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ORIGINAL CONTRIBUTION

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A Recurrent Mutation in Growth Hormone Receptor (*GHR*) Gene Underlying Laron-type Dwarfism in a Pakistani Family

Rana Muhammad Kamran Shabbir[a,1], Gökhan Nalbant[b,1], Qamar Zaman[c], Aslıhan Tolun[b], Sajid Malik[c,*], and Sara Mumtaz[d,*]

[a]Department of Zoology, Division of Science and Technology, University of Education, Lahore, Pakistan; [b]Department of Molecular Biology and Genetics, MOBGAM, Istanbul Technical University, Istanbul, Türkiye; [c]Human Genetics Program, Department of Zoology, Faculty of Biological Sciences, Quaid-i-Azam University, Islamabad, Pakistan; [d]Department of Biological Sciences, National University of Medical Sciences, Rawalpindi, Pakistan

Laron syndrome (LS) is a rare autosomal recessively segregating disorder of severe short stature. The condition is characterized by short limbs, delayed puberty, hypoglycemia in infancy, and obesity. Mutations in growth hormone receptor (*GHR*) have been implicated in LS; hence, it is also known as growth hormone insensitivity syndrome (MIM-262500). Here we represent a consanguineous Pakistani family in which three siblings were afflicted with LS. Patients had rather similar phenotypic presentations marked with short stature, delayed bone age, limited extension of elbows, truncal obesity, delayed puberty, childish appearance, and frontal bossing. They also had additional features such as hypo-muscularity, early fatigue, large ears, widely-spaced breasts, and attention deficit behavior, which are rarely reported in LS. The unusual combination of the features hindered a straightforward diagnosis and prompted us to first detect the regions of shared homozygosity and subsequently the disease-causing variant by next generation technologies, like SNP genotyping and exome sequencing. A homozygous pathogenic variant c.508G>C (p.(Asp170His)) in *GHR* was detected. The variant is known to be implicated in LS, supporting the molecular diagnosis of LS. Also, we present detailed clinical, hematological, and hormonal profiling of the siblings.

INTRODUCTION

With next generation sequencing (NGS) millions of sequence reads can be processed in a time- and cost-effective manner [1]. NGS technologies have been applied in numerous studies with positive results [2,3]. Both whole genome sequencing (WGS) and whole exome sequencing (WES) are included in NGS. Though WGS is a more powerful technique than WES, the technology of WGS is very costly compared to WES [4]. So in many

*To whom all correspondence should be addressed: Dr. Sara Mumtaz, PhD, National University of Medical Sciences, Rawalpindi, Pakistan; Email: sara.mumtaz@numspak.edu.pk. Prof. Dr. Sajid Malik, PhD, Quaid-i-Azam University, Islamabad, Pakistan; Email: malik@qau.edu.pk.

Abbreviations: LS, Laron syndrome; GHR, growth hormone receptor; GH, growth hormone; NGS, next generation sequencing; WGS, whole genome sequencing; WES, whole exome sequencing.

Keywords: short stature, truncal obesity, widely-spaced breasts, delayed puberty, facial dysmorphism, growth hormone insensitivity

Author Contributions: SMk and AT conceived and designed the study; RMKS and QZ performed data collection; GN did molecular analysis; SMk, SMz, and RMKS compiled data and drafted manuscript. [1]These authors contributed equally.

studies WES is used and thereby, instead of sequencing the entire genome, only 2% of the protein-coding genome is sequenced that contains most of the disease-causing mutations [5]. WES can be applied with high efficiency in the identification of mutations in genetic cases of short stature.

Short stature can be characterized as the height below the third percentile of the general population. Growth of an individual is affected by numerous factors such as lifestyle, ethnicity, cultural and socio-economic, and nutritional aspects. Therefore, the prevalence and causes of short stature vary between low- and high-income countries [6].

Hereditary forms of short stature are attributed to monogenic genetic defects which cause skeletal dysplasia or endocrinological abnormalities in the growth hormone-insulin-like growth factor 1 (IGF-1). *ACAN*, *FGFR3*, *NPR2*, and *SHOX* are known genes related to skeletal dysplasia whereas *GHRHR*, *GHR*, *GH1*, *IGF1*, *STAT5B*, *IGFALS*, and *IGF1R* are known for their role in GH-IGF1 axis [7,8].

