# The original Lujan syndrome family has a novel missense mutation (p.N1007S) in the MED12 gene

Charles E Schwartz, Patrick S Tarpey, Herbert A Lubs, Alain Verloes, Melanie M May, Hiba Risheg, Michael J Friez, P Andrew Futreal, Sarah Edkins, Jon Teague, Sylvain Briault, Cindy Skinner, Astrid Bauer-Carlin, Richard J Simensen, Sumy M Joseph, Julie R Jones, Josef Gecz, Michael R Stratton, F Lucy Raymond and Roger E Stevenson

*J. Med. Genet.* 2007;44;472-477; originally published online 16 Mar 2007; doi:10.1136/jmg.2006.048637

LETTER TO JMG

# The original Lujan syndrome family has a novel missense mutation (p.N1007S) in the *MED12* gene

**Charles E Schwartz, Patrick S Tarpey, Herbert A Lubs, Alain Verloes, Melanie M May, Hiba Risheg, Michael J Friez, P Andrew Futreal, Sarah Edkins, Jon Teague, Sylvain Briault, Cindy Skinner, Astrid Bauer-Carlin, Richard J Simensen, Sumy M Joseph, Julie R Jones, Josef Gecz, Michael R Stratton, F Lucy Raymond, Roger E Stevenson**

*J Med Genet* 2007;**44**:472–477. doi: 10.1136/jmg.2006.048637

A novel missense mutation in the mediator of RNA polymerase II transcription subunit 12 (*MED12*) gene has been found in the original family with Lujan syndrome and in a second family (K9359) that was initially considered to have Opitz–Kaveggia (FG) syndrome. A different missense mutation in the *MED12* gene has been reported previously in the original family with FG syndrome and in five other families with compatible clinical findings. Neither sequence alteration has been found in over 1400 control X chromosomes. Lujan (Lujan–Fryns) syndrome is characterised by tall stature with asthenic habitus, macrocephaly, a tall narrow face, maxillary hypoplasia, a high narrow palate with dental crowding, a small or receding chin, long hands with hyperextensible digits, hypernasal speech, hypotonia, mild-to-moderate mental retardation, behavioural aberrations and dysgenesis of the corpus callosum. Although Lujan syndrome has not been previously considered to be in the differential diagnosis of FG syndrome, there are some overlapping clinical manifestations. Specifically, these are dysgenesis of the corpus callosum, macrocephaly/relative macrocephaly, a tall forehead, hypotonia, mental retardation and behavioural disturbances. Thus, it seems that these two X-linked mental retardation syndromes are allelic, with mutations in the *MED12* gene.

Identification of the gene mutations responsible for X-linked mental retardation (XLMR) syndromes has been the dominant force in linking syndromes previously considered as separate entities on clinical criteria alone.[1] Notable among the XLMR syndromes so linked are those associated with mutations in L1 cell-adhesion molecule , aristaless-related homoeobox, X-linked nuclear protein, filamin A and polyglutamine tract binding protein 1 genes.[1–7] In some instances, the linked syndromes have overlapping clinical manifestations (eg, L1 cell-adhesion molecule gene mutations in MASA (mental retardation, aphasia, shuffling gait, adducted thumbs) syndrome, X-linked hydrocephaly and spastic paraplegia type 1), and in other instances the linked entities exhibit rather disparate clinical presentations (eg, filamin A gene mutations in periventricular nodular heterotopia, Melnick–Needles syndrome and otopalatodigital syndrome).[1 6 7]

A recurrent mutation (c.2881C→T, p.R961W) in exon 21 of the mediator subunit 12 gene (*MED12*, also known as *HOPA* and *TRAP230*) has been found in the original family with FG syndrome and in five other families with compatible clinical findings.[8] In this communication, we report that the original family with Lujan syndrome (also known as Lujan–Fryns syndrome and XLMR with Marfanoid features) has a separate sequence alteration (c.3020A→G, p.N1007S) in exon 22 of the *MED12* gene. It seems that these two XLMR syndromes, previously considered separate and phenotypically distinct, are allelic, with different mutations in the *MED12* gene.

## CASE REPORTS

### Kindred 8295

Figure 1 shows an updated partial pedigree of kindred 8295 (K8295), the original family described as having Lujan syndrome.[9] An additional affected individual (V-9) has been born since the initial family report, and one individual (IV-9) previously considered to be affected is now found to be phenotypically different from the affected males. Table 1 summarises the measurements, clinical findings and intelligence quotient (IQ; as determined by the Stanford–Binet Intelligence Scale[10]) in affected males. The affected males IV-2, IV-5 and V-9 were ⩾8 cm taller than their fathers, and IV-12 was as tall as his father. Table 2 gives a comparison of the findings in Lujan syndrome with those in FG syndrome. Carriers had normal craniofacies, ranged in height from 160 to 173 cm (35–95th centile) and had head circumferences from 54.9 to 57.6 cm (60–97th centile). Their IQ measurements (Kaufman Brief Intelligence Test)[11] ranged from 83 to 102. Four affected males and two carrier females had thyroid function studies (serum thyroid-stimulating hormone, free and total triiodothyronine, free and total thyroxine), all of which were normal.

