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Prenatal and Postnatal 10q24.32 Duplications Detected by SNP Microarray

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I. Introduction

Split-hand/split foot malformation (SHSF) also called ectrodactyly is a limb malformation syndrome involving missing, clefting and/or fusion of the hands and/or the feet and variable syndactyly of the remaining digits. Most cases occur sporadically with familial forms being uncommon. SHSF is a heterogenous condition with at least 7 different loci associated with a variety of etiologies and different causative genes. SHFM3 is one type, caused by a duplication of 10q24.32 and include the BTRC and FBXW4 genes. This is inherited in an autosomal dominant fashion with variable expression and penetrance. The clinical features may include limb defects, intellectual disability, craniofacial and orofacial findings. The duplication has been increasingly identified by the utilization of microarray analysis over the past decade. Analysis of over 180,000 postnatal patients and 50,000 prenatal patients has provided interesting differences between prenatal and postnatal cases information and a better understanding of this syndrome. We report a series of cases with interstitial duplications/triplications of 10q24.32 including 12 postnatal and 9 prenatal cases.

II. Results

Table 1. Postnatal cases with interstitial 10q24.32 duplications/triplications

Case	Sex	Age at Time of Testing	Size (Mb)	Band Designation	Inheritance	Secondary CNV	Clinical Indication	Genes within Interval
Case 1	M	3y 10m	0.251	arr[hg19] 10q24.32q24.32(103157780-103409070)x3	—	none	Developmental delay, speech and gross motor delays, normal growth, history of pyloric stenosis, no dysmorphic facial features, suspected autism spectrum disorder	partial BTRC, POLL, DPCD, partial FBXW4
Case 2	M	1d	0.247	arr[hg19] 10q24.32q24.32(103185243-103432420)x3	—	arr[hg19] 17p131p12(10,090,587-11,676,911)x1	Previous sibling with 1.59Mb deletion of 17p13.1p12; no abnormality in baby	partial BTRC, POLL, DPCD partial FBXW4
Case 3	M	15y 7m	0.234	arr[hg19] 10q24.32q24.32(103197122-103431579)x3	—	arr[hg19] 16p13.3(85,880-6,572,606)x3, 16q24.3(89,656,346-90,155,062)x1	Developmental delay autism, facial dysmorphism, non-verbal sounds only	partial BTRC, POLL, DPCD, partial FBXW4
Case 4	M	8y 1m	0.235	arr[hg19] 10q24.32q24.32(103197122-103432420)x3	Maternal	arr[hg19] 7q11.23(72,589,903-74,242,132)x3	Speech delay, mixed developmental disorder	partial BTRC, POLL, DPCD, partial FBXW4
Case 5	M	4y 9m	0.235	arr[hg19] 10q24.32q24.32(103197122-103432420)x3	Maternal	none	Speech delay, suspected autism spectrum disorder	partial BTRC, POLL, DPCD, partial FBXW4
Case 6	M	7y 4m	0.229	arr[hg19] 10q24.32q24.32(103203244-103432420)x3	—	none	—	partial BTRC, POLL, DPCD, partial FBXW4
Case 7	F	4y 5m	0.162	arr[hg19] 10q24.32q24.32(103220600-103382665)x3	Maternal	arr[hg19] 2p11.2(86,285,942-86,506,131)x3 mat	Conditions due to anomaly of unspecified chromosome, encephalopathy, insomnia	partial BTRC, POLL, DPCD, partial FBXW4
Case 8	M	5y 9m	0.208	arr[hg19] 10q24.32q24.32(103258780-103467022)x3	Maternal	none	Unspecified disturbance of conduct	partial BTRC, POLL, DPCD, FBXW4
Case 9	M	6y	0.442	arr[hg19] 10q24.32q24.32(103204913-103646574)x4	Normal mother Father not tested	none	—	BTRC, POLL, DPCD, FBXW4, FGF8, NPM3, MGEA5, KCHIP2
Case 10	M	7y 11m	0.233	arr[hg19] 10q24.32q24.32(103212407-103444938)x4	—	none	Unspecified lack of expected normal physiological development in childhood	partial BTRC, POLL, DPCD, partial FBXW4
Case 11	M	13y 4m	0.535	arr[hg19] 10q24.31q24.32(102924566-103459548)x3	Paternal	none	Psychological issues. Neither dad nor the child have split hand/split foot. The child has small hands, brachydactyly, but no SHFM.	LBX1, BTRC, POLL, DPCD, FBXW4
Case 12	M	8y 2m	0.26	arr[hg19] 10q24.32q24.32(103014631-103275093)x3	—	none	Mild intellectual disability, history of motor and developmental delay, currently in a special education class. Otherwise normal.	partial BTRC