Laron syndrome (LS, MIM 262500), a very rare type of short stature, is caused by mutation in growth hormone receptor (*GHR)* and has a prevalence of 1-9/1000000 [9]. An estimated 350 patients with Laron syndrome (LS) have been reported in the medical literature, with geographic aggregation of this anomaly in few regions. Of those cases two-thirds have Jewish origin and the majority of the remaining are of South Asian or Mediterranean descent. The most genetically homogenous group lives in Southern Ecuador where the disease is due to the ss180 mutation (splice site recessive mutation at codon 180 of exon 6) in *GHR* [10].

LS is characterized by short stature, truncal obesity, sparse hair, small head circumference, frontal bossing, "sunset eyes," crowded teeth, acromicria, small gonads or genitalia, high-pitched voice, delayed skeletal maturation, and slow motor development [11]. Additional symptoms include protruding forehead, weak muscles, delayed puberty, saddle nose, and blue sclera [12,13]. At a biochemical level, LS is diagnosed with hypoglycemia in infancy, low levels of IGFBP-3 or IGF, serum GHBP (- or +), high serum hGH, and progressive hyperlipidemia [11].

LS is also known as hormone insensitivity syndrome and its inheritance pattern is autosomal recessive [14], caused by mutations in the *GHR*. In the literature more than 120 mutations in the *GHR* have been reported [14]. These mutations affect GHR dimerization and/or ligand binding which ultimately halts growth of the bones [15-17]. These mutations include RNA processing defects, deletion, missense, or truncating mutations. Mostly mutations are reported in the extracellular domain followed by intracellular domain and least in intronic regions.

Growth hormone (GH) or somatotropin is secreted from somatotroph cells of the anterior pituitary gland. It is a peptide hormone and plays an important role in growth, cell progression, and renewal [18,19]. It is essential for the regulation of the brain and different human systems eg, cardiovascular, metabolism, immune, and reproductive [20]. GHR and IGF-1 regulate the effects of GH directly and indirectly, respectively. GH is released in pulsatile nature and is influenced by a variety of hormones such as stimulatory ghrelin and sex steroids, hypothalamic GH-releasing hormone, inhibitory somatostatin, glucocorticoids, and IGF. A complex feedback system is involved in GH secretion consisting of leptin, ghrelin, free fatty acids, IGF-1, and the central nervous systems. After releasing from pituitary, GH binds to GHR in cartilage and liver. This phenomenon initiates the production of IGF-1 that stimulates linear bone growth. Other functions via endocrine and paracrine or autocrine mechanisms are also initiated [21,22].

GHR has a vital role in the GH-GHR-IGF-1 axis and individual growth. In the interaction of GH-GHR-IGF-1, GHR acts as an important cytokine. It controls the individual growth by regulating the expression of IGFs via GH signal into the cell. Consequently, GH physiological activity is directly dependent upon GHR's level of expression and functioning in cells and tissues [23]. People afflicted with dysfunctional GHR are very short as they experience a loss or malfunctioning in the GHR response. Such people have increased adiposity and low bone mineral density which can lead to increased risk of osteoporosis, lipid malformations, and/or cardiovascular diseases [24].

We report clinical and genetic findings of a Pakistani family afflicted with LS. The family has features of LS with certain additional peculiarity in clinical presentation. A known variant in *GHR* was detected by SNP-based mapping coupled with WES, supporting the molecular diagnosis of LS.

MATERIALS AND METHODS

The Helsinki II declaration was followed to collect all information and biological material. The approval of study was taken by institution review boards of Quaid-i-Azam University, Islamabad, Pakistan and Boğaziçi University, Istanbul. The family originates from Southern Punjab, Pakistan. A four-generation family pedigree strongly illustrates the autosomal recessive pattern of inheritance (Figure 1). With the help of a local physician, six (two male and four female) family members were physically examined. Among them, one male and a pair of female twins were affected. Anthropometric measurements and pictures depicting the phenotype were obtained. Hand roentgenograms of patient 401 were ob-