IV-2 was aged 17 years when initially reported. He was re-evaluated at ages 27 and 41 years. He had no malformations, but did have dysmorphic facies, broad thumbs, hyperextensible joints, mild pectus excavatum, flexion contractures at the right elbow and both knees, global developmental delay, seizures, hypotonia and hypernasal speech (fig 2). In addition, he had macrocephaly, a keel-shaped forehead, a long narrow face, minimally downslanted palpebrae, an open mouth, a tall narrow palate, crowded teeth, a small chin and abnormal ears (flattened superior helix on the right, deficient folding of lateral helix on the left, absent lobes). Testes were small (13 ml, 6 ml). In his youth he was aggressive, but is now more passive. He lives in a group home. His IQ was 42.

IV-5 was evaluated multiple times between the ages of 4 and 35 years. He had global developmental delay, hypotonia, hypernasal speech and an easy-going personality. He had a febrile seizure in infancy. He had macrocephaly and a long narrow face with high nasal root, ptosis, unfolded left helix, irregular right lateral helix, a short philtrum with prominent philtral pillars, an open mouth, a tall narrow palate, crowded teeth and a small jaw (fig 2). He was tall and asthenic, the wrists and fingers were mildly hyperextensible, the thumbs

**Abbreviations:** FG syndrome, Opitz–Kaveggia syndrome; IQ, intelligence quotient; K8295, kindred 8295; MED12, mediator of RNA polymerase II transcription subunit 12; XLMR, X-linked mental retardation

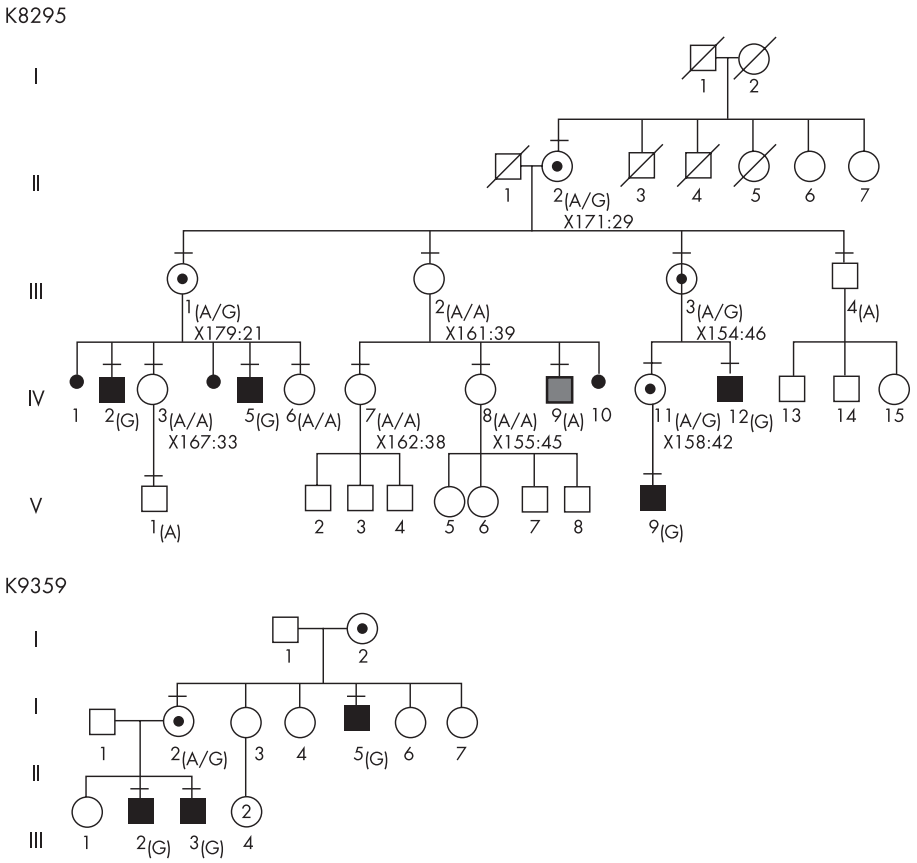


**Figure 1** Partial pedigrees of kindred 8295 showing four affected males in two generations, and K9359 showing three affected males in two generations. The numbering in K8295 is the same as in Lujan *et al*.[9] Note that individual IV-9 (hatched square) has mental retardation, but is different phenotypically from the affected males and does not have the p.N1007S *MED12* mutation. The horizontal bar above a symbol indicates an individual evaluated. A, wild-type allele at nucleotide 3020; G, mutant allele at nucleotide 3020; A/G, carrier female. XI indicates the ratio of active to inactive allele in female carriers.

were not broad and there was no pectus abnormality. He lives in a group home. His IQ was 60.