Figure 1. Postnatal cases with interstitial 10q24.32 duplications/triplications

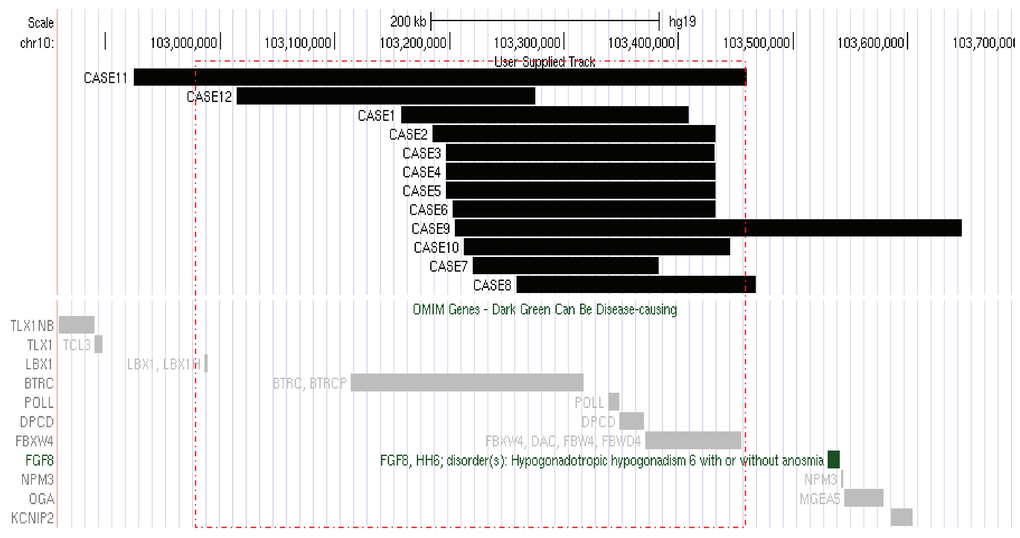
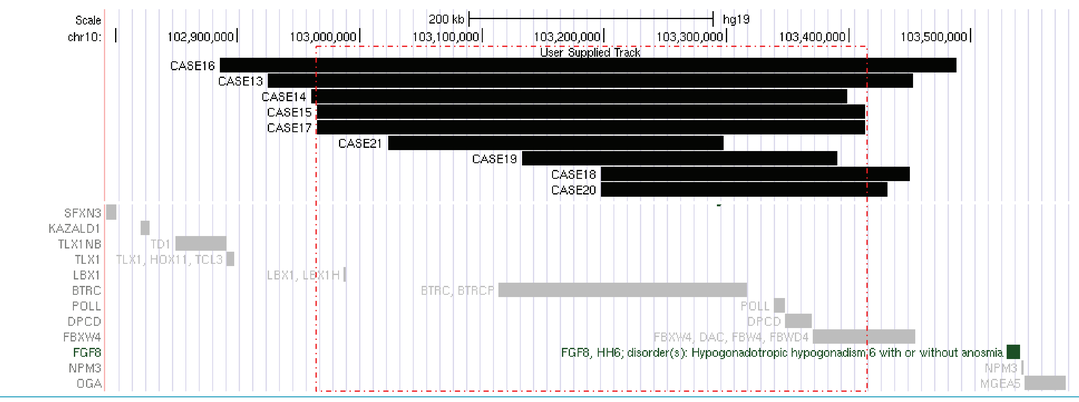