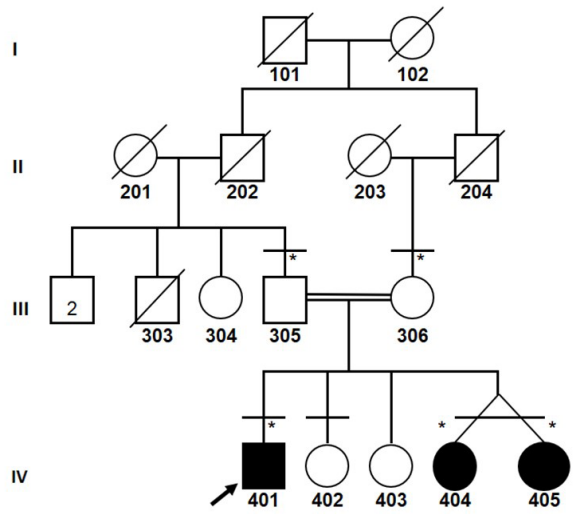

Figure 1. Pedigree of the family. Horizontal lines above individuals indicate that physical examination was performed. * indicates subjects participated in genetic study.

tained. Three of the patients underwent hematological and hormonal examinations.

A mixture of DNA samples of the three affected siblings were used for generating SNP-genotyping with 710K markers using Illumina Human OmniExpress-24 BeadChip. In order to detect homozygous regions, the data were analyzed through HomozygosityMapper and the regions were evaluated in Excel. Regions with >1 Mb were scrutinized for candidate genes through GeneDistiller (as described in [25]).

The Agilent SureSelect Target Enrichment System and the Illumina HiSeq2000 platform were used for WES of affected son 401. The data generated were analyzed by bioinformatics pipeline. For this purpose, the UCSC Genome Bioinformatics site was retrieved for downloading of human reference genome sequence (assembly GRCh37/hg19). The downloaded assembly was unzipped; individually assembled chromosomes were concatenated to each other and were indexed. The Burrows-Wheeler Aligner (BWA) program was used to align the pair-end reads to the reference genome and the final alignment was generated in SAM (Sequence Alignment/Map) format. Quality control (QC) on raw data was through FASTX-Toolkit (Gordon A, Hannon GJ. FASTX-Toolkit [26]). SAMTools package was used to convert the SAM file into BAM (Binary Alignment Map) format and aligned BAM files were subjected to alignment QC. The resulting file was sorted, indexed, and subjected to Variant Calling File (VCF) by using Genome Analysis Tool Kit (GATK), which outputs a list of variants that were different from the reference genome. ANNOVAR was used to annotate the list of variants which denotes the

Figure 2. **Phenotypes of patients**. Short stature, truncal obesity, widely-spaced breasts, protruding forehead, depressed nose, large ears, and blue sclera. X-ray image of hands depicting the delayed bone age and late epiphyseal closure at the age of 19 of subject 401.

chromosomal location, dbSNP ID, region of the nucleotide change, exonic nucleotide change, or splicing mutation. Regions of the exonic nucleotide change includes exonic, intronic, UTR, non-coding RNA, or intergenic while type of exonic nucleotide change includes synonymous, non-synonymous, frameshift, stop gain, or stop loss. Integrative Genomic Viewer (IGV) was used for the visualization of alignments. Various commands were used for data analysis (Appendix A: Supplemental Table 1). Candidate homozygous regions detected through SNP genotyping were searched for homozygous, novel, and rare variants with frequency <0.01 (variants with read to total read ratios >0.50 were retained). Variants with possibly damaging protein function were considered. The variants found in-lab exome files were not considered. All rare variants were scrutinized through public databases (1000 Genome and gnomAD that have numerous Pakistani exomes). Sanger sequencing was performed to validate the identified mutation, and segregation in the family was done by single-strand conformational polymorphism analysis. Pathogenicity of the detected variant was assessed through *in silico* toolsPolyPhen-2, MutationTaster, PROVEAN, SIFT, and M-CAP.

RESULTS

All unaffected individuals examined were normal and showed no remarkable phenotype. All affected individuals had proportionately short stature and childish appearance (Figure 2). They also had hypo-muscularity, limited elbow extensibility, truncal adiposity, and widely-spaced breasts. The cranio-facial features included protruding forehead, blue sclerae, large ears, saddle nose, and crowded teeth. Sparse hair, thin and prematurely aged skin, and high-pitched voice were noted. Patients were not able to perform rigorous activities and had symptoms of early fatigue and muscle weakness. Patients