IV-12 was aged 19 years when initially reported and was re-evaluated at ages 29 and 42 years (fig 2). He had global developmental delay and behavioural problems. He had macrocephaly, dolichocephaly, a tall narrow face with prominent forehead, a high nasal root, hypotelorism, a narrow nose, a flat mid-face, a high narrow palate, crowded teeth and a swollen lower face (due to dental infection, at least on the right). The hands and fingers were long, and the thumbs were broad. The large joints were not hyperextensible, but the fingers were. Testes measured 26.5 ml bilaterally, and bilateral varicoceles are present. IV-12 is married to an intellectually impaired woman and they live alone, but under supervision. He is quite anxious, obsessive–compulsive, talks constantly and seeks attention. His IQ was 59.

V-9 was born after the initial report and was evaluated at ages 10 and 23 years. He has been diagnosed with Asperger syndrome. He was hyperactive, spoke loudly with a projected voice, and was attention seeking and aggressive. He was tall (>97th centile), with a large head (85th centile), and had large hands and feet. The face was tall and narrow with a normal nose, short philtrum and tall palate (fig 2). There was no chest deformity. There was no history of hypotonia; the joints were not hyperextensible but the feet were flat. The testes were approximately 25 ml (comparison with Prader beads). His IQ was 78.

In the original report, IV-9 was considered to be affected, although he differed from the other affected males in that he lacked an asthenic habitus and long hyperextensible digits and had more severely impaired cognitive function. He was re-evaluated at 42 years and was found to be quite different from IV-2, IV-5, IV-12 and V-9. He never developed speech and was unable to attend school or undergo cognitive testing. He was not hypotonic nor did he drool. He was considered aloof, had a fixation on newsprint and shapes, rocked from side to side, had a high level of anxiety, was constantly moving and was not aggressive. He had normal height (65th centile) and head size (55th centile), normal hand length (50th centile) and was said to have the facial appearance of his father. He had male pattern balding, downslanting palpebral fissures, a prominent nasal root, and no facial hypotonia. Musculoskeletal examination was normal. Vineland Adaptive Behavior Scale assessment gave a score of <20.[12]

## K9359

The proband was one of six siblings (partial pedigree shown in fig 1). One sister required special education and two maternal nephews (III-2 and III-3) had mental retardation.

II-5, the proband, had global developmental delay. Agenesis of the corpus callosum was found on cranial tomography. Examination at 19 years of age showed a small head (54 cm, 3rd centile), a long narrow face with high square forehead, a bulbous nasal tip, flat malar area, a short philtrum, a bowed upper lip, a prominent lower jaw and a hairy nevus on the right forearm. The testes appeared large. He was considered to have moderate to severe cognitive impairment. His speech was limited and difficult to understand. Behaviour was marked by temper tantrums and aggressiveness. His findings were initially considered to be consistent with FG syndrome.

III-2 had a birth weight of 3450 g and a length of 50 cm at term delivery. He experienced global developmental delay of moderate severity and had a tendency to opisthotonic posturing during early childhood. As a teenager he was tall and slender, with a long face and high forehead, short philtrum, small mouth and narrow palate, and crowded teeth (table 1 and fig 3).