Table 2. Prenatal cases with interstitial 10q24.32 duplications

Case	Specimen Type	Size (Mb)	Band Designation	Inheritance	Secondary CNV	Clinical Indication	Genes within Interval
Case 13	Amniotic Fluid	0.528	arr[hg19] 10q24.3 1q24.32(102,924,566-103,452,974)x3	*de novo*	none	Ectrodactyly, split hand split foot, syndactyly	LBX1, BTRC, POLL, DPCD, partial FBXW4
Case 14	Amniotic Fluid	0.439	arr[hg19] 10q24.3 1q24.32(102,960,151-103,398,999)x3	*de novo*	none	bilateral ectrodactyly in hands; possible split hand, split foot malformation, missing digits (3 toes total, two fingers total)	LBX1, BTRC, POLL, DPCD, partial FBXW4
Case 15	Amniotic Fluid Culture	0.448	arr[hg19] 10q24.3 1q24.32(102,964,977-103,413,254)x3	*de novo*	15q13. 2q13.3(31,112,919-32,439,524)x3 pat	Ectrodactyly, bilateral split hand split foot	LBX1, BTRC, POLL, DPCD, partial FBXW4
Case 16	Amniotic Fluid	0.603	arr[hg19] 10q24.3 1q24.32(102,885,609-103,488,168)x3	*de novo*	none	Diagnosis confirmed after birth for ectrodactyly no other issues. Both hands and feet bilaterally have the thumb/big toe larger then a split w/other 4 digits fused.	TLX1NB, TLX1, LBX1, BTRC, DPCD, POLL, FBXW4
Case 17	Amniotic Fluid	0.449	arr[hg19] 10q24.3 1q24.32(102,964,977-103,413,960)x3	*de novo*	none	Ectrodactyly, bilateral split hand split foot	LBX1, BTRC, POLL, DPCD, partial FBXW4
Case 18	Amniotic Fluid Culture	0.253	arr[hg19] 10q24.32(103,197,122-103,449,778)x3	Paternal	none	Prior pregnancy with holoprosencephaly, bilateral cleft lip and palate	partial BTRC, POLL, DPCD, partial FBXW4
Case 19	Amniotic Fluid	0.259	arr[hg19] 10q24.32(103,132,508-103,391,106)x3	—	none	Abnormal prenatal screen	partial BTRC, POLL, DPCD, partial FBXW4
Case 20	Amniotic Fluid	0.234	arr[hg19] 10q24.32(103,197,493-103,431,579)x3	Maternal	none	increased nuchal translcency, polyhydramnios later developed requiring 2 amnio fluid reductions. Mom normal and had 3 prior children all normal	partial BTRC, POLL, DPCD, partial FBXW4
Case 21	Amniotic Fluid Culture	0.274	arr[hg19] 10q24.32(103,023,320-103,297,585)x3	Paternal	none	Symmetrical Intra-uterine growth restriction, Choroid plexus cyst, micrognathia, clenched hands. Termination of pregnancy. No family history of split hand split foot	partial BTRC

Figure 2. Prenatal cases with interstitial 10q24.32 duplications



III. Summary

- Five of the 9 prenatal 10q24.32 duplications cases (cases 13-17) were ascertained due to an ultrasound indication of skeletal anomaly.
- The 5 prenatal cases with an indication of skeletal anomaly were consistent with SHSF and were *de novo* in origin.
- The prenatal *de novo* duplications ranged in size between 439-603 kb with and all included the LBX, BTRC, POLL, DPCD, and at least a partial or complete duplication of FBXW4 and were consistently larger in size than the prenatal cases with no ultrasound findings consistent with SHSF.
- The remaining 4 prenatal specimens showed no ultrasound findings suggestive of SHSF and had overlapping duplications that ranged in size from 234-237 kb with a common region that partially includes the BTRC, POLL, DPCD, and FBXW4.
- The remaining 4 prenatal cases, three of which had parental follow-up testing (cases 18, 20 ,21) showed inheritance from a parent with no clinical history of SHSF.
- None of the postnatal duplications or triplication cases showed features of SHSF based on clinical phenotype provided and ranged in size from 162-535 kb .
- Five (cases 4, 5, 7, 8, 9, 11) of the 12 postnatal cases with available parental follow-up were inherited from parents with no phenotypic features of SHSF.
- Only one of the postnatal cases (case 11) showed a similar duplication size and gene content as the prenatal *de novo* cases with skeletal anomalies, suggesting reduced penetrance.

IV. Discussion and Conclusions

The case series highlight that 10q24.1 duplications which at a minimum include the genes LBX, BTRC, POLL, DPCD, and at least partially or completely include the FBXW4 present with features SHSF with a reduced penetrance as suggested by case 11. The features of SHSF were predominantly seen in the prenatal group and are often *de novo*. Both prenatal and postnatal inherited cases are smaller in size than *de novo* cases. These results highlight that the ascertainment of an affected has important counseling significance for future pregnancies. Although this is a rare disorder, the detection of affected prenatal patients is likely a result of ascertainment, but demonstrates a correlation between the duplication and the disorder.

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