Table 1. Clinical Features of Affected Siblings

Features	401	404	405
Sex, age (years)	M, 19	F, 10	F, 10
Skeletal features			
Short stature	+	+	+
Short limbs	+	+	+
Hypo-muscularity	+	+	+
Limited elbow extensibility	+	+	+
Cranio-facial features			
Protruding forehead	+	+	+
Blue sclerae	+	+	+
Shallow orbits of eye	-	+	+
Large ears	+	+	+
Saddle nose	+	+	+
Crowded teeth	+	+	+
Ectodermal features			
Thin and prematurely aged skin	+	+	+
Sparse hair	+ in childhood	+	+
Decreased sweating	+	+	+
Others			
Truncal adiposity	+	+	+
Widely-spaced breasts	+	+	+
Early fatigue, muscle weakness	+	+	+
High-pitched voice	+	+	+
Delayed walking in infancy	+	+	+
Heart problem	+	NA	NA
Micro-penis and small testicles	+	NR	NR
Laboratory findings			
Hypoglycemia	-	+	+
GH levels	Low	High	NA
Macrocytic anemia	+	+	+

+, feature present; -, feature absent; NA, not assessed; NR, not relevant.

Table 2. Anthropometric Measurements of Affected Siblings

Features	401	404	405
Sex, age (years)	M, 19	F, 10	F, 10
Standing height*	139 (<0.1)	102 (<0.1)	100 (<0.1)
Sitting height [36]	75 (<1)	52 (<1)	49 (<1)
Arm span [37]	146 (<1)	105 (<5)	102 (<5)
Head circumference [38]	52 (<5)	47 (<1)	46 (<1)
Chest circumference	78	51	50
Neck circumference	32	23	23

Percentiles are given in parentheses. All measurements are in cm. Head circumference is with respect to age and sex. *Percentiles are from WHO Growth Reference: http://www.who.int/growthref/who2007_height_for_age/en/.

Table 3. Hematologic and Endocrinologic Parameters of Affected Siblings

Variables	401	404	405	Reference ranges (units)
Sex/age	M, 19	F, 10	F, 10	
Blood Glucose Fasting	76	**59**	**52**	60-100 mg/dl
Hematological Report				
Hb	14.5	11.5	12.1	13-18 (M); 11.5-14.5 (F) mg/dl
Total RBC	5.7	4.9	5.0	4.5-6.5 (M); 4-5.3 (F) x 10^12/l
Hct	48	39	40	38-52 (M); 33-43 (F)%
MCV	85	79	80	75-95 (M); 76-90 (fl)
MCH	**25**	**23**	**24**	26-32 (M); 25-31 (F) pg
MCHC	30	30	30	30-35 g/dl
Platelet Count	326	393	198	150-400 x ^10^9/l
WBC Count (TLC)	**12.3**	**14.1**	**12.1**	4-11 x ^10^9/l
Neutrophils	54	60	60	40-75%
Lymphocytes	28	35	33	20-50%
Monocytes	08	04	05	2-10%
Eosinophils	10	01	02	1-6%
Growth Hormone	**1.50**	**9.91**	-NA	2.0-5.0 (M); < 6.0 (F) ng/mL
T3	127.15	120.77	-NA	80-210 (M); 94-241 (F) ng/dl
T4	7.48	8.98	-NA	4.6-10.5 (M); 6.4-13.3 (F) ug/dl
TSH	2.7160	2.6179	-NA	0.51-5.27 (M); 0.55-5.46 (F) uIU/ml

M, male; F, female; Values in boldface deviate from the normal ranges; NA, not assessed.

404 and 405 were so weak that they were unable to lift more than 2kg of weight. Delayed puberty and large ears in all, no menarche in female patients and small genitalia in male were also remarkable features; patients also have attention deficit behavior (Table 1). Anthropometric measurements of patients showed significantly short stature (Table 2). Hormonal assays showed that GH level was remarkably lower in male patient 401 and higher in female 404, whereas in both thyroid hormone level was unremarkable (Table 3).

SNP-based HomozygosityMapper analysis led to the detection of 45 autosomal homozygous intervals (size >1 Mb) (Figure 3; Appendix A: Supplemental Table 2). The largest homozygous interval (45 Mb) was on chromosome 5 (Appendix A: Supplemental Table 2). In the exome data, there were 22 rare exonic, nonsynonymous variants detected through the filtration scheme (Figure 4). There was only one candidate which falls in the regions of homozygosity, namely *GHR*: c.508G>C (p.(Asp170His)) in exon 6 (NM_000163.5) (Appendix A: Supplemental Figure 1). This variant is known to be associated with LS and was predicted to be pathogenic (damaging or deleterious) through various *in silico* tools (Appendix A: Supplemental Table 3). The second variant *DYM* c.980C>A (p.Ala327Asp; NM_017653) was listed as uncertain significance in ClinVar and did not fall in a SNP-based shared homozygous interval.