**Table 1** Measurements and clinical manifestations in affected males in kindred 8295

| | K8295 | | | | | | | | | | | K9359 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | IV-2 | | | IV-5 | | | IV-12 | | | V-9 | | II-5 | III-2 | III-3 |
| Age, years | 14 | 27 | 41 | 8 | 19 | 29 | 21 | 35 | 42 | 19 | 29 | 19 | 15 | 11 |
| Height, cm (centile) | 164 (60) | 175 (45) | 177.8* (65) | 132 (50) | 190 (>98) | 186.7 (95) | 181 (80) | 182.9 (85) | 185 (95) | 190 (>98) | 186.7 (95) | NA | 177 (90) | 149 (80) |
| Span, cm (centile) | – | – | 177.8 (30) | – | – | 193 (90) | – | – | – | – | 190.5 (85) | NA | 178 | 150 |
| Weight, kg (centile) | 50 (50) | 60.75 (5) | 75 (25) | 25 (50) | 57.7 (10) | – | 70.2 (40) | 85 (65) | 77.7 (35) | 57.7 (10) | – | NA | 52 (40) | 34 (40) |
| Head circumference, cm (centile) | 58 (>98) | 61.5 (>98) | 61.9 (>98) | 54 (80) | 59 (80) | 59 (90) | 58.5 (80) | 59.5 (95) | 59.7 (97) | 59 (80) | 59 (90) | 54 (3) | 56.5 (75) | 53.5 (45) |
| Interpupillary, cm (centile) | – | 5.5 (<3) | 6.1 (15) | – | – | 5.5 (<3) | 5.5 (<3) | 6.2 (25) | 5.4 (<3) | – | 5.5 (<3) | NA | NA | NA |
| Hand length, cm (centile) | – | 20.5 (85) | 20.0 (75) | – | – | – | 20.5 (85) | 20.5 (85) | 21.6 (>98) | – | – | NA | NA | NA |
| Ear length, cm (centile) | – | 6.1 (20) | 6.4 (45) | – | – | 5.5 (<3) | 6.3 (35) | 6.6 (65) | 6.1 (20) | – | 5.5 (<3) | NA | NA | NA |
| Agenesis of corpus callosum | + | | | † | | | NA | | | NA | | + | – | – |
| Tall narrow face | + | | | + | | | + | | | + | | + | + | + |
| High full nasal root | + | | | + | | | + | | | + | | + | + | + |
| Thin nose | + | | | + | | | + | | | – | | – | + | – |
| Ptosis | – | | | + | | | – | | | – | | + | – | – |
| Short philtrum | + | | | + | | | + | | | + | | + | + | + |
| Open mouth | + | | | + | | | – | | | – | | + | – | – |
| High narrow palate | + | | | + | | | + | | | + | | NA | + | NA |
| Crowded teeth | + | | | + | | | + | | | + | | NA | + | – |
| Micrognathia/retrognathia | + | | | + | | | + | | | – | | – | + | + |
| Broad thumbs | + | | | – | | | + | | | – | | – | NA | + |
| Hyperextensible fingers | – | | | + | | | + | | | – | | NA | NA | NA |
| Second toe longer | + | | | – | | | + | | | + | | NA | NA | NA |
| Testicular volume, ml | 13/6 | | | 30/30 | | | 26/26 | | | 25/22 | | ‡ | NA | NA |
| Behavioral disturbances | – | | | – | | | + | | | + | | + | + | + |
| IQ (Stanford–Binet IV) | 42 | | | 60 | | | 59 | | | 78 | | NA | NA | NA |

IQ, intelligence quotient; K8295, kindred 8295; NA, not applicable.
*Knees flexed.
†CT suggestive of agenesis of the corpus callosum.
‡Appeared large; not measured.

He was moderately mentally retarded and was hyperactive with outbursts of aggressiveness. Brain CT, EEG and hearing tests were normal.

III-3 was born at 34 weeks with a weight of 2450 g and a length of 48 cm. Development was globally delayed with walking at 2 years and first words at 4½ years. He was tall and thin, had scaphocephaly with a narrow face, upslanting palpebral fissures, a short philtrum and micrognathia (table 1 and fig 3). He had moderate mental retardation with limited verbal abilities and attention deficit hyperactivity disorder. Cranial MRI was normal.

**Table 2** Comparison of clinical findings in Lujan syndrome and Opitz–Kaveggia syndrome

| Major distinguishing findings | Lujan syndrome | FG syndrome |
|---|---|---|
| Tall stature | + | – |
| Hypernasal voice | + | – |
| High nasal root | + | – |
| Long hyperextensible digits | + | – |
| Macrocephaly | + | ± |
| Broad thumbs | ± | + |
| Frontal hair upsweep | – | + |
| Hypertelorism/telecanthus | – | + |
| Small ears | – | + |
| Persistent fetal finger pads | – | + |
| Horizontal palmar creases | – | + |
| Syndactyly | – | + |
| Anal anomalies | – | + |
| Childhood constipation | – | + |
| Genitourinary problems | – | + |
| Spasticity | – | + |
| **Major findings that overlap** | | |
| Agenesis of corpus callosum | High narrow palate, dental crowding | |
| Tall prominent forehead | Micrognathia/retrognathia | |
| Downslanting palpebrae | Hypotonia | |
| Strabismus | Seizures | |
| Maxillary hypoplasia | Mental retardation | |
| Open mouth | Behavioural disturbances | |

FG, Opitz–Kaveggia syndrome.

## MOLECULAR FINDINGS

As part of a systematic sequencing screen of 737 Vega annotated genes in 250 families with XLMR, a base alteration, c.3020A→G, was observed in the proband from the original Lujan syndrome family, K8295.[9 13] This change was subsequently confirmed to segregate with the Lujan phenotype in the family. Additionally, the alteration was not observed in 734 X chromosomes from normal males studied at the Greenwood Genetic Center, Greenwood, South Carolina, USA, nor in 719 control X chromosomes (227 males, 246 females) sequenced at the Wellcome Trust Sanger Institute, Hinxton, UK. X-Inactivation studies of carrier mothers did not detect skewing. The same alteration was found in the three affected males and the one available carrier female in K9359.

The c.3020A→G change results in the substitution of a serine residue for an asparagine at position 1007 (p.N1007S) in exon 22. The asparagine residue is contained within a region that is highly conserved in vertebrates.

