX, RAB7A,SBF2, SH3TC2, TRPV4*
RHIZOMELIC CHONDRODYSPLASIA PUNCTATA, TYPE 1	*PEX7*

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COFFIN-LOWRY SYNDROME	*RPS6KA3*
CORNELIA DE LANGE SYNDROME 1	*NIPBL*
CORNELIA DE LANGE SYNDROME 2	*SMC1A*
COSTELLO SYNDROME	*HRAS*
CROUZON SYNDROME	*FGFR2*
DYSAUTONOMIA, FAMILIAL	*IKBKAP*
CORTICAL DYSPLASIA, COMPLEX, WITH OTHER BRAIN MALFORMATIONS 1	*TUBB3*
CAMPOMELIC DYSPLASIA WITH AUTOSOMAL SEX REVERSAL	*SOX9*
EHLERS-DANLOS SYNDROME, TYPE VIIC/TYPE I/AUTOSOMAL RECESSIVE, CARDIAC VALVULAR FORM/TYPE IV/TYPEVI	*ADAMTS2/COL1A1/COL1A2/COL3A1/COL5A1/COL5A2/PLOD1*
ELLIS-VAN CREVELD SYNDROME	*EVC*
EPIDERMOLYSIS BULLOSA SIMPLEX, DOWLING-MEARA TYPE/GENERALIZED	*KRT5/KRT14*
PHENYLKETONURIA	*PAH*
CYSTIC FIBROSIS	*CFTR*
GALACTOSEMIA	*GALT*
HOLT-ORAM SYNDROME	*TBX5*
HYPOCHONDROPLASIA	*FGFR3*
HYPOPHOSPHATASIA, INFANTILE	*ALPL*

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LISSENCEPHALY, X-LINKED, 1	*DCX*
LISSENCEPHALY 3	*TUBA1A*
JOUBERT SYNDROME 3/5/6/8/7/9/2	*AHI1/CEP290/TMEM67/ALR13B/RPGRIP1L/CC2 D2A/TMEM216*
KABUKI	*KMT2D*
MARFAN DISEASE	*FBN1*
MECKEL SYNDROME	*MKS1*
MICROCEPHALY	*ASPM*
MUCOLIPIDOSIS	*MCOLN1*
NAIL-PATELLA SYNDROME	*LMX1B*
NOONAN SYNDROME	*PTPN11/SOS1/KRAS/RAF1/BRAF/NRAS/CBL*
HOLOPROSENCEPHALY	*SHH/SIX3*
OSTEOGENESIS IMPERFECTA, TIPO I/II/III/IV/VII	*COL1A1/COL1A2/CRTAP/LEPRE1*
POLYMICROGYRIA	*TUBB2B*
POLYCISTIC KIDNEY DISEASE	*PKD1/PKD2/PKHD1*
PFEIFFER SYNDROME	*FGFR1*
RETT SYNDROME	*MECP2*
SAETHRE-CHOTZEN SYNDROME	*TWIST1*
SECKEL SYNDROME	*ATR*
SMITH-LEMLI-OPITZ SYNDROME	*DHCR7*

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DEAFNESS	*GJB2/GJB6*
SOTOS SYNDROME	*NSD1*
TAY-SACHS DISEASE	*HEXA*
TIROSINEMIA	*FAH*
TREACHER COLLINS SYNDROME	*TCOF1*
WILSON SYNDROME	*ATP7B*
ZELLWEGER SYNDROME	*PEX1*

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Figure 1

MFN2 c.1126A>G on CVS sample: a. NGS result displayed by Integrative Genome Viewer (IGV); b. variant confirmation by Sanger sequencing.

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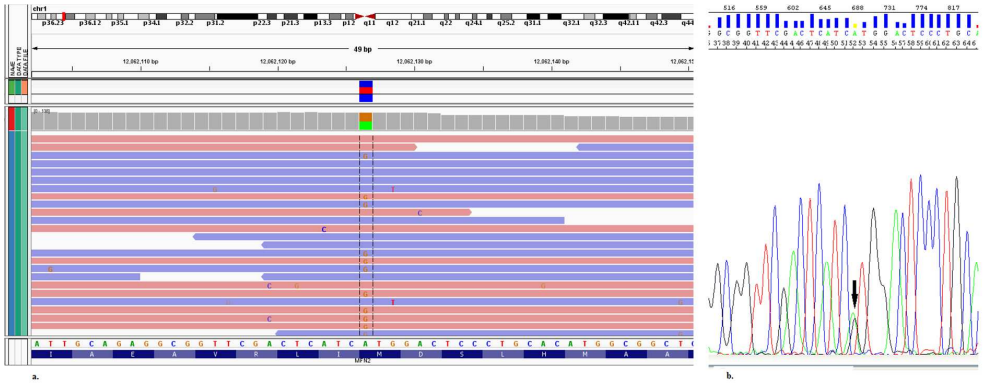

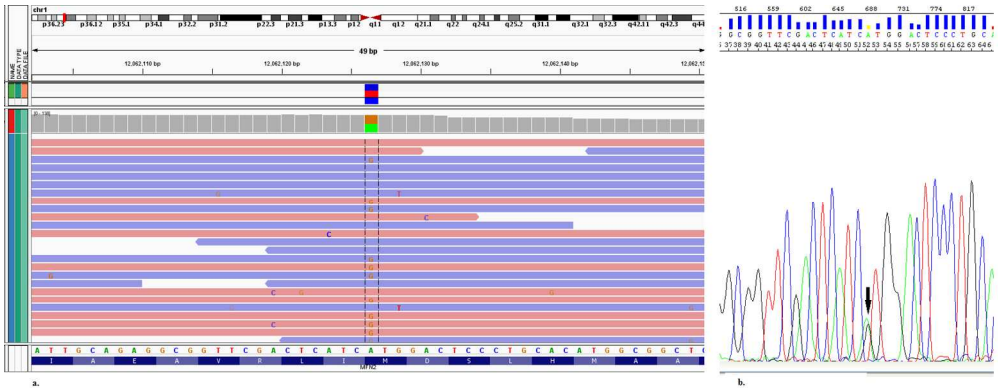

MFN2 c.1126A>G: a. NGS result displayed by Integrative Genome Viewer (IGV); b. variant confirmation by Sanger sequencing.