DISCUSSION

This study presents a family with Laron type dwarfism. The primary presentation and the phenotypic data alone may not be sufficient to reach a correct diagnosis for this disorder, and a clinician with not much experience might not be able to reach the correct differential diagnosis, which can in turn compromise genetic counseling and therapeutic approaches. Characteristics of LS overlap with other well-characterized disorders such as severe GH deficiency (types IA, IB, II, III, IV), growth delay due to IGF-I resistance (MIM-270450), Noonan syndrome (many types), hypothyroidism (types 1-9), and panhypopituitarism (MIM-312000). Most of these disorders are recessively segregating except for the Noonan syndromes which are predominantly autosomal dominant. Further, the GH deficiency is an etiologically heterogeneous condition.

GH-gene deletion syndrome, another inherited condition, has similar clinical symptoms as LS, including organomicria, acromicria, delayed development of the muscular systems, and skeletal and cranio-facial disproportion, and obesity [27,28]. Major similarity of these syndromes at the biochemical level includes an unde-

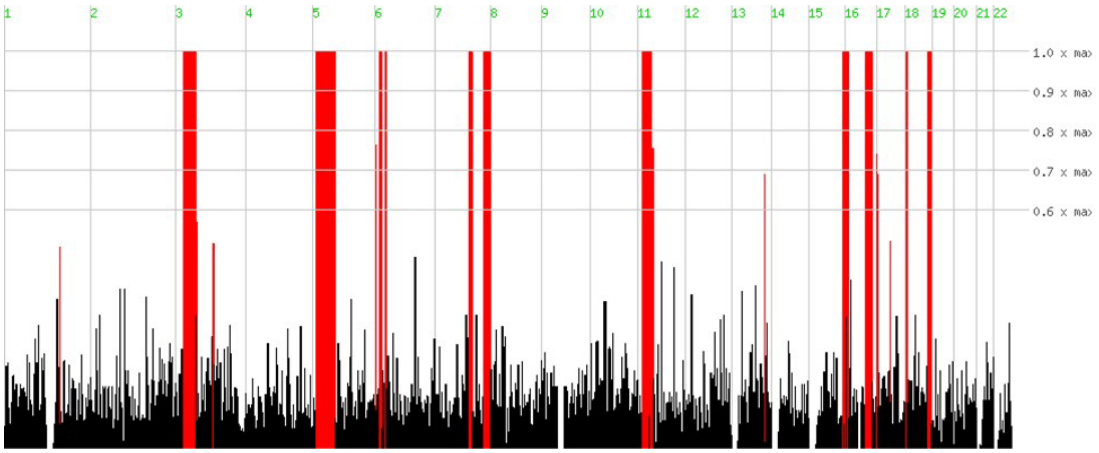

Figure 3. **Graphical representation of homozygosity intervals obtained by HomozygosityMapper with default parameters**. Red bars depict the longer stretches of homozygous genotypes on chromosomes and black bars revealed short intervals of homozygous genotypes. Note the largest interval at chromosome 5.

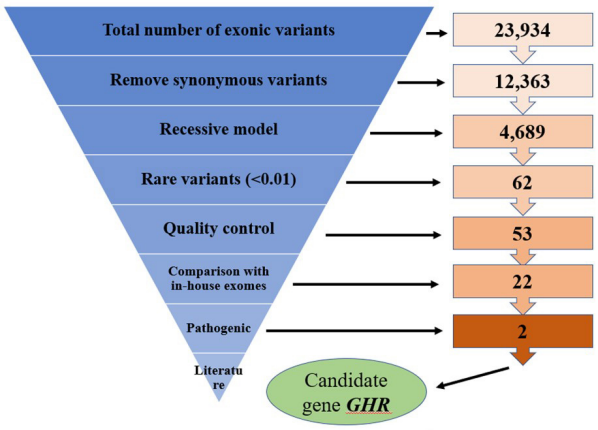

Figure 4. **Summary of Exome filtration scheme**.

tectable level of circulating IGF-1 whereas the major discrimination can be made between GH-gene deletion and LS depending upon the level of GH in patient serum. A higher level of GH is found in LS due to insensitivity of GH receptors, but in GH-gene deletion syndrome GH level is undetectable [27]. The hormonal profiling of the patients in the presented family revealed that GH level was low in male patient 401 and remarkably higher in female 404, whereas thyroid hormone test was unremarkable. Hence, GH-gene deletion syndrome could be excluded which shows absence of basal GH. In order to molecularly diagnose the condition afflicting this family we applied SNP-based genotyping and WES. The data from these methods corroborated to uniquely pinpoint the pathogenic variant.