## DISCUSSION

Lujan syndrome and FG syndrome are among the XLMR syndromes that have posed the greatest diagnostic challenges for clinicians.[9 14–18] Individuals with Lujan syndrome have tall stature with asthenic build, macrocephaly, a tall narrow face, maxillary hypoplasia, a high narrow palate with dental crowding, a small or receding chin, long hands with hyperextensible digits, hypernasal speech, hypotonia, mild-to-moderate mental retardation, behavioural abnormalities (hyperactivity, emotional lability, shyness, aggressiveness, autistic mannerisms and/or psychoses) and agenesis/dysgenesis of the corpus callosum. In FG syndrome, the major findings are agenesis of the corpus callosum, relative macrocephaly, facial dysmorphism (frontal hair upsweep, a high prominent

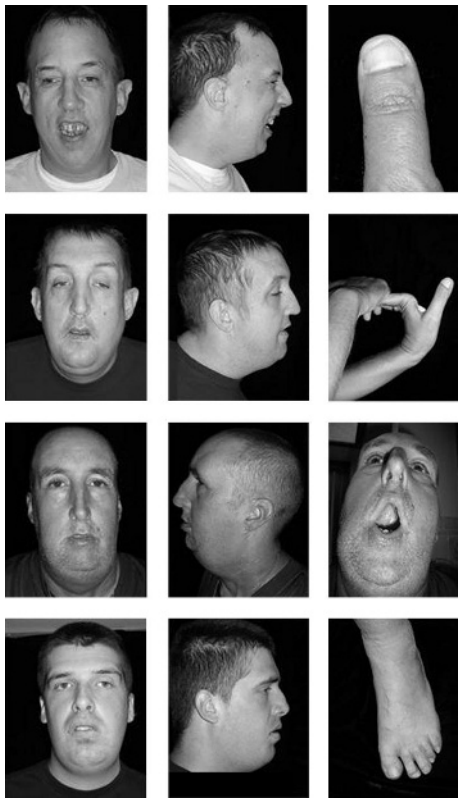

**Figure 2** Left and middle columns from top to bottom: frontal and profile views of IV-2, IV-5, IV-12, and V-9. Right column, top to bottom: broad thumb of IV-12, hand of IV-12 showing hyperextensible joints, narrow alveolar ridge of IV-12, foot of IV-2 showing the second toe slightly longer than the big toe. The patients and their legal guardians have provided consent for publication of these photographs.

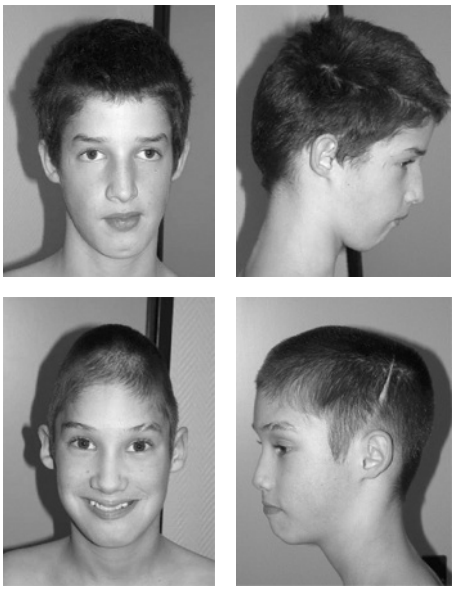

**Figure 3** K9359. Facial appearance of III-2 (top) and III-3 (bottom). III-2 at age 17 years has a tall thin face, full nasal root, thin nose, short philtrum and small mouth. III-3 at age 11 years has scaphocephaly, upslanting palpebral fissures, short philtrum and micrognathia. The patients and their legal guardians have provided consent for publication of these photographs.

forehead, hypertelorism, downslanting palpebrae, small cupped ears, a thin upper lip and a full lower lip), short hands with broad thumbs, broad big toes, anal anomalies/constipation, hypotonia, variable mental retardation and behavioural disturbances. Anal anomalies or constipation, which occur commonly in FG syndrome, have not been reported in Lujan syndrome. Tall stature, long hands and fingers, and hypernasal speech are to be expected in Lujan syndrome, but are absent or less notable in FG syndrome.

Certain findings—macrocephaly/relative macrocephaly, tall forehead, tall narrow palate with dental crowding, hypotonia, mental retardation, behavioural disturbances and dysgenesis of the corpus callosum—are shared by both syndromes (table 2). Apart from these similarities, neither of the syndromes has been considered in the differential diagnosis of the other.[19 20] None of the somatic findings is obligatory in either syndrome and some seem to be common among people with mental retardation.

Fryns and van den Berghe[16] have commented that the muscle hypotrophy, hypotonia, developmental delay and shyness were more notable in individuals with Lujan syndrome before puberty, whereas the Marfanoid habitus, more specifically the excess of span over height, became obvious only after puberty. Unfortunately, we do not have span measurements at various ages in the original family (K8295) to support this observation. Span centiles were less than height centiles in all the three adult males in whom measurements were available (table 1). In K9359, measurements during the teenage years showed that the span exceeded the height by only 1 cm in the two affected brothers.

A spectrum of behavioural disturbances, ranging from shyness to frank psychosis, has been noted among individuals with Lujan syndrome.[15 16 21] Some individuals, however, seem to be friendly, jovial and outgoing, without overt signs of behavioural disturbances.[22] In K8295, emotional lability, excessive talkativeness, attention seeking and anxiety were evident in two individuals (IV-12, V-9), whereas two others were more passive and cooperative, at least in adult life. In K9359, the males were hyperactive and prone to outbursts of aggression and tantrums.

The occurrence of mental retardation of apparently unrelated cause in the original family with Lujan syndrome reported here may be unsettling. Yet, the prevalence of mental retardation among males in the population (~3%) makes it probable that at least 1 out of 30 kindreds with XLMR will contain a minimum of one male with mental retardation of a different cause than other affected males in the kindred. An additional ascertainment bias may be seen among kindreds with multiple males with mental retardation.

The highly conserved MED12 protein, also known as HOPA and TRAP230, is the largest component of the mediator complex, which has an essential role in regulating RNA polymerase II activity.[23 24] The mediator complex contains a large number of subunits, some core elements and others like MED12, that serve as transcriptional facilitators for specific pathways. A number of studies highlight the importance of MED12 in model organisms where it seems to be essential for normal development.[25–27] Other studies have also implicated MED12 in specific developmental pathways. Boyer and colleagues have reported two specific findings that link MED12 to the Wnt/B-catenin pathway and to the sonic hedgehog pathway through direct interaction with Gli3.[28 29] Another report by Lehner *et al*[30] has also featured MED12 (*dpy-22* in *Caenorhabditis elegans*) as a highly connected ''hub'' gene with the potential to enhance phenotypic consequences of many different forms of genetic variation. The current data, along with other substantial functional studies, suggest that

## Key points

- A novel missense mutation (p.N1007S) in the *MED12* gene is present in the original family with Lujan syndrome and in a second family with compatible findings.
- Lujan syndrome is thus allelic to Opitz–Kaveggia (FG) syndrome, another X-linked mental retardation syndrome previously found to have mutations in the *MED12* gene.
- Lujan syndrome and FG syndrome share certain clinical findings (dysgenesis of the corpus callosum, macrocephaly, a tall forehead, a high palate, hypotonia, mental retardation and behavioural disturbances). Anal anomalies/constipation are common in FG syndrome, and tall stature, long hands and fingers, and hypernasal speech are common in families with Lujan syndrome.

MED12 and the entire mediator complex are involved in a broad range of developmental processes.

The p.N1007S alteration found in Lujan syndrome seems to significantly affect predicted protein folding domains within the MED12 protein. The presence of a serine at position 1007 removes a coiled region while also reducing the length of a β-pleated sheet based on Protean analysis (DNA Star package, Lasergene, Madison, Wisconsin, USA). Additionally, PolyPhen (http://tux.embl-heidelberg.de/ramensky/) analysis predicts the p.N1007S substitution to be possibly deleterious.

The evidence that Lujan syndrome is caused by the p.N1007S alteration in *MED12* rests with (1) identification of the alteration in the original family with Lujan syndrome, (2) identification of the same alteration in a second family with compatible clinical findings, (3) an earlier report of another missense variant in *MED12* in FG syndrome, an XLMR syndrome with clinical findings overlapping those of Lujan syndrome, (4) absence of the missense variation in over 1400 control X chromosomes, and (5) computer protein modelling, which indicates that the alteration is probably pathogenic.

A certain deference should be accorded kindred 8295, which is the prototype for Lujan syndrome.[9] Only those kindreds/cases with a compatible clinical phenotype and mutations in the *MED12* gene should retain the diagnosis of Lujan syndrome. Consideration should be given to reclassification for those kindreds/cases reported subsequent to K8295 that do not have mutations in the *MED12* gene. With this approach, the phenotypic boundaries of Lujan syndrome (ie, those cases with mutations in the *MED12* gene) may be determined.

## ACKNOWLEDGEMENTS

We thank the family K8295 for their cooperation over a period of more than two decades. This work was supported by grants from the National Institute of Child Health and Human Development (HD 26202 to CES), the South Carolina Department of Disabilities and Special Needs, the Wellcome Trust, and the Australian NH and MRC Programs (400121 to JG). This paper is dedicated to the memory of Ethan Francis Schwartz, 1996–1998.