Variant *GHR* c.508G>C detected in this presented family is already reported in a Pakistani and an Indian family [29]. Hormonal assays of these families were previously reported by Savage et al. (1993), but no phenotypic features or roentgenograms were presented [30]. We report detailed phenotypical, radiological, biochemical, and molecular analysis of an LS family. Clinical features unique to this family are large ears, early fatigue during normal activities, muscle weakness, widely-spaced breasts, sparse hair, prematurely aged skin, attention deficit behavior, and macrocytic anemia. The presence of these peculiar features prompted us to carry our genetic characterization of this condition. To the best of our knowledge, this is the first report of LS with detailed clinical and molecular analysis from Pakistan.

Height below than third percentile or lower than the normal average by 2 or more standard deviation (SD) is characterized as short stature. Based on this classification, cases can be divided into proportionate and disproportionate short stature such as achondroplasia, hypochondroplasia, and multiple epiphyseal dysplasia [31,32]. Further etiology includes nutritional, gastrointestinal, and endocrinal factors [6]. Endocrine cause of short stature may be due to GH deficiency, of which LS is a subtype [31,32].

Certain characteristic features of LS remain common among patients from diverse origins. For instance, patients in their early childhood were observed with hypoglycemia due to low glucose level as output from the liver in the absence of IGF-1. A similar observation in our study family is that females in early childhood have been observed with hypoglycemia but not in males [13,33]. Other symptoms include delayed fontanel closure, “sunset eyes,” and shallow eye orbits. Patients from Mediterranean or Middle Eastern regions were noted with blue sclera [13]. Among these symptoms, shallow eye orbits and mild blue sclera were observed in our study family. Hair was silky and growth was sparse in 401 in early

childhood. Similar conditions were observed in our study family.

In the current study, nucleotide substitution c.508G>C is detected which substituted amino acid aspartic acid at codon 170 with histidine. Another missense variant in the same codon (c.509A>G; p.(Asp170Gly)) has been reported in a Taiwanese family [34]. We concluded that the mutation underlies the pathogenesis since it segregates with the malformation in the family and has already been reported in two LS families of Asian origin [29] and another family from Pakistan [35]. Furthermore, the online bioinformatics tools predict this variant as pathogenic (Appendix A: Supplemental Table 3). This variant falls in the dimerization domain of GHR and is likely to perturb the expression, dimerization, and signaling of GHR [29]. At least 120 mutations are reported in *GHR* (HGMD; reviewed in Lin et al. 2018 [14]).

CONCLUSION

The strength of this study is that we present detailed clinical, hematological, and hormonal profiling of an LS family. Further, we applied high throughput genetic analysis methods of SNP-based genotyping and WES technology and successfully identified a pathogenic variant in *GHR*. This will help in genetic counseling of the studied family to prevent reoccurrence of disease in future generations. So, we concluded that SNP-based genotyping coupled with WES is a powerful technique to reach correct molecular diagnosis, particularly when there is no straightforward clinical diagnosis is available.

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Appendix A

Supplemental Table 1. Command line used in bioinformatics analysis of exome sequencing data and their purposes.

Purpose	Command
To download the reference genome assembly from UCSC	http://hgdownload.soe.ucsc.edu/goldenPath/hg19/bigZips/hg19.fa.gz
To unzip the file	gunzip file.fa
Concatenates all chromosomes of the reference genome sequence	cat file.fa > file.fasta
Indexes the references genome	bwa index -a bwtsw file.fasta
Aligns paired end reads to the reference genome	bwa mem -M -t 8 file.fasta File_1.fastq File_2.fastq > file.sam
Cleans up unusual FLAGs such as read pairing information in the sam records created by BWA	samtools fixmate -O bam file.sam file.bam
Sorts the bam file with chromosomal coordinates	samtools sort -O bam -o file.sorted.bam file.bam
For adding or replacing the Read Groups	java -jar picard.jar AddOrReplaceReadGroups I=file_sorted.bam O=file_sorted.RG.bam RGID=1 RGLB=lib RGPL=illumina RGPU=index RGSM=file_sorted.RG.bam
To create the .fai file	samtools faidx hg19.fasta
To generate the .dict file	java -jar picard.jar CreateSequenceDictionary R=hg19.fasta O=hg19.dict