## Authors' affiliations

**Charles E Schwartz, Herbert A Lubs, Melanie M May, Hiba Risheg, Michael J Friez, Cindy Skinner, Astrid Bauer-Carlin, Richard J Simensen, Sumy M Joseph, Julie R Jones, Roger E Stevenson,** JC Self Research Institute of Human Genetics, Greenwood Genetic Center, Greenwood, South Carolina, USA
**Patrick S Tarpey, P Andrew Futreal, Sarah Edkins, Jon Teague, Michael R Stratton,** Cancer Genome Project, Wellcome Trust Sanger Institute, Hinxton, UK
**Alain Verloes,** Department of Genetics, Clinical Genetics Unit, Robert Debre University Hospital, Serurier, France
**Sylvain Briault,** Laboratoire de Génétique Chromosomique, Centre Hospitalier Régional d'Orléans, Orléans, France
**Josef Gecz,** Departments of Paediatrics and Molecular Biosciences, University of Adelaide, Adelaide, Australia
**F Lucy Raymond,** Cambridge Institute of Medical Research, University of Cambridge, Addenbrookes Hospital, Cambridge, UK

Competing interests: None.

The patients and their legal guardians have provided consent for publication of the patient images in figs 2 and 3.

Correspondence to: Dr R E Stevenson, JC Self Research Institute of Human Genetics, Greenwood Genetic Center, 113 Gregor Mendel Circle, Greenwood, SC 29646, USA; res@ggc.org

Received 20 December 2006
Revised 23 February 2007
Accepted 27 February 2007
**Published Online First 16 March 2007**

## REFERENCES

1 **Stevenson RE**. Splitting and lumping in the nosology of XLMR. *Am J Med Genet* (*Semin Med Genet*), 2000;**97**:174–82.
2 **Vits L**, Van Camp G, Coucke P, Fransen E, De Boulle K, Reyniers E, Korn B, Poustka A, Wilson G, Schrander-Stumpel C, Winter RM, Schwartz C, Willems PJ. MASA syndrome is due to mutations in the neural cell adhesion gene L1CAM. *Nat Genet* 1994;**7**:408–13.
3 **Strømme P**, Mangelsdorf ME, Shaw MA, Lower KM, Lewis SM, Bruyere H, Lutcherath V, Gedeon AK, Wallace RH, Scheffer IE, Turner G, Partington M, Frints SG, Fryns JP, Sutherland GR, Mulley JC, Gecz J. Mutations in the human ortholog of Aristaless cause X-linked mental retardation and epilepsy. *Nat Genet* 2002;**30**:441–5.
4 **Bienvenu T**, Poirier K, Friocourt G, Bahi N, Beaumont D, Fauchereau F, Ben Jeema L, Zemni R, Vinet MC, Francis F, Couvert P, Gomot M, Moraine C, van Bokhoven H, Kalscheuer V, Frints S, Geca J, Ohzaki K, Chaabouni H, Fryns JP, Desportes V, Beldjord C, Chelly J. ARX, a novel Prd-class-homeobox gene highly expressed in the telencephalon, is mutated in X-linked mental retardation. *Hum Mol Genet* 2002;**11**:981–91.
5 **Kitamura K**, Yanazawa M, Sugiyama N, Miura H, Iizuka-Kogo A, Kusaka M, Omichi K, Suzuki R, Kato-Fukui Y, Kamiirisa K, Matsuo M, Kamijo S, Kasahara M, Yoshioka H, Ogata T, Fukuda T, Kondo I, Kato M, Dobyns WB, Yokoyama M, Morohashi K. Mutation of ARX causes abnormal development of forebrain and testes in mice and X-linked lissencephaly with abnormal genitalia in humans. *Nat Genet* 2002;**32**:359–69.
6 **Robertson SP**, Twigg SR, Sutherland-Smith AJ, Biancalana V, Gorlin RJ, Horn D, Kenwrick SJ, Kim CA, Morava E, Newbury-Ecob R, Orstavik KH, Quarrell OW, Schwartz CE, Shears DJ, Suri M, Kendrick-Jones J, Wilkie AO. OPD-spectrum Disorders Clinical Collaborative Group. Localized mutations in the gene encoding the cytoskeletal protein filamin A cause diverse malformations in humans. *Nat Genet* 2003;**33**:487–91.
7 **Stevenson RE**, Bennett CW, Abidi F, Kleefstra T, Porteous M, Simensen RJ, Lubs HA, Hamel BC, Schwartz CE. Renpenning syndrome comes into focus. *Am J Med Genet A* 2005;**134**:415–21.
8 **Risheg H**, Graham JM Jr, Clark RD, Rogers RC, Opitz JM, Moeschler JB, Peiffer AP, May M, Joseph SM, Jones JR, Stevenson RE, Schwartz CE, Friez MJ. A recurrent mutation in MED12 leading to R961W causes Opitz–Kaveggia syndrome. *Nat Genet* 2007;**39**:451–3.
9 **Lujan JE**, Carlin ME, Lubs HA. A form of X-linked mental retardation with Marfanoid habitus. *Am J Med Genet* 1984;**17**:311–22.
10 **Thorndike RL**, Hagen EP, Sattler JM. *The Stanford–Binet Intelligence Scale*, 4th edn. Chicago: Riverside Publishing Company, 1986.
11 **Kaufman AS**, Kaufman NL. *Kaufman Brief Intelligence Test*, 2nd edn. Circle Pines, Minnesota: American Guidance Service, 2004.
12 **Sparrow SA**, Balla DA, Cicchetti DV. *Vineland Adaptive Behavior Scale*. Circle Pines, Minnesota: American Guidance Service, 1984.
13 **Tarpey PS**, Stevens C, Teague J, Edkins S, O'Meara S, Avis T, Barthorpe S, Buck G, Butler A, Cole J, Dicks E, Gray K, Halliday K, Harrison R, Hills K, Hinton J, Jones D, Menzies A, Perry J, Raine K, Shepherd R, Small A, Tofts C, Varian J, Widaa S, Yates A, Catford R, Brant J, Mallya U, Moon J, Luo Y, Dorkins H, Thompson D, Easton DF, Wooster R, Bobrow M, Carpenter N, Simensen RJ, Schwartz CE, Stevenson RE, Turner G, Partington M, Gecz J, Stratton MR, Futreal PA, Raymond FL. Mutations in the gene encoding the sigma 2 subunit of the adaptor protein 1 complex, AP1S2, cause X-linked mental retardation. *Am J Hum Genet* 2006;**79**:1119–24.
14 **Fryns JP**, Buttiens M. X-linked mental retardation with Marfanoid habitus. *Am J Med Genet* 1987;**28**:267–74.
15 **Lalatta F**, Livini E. Selicornia A, Brisciolo V, Vita A, Lugo F, Zollino M, Gurrieri F, Neri G. X-linked mental retardation with Marfanoid habitus: first report of four Italian patients, *Am J Med Genet* 1991;**38**:228–32.
16 **Fryns JP**, Van Den Berghe H. X-linked mental retardation with Marfanoid habitus: a changing phenotype with age? *Genet Couns* 1991;**2**:241–4.

17 **Opitz JM**, Kaveggia EG. Studies of malformation syndromes of man XXXIII: the FG syndrome. An X-linked recessive syndrome of multiple congenital anomalies and mental retardation. *Z Kinderheilk* 1974;**117**:1–18.
18 **Battaglia A**, Chines C, Carey JC. The FG syndrome: report of a large Italian series. *Am J Med Genet A* 2006;**140**:2075–9.
19 **Stevenson RE**, Schwartz CE, Schroer RJ. *X-linked mental retardation*. New York: Oxford University Press, 2000.
20 **Van Buggenhout G**, Fryns J-P. Lujan–Fryns syndrome (mental retardation, X-linked, Marfanoid habitus). *Orphanet J Rare Dis* 2006;**1**:26.
21 **Lerma-Carrillo I**, Molina JD, Cuevas-Duran T, Julve-Correcher C, Espejo-Saavedra JM, Andrade-Rosa C, Lopez-Muñoz F. Psychopathology in the Lujan–Fryns syndrome: report of two patients and review. *Am J Med Genet A* 2006;**140**:2807–11.
22 **Rivera H**, Ramírez-Dueñas ML, García-Ochoa C. Lujan syndrome in a Mexican boy. *Am J Med Genet* 1992;**43**:626–7.
23 **Fondell JD**, Ge H, Roeder RG. Ligand induction of a transcriptionally active thyroid hormone receptor coactivator complex. *Proc Natl Acad Sci USA* 1996;**16**:8329–33.
24 **Blazek E**, Mittler G, Meisterernst M. The mediator of RNA polymerase II. *Chromosoma* 2005;**113**:399–408.
25 **Zhang H**, Emmons SW. A *C. elegans* mediator protein confers regulatory selectivity on lineage-specific expression of a transcription factor gene. *Genes Dev* 2000;**14**:2161–72.
26 **Treisman J**. Drosophila homologues of the transcriptional coactivation complex subunits TRAP240 and TRAP230 are required for identical processes in eye-antennal disc development. *Development* 2001;**128**:603–15.
27 **Hong SK**, Haldin CE, Lawson ND, Weinstein BM, Dawid IB, Hukriede NA. The zebrafish kohtalo/trap230 gene is required for the development of the brain, neural crest, and pronephric kidney. *Proc Natl Acad Sci USA* 2005;**102**:18473–8.
28 **Zhou H**, Kim S, Ishii S, Boyer TG. Mediator modulates Gli3-dependent Sonic hedgehog signaling. *Mol Cell Biol* 2006;**26**:8667–82.
29 **Kim S**, Xu X, Hecht A, Boyer TG. Mediator is a transducer of Wnt/beta-catenin signaling. *J Biol Chem* 2006;**281**:14066–75.
30 **Lehner B**, Crombie C, Tischler J, Fortunato A, Fraser AG. Systematic mapping of genetic interactions in Caenorhabditis elegans identifies common modifiers of diverse signaling pathways. *Nat Genet* 2006;**38**:896–903.