To generate the .idx file	java -jar gatk-package-4.0.4.0-local.jar IndexFeatureFile -F dbsnp_138.hg19.vcf
To generate the .idx file	java -jar gatk-package-4.0.4.0-local.jar IndexFeatureFile -F 1000G_phase1.indels.hg19.sites.vcf
For Base Recalibrator	java -Xmx4g -jar gatk-package-4.0.4.0-local.jar BaseRecalibrator -R hg19.fasta --known-sites dbsnp_138.hg19.vcf --known-sites 1000G_phase1.indels.hg19.sites.vcf -I file_sorted.RG.bam -O file_recal_data.table
For Base Quality Score Recalibration	java -Xmx4g -jar gatk-package-4.0.4.0-local.jar ApplyBQSR -R hg19.fasta -I file_sorted.RG.bam --bqsr-recal-file file_recal_data.table -O file_sorted.realigned.recal.bam
For marking and removing the duplications	java -Xmx4g -jar picard.jar MarkDuplicates REMOVE_DUPLICATES=TRUE INPUT=file_sorted.realigned.recal.bam OUTPUT=file_sorted.realigned.recal.rmdup.bam METRICS_FILE=file_marked_dup_metrics.txt
For Bam Indexing	java -jar picard.jar BuildBamIndex I=file_sorted.realigned.recal.rmdup.bam O=File_sorted.realigned.recal.rmdup.bam.bai
For generation of ".vcf" file	java -jar gatk-package-4.0.4.0-local.jar HaplotypeCaller --genotyping-mode DISCOVERY -R hg19.fasta -I file_sorted.realigned.recal.rmdup.bam --dbsnp dbsnp_138.hg19.vcf -stand-call-conf 30 -O alam_raw_variants-new.vcf
For annotation	Upload the data at http://wannovar.wglab.org/

Supplemental Table 2. Homozygous intervals (>1 Mb) detected through SNP genotype analysis.

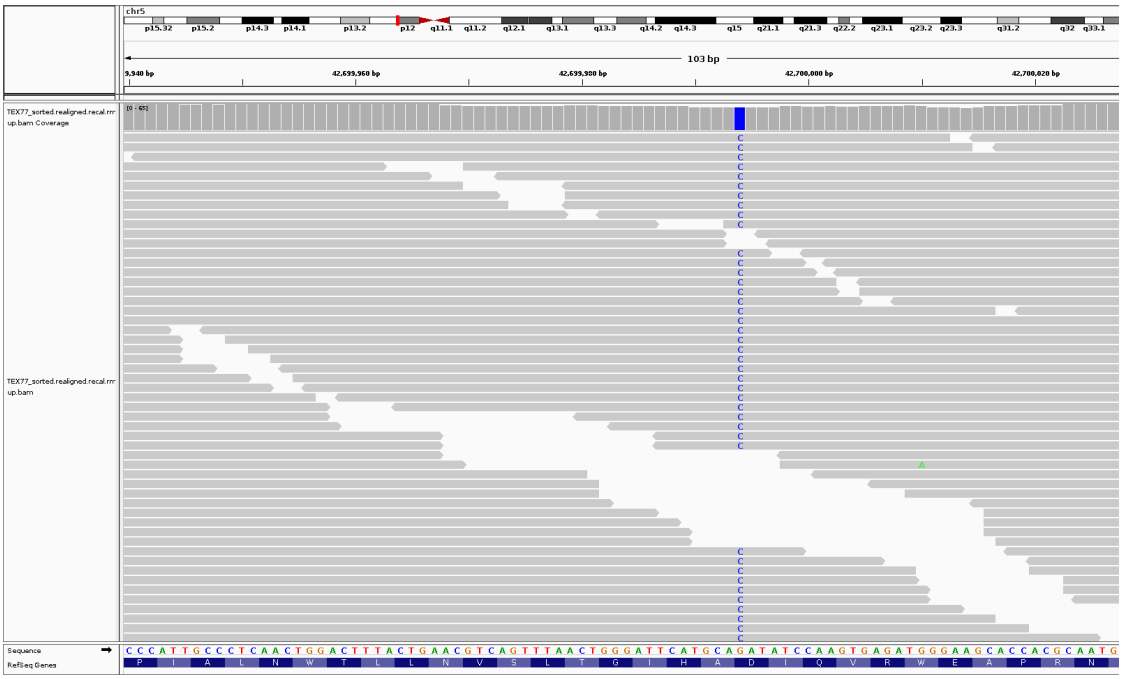
Chr	Start SNP	End SNP	Start position	End position	interval (Mb)	No. of genes in interval
1	rs10489636	rs2840310	160651750	161700827	1.05	79
2	rs12470303	rs890682	24619883	25948600	1.33	15
2	rs6436290	rs267993	157148002	158314418	1.17	10
3	rs9310681	rs7647724	22153897	29725062	7.57	58
3	rs7647724	rs6800757	29725062	31980606	2.26	13
3	rs6800757	rs2564926	31980606	53094730	21.11	426
3	rs2564926	rs3924042	53094730	57020736	3.93	29
3	rs9828514	rs4855586	107722014	108989277	1.27	17
4	rs7434819	rs7660477	158731019	159948180	1.22	16
5	**rs2930059**	**rs30364**	**10753399**	**55829376**	**45.08**	**288**
5	rs30364	rs317969	55829376	66686570	10.86	82
5	rs299099	rs7732361	68720419	70749745	2.03	45
6	rs7750580	rs1772987	1211523	2512075	1.30	8
6	rs1990665	rs4712274	13755585	16036551	2.28	12
6	rs4712274	rs10946363	16036551	20163330	4.13	39
6	rs9374450	rs10485113	114588786	116147191	1.56	2
7	rs17168173	rs10953348	96725713	101169691	4.44	143
7	rs10953348	rs39334	101169691	103453099	2.28	46
7	rs39334	rs2893638	103453099	106055504	2.60	27
7	rs12056021	rs17520243	118489794	119672864	1.18	2
7	rs17520243	rs10251692	119672864	120714700	1.04	5
7	rs10435433	rs11771946	138494588	140432893	1.94	38
7	rs11771946	rs929289	140432893	144112357	3.68	167
7	rs929289	rs826790	144112357	147027426	2.92	12
8	rs7388463	rs2945251	6974050	8094406	1.12	73
8	rs10105616	rs7003452	33906372	35021424	1.12	2
9	rs7853023	rs4275319	38772575	68513625	29.74	184
10	rs10751387	rs11259820	46141837	47588324	1.45	35
11	rs6486167	rs1792537	14114334	15168799	1.05	15
11	rs12275191	rs1532286	24087672	25818836	1.73	3
11	rs10767859	rs224612	30571347	32063229	1.49	12
11	rs10836878	rs4755505	37883072	39283877	1.40	4
11	rs687558	rs260864	102833618	103876114	1.04	8
14	rs9671696	rs6576199	105932544	107124500	1.19	168
15	rs4508302	rs748385	97218758	99143471	1.92	19

16	rs9930089	rs8048667	59208069	71048669	11.84	164
16	rs8048667	rs11859772	71048669	78965188	7.92	94
17	rs12943234	rs4796691	38861655	39883789	1.02	75
17	rs3999623	rs3785859	58308456	59379738	1.07	17
18	rs9948893	rs7235529	5190554	7369572	2.18	23
18	rs9946136	rs7239116	18249729	19486725	1.24	14
18	rs2156439	rs4464167	64724538	73303404	8.58	50
19	rs10413586	rs775883	59071321	60143609	1.07	5

Interval in bold indicates *GHR* gene locus

Supplemental Table 3. Pathogenicity score of detected variant through *in silico* tools.

No.	Tool	Pathogenicity score
1	Polyphen-2	Damaging; 0.899
2	MutationTaster	Disease causing automatic; 0.81
3	PROVEAN	Deleterious; -3.3
5	SIFT	Damaging; 0.912
6	M-CAP	Damaging; 0.041



Supplemental Figure 1. Integrative Genomics Viewer (IGV) snapshot of exome capture sequencing reads and alignment showing the detected variant (*GHR* c.508G>C) in patient